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Review article

The importance of preclinical diagnostics in Parkinson disease

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ABSTRACT

Given the increasing recognition that neurodegeneration begins decades before the appearance of motor symptoms of Parkinson disease (PD), recent attention has turned to methods of preclinical or prodromal diagnosis. Accurate preclinical diagnosis of individuals at high risk of developing manifest motor PD can improve clinical counseling as well as provide an enriched cohort for studies of possible disease-modifying therapies. In this review article, the authors synthesize the myriad clinical, radiographic, and biochemical signatures of preclinical PD, with an emphasis on biomarkers that may provide accurate population screening for the disease. As individual biomarkers have relatively lowsensitivity and specificity, any population-based approach to preclinical diagnosis will likely combine multiple biomarkers to improve both negative and positive predictive value.

1. Introduction

Since its initial description in 1817 [1], the diagnosis of Parkinson disease (PD) has centered on motor impairment. Currently accepted diagnostic criteria [2,3] require the presence of bradykinesia in addition to at least one other motor symptom, such as cogwheel rigidity or rest tremor. However, by the time motor signs appear, an estimated 60–80% of striatal dopamine neurons have already been lost [4,5]. Therefore, neurodegeneration and associated pathology appear to begin long before the onset of motor symptoms that lead to a clinical diagnosis of PD. Indeed, the Braak staging hypothesis [6] suggests that alpha-synuclein deposition begins in the olfactory bulb and the dorsal motor nucleus of the vagus nerve before propagating in a caudal-rostral fashion into the brainstem, the midbrain/substantia nigra (thus producing motor PD), and finally into the cortex. In this model, motor symptoms appear relatively late in the natural history of Lewy body-PD and indicate disease progression rather than onset of neurodegeneration.

The recognition that extensive, and perhaps irrevocable, pathology is already present once motor symptoms appear has led to the development of preclinical diagnostic tools for early identification of at-risk individuals. The long latent period of neurodegeneration may be subdivided into multiple phases, ranging from truly preclinical (completely asymptomatic and no clinical signs evident) to prodromal (evidence of non-motor or subtle motor dysfunction) to manifest motor PD. Early identification of incipient PD will allow for not only better prognostic counseling but also initiation of any possible neuroprotective therapies at a stage where they might be most effective. Here, we will review the major approaches to preclinical PD diagnosis tools, ranging from prodromal symptoms to advanced imaging techniques to blood and tissue based biomarkers. Additionally, we will examine the promise of multimodal approaches that combine these screening tools for preclinical PD and avenues for future investigation.

2. Prodromal symptoms

Prodromal PD [7] refers to individuals who do not currently fulfill diagnostic criteria for PD but who exhibit signs and symptoms indicating they may be at higher than average risk of developing motor PD in future. Since the onset of motor symptoms currently defines clinically manifest disease, most work in prodromal PD focuses on non-motor symptoms, which often predate the diagnosis of motor PD by years to decades and are major contributors to health-related quality of life [8–10]. Additionally, early identification of patients with prodromal symptoms provides an enriched cohort for studies of imaging or biochemical diagnostic tools, as well as for studies of putative neuroprotective strategies. The best-characterized markers of prodromal PD include hyposmia, constipation, sleep disturbances, and mood disorders.

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2.1. Hyposmia

Olfaction is impaired in over 90% of patients with motor PD at the time of diagnosis [11], compared to a prevalence of about 20% in the general population [12,13] and up to 50% in adults over 65 without PD [14]. Increasing evidence suggests that hyposmia begins several years before the onset of motor symptoms. In the Honolulu-Asia Aging study, individuals in the lowest quartile of smell identification (i.e. correctly identifying fewer than 5 of 12 odors on the Brief Smell Identification Test) had a 5.2-fold increased risk over developing PD over 4 years [15]. Similarly, a Dutch study of first degree relatives of individuals with PD found that 10% of subjects in the lowest decile of olfactory function developed PD within 2 years, compared to none of the normosmic subjects [16]. By contrast, olfaction is relatively preserved or normal in atypical parkinsonian syndromes, including multiple system atrophy, progressive supranuclear palsy, and corticobasal syndrome [17,18] and in drug-induced parkinsonism [19]. Additionally, olfaction is less impaired in certain monogenic PD cohorts, such as LRRK2 mutation carriers, than in sporadic PD [20], although it is still significantly different from non-mutation controls [21–23]. Thus, hyposmia appears to be a sensitive, though nonspecific, prodromal feature.

Olfactory loss may be measured in multiple ways, including odor identification (naming a specific odor, which may be free or cued from a list of choices), odor detection (perceiving odors at low concentrations), and odor discrimination (distinguishing between multiple odors); impairment in any of these is associated with future risk of PD. However, some studies suggest that odor discrimination is the best predictor for future PD and is inversely correlated with disease severity [24,25]. It is important to note that 63% of PD subjects are unaware of their hyposmia [26]; therefore objective testing is necessary to quantify the presence/absence and the degree of hyposmia. Notably, longitudinal or repeated assessment of olfaction reveals low levels of agreement between tests [27,28], suggesting that hyposmia reflects underlying disorganization of the olfactory system rather than dysfunction of specific odor pathways.

A number of bedside tests for hyposmia/microsmia have been developed. One of the earliest examples is the University of Pennsylvania Smell Identification Test (UPSIT) [29], a 40-item forced multiple choice “scratch-and-sniff” test, in which higher scores indicated better odor identification. The UPSIT can be self-administered and is both sensitive and specific for the detection of hyposmia in PD subjects [30], although differential item functioning analysis has identified poor performance of specific items such as rose, lemon, and turpentine [31–33]. This may be related to cultural factors rather than intrinsic item performance, as other studies have failed to identify PD-specific odorants [27,34]. The 12-item Brief Smell Identification Test (B-SIT) [35], previously called the Cross-Cultural Smell Identification Test (CC-SIT) [36], is derived from UPSIT items with high discrimination between PD subjects and controls and has been validated across multiple cultural and ethnic groups. Another modality for assessing olfaction is the Sniffin’ Sticks Test [37], a 16-item test incorporating odor threshold, discrimination, and identification. Sniffin’ Sticks may be more sensitive for the detection of hyposmia in prodromal PD [38] but requires a trained examiner to administer the test. For all tests of hyposmia, published normative values vary by age and gender.

2.2. Constipation

Another commonly noted prodromal PD feature is constipation, which may be related to Lewy body deposition in the dorsal motor nucleus of the vagus nerve and in the enteric nervous system [39]. After adjustment for diet, exercise, and cigarette smoking, the increased odds of developing PD for individuals with fewer than one bowel movement per day are between 2.3 and 4.5 compared to individuals with more frequent bowel movements [40–42]. Constipation is apparent as early as 25 years before the diagnosis of motor PD [41], making it one of the earliest recognizable prodromal features. Conversely, constipation may be a risk factor for PD, due to increased gut transmission of pathogens [43,44] which spread, prion-like, to the central nervous system by way of the vagus nerve. This view is supported by the fact that vagotomy appears to arrest the spread of synuclein from the enteric to the central nervous system [45]. Like olfactory loss, however, constipation is nonspecific [46] and may have a myriad of causes; the positive predictive value is therefore too low to be used in isolation as a preclinical marker of PD.

2.3. Sleep disturbance

REM sleep behavior disorder (RBD) is one of the best studied features of prodromal PD and is associated with the highest risk of conversion to motor PD. Multiple cohort studies of individuals with polysomnography-confirmed RBD indicate that between 50 and 70% will progress to develop a synucleinopathy over time [47–50], and the rate of conversion increases with age. Risk is about equally divided between idiopathic PD, often with prominent cognitive impairment, and dementia with Lewy bodies; a minority are diagnosed with multiple system atrophy [51]. Prediction of which synucleinopathy is likely to develop can be enhanced by metabolic imaging with radiolabeled fluorodeoxyglucose positron emission tomography (FDG-PET) [52] or metaiodobenzylguanidine single-photon emission computed tomography (MIBG-SPECT) [53] (discussed in detail below).

The dream enactment symptoms of RBD typically involve vocalizations and movements of the upper extremities [54] and may lead to inadvertent injury to the patient or their bed-partner. Patient-reported questionnaires have been developed for identification of individuals with RBD [55–57], but like patients with hyposmia, patients with RBD are typically not aware of their symptoms. Accurate collateral history from a bed-partner is usually sufficient to make the diagnosis; the freely available Mayo Sleep Questionnaire [http://www.mayoclinic.org/pdfs/MSQ-copyrightfinal.pdf], for instance, specifically enquires about dream enactment and has high sensitivity and specificity [58]. In questionable cases, polysomnography can be obtained, which will show decreased sleep spindle density in stage II sleep [59] along with absence of expected REM atonia on chin EMG. Given the specificity of RBD as a marker of synuclein deposition and the high risk of progression to a neurodegenerative syndrome, appropriate workup of suspected RBD is imperative.

2.4. Mood disorders

Mood changes are commonly noted prior to the onset of motor PD, perhaps due to involvement of the serotonergic raphé nuclei and the adrenergic locus coeruleus in Braak stage 2 [6]. Retrospective chart review demonstrates a higher risk of developing PD among individuals previously treated with antidepressants [60]; additionally multiple population-based registries have found a 2.4–2.7 fold odds ratio of depression in the years preceding incident PD diagnosis, with average time of 10.1 years between first depressive episode and PD diagnosis [61,62]. Similarly, individuals with prescriptions for anxiolytics or higher anxiety scores on the Minnesota Multiphasic Personality Inventory have a 1.6-fold increased risk of PD [63,64], lending credence to the anecdotal concept of a “premorbid parkinsonian personality” characterized by risk aversion and neuroticism [65]. Both apathy and anxiety are associated with reduced dopamine transporter levels, particularly in the right caudate nucleus [66,67], suggesting early dysfunction of the nigrostriatal system could manifest as behavioral symptoms in these individuals. Retrospective case-control analysis of the population-based Rotterdam study suggests that both anxiety and depression become significantly more common in cases only about 1–2 years before PD diagnosis [68]. Thus, mood disorders may be a relatively late preclinical marker of impeding motor PD.

In summary, a number of prodromal symptoms have been identified

in PD. Of these, RBD appears to have the highest positive predictive value for PD, while hyposmia, constipation, and mood disorders are relatively sensitive although non-specific. A combination of these symptoms may be used to identify individuals at higher risk of PD. For instance, an individual with RBD who develops hyposmia can then be assessed further with more advanced or refined tools to better quantify his risk of PD. Additionally, better defining these high-risk cohorts will be useful for providing enriched populations for studies of imaging and other diagnostic biomarkers.

3. Preclinical diagnostic imaging

3.1. Dopaminergic imaging

There are multiple potential imaging biomarkers for preclinical PD, encompassing structural, functional, and molecular approaches. Of these, perhaps the most widely studied is dopamine-based imaging. L-6-[^{18}F] fluoro-3,4-dihydroxyphenylalanine positron emission tomography (^{18}F-DOPA PET) assesses the activity of amino acid decarboxylase, which converts ^{18}F-DOPA to ^{18}F-dopamine. ^{18}F-DOPA PET imaging is both highly sensitive and specific for the diagnosis of PD [69]. However, the most widely used and commercially available modality is dopamine transporter (DAT) imaging. This technique involves the use of a radio-iodinated ligand, which binds to DAT on dopaminergic terminals in the striatum. Binding is then detected through single photon emission computed tomography (SPECT) scanning. In this way, a DAT scan directly assesses the integrity of the presynaptic nigrostriatal system, which is impaired in PD and other degenerative parkinsonisms yet preserved in other forms of tremor and in drug-induced parkinsonism. DAT scans identify areas of neuronal loss and predict post-mortem nigral cell counts [70]. In patients with early PD, DAT deficits are correlated with severity of bradykinesia and rigidity [71] and with the presence of cognitive impairment [72]. DAT scans have also been used to examine nigrostriatal integrity in individuals with suspected prodromal PD. In one cohort study of 20 individuals with idiopathic RBD and 20 controls, serial DAT imaging showed a progressive decline in presynaptic dopamine binding [73]; individuals ultimately diagnosed with PD within 3 years had both the lowest DAT binding at baseline and also a more rapid rate of decline compared to controls. Additionally, dopamine transporter imaging abnormalities have been detected in asymptomatic carriers of genetic mutations in LRRK2, a high-risk gene for PD [74], and in asymptomatic but hyposmic relatives of PD patients [75]. The sensitivity of DAT scan for the diagnosis of a neurodegenerative parkinsonian syndrome is about 92% with a specificity of 100% [76], although it should be noted that DAT does not distinguish between PD and atypical parkinsonian syndromes.

The strong physiologic correlation between DAT imaging and PD pathology makes it an attractive imaging biomarker candidate; however some important considerations, including cost, availability, and use of a radio-ligand, may limit its use in a clinical setting. Notably, longitudinal analysis of DAT deficit can be discordant with clinical severity and disease progression [77,78], potentially limiting its utility in the diagnosis of prodromal or preclinical PD, or as an endpoint for disease modification trials. Additionally, DAT scans can be falsely positive in the presence of certain drugs [79], most notably cocaine, amphetamines or amphetamine derivatives, buproprion, and benztropine. Washout periods for range from one day for methylphenidate to as long as 45 days for long-acting selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine. It is important to note that these common drugs do not necessarily preclude a diagnostic (qualitative) scan, though they should be discontinued prior to a research (quantitative) scan. From a logistical standpoint, long washout periods may limit both interpretation and ease of incorporating DAT scans into a diagnostic algorithm for preclinical PD. In light of this, tiered screening approaches may be preferable.

3.2. Transcranial sonography

Another promising candidate imaging biomarker for preclinical PD is non-invasive visualization of the substantia nigra using transcranial sonography through temporal bone windows [80]. Hyperechogenicity of the nigra suggests iron deposition [81] and microglial activation [82], both of which are important in the pathogenesis of PD; a positive scan is both sensitive and specific for preclinical PD compared to healthy controls [83]. In longitudinal cohort studies, a positive scan indicates a 21-fold increased risk of developing motor PD within 5 years [84]. Additionally, nigral echogenicity adequately distinguishes between PD and other movement disorders [85], as well as between subtypes of PD [86], which may have important implications in monitoring disease progression and response to therapy. One limitation of this technique is that some individuals may not have bone windows that allow adequate visual ultrasound visualization of midbrain structures. Additionally, nigral hyperechogenicity does not change over time [87] and can be seen in 9% of healthy controls [88], limiting its utility as a longitudinal clinical biomarker.

3.3. Magnetic resonance imaging

Iron deposition can also be assessed with advanced MRI techniques. On high resolution scanners, neuromelanin-sensitive T1-weighted spin echo sequences demonstrate attenuated signal in the lateral substantia nigra and the locus coeruleus for patients with both early and late motor PD compared to healthy controls [89,90], with a small but detectable effect of disease stage. Similarly, on susceptibility-weighted imaging sequences, nigrosome-1 in the posterior substantia nigra produces a characteristic hyperintense “swallow-tail sign” in healthy individuals, which is lost in early PD [91]. Loss of the normal swallow-tail has high sensitivity and specificity, as well as high inter-rater reliability, for the diagnosis of PD [91,92] and has been demonstrated in RBD [93]. Conceivably, a study in a preclinical cohort would demonstrate early changes in the locus coeruleus (Braak stage 2), possibly years before involvement of the lateral substantia nigra (Braak stage 3). Indeed, a recent cross-sectional analysis of patients with idiopathic RBD demonstrated loss of neuromelanin signal intensity in the locus coeruleus and subcoeruleus complex compared to healthy controls [94]; a prospective cohort study will be needed to identify how many of these patients later convert to motor PD. Other MR techniques, including diffusion tensor imaging [95] and voxel based morphometry [96], can adequately distinguish early PD from healthy controls on the basis of white matter tractography and gray matter volume respectively. Like neuromelanin sequences, however, investigations into preclinical disease are currently limited and prospective studies in prodromal cohorts will be needed to define the role of these markers [97,98].

3.4. Cardiac scintigraphy

Unlike imaging directed at CNS evidence of PD, cardiac scintigraphy with radiolabeled metaiodobenzylguanidine (MIBG) offers an opportunity to assess the integrity of the sympathetic nervous system that may be affected in prodromal disease. MIBG, an analog of norepinephrine [99], is taken up into the synaptic terminal and released in response to adrenergic stimuli but is not broken down. It is therefore a good marker of presynaptic post-ganglionic sympathetic innervation [100]. The ratio of heart-to-mediastium accumulation of radiolabeled MIBG at both early (20 min after administration) and late (4 h after administration) intervals may suggest relative sympathetic denervation. In PD, early involvement of the dorsal motor nucleus of the vagus nerve in Braak stage 1 leads to relative denervation of the cardiac sympathetic structures [101], and serial imaging demonstrates progressive sympathetic degeneration [102]. By contrast, in other degenerative parkinsonian syndromes, such as multiple system atrophy or progressive supranuclear palsy, cardiac sympathetic tone is thought to

remain normal [103], although recent studies have suggested that MIBG can be abnormal in up to 30% of individuals with multiple system atrophy [104]. MIBG scintigraphy is therefore both a sensitive and fairly specific biomarker of PD [105]. There is growing evidence that MIBG is reduced in prodromal cohorts prior to the onset of motor PD [106–109].

Some important limitations in MIBG scintigraphy should be acknowledged. Medications that interfere with sympathetic/parasympathetic balance, such as tricyclic antidepressants, sympathomimetic amines, or serotonin-norepinephrine reuptake inhibitors, can lead to a false positive MIBG scan [110]. Additionally, cardiac MIBG ratios in patients with genetic forms of PD appear to be more heterogenous or even normal [111–113], suggesting an alternative disease mechanism, such as autonomic neuropathy, may be contributing to sympathetic drive in these individuals compared to those with sporadic PD.

4. Biochemical biomarkers

4.1. Alpha-synuclein

As the molecular driver of PD pathology, alpha-synuclein (aSyn) has been heavily investigated as a potential biomarker for PD. However, despite intense study, aSyn assays in from blood and CSF have yielded disparate results [114,115]. Additionally, recent work [116,117] suggests that aSyn begins to aggregate in oligomers prior to the formation of Lewy bodies, and that oligomers might themselves be neurotoxic. Therefore, a PD vaccine targeting aSyn may be most effective if it is selective for the oligomeric form of the protein [118]. The ratio of oligomeric to total aSyn in red blood cells is higher in PD patients than in controls, although both sensitivity and specificity of the ratio are relatively poor and vary across studies [119,120]. Other groups have suggested that the key pathogenic step in the aggregation of aSyn into Lewy bodies involves post-translational phosphorylation [121,122], suggesting that assays specific to phosphorylated aSyn may improve sensitivity and specificity of disease detection [123,124]. Analysis of aSyn in the cerebrospinal fluid (CSF) has demonstrated increased oligomeric aSyn and decreased total aSyn in PD subjects compared to controls [114,115,125,126], and specificity may be enhanced with newer assays such as RT-QuiC [127] or PMCA [128]. Importantly, however, CSF aSyn does not appear to change in longitudinal cohorts [129], potentially limiting its utility as a biomarker.

Similarly, the sensitivity and specificity of tissue diagnosis is heavily influenced by surgical technique and site selection. Colonic biopsies have shown variable sensitive and specificity [130–132], possibly due to differences in local staining techniques [133]. Similarly, biopsy of the minor salivary or submandibular glands has shown mixed results [134–136], although biopsy in a higher-risk population, such as those with RBD, will increase the yield [137]. More recently skin biopsies stained for phosphorylated synuclein (pSyn) demonstrate high sensitivity and specificity for PD [138,139] and RBD [140]. Development of accurate and reproducible biofluid or tissue assays for aSyn that reflect important post-translational modifications including phosphorylation or oligomeric state remains elusive and represents one of the greatest unmet needs in PD biomarker research.

4.2. Other markers

Another protein which has been investigated as a potential PD biomarker is DJ-1, a marker of oxidative stress. Mutations in the gene encoding DJ-1 have been linked to early-onset recessive PD [141], and levels of DJ-1 are elevated in the blood and CSF in sporadic PD, distinguishing it from multiple system atrophy [142–144]. However, specificity is relatively low, perhaps because DJ-1 levels, as a marker of oxidative stress, are also elevated in multiple cancers [145–147], sepsis [148], and cardiac ischemic preconditioning [149]. Thus, DJ-1 may be a bystander marker of overall inflammation and cell death rather than a direct player in the pathogenesis of PD. However, development of a reliable biofluid DJ-1 assay remains of interest and is under active investigation.

Like DJ-1, uric acid is a marker of oxidative stress and is inversely correlated with PD risk and PD progression in men, but not women [150–152]. The reason for the sex difference is unclear and does not seem to be related to circulating estrogen levels [153]. There does not appear to be a racial or geographic difference in urate levels among PD subjects or healthy controls [154]. The consistent relationship between serum urate and PD risk has led to trials of inosine, a urate precursor, as a possible disease-modifying agent [155]. Administration of inosine has shown a measurable and dose-dependent increase in serum urate without obvious safety concerns [155,156]. Additional prospective studies including follow up in prodromal cohorts treated with inosine will be needed to determine whether increasing serum urate reduces PD risk.

Apolipoprotein A1 (ApoA1), which is involved in lipid metabolism, is associated with PD phenotype and age of onset, with low levels of ApoA1 predicting more severe disease and younger development of motor symptoms [157]. Additionally, in the Parkinson's Associated Risk Study (PARS) cohort (see below also) of hyposmic individuals, lower levels of ApoA1 were associated with decreased putaminal dopamine transporter binding [158], suggesting that serum apolipoprotein A1 may identify individuals at highest risk of developing PD. The sensitivity and specificity of plasma ApoA1 for conversion to manifest motor PD is moderate at 71% and 60% respectively [159]. It should be noted, however, that ApoA1 is a component of high density lipoproteins and thus may be falsely elevated in statin users [160]; data on the impact of statin therapy on the risk of Parkinson disease has been mixed [161–164].

5. Multimodal screening tools for prodromal PD

Given the mixed sensitivity and specificity of any one preclinical diagnostic tool for PD, it is apparent that an effective screening algorithm will have to be multimodal. The MDS prodromal criteria [7] specifically address this by combining likelihood ratios of various prodromal and risk factors in Bayesian analysis to determine a final probability of PD. Building off this model, Winkler et al. have proposed a “PD risk score” [165] identifying individuals with non-motor symptoms (hyposmia, RBD, depression, constipation, urinary dysfunction, orthostasis) and refining risk assessment with increasingly advanced technology. Similarly, Meles et al. used a combination of RBD, hyposmia, and DAT deficit to identify “Parkinson Disease Related Pattern” (PDRP) [166]; their ongoing cohort study of high and low PDRP clusters will show whether or not this is an effective preclinical screening tool. The PREDICT-PD algorithm [167] synthesizes mood symptoms, RBD, smell testing, genotyping, and keyboard-tapping tasks to divide individuals into high-, middle-, and low-risk groups. Recently published interim analysis at 3 years of follow-up [168] demonstrates a hazard ratio of 4.39 (95% confidence interval 1.03–18.68) for the diagnosis of PD in the high-risk group compared to the low-risk group. If found to be an effective screening tool, the online recruitment strategy of PREDICT-PD can be scaled up relatively easily to reach populations that may not have regular access to movement disorders specialty care.

The goal of these and other multimodal screening tools is to identify a population at significant risk of Parkinson disease both to improve counseling for individual patients as well as to identify a potential population for clinical trials of disease modifying agents. Because neurodegeneration begins years to decades before the onset of motor PD, the most appropriate time to start a disease modifying therapy is presumably during the asymptomatic or prodromal phase. Observational cohorts such as the Parkinson Progression Markers Initiative (PPMI) [169] and the PARS cohort [170] provide prospective data on prodromal and early PD in order to better enhance

understanding of disease risk and progression, and provide large multicenter samples for testing of biomarkers and advanced imaging techniques to refine the diagnosis of PD. While PPMI historically has recruited early PD, there is also a growing cohort of individuals with prodromal symptoms, who undergo serial imaging and biomarker assessment in order to determine rates of conversion. The PARS study, meanwhile, included 203 hyposmic individuals and 100 normosmic individuals without a diagnosis of PD. Hyposmic individuals with a baseline DAT deficit had a relative risk of conversion of 17.5 at four years compared to hyposmic individuals without DAT deficit [171].

With recent advances in genetic screening, there has been growing interest in genetic risk markers for PD [172,173]. Several recent studies [174,175] have assessed the influence of common mutations on PD risk. Most PD-related genes have incomplete penetrance; large genome-wide association studies [176,177] have attempted to derive a polygenic risk score, and ongoing genetic cohort studies [178] will prospectively determine the conversion risk for those with a strong family history or a known genetic mutation. As genetic technology becomes increasingly refined, it may be appropriate to incorporate genetic testing into the clinical assessment of preclinical and prodromal PD.

Currently, there exist multiple preclinical diagnostic tools and biomarkers for the detection of preclinical PD, ranging from non-invasive assessment of early non-motor symptoms such as hyposmia, sleep disturbances, and constipation, to advanced and potentially expensive imaging modalities and biochemical assays. Each of these carries some value in assessing an individual's risk of developing manifest motor PD; multimodal biomarkers provide additional insight into the onset and progression of neurodegeneration, which can in turn be used to further refine our understanding of the biomarkers themselves. However, high variation in sensitivity and specificity confounds the ability to use them effectively in screening individual patients. What are now needed are reliable and reproducible tests, administered in longitudinal studies of prodromal or other high-risk cohorts, in order to define a plausible and informative algorithm combining markers for the diagnosis of preclinical PD. In this way, effective treatments and disease-modifying interventions can be developed, in order, we hope, to halt neurodegeneration before the development of motor disability.

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