The search for markers of preclinical Parkinson disease (PD) is becoming increasingly important because pathogenesis-targeted neuroprotective strategies are being developed for future use in at-risk populations, even before clinical onset of disease. Advances in clinical recognition of early symptoms and signs, development of new neuroimaging probes and technologies, identification of new neuropathological markers of PD, and breakthroughs in genetics and basic neuroscience are gradually translating into better understanding of predisposing and preclinical factors that lead to progressive neurodegeneration. Coupled with system biology tools, progress is being made in the identification of new genomic, transcriptomic, proteomic, lipidomic, and metabolomic molecules and new signaling pathways that are relevant to the pathogenesis of neurodegeneration in PD. These new tools will be critical not only in the discovery of sensitive, specific, and reliable biomarkers of preclinical PD but also in the development of tests that will aid in the early detection and differential diagnosis of parkinsonian disorders and in monitoring disease progression.
CLINICAL BIOMARKERS OF PRECLINICAL PD

Growing evidence suggests that a variety of conditions can precede the classic motor features of PD. Symptoms and signs, suggested as possible premonitory features of PD, include essential tremor (ET), olfactory dysfunction, sleep disturbances, depression, anxiety, apathy, low impulsiveness, constipation, and other dysautonomic features.

Essential Tremor

Although a link between ET and PD has been debated for a long time, recent neuropathological studies provide additional support for the association of the 2 disorders. Furthermore, clinical epidemiological studies have indicated that a higher-than-expected proportion of patients with ET have coexistent PD; patients with PD often have preexisting ET, even since childhood; and there is a high prevalence of ET among their first-degree relatives. More recently, a large cohort study of 3813 older people in central Spain found that patients with ET are 4 times more likely than controls to develop PD.

Olfactory Dysfunction

Olfactory loss (hyposmia or anosmia) occurs in up to 90% of patients with PD and involves several impairments of odor detection, identification, and discrimination. An association between impaired olfaction and the future development of PD has also been found in population-based prospective studies. Furthermore, results of odor discrimination measures have been found to be related to disease severity, possibly indicating that at least some aspects of olfactory dysfunction in PD may be secondary to ongoing degenerative processes in PD. These and other studies support that olfactory dysfunction is a very early sign of idiopathic PD. Olfactory testing, combined with neuroimaging and neurochemical markers of central DA measured by the ratio of 6-fluorodopa F 18 uptake between the putamen and SN and between the putamen and caudate, and peripheral DA levels, indicated by cardiac 6-[18F]Fluorodopamine–derived radioactivity, distinguished PD from multiple-system atrophy. These results suggest that olfactory loss can predate the development of clinical PD by 2 to 7 years. The mechanism of olfactory loss in PD is not well understood, but it appears to be of central origin rather than due to damage to the olfactory epithelium.

Sleep Disturbances

Many studies have found that patients with PD have a variety of sleep disturbances, including rapid eye movement behavioral disorder (RBD), that precede the onset of motor symptoms by many years or even decades. In a long-term clinical follow-up of 93 patients with RBD, 14 developed parkinsonism, 7 met clinical criteria for Lewy body (LB) dementia, 4 met clinical criteria for Alzheimer disease, and 1 developed multiple-system atrophy. Patients with RBD are significantly less likely to have a tremor-dominant form of PD, have higher frequency of cognitive impairment and falls, and are less responsive to medications. Furthermore, in addition to motor impairment, patients with RBD have been found to have a high incidence of impaired color discrimination, olfactory dysfunction, and dysautonomia.

Oculomotor Disturbances

Loss of central dopaminergic pathways involved in oculomotor control probably accounts for the impairment of saccades, observed even in early PD, but saccadic latency and amplitude have not been found to be particularly sensitive measures of disease progression, chiefly because of marked intrasubject and intersubject variability and low reproducibility over time.

Constipation and Other Dysautonomic Features

Severe dysautonomia is generally present in the advanced stages of PD, when progression of the disease and adverse effects of treatment play a role in the development of these symptoms. When prominent dysautonomia occurs early...
In untreated patients with early PD, depression (37%), apathy (27%), sleep disturbances (18%), and anxiety (17%) are the most common neuropsychiatric symptoms. Other gastrointestinal tract motility problems such as regurgitation, nausea, and epigastric discomfort, likely related to gastroparesis, have also been reported to predate motor symptoms in some cases of PD. Sexual disturbances, orthostatic hypotension, and urinary disturbances are common in advanced stages of PD, but these autonomic features occasionally precede motor symptoms of PD. Because these various dysautonomic symptoms are very common in the general population and relatively nonspecific for neurodegenerative disorders, it is unlikely that they will emerge as reliable biomarkers of PD.

Mood Disorders and Other Neurobehavioral Abnormalities

In untreated patients with early PD, depression (37%), apathy (27%), sleep disturbances (18%), and anxiety (17%) are the most common neuropsychiatric symptoms. Several lines of evidence support the concept that depression in PD probably has a biological rather than a purely psychological reactive basis because it is detected in up to 27.6% of patients with PD in the early stages of the disease and it may precede the development of motor manifestations by several years. Several investigators have also commented on premorbid parkinsonian personality. Twin and other studies have suggested that patients with PD, even since childhood, are more introverted, serious, cautious, tense, nervous, obsessive-compulsive, inflexible, industrious, and honest; that they avoid risk-seeking behavior such as smoking; and that they are less likely to exhibit impulsive or novelty-seeking behavior compared with controls. Despite these characteristic psychological and personality changes occurring in early stages of PD, they are relatively nonspecific, and it is unlikely that these traits can be used to reliably predict increased risk of PD in the general population.

PATHOLOGICAL BIOMARKERS OF PRECLINICAL PD

The pathological hallmark of PD is degeneration of dopaminergic neurons in the SN pars compacta, coupled with intracytoplasmic proteinaceous inclusions known as LBs. Braak et al. have suggested that neurodegeneration of nondopaminergic neurons, particularly those in the caudal brainstem such as the dorsal motor nucleus of the vagus, precedes the onset of dopaminergic pathological changes in the SN pars compacta. This Braak hypothesis, which proposes that synuclein pathological changes in PD start in the lower brainstem and progress following a predictable caudal-rostral pattern, has been supported by the finding of reduced immunoreactivity for α-synuclein in the dorsal motor nucleus of the vagus. This Braak hypothesis has been challenged by the observation that α-synuclein may act like a prion and spread, possibly even from the periphery, and propagate throughout the nervous system in PD.

Incidental LB Disease

Lewy bodies are detected in the brains of about 10% of clinically normal people older than 60 years, and some have suggested that cases with such incidental LBs (ILBs) represent preclinical PD. This hypothesis is supported by the finding of reduced immunoreactivity for tyrosine hydroxylase and vesicular monoamine trans...
porter 2 in the putamen of these brains compared with those of healthy controls, and the decline in dopaminergic immunoreactivity correlates inversely with SN neuronal loss and PD stages. Decreased tyrosine hydroxylase immunoreactivity in the striatum and in the epicardial nerve fibers of the same individuals was also found in another study that compared the brains and hearts of patients with iLBs with those of healthy controls. The distribution of LBs in iLB disease is similar to the distribution in PD, but neuronal populations vulnerable to LB pathological changes do not show significant neuronal loss in brains with iLBs. These findings indicate that brains with iLBs have nigrostriatal pathological features that are intermediate between those found in healthy controls and those with PD and provide evidence that the presence of iLBs might represent preclinical PD.

### Olfactory Pathological Features

The anterior olfactory region in particular has been suggested to be one of the earliest sites of neurodegeneration in PD. Hawkes et al have revised the original LB staging scheme and proposed that synucleinopathy in PD begins in the olfactory bulb and within enteric cellplexuses. This has led to the so-called dual-hit hypothesis, which proposes that an unknown neurotropic pathogen initiates the pathological process underlying sporadic PD in an anterograde direction via olfactory pathways and in a retrograde direction, via enteric plexuses and preganglionic vagal fibers. The pathogen will then presumably enter the pons and then midbrain until the SN is reached and typical changes associated with PD emerge.

### Autonomic Nervous System

Several studies have provided evidence that the paravertebral sympathetic ganglia, the enteric system, and the epicardium are affected by synuclein pathological changes at early stages of PD. In an autopsy cohort of 98 neurologically unimpaired subjects 64 years or older, examination of the brain, the sacral and thoracic autonomic nuclei of the spinal cord, and several components of the peripheral autonomic nervous system with α-synuclein immunostaining showed that the autonomic nuclei of the spinal cord and the peripheral autonomic nervous system are consistently the earliest affected regions, after medullary structures and the olfactory nerves in neurologically unimpaired older individuals. This provides a pathological basis for early premotor autonomic dysfunction at a prodromal stage of PD. The frequent presence of α-synuclein aggregates in peripheral autonomic neurons (eg, abdominopelvic autonomic plexuses) may represent an early presymptomatic phase in the development of LB disorders. The involvement of the peripheral autonomic nervous system in PD is also supported by decreased cardiac uptake of iodine 123–labeled metaiodobenzylguanidine in single-photon emission computed tomography (SPECT) studies.

### Skin Changes

With the use of punch skin biopsy with immunostaining and a panneuronal marker for protein gene product 9.5, PD-related changes are found in the small-caliber cutaneous fibers, indicating involvement of the peripheral (skin) autonomic nervous system in early PD. There is no difference in skin biopsy scores between treated and untreated patients; therefore, the morphological findings are not related to anti-PD medications and probably reflect peripheral manifestation of PD. The presence of α-synuclein deposits in the dermis of a patient with pure autonomic failure provides evidence that this disorder and others associated with autonomic failure, including PD, dementia with LBs, and multiple-system atrophy, should be viewed as variant synucleinopathies.

### Neuroimaging Biomarkers of Preclinical PD

<table>
<thead>
<tr>
<th>Method</th>
<th>Biomarker</th>
<th>Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPECT</td>
<td>DAT SPECT</td>
<td>Helpful in diagnosis of preclinical PD, but not clear whether it changes with disease progression</td>
<td>Booij and Knol, 2007; Berti et al, 2008</td>
</tr>
<tr>
<td>PET</td>
<td>18F-fluorodopa and DAT PET</td>
<td>Very sensitive to detect preclinical PD but expensive and could be affected by levodopa</td>
<td>Panzacchi et al, 2008; Bolin et al, 2006; Hilker et al, 2005; Stoessel, 2007</td>
</tr>
<tr>
<td>Sonography</td>
<td>SN hyperchogenicity</td>
<td>Helpful in diagnosis of preclinical PD, but not clear whether it changes with disease progression</td>
<td>Zecca et al, 2005; Berg et al, 2008</td>
</tr>
<tr>
<td>fMRI</td>
<td>Iron in SN; fractional anisotropy in DTI</td>
<td>Helpful in diagnosis of preclinical PD, especially combined with using clinical biomarkers, but needs more prospective studies</td>
<td>Martin et al, 2008; Vaillancourt et al, 2009</td>
</tr>
<tr>
<td>Scintigraphy</td>
<td>MIBG</td>
<td>Helpful in diagnosis of preclinical PD but insensitive</td>
<td>Spiegel et al, 2007</td>
</tr>
</tbody>
</table>

Abbreviations: DAT, dopamine transporter; DTI, diffusion tensor imaging; fMRI, functional magnetic resonance imaging; MIBG, meta-iodobenzyl guanidine I 123; PET, positron emission tomography; PD, Parkinson disease; SN, substantia nigra; SPECT, single-photon emission computed tomography.
DAT SPECT

SPECT used to image DAT has consistently found reduced binding in patients with PD, which correlates with the severity and asymmetry of motor clinical scores.\(^6\)\(^\text{a}\)\(^4\) Measures of striatal N-\(\omega\)-fluoropropyl-2\(\beta\)-carbethoxy-3\(\beta\)-4\(\text{I}\)iodophenyl-nortropane (\(^{123}\text{I}\)FP-CIT) binding in patients with de novo PD correlated well with clinical scales of disease severity, even in the initial phases of the disease, suggesting that this imaging abnormality is a useful biomarker of early PD.\(^6\)\(^\text{d}\) DAT SPECT is also helpful for differentiating patients with PD from those who exhibit parkinsonian symptoms but have scans without evidence of dopaminergic deficit (SWEDDs).\(^6\)\(^\text{a}\)

Positron Emission Tomography

Positron emission tomography (PET) using carbon 11-labeled dihydroetrenzamine to label the vesicular monoamine transporter 2, a variety of \(^{11}\text{C}\)- or \(^{18}\text{F}\)-labeled ligands for DAT, or \(6\)-fluorodopa F 18, which assesses uptake and decarboxylation of levodopa and vesicular storage of radiolabeled dopamine, can all be used to detect premotor PD or the preclinical period of PD.\(^7\)\(^,\)\(^6\)\(^\text{1}\)\(^6\)\(^\text{4}\)\(^\text{b}\) Reduced DAT binding was the earliest indication of dopaminergic dysfunction in these individuals, indicating that DAT imaging provides a very sensitive index of subclinical deficits related to abnormalities in the nigrostriatal pathway.\(^6\)\(^\text{a}\) Imaging presynaptic dopaminergic terminals with \(^{11}\text{C}\)-dihydroetrenzamine PET can also show nigrostriatal deficits in preclinical PD and might serve as an objective biomarker of PD severity.\(^7\)

Although using PET for the preclinical diagnosis of PD is expensive and not widely available, continued longitudinal follow-up of the asymptomatic at-risk subjects is essential in studying the phenocconversion from preclinical dopaminergic dysfunction to clinical disease, in improving the estimate of the duration of the preclinical period, and in better characterizing the progression of PD.

Sonography

Several studies have indicated that SN hyperechogenicity, typically found in clinically manifest PD, might also be seen in subjects with a preclinical impairment of the nigrostriatal system. A significant positive correlation was found between the echogenic area of the SN and the concentration of iron and of H- or L-chain ferritins in postmortem brains compared with healthy subjects at different ages.\(^6\)\(^\text{a}\) The use of a combined approach, such as identification of olfactory and autonomic dysfunction, depression, RBD, and other premotor symptoms and detection of hyperechogenicity of the SN, may be an effective strategy for early diagnosis of PD.\(^6\)\(^\text{a}\)

Magnetic Resonance Imaging

Similar to sonography, high-field-strength magnetic resonance imaging (MRI) demonstrated abnormalities in the lateral SN pars compacta of early PD consistent with increased iron content, corresponding to the known distribution of neuronal loss.\(^6\)\(^\text{a}\) Furthermore, using high-resolution diffusion tensor imaging, fractional anisotropy was found to be reduced in the SN of patients with early untreated PD compared with controls.\(^6\)\(^\text{e}\) Post hoc analysis showed, as expected, that reduced fractional anisotropy in patients with PD was greater in the caudal compared with the rostral region of interest. A receiver operator characteristic analysis in the caudal SN showed that sensitivity and specificity were 100% for distinguishing patients with PD from healthy individuals. These findings provide evidence that high-resolution diffusion tensor MRI focusing on the SN distinguishes patients with mild PD from healthy individuals and has the potential to serve as a noninvasive biomarker of early PD.

GENETIC AND NEUROCHEMICAL BIOMARKERS OF PRECLINICAL PD

Although the presymptomatic phase of PD has not been well characterized, there is a general consensus that neuronal damage, as a result of complex genetic, environmental, and other factors, starts years or even decades before the onset of symptoms.\(^14\)\(^,\)\(^4\)\(^4\) Understanding these interactions may enable identification of early biomarkers of degeneration and aid in preclinical screening and, eventually, identification of molecules that can halt or delay the neurodegenerative process.\(^6\)\(^9\)\(^,\)\(^7\)\(^0\) This research will also provide insights into the variable penetrance of the various genetic forms of PD.\(^7\)\(^1\)

Using a variety of assays to measure \(\alpha\)-synuclein protein concentrations, several studies have shown that patients with PD have significantly lower \(\alpha\)-synuclein levels in their cerebrospinal fluid (CSF) than the control groups, even after adjusting for sex and age.\(^7\)\(^2\)\(^,\)\(^7\)\(^3\) Levels of \(\alpha\)-synuclein in the CSF have been found to be decreased in patients with parkinsonism linked to synucleinopathy, such as PD and dementia with LBs,\(^7\)\(^4\) and in patients with PD (\(n=177\)) compared with patients with Alzheimer disease (\(n=50\)) and healthy controls (\(n=132\)).\(^7\)\(^3\) One study suggested that \(\alpha\)-synuclein levels in lymphomonocytes are affected by age, sex, and 20S proteasome activity in controls.\(^7\)\(^5\) However, further studies are needed before quantification of \(\alpha\)-synuclein levels in the CSF or blood can be adopted as a potential laboratory marker in the clinical diagnosis of PD.\(^7\)\(^6\) (Table 2).

Although much attention has focused on the role of \(\alpha\)-synuclein in the pathogenesis of PD, a more common autosomal dominant PD detected in about 10% to 15% of familial cases is caused by mutations in \(LRRK2\) (OMIM *609007).\(^7\)\(^7\) Although responsible for only 1% to 2% of sporadic cases of PD, in some genetically isolated populations such as the Ashkenazi Jews\(^6\)\(^6\) and North African Arabs,\(^8\) the prevalence of some \(LRRK2\) mutations, such as G2019S, is much higher and reaches 30% to 40% in familial cases. Testing for such common gene mutations may evolve into a valuable screening tool in these enriched populations.

Levels of DJ-1 (OMIM *602533), another multifunctional protein with loss of its function in gene mutations associated with familial, autosomal recessive PD, have been found to be decreased in the CSF of patients with PD as determined by highly sensitive and quantitative assays (Luminex Corporation, Austin, Texas).\(^7\)\(^3\)
When combined with other CSF markers, including β-amyloid 1-42, total tau, and interleukin (IL) 8, these assays seem to be able to differentiate patients with PD from those with other neurodegenerative disorders, such as Alzheimer disease and multiple-system atrophy, and from healthy controls.84 Mutations in the parkin gene (OMIM *602544), identified as the major cause of autosomal recessive early-onset PD and several types of tumors,85 may result in an early-onset PD, and detection of such mutations may serve as a potential biomarker of PD.86 NURR1 (NR4A2) (OMIM *601828), encoding a member of nuclear receptor superfamily, is a transcription factor essential for the development, survival, and functional maintenance of midbrain dopaminergic neurons.10 We studied 278 patients with PD, 166 healthy controls, and 256 controls with neurological disease and found that NURR1 gene expression in human peripheral blood lymphocytes, as measured by quantitative real-time polymerase chain reaction analysis, was significantly decreased in patients with PD.79 Although it is unlikely that this will evolve into a reliable test for preclinical PD because of moderate overlap between the various study populations, measuring gene expression signals in blood is a potentially fruitful area of research into biomarkers for the prediction of PD. A transcriptome-wide scan in 105 individuals to interrogate the molecular processes perturbed in the cellular blood of patients with early-stage PD identified a pattern of 22 differentially regulated genes in peripheral blood leukocytes of patients with PD.80 These include the cochaperone ST13 (OMIM *606796), which stabilizes heat shock protein 70, a modifier of α-synuclein misfolding and toxicity. The investigators found that the number of ST13 messenger RNA copies is lower in patients with PD than in controls (mean [SE], 0.59 [0.05] vs 0.96 [0.09] copies; P = .002) in 2 independent populations. Thus, measuring gene expression signals in the blood can facilitate the search for biomarkers of PD. Furthermore, the simultaneous detection of multiple misregulated genes and their messenger RNA or protein expressions may have advantages compared with the determination of single proteins and may allow the identification of networks of interacting proteins that reflect the underlying disease process.

**OTHER POTENTIAL PD-RELATED BIOMARKERS**

There are many other clinical or laboratory abnormalities that can potentially serve as biomarkers for the prediction of PD. For example, several studies have found that urate, a potent antioxidant, could be a protective factor or a biomarker in the diagnosis of PD (Table 2).78,81,91-93 Using metabolomic profiling with high-performance liquid chromatography coupled with electrochemical coulometric array detection, Bogdanov et al81 found that uric acid levels were significantly reduced in patients with PD. Other studies have shown that higher urate levels in the blood and CSF may decrease the risk of PD and predict slow progression.78,81 These findings have led to a prospective, longitudinal study of inosine—a nutritional supplement known to raise urate levels—designed to determine whether pharmacologically elevating serum urate levels could be an effective disease-modifying therapy in PD.92 Despite its many limitations, this study is an example of how discovery of a potential biomarker can lead to an early therapeutic intervention.93

One study found that men with high plasma concentrations of IL-6, an index of inflammation thought to be important in the pathogenesis of PD, have an increased risk of developing PD.94 However, this finding should be interpreted with caution because of the small sample size and the lack of associations with other biomarkers of inflammation. More recently, another study also indicated that the elevation of IL-10 levels and the significant correlation between IL-10 and IL-12, a proinflammatory cytokine, suggests that immunological disturbances are involved in patients with PD,95 but its role as a biomarker for the early diagnosis of PD needs to be validated.

Other studies provide a signal for a potentially increased risk of PD. In a study of 236 patients, low levels of low-density lipoprotein were associated with a 3.5 times higher-than-expected risk for development of PD, and the follow-up study confirmed the association between low cholesterol levels and the risk of PD.96 Increased PD risk has been associated with decreasing darkness of hair color, with highest risk in red-haired and blond individuals, suggesting a role of pigmentation in the pathogenesis of PD.97 These reports, although interesting and worth pursuing, require validation before the findings can be considered as potential biomarkers of PD.

### NEW POTENTIAL TOOLS TO DISCOVER BIOMARKERS OF PRECLINICAL PD

Progress in our knowledge of the system biology tools, including genomics, proteomics, lipidomics, and metabolomics, and the use of microarray, spectroscopy, and...
other techniques to measure multiple-gene messenger RNA expression signals in various tissues, including blood, should facilitate the development of more sensitive and specific biomarkers for the prediction of PD. These advances should provide the basis for the development of new and reliable biomarkers of PD that eventually may be instrumental in the development of new treatment strategies. More recently, glycoproteomics, a branch of proteomics that catalogs and quantifies glycoproteins, provides a powerful means to systematically profile the glycopeptides or glycoproteins of a complex mixture that are highly enriched in body fluids, with the great potential to be diagnostic and even prognostic markers of neurodegenerative disorders such as PD. Metabolic profiling that uses electrophoresis and electrospray array detection to search for biomarkers in plasma may also uncover potentially useful biomarkers. One study, for example, showed that 8-hydroxy-2-deoxyguanosine levels (a marker of oxidative damage to DNA) were significantly increased in patients with PD but overlapped with those of controls. Novel methods involving the validation of blood transcriptomic markers for PD could also be promising avenues of future research.

SUMMARY

Development and validation of disease-specific biomarkers for the diagnosis of early PD represents one of the most urgent unmet needs in neurology. Most of the current markers of the disease, such as neuroimaging abnormalities detected by SPECT, meta-iodobenzylguanidine I 123, sonography, PET, or MRI, have been tested in patients with moderate or advanced disease, are not disease specific, and have not been validated in early preclinical stages of the disease. The sensitivity and specificity of the various imaging techniques are currently too low and the cost is too high to use these techniques as screening tools in the general population. The search for biomarkers is hampered by a number of challenges, including the difficulties in collecting postmortem specimens for validation studies. The future goal is to find a reliable biomarker of neurodegenerative diseases in peripheral blood, the CSF, or other readily accessible tissue. Such preclinical biomarkers are essential in identifying at-risk populations that might be potential targets for neuroprotective or disease-modifying therapeutic strategies. Although the concept of preclinical PD as a natural target for neuroprotective therapies and primary prevention is not new, neuroprotective trials have yet to be performed in at-risk individuals, not only because of the lack of reliable predictive risk markers for PD but primarily because of the lack of proven disease-modifying therapies.

In addition to sensitive and specific diagnostic biomarkers, there is also an urgent need for reliable surrogate biomarkers that can be used to accurately track progression of the disease. The progress in developing sensitive, specific, accurate, and reliable biomarkers of PD has been rather slow. However, with further refinements of various clinical, neurophysiological, and neuroimaging tests and when coupled with other laboratory biomarkers using blood, CSF, or other tissues and applying novel techniques in genomics, proteomics, lipidomics, and metabolomics, it is likely that clinically useful biomarkers for the prediction of PD will eventually be developed. Currently, a multicenter biomarker study (Parkinson's Progression Markers Initiative [PPMI]) is under way in North America and Europe, a landmark observational clinical study designed to comprehensively evaluate a cohort of recently diagnosed patients with PD and healthy subjects using advanced imaging, biological sampling, and clinical and behavioral assessments to identify biomarkers of Parkinson disease progression (http://www.ppmi-info.org). These biomarkers can then be used effectively to aid in detecting asymptomatic individuals with early disease who may benefit from early therapeutic intervention.

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