WHITE PAPER

Improving standard of care:

The Neuromotor Pen™ as a diagnostic aid

for differentiation between Parkinson's disease and other tremor disorders

to improve the diagnostic accuracy in early Parkinson's.

Performance requirements and evidence.

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Background

Parkinson's disease (PD) is a neurodegenerative disorder that affects predominantly the dopamine-producing ("dopaminergic") neurons in a specific area of the brain called substantia nigra. Lewy bodies (accumulation of abnormal alpha-synuclein) are found in substantia nigra neurons of people with PD. When alpha-synuclein misfolds and aggregates in specific areas of the brain, it diminishes the brain's production of dopamine. Dopamine is vital to smooth, coordinated movements and other body processes. Parkinson's symptoms arise from dopamine declines.[1,2]

Dopamine is a chemical messenger (neurotransmitter) that is primarily responsible for controlling movement, emotional responses and the ability to feel pleasure and pain. In people with Parkinson's, the cells that make dopamine are impaired. As PD progresses, more dopamine-producing brain cells die. The brain eventually reaches a point where it stops producing dopamine in any significant amount, causing increasing problems with movement.[1,2]

The prevalence of PD is 1% at age 60 years and doubles to 2% by 70 – 80 years. Symptoms generally develop slowly over years. The progression of symptoms vary across individuals due to the diversity of the disease.[3] People with PD may experience: Tremor, a 'to and fro movement', usually with one specific frequency, which can appear in the extremities as well as in the neck/head; this tremor typically starts asymmetrically, and may be accompanied by slowness and paucity of movement (called bradykinesia and hypokinesia), limb stiffness (rigidity), and gait and balance problems (postural instability). In addition to rest tremor, a significant subset of patients also present with postural tremor. This postural tremor can have the same frequency as the rest tremor (typical frequency of rest tremor: 4-7 Hz), or it can have a different, most commonly a faster frequency.[4]

In addition to movement-related ("motor") symptoms, Parkinson's symptoms may be unrelated to movement ("non-motor"). Examples of non-motor symptoms include: depression, anxiety, apathy, hallucinations, constipation, orthostatic hypotension, sleep disorders, loss of sense of smell, and a variety of cognitive impairments. Importantly, motor symptoms of PD only become evident later in the course of the disease, after 60% to 80% of the substantia nigra neurons have already been lost or impaired.[5]

Early signs of PD include tremor (slight shaking or tremor in finger, thumb, hand or chin while at rest), micrographia (decreased letter size and spacing), constipation, loss of smell, trouble sleeping, dizziness or fainting upon standing from a seated position, stooping or hunching over, trouble moving or walking, facial masking, and voice changes to a soft or low voice.[5]

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[1] Dickson DW. Parkinson's disease and parkinsonism: neuropathology. Cold Spring Harb Perspect Med. 2012 Aug 1;2(8):a009258. doi: 10.1101/cshperspect.a009258. PMID: 22908195; PMCID: PMC3405828.

[2] Stoker TB, Greenland JC, editors. Parkinson's Disease: Pathogenesis and Clinical Aspects [Internet]. Brisbane (AU): Codon Publications; 2018 Dec 21. Section I, Pathology.

[3] Driver JA, Logroscino G, Gaziano JM, Kurth T. Incidence and remaining lifetime risk of Parkinson disease in advanced age. Neurology. 2009 Feb 3;72(5):432-8. doi: 10.1212/01.wnl.0000341769.50075.bb. PMID: 19188574; PMCID: PMC2676726.

[4] Gironell A, Pascual-Sedano B, Aracil I, Marín-Lahoz J, Pagonabarraga J, Kulisevsky J. Tremor Types in Parkinson Disease: A Descriptive Study Using a New Classification. Parkinsons Dis. 2018 Sep 30;2018:4327597. doi: 10.1155/2018/4327597. PMID: 30363956; PMCID: PMC6186312.

[5] Armstrong MJ, Okun MS. Diagnosis and Treatment of Parkinson Disease: A Review. JAMA. 2020 Feb 11;323(6):548-560. doi: 10.1001/jama.2019.22360. PMID: 32044947.

Stages of Parkinson's

In 1967, Hoehn & Yahr defined five stages of PD based on the level of clinical disability. Clinicians use this scale to describe how motor symptoms progress in PD. On this scale, stages 1 and 2 represent early-stage, 2 and 3 mid-stage, and 4 and 5 advanced-stage PD.[6]

During stage one, the person has mild symptoms that generally do not interfere with daily activities. Tremor and other movement symptoms occur on one side of the body only (symptoms will usually remain worse on that side, even after symptoms begin to affect the limbs on both sides in later stages). Changes in posture, walking and facial expressions occur.

In stage two, symptoms start worsening. Tremor, rigidity and other movement symptoms affect both sides of the body or the midline (such as the neck and the trunk). Walking problems and poor posture may be apparent. The person is able to live alone, but daily tasks are more difficult and lengthier.

Stage three is considered mid-stage, and loss of balance (such as unsteadiness as the person turns or when he/she is pushed from standing) is the hallmark. Falls are more common. Motor symptoms continue to worsen. Functionally, the person is somewhat restricted in his/her daily activities, but is still physically capable of leading an independent life. Disability is mild to moderate at this stage.

By stage four, symptoms are fully developed and severely disabling. The person is still able to walk and stand without assistance, but may need to ambulate with a cane/walker for safety. The person needs significant help with activities of daily living and is unable to live alone.

Stage five is the most advanced and debilitating stage. Stiffness in the legs may make it impossible to stand or walk. The person is bedridden or confined to a wheelchair unless aided. Around-the-clock care is required for all activities.[6]

In a study[7] published in 2010 by the Movement Disorder Society on a total of 695 patients (mean age: 65.2, male: 57.3%), the progression time from one Hoehn and Yahr (H&Y) stage to the next stage, was evaluated. The median time to progress from H&Y stage 1 to 2, 2 to 2.5, and 2.5 to 3 were 20, 62, and 25 months, respectively, whereas the median time taken to progress from stage 3 to 4 and 4 to 5 were 24 and 26 months, respectively.

Recently, the Movement Disorder Task Force also recognized three stages in early PD, preclinical, prodromal and clinical PD.[8] During the preclinical phase, pathology has initiated and biomarkers can be found that are suggestive of PD; however, no significant symptoms of disease have yet arisen. Currently, the predictive ability of preclinical biomarkers for future PD diagnosis is limited, but research is ongoing. The prodromal phase can last over a decade and is mainly characterized by non-motor symptoms, although recent studies have also shown subtle motor deficits years before the diagnosis. Symptoms in the prodromal phase of PD are often not yet recognized as belonging to PD because of

[6] Goetz CG, Poewe W, Rascol O, Sampaio C, Stebbins GT, Counsell C, Giladi N, Holloway RG, Moore CG, Wenning GK, Yahr MD, Seidl L; Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease. Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: status and recommendations. Mov Disord. 2004 Sep;19(9):1020-8. doi: 10.1002/mds.20213. PMID: 15372591.

[7] Zhao YJ, Wee HL, Chan YH, Seah SH, Au WL, Lau PN, Pica EC, Li SC, Luo N, Tan LC. Progression of Parkinson's disease as evaluated by Hoehn and Yahr stage transition times. Mov Disord. 2010 Apr 30;25(6):710-6. doi: 10.1002/mds.22875. PMID: 20213822.

their low specificity. In the clinical phase, clinical signs of PD are readily apparent and this is when a diagnosis is typically made.[8]

Atypical Parkinsonism

Parkinsonism is a general term that refers to a group of neurological disorders that cause movement problems similar to those seen in PD such as tremors, slow movement and stiffness. Under the category of parkinsonism there are a number of disorders, some of which have yet to be clearly defined or named. Early in the disease process, it is often difficult to determine whether a person has idiopathic (meaning "of unknown origins") PD or a syndrome that mimics it. Atypical parkinsonism represents about 10-15% of all diagnosed cases of parkinsonism. These syndromes tend to progress more rapidly than PD, and present with additional symptoms such as early falling, dementia or hallucinations.[9]

Like primary PD, atypical parkinsonian disorders can also be sporadic or familial. The sporadic cases include progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal degeneration (CBD), and dementia with Lewy bodies (DLB), as well as other rare causes. Familial (heredodegenerative) disorders that may present with atypical parkinsonism include Huntington disease, spinocerebellar ataxias, X-linked dystonia-parkinsonism (Lubag disease) and neuronal brain iron accumulation disorders.[9]

There are also secondary, or acquired, causes of parkinsonism including drug-induced parkinsonism,[10] vascular parkinsonism,[11] as well as other secondary causes of parkinsonism.

Current Methods of Diagnosis

Diagnosis of PD requires referral to a movement disorders neurologist. It may take years for a general practitioner (GP) to refer patients to a neurologist with movement disorder knowledge. In a 2005 publication by Kang et al, the authors studied the clinical characteristics of individuals diagnosed with clinically probable PD in central California. Their results showed that, for a total of 153 patients, only 23% were diagnosed with PD at stage 1, 37% had reached stage 1.5-2, another 37% were at stages 2.5-3, and 2% were first diagnosed at stages 4 or 5.[12] Thus, for the vast majority of patients, diagnosis is delayed until stages 2-3 are reached. This can be up to 8-10 years after onset of clinical signs. [13]

[8] Dommershuijsen LJ, Boon AJW, Ikram MK. Probing the Pre-diagnostic Phase of Parkinson's Disease in Population-Based Studies. Front Neurol. 2021 Jul 1;12:702502. doi: 10.3389/fneur.2021.702502. PMID: 34276552; PMCID: PMC8284316.

[9] Levin J, Kurz A, Arzberger T, Giese A, Höglinger GU. The Differential Diagnosis and Treatment of Atypical Parkinsonism. Dtsch Arztebl Int. 2016 Feb 5;113(5):61-9. doi: 10.3238/arztebl.2016.0061. PMID: 26900156; PMCID: PMC4782269.

[10] Shin HW, Chung SJ. Drug-induced parkinsonism. J Clin Neurol. 2012 Mar;8(1):15-21. doi: 10.3988/jcn.2012.8.1.15. Epub 2012 Mar 31. PMID: 22523509; PMCID: PMC3325428.

[11] Gupta D, Kuruvilla A. Vascular parkinsonism: what makes it different? Postgrad Med J. 2011 Dec;87(1034):829-36. doi: 10.1136/postgradmedj-2011-130051. PMID: 22121251.

[12] Kang GA, Bronstein JM, Masterman DL, Redelings M, Crum JA, Ritz B. Clinical characteristics in early Parkinson's disease in a central California population-based study. Mov Disord. 2005 Sep;20(9):1133-42. doi: 10.1002/mds.20513. PMID: 15954133; PMCID: PMC3643967.

[13] Zhao YJ, Wee HL, Chan YH, Seah SH, Au WL, Lau PN, Pica EC, Li SC, Luo N, Tan LC. Progression of Parkinson's disease as evaluated by Hoehn and Yahr stage transition times. Mov Disord. 2010 Apr 30;25(6):710-6. doi: 10.1002/mds.22875. PMID: 20213822.

Even once the patient reaches the correct specialist, correct diagnosis remains uncertain. Despite recent research and diagnostic advances, the diagnosis of PD and types of atypical parkinsonian still relies primarily on a clinical evaluation by a specialist. There are many overlapping signs and symptoms among PD, atypical parkinsonisms, and secondary parkinsonisms, making it difficult to diagnose.[14] There is no definitive test to detect Parkinson's disease or parkinsonism. For these reasons, an accurate diagnosis can take up to 10 years since onset of symptoms, to determine.[15]

Parkinson's disease (PD) is called a movement disorder because of the tremors, slowing and stiffening movements it can cause, and these are the most obvious symptoms of the disease. While there is no single test or scan for Parkinson's, there are three telltale symptoms that help specialists make a diagnosis:[16]

- Bradykinesia (slowness of movement)
- Tremor
- Rigidity

Bradykinesia plus either tremor or rigidity must be present for a PD diagnosis to be considered. Another movement symptom, postural instability (trouble with balance and falls), is another primary symptom, but it does not occur until later (H&Y scale stage three) in the disease progression. In fact, problems with walking, balance and turning around early in the disease are likely a sign of an atypical parkinsonism. The Movement Disorder Society Clinical Diagnostic Criteria for Parkinson's requires an individual to meet at least 2 of 4 supportive criteria for a clinical diagnosis of PD: [17]

- rest tremor,
- a dramatic improvement with dopaminergic therapy,
- the presence of levodopa-induced dyskinesias, or
- the presence of either olfactory loss or cardiac sympathetic denervation on iodine-123-meta-iodobenzylguanidine myocardial scintigraphy.

For diagnosis, the specialist takes a thorough medical history and may request a number of movement tests. Rating Scales for the diagnosis of PD have been developed, most importantly the Unified Parkinson's Disease Rating Scale (UPDRS).[18] Assessment of motor cardinal signs, typically starting asymmetrically, and inquiring about autonomous symptoms like gastrointestinal signs or orthostasis is currently used to diagnose PD. Testing for micrographia and drawing of a spiral are additional tools

[14] Jankovic J. Parkinson's disease: clinical features and diagnosis. J Neurol Neurosurg Psychiatry. 2008 Apr;79(4):368-76. doi: 10.1136/jnnp.2007.131045. PMID: 18344392.
[15] Pahwa R, Lyons KE. Early diagnosis of Parkinson's disease: recommendations from diagnostic clinical guidelines. Am J Manag Care. 2010 Mar;16 Suppl Implications:S94-9. PMID: 20297872.
[16] Jankovic J. Parkinson's disease: clinical features and diagnosis. J Neurol Neurosurg Psychiatry. 2008 Apr;79(4):368-76. doi: 10.1136/jnnp.2007.131045. PMID: 18344392.
[17] Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, Obeso J, Marek K, Litvan I, Lang AE, Halliday G, Goetz CG, Gasser T, Dubois B, Chan P, Bloem BR, Adler CH, Deuschl G. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord. 2015 Oct;30(12):1591-601. doi: 10.1002/mds.26424. PMID: 26474316.
[18] Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease. The Unified Parkinson's Disease Rating Scale (UPDRS): status and recommendations. Mov Disord. 2003 Jul;18(7):738-50. doi: 10.1002/mds.10473. PMID: 12815652.

used in the diagnosis of PD.[19] However, this testing may occur with a long delay in a large number of patients, if symptoms are not noticed or are associated with a different disease in error.

Because of the observational nature of the diagnosis, PD can sometimes be confused with other movement disorders with parkinsonism, and the diagnosis may need to be revised over time based on speed of disease progression, response to medications and other factors. All parkinsonisms show a changes in the dopaminergic system or in the amount of dopaminergic neurons and/or postsynaptic dopamine receptors., meaning that imaging methods that are based on this feature cannot be used to differentiate between them and idiopathic PD.[20] As symptoms continue to worsen and develop over time, correct diagnosis of Parkinson's becomes easier. Once diagnosed with PD, many patients present good treatment response after initiating medication with dopamine agonists or levodopa, especially in early disease stages.[21]

Unfortunately, early signs of PD are often wrongly diagnosed as symptoms of disability, and may be incorrectly attributed to normal aging in older patients or to essential tremor or a functional disorder (especially in younger patients). Using neuropathologic findings as the gold standard, a study by Adler et al (2014) found that the accuracy for a clinical diagnosis of PD in untreated or subjects not clearly responsive to levodopa treatment was only 26%, and the accuracy in subjects with early PD, as defined as onset of first symptom <5 years prior to diagnosis, who showed levodopa responsiveness, was only 53%.[22],[23]

It is important to note that many people will not exhibit the cardinal symptoms necessary for a diagnosis of a specific disorder and will simply be labeled as having "parkinsonism". For these people, a definite diagnosis may only come if the family requests a brain autopsy at time of death.[24]

Difficulty with the Differentiation from Parkinsonian vs. Non-Parkinsonian Disorders

While tremor is a key component to a correct PD diagnosis, tremors can manifest for a variety of reasons that are not PD related making differential diagnosis difficult. Tremor disorders that may be particularly difficult to distinguish from PD tremor are essential tremor (ET), enhanced physiological

[19] Wagle Shukla A, Ounpraseuth S, Okun MS, Gray V, Schwankhaus J, Metzer WS. Micrographia and related deficits in Parkinson's disease: a cross-sectional study. BMJ Open. 2012 Jun 25;2(3):e000628. doi: 10.1136/bmjopen-2011-000628. PMID: 22734114; PMCID: PMC3383984.

[20] Bajaj N, Hauser RA, Grachev ID. Clinical utility of dopamine transporter single photon emission CT (DaT-SPECT) with (123I) ioflupane in diagnosis of parkinsonian syndromes. J Neurol Neurosurg Psychiatry. 2013 Nov;84(11):1288-95. doi: 10.1136/jnnp-2012-304436. Epub 2013 Mar 13. PMID: 23486993; PMCID: PMC3812862.

[21] Martin WRW, Miles M, Zhong Q, Hartlein J, Racette BA, Norris SA, Ushe M, Maiti B, Criswell S, Davis AA, Kotzbauer PT, Cairns NJ, Perrin RJ, Perlmutter JS. Is Levodopa Response a Valid Indicator of Parkinson's Disease? Mov Disord. 2021 Apr;36(4):948-954. doi: 10.1002/mds.28406. Epub 2020 Nov 30. PMID: 33253432; PMCID: PMC8046721.

[22] **Adler CH**, Beach TG, Zhang N, Shill HA, Driver-Dunckley E, Mehta SH, Atri A, Caviness JN, Serrano G, Shprecher DR, Sue LI, Belden CM. Clinical Diagnostic Accuracy of Early/Advanced Parkinson Disease: An Updated Clinicopathologic Study. Neurol Clin Pract. 2021 Aug; 11 (4):e414-e421

[23] Adler CH, Beach TG, Hentz JG, Shill HA, Caviness JN, Driver-Dunckley E, Sabbagh MN, Sue LI, Jacobson SA, Belden CM, Dugger BN. Low clinical diagnostic accuracy of early vs advanced Parkinson disease: clinicopathologic study. Neurology. 2014 Jul 29;83(5):406-12. doi: 10.1212/WNL.0000000000000641. Epub 2014 Jun 27. PMID: 24975862; PMCID: PMC4132570.

[24] Rajput AH, Rozdilsky B, Rajput A. Accuracy of clinical diagnosis in parkinsonism--a prospective study. Can J Neurol Sci. 1991 Aug;18(3):275-8. doi: 10.1017/s0317167100031814. PMID: 1913360.

tremor (EPT), functional tremor, different forms of cerebellar tremor, and dystonic tremor. Differentiating between a parkinsonian tremor and other tremor disorders is challenging even for experienced neurologists.[25] The separation of PD from ET is the most relevant clinically as misdiagnosis of ET as PD is common, accounting for about half of the misdiagnoses.[26] This occurs in the US and other highly developed European countries such as Germany.

The lack of tremor measurement equipment in the clinic and the inability to identify subtle tremors is partly responsible for the difficulty with differentiation between PD and ET. Importantly, subtle tremors, are often already present in the prodromal stage before a clinical diagnosis can be made.[27] Thus, use of a device that can differentiate between PD related tremor and ET during early stage diagnosis would be of meaningful benefit to patients.

Dopamine transporter single-photon emission computed tomography (DaT) scans have been approved by FDA to differentiate between PD and non-PD tremors. DaTscan works by showing decreased putaminal tracer uptake in PD and other parkinsonian syndromes (detecting nigrostriatal cell loss), but they show normal uptake in essential tremor. These scans were approved for use when a diagnosis is unclear and the differential diagnosis includes both essential tremor and Parkinson disease. Use of DaTscan does *not* extend to the diagnostic distinction between PD and atypical parkinsonian conditions because while it adds information to diagnostic report, but it does not increase efficacy of differential diagnosis.

The FDA-approved indication for DaTscan is: 'DaTscan is a radiopharmaceutical indicated for striatal dopamine transporter visualization using single photon emission computed tomography brain imaging to assist in the evaluation of adult patients with suspected parkinsonian syndromes. In these patients, DaTscan may be used to help differentiate ET from tremor due to parkinsonian syndromes (idiopathic Parkinson's disease, multiple system atrophy and progressive supranuclear palsy). DaTscan is an adjunct to other diagnostic evaluations.' Depending on the disease stage and setting of use, the scan has up to a 80%-95% sensitivity and > 90% specificity. However, as reported by the American Parkinson's Disease Association, "Despite the DaTscan being available to help make a differential diagnistic decision in clinical situations, a DaTscan will not always add information to what can be gleaned from the clinical exam. Some studies actually demonstrated that the accuracy of diagnosis in early PD was the same whether the diagnosis was reached using clinical exam or using DaTscan."[28]* Although approved for use in the US and Europe, DaTscans are not part of routine testing even if a patient presents with PD symptoms.[29] They are used only when a patient presents with PD symptoms, and diagnosis is uncertain. Even so, diagnosis ultimately relies on clinical assessments of symptoms, with the scan assisting the clinician in diagnosis.

[25] Aly N. Parkinson's disease tremor: differential diagnosis and management. Geriatric Medicine, 47 (4), April, 2017

[26] Meara J, Bhowmick BK, Hobson P. Accuracy of diagnosis in patients with presumed Parkinson's disease. Age Ageing. 1999 Mar;28(2):99-102. doi: 10.1093/ageing/28.2.99. PMID: 10350403.

[27] Schrag A, Horsfall L, Walters K, Noyce A, Petersen I. Prediagnostic presentations of Parkinson's disease in primary care: a case-control study. Lancet Neurol. 2015 Jan;14(1):57-64. doi: 10.1016/S1474-4422(14)70287-X. Epub 2014 Nov 27. PMID: 25435387.

[28] What is a DaTscan and should I get one? | American Parkinson Disease Association (apdaparkinson.org)

[29] This is apparent from various PD-dedicated websites, e.g., Ask the MD: DaTscan and Parkinson's | Parkinson's Disease (michaeljfox.org); Parkinson's disease - Diagnosis and treatment - Mayo Clinic; How is Parkinson's Disease Diagnosed? | ParkinsonsDisease.net).

DaTscans also present non-trivial risks and have several limitations. The scan itself exposes the patient to a significant amount of radiation, resulting in a cancer risk of 1 in 5000 to 7500, as suggested by de la Fuente-Fernández.[30] There is also no quantitative output (score), and the scan therefore requires expert visual interpretation. The procedure itself is invasive and unpleasant, with patients often being reluctant to undergo scans. Finally, the scans are costly and are not used unless PD is already suspected. Accordingly, there remains a need for a non-invasive, readily accessible, low risk, less costly, and easy to use diagnostic to assist in the differentiation between PD and ET in early stage PD patients.

Performance of Current Diagnostic Methods

- **Overview and Rationale**

In order to support the Manus Neurodynamica selected performance goals (60% sensitivity and 45% specificity) for the proposed clinical study for NMP (Neuromotor Pen), a literature search has been conducted to assess the performance in early stage PD diagnosis with current standard of care (SOC).

In 2016, Rizzo et al. published a comprehensive, systematic review and meta-analysis entitled: ”Accuracy of clinical diagnosis of Parkinson Disease”.[31] This extensively cited review aimed to evaluate the accuracy of clinical diagnosis of PD reported in the last 25 years by way of systematic review and meta-analysis. The authors included all articles reporting diagnostic parameters regarding clinical diagnosis of PD or crude data. The selected studies were subclassified based on different study setting, type of test diagnosis, and gold standard. Bayesian meta-analyses of available data were performed. The authors, based on relevant search criteria, selected 20 studies for the meta-analysis, including 11 using pathologic examination as gold standard.

This meta-analysis covers studies that vary in the setting (community/clinic-based diagnosis), the type of diagnosis performed (initial/refined clinical diagnosis by nonexperts or experts, or using United Kingdom PD Society Brain Research Center (UKPDSBRC) clinical criteria), and the gold standard used to truth this diagnosis (pathological diagnosis/UKPDSBRC clinical criteria/refined clinical diagnosis by expert). Overall, the meta-analysis showed a sensitivity of 89.5% [84.2%, 93.2%] and a specificity of 68.3% [59.6%, 75.7%]. However, these performance parameters reflect the performance in situations that are different from the intended use situation for the proposed clinical study for NMP. As discussed below, the NMP study represents a more challenging situation compared to many of the studies included in the meta-analysis. As such, the overall performance parameters from the meta-analysis would over-estimate the actual performance of SOC in the intended use scenario for NMP.

For example, only a subset of the studies in the meta-analysis focus on the performance of *initial* diagnosis. PD diagnosis is often updated during the disease course as patients gradually develop symptoms, and the final refined diagnosis of a patient, often after several years of follow-up, has been

[30] de la Fuente-Fernández R. Role of DaTSCAN and clinical diagnosis in Parkinson disease. Neurology. 2012 Mar 6;78(10):696-701. doi: 10.1212/WNL.0b013e318248e520. Epub 2012 Feb 8. PMID: 22323748.

[31] Rizzo G, Copetti M, Arcuti S, Martino D, Fontana A, Logroscino G. Accuracy of clinical diagnosis of Parkinson disease: A systematic review and meta-analysis. Neurology. 2016 Feb 9;86(6):566-76. doi: 10.1212/WNL.0000000000002350. Epub 2016 Jan 13. PMID: 26764028.

shown to be significantly more accurate than the initial diagnosis.[32] In another study that evaluated the performance of the UPDRS rating scale,[33] it was shown that the UPDRS cutoff had a sensitivity of 16.7% for the initial assessment (6 years before clinical conversion), but reaching 60.5% sensitivity at 2 years before and 92.6% only at the time of clinical diagnosis.

The performance of SOC in detecting PD is also highly dependent on the stage of the disease. Studies have shown that it is much more difficult to diagnose PD at the early stage. In the meta-analysis, only one study (Adler and Beach, 2014) specifically analyzed the difference between early-stage disease diagnosis (patients diagnosed within <5 years of initial symptoms) and later-stage diagnosis (>5y). A major difference is noted in this study, showing that when the initial PD diagnosis was performed in the earliest stages, the diagnostic error was high, with accuracy of 53% in patients with <5 years of disease duration, compared to >85% diagnostic accuracy for disease of longer duration. [34] Similarly, in another review of studies of diagnostic accuracy in early PD,35 the above study was analyzed together with two additional studies, [36,37] focusing on initial, early diagnosis as assessed against a pathologic gold standard. In the three studies that included initial, early diagnosis, only 5 of 13 (38%), 28 of 43 (65%), and 8 of 15 (53%) patients clinically diagnosed with early PD were confirmed to have PD at autopsy. Taken together, these data from three different research groups report a diagnostic accuracy of only 58% (41 of 71) for parkinsonian subjects with an initial, early diagnosis of PD. While sensitivity and specificity data for the early stage PD were not discussed in these studies, the reported lower accuracy is indicative of a worse performance of the SOC for initial detection of early stage PD. These studies are summarized in Table 1 below.

Adler-Beach 2014[38]	Subjects enrolled from 1997 to 2013 in an ongoing longitudinal clinical-neuropathologic study, the Arizona Study of Aging and Neurodegenerative Disorders	15	Initial visit Early-stage disease (<5 y duration) (age: mean 76 years)	Clinical (UPDRS), 2/3 cardinal signs + responsive to medication	Movement disorder specialist	Neuro-pathology	53%

[32] Jankovic J, Rajput AH, McDermott MP, Perl DP. The evolution of diagnosis in early Parkinson disease. Parkinson Study Group. Arch Neurol. 2000 Mar;57(3):369-72. doi: 10.1001/archneur.57.3.369. PMID: 10714663.
[33] Fereshtehnejad SM, Yao C, Pelletier A, Montplaisir JY, Gagnon JF, Postuma RB. Evolution of prodromal Parkinson's disease and dementia with Lewy bodies: a prospective study. Brain. 2019;142(7):2051-2067.
[34] Adler CH, Beach TG, Hentz JG, Shill HA, Caviness JN, Driver-Dunckley E, Sabbagh MN, Sue LI, Jacobson SA, Belden CM, Dugger BN. Low clinical diagnostic accuracy of early vs advanced Parkinson disease: clinicopathologic study. Neurology. 2014 Jul 29;83(5):406-12. doi: 10.1212/WNL.0000000000000641. Epub 2014 Jun 27. PMID: 24975862; PMCID: PMC4132570.
[35] Beach TG, Adler CH. Importance of low diagnostic Accuracy for early Parkinson's disease. Mov Disord. 2018 Oct;33(10):1551-1554. doi: 10.1002/mds.27485. Epub 2018 Oct 4. PMID: 30288780; PMCID: PMC6544441.
[36] Rajput AH, Rozdilsky B, Rajput A. Accuracy of clinical diagnosis in parkinsonism--a prospective study. Can J Neurol Sci. 1991 Aug;18(3):275-8. doi: 10.1017/s0317167100031814. PMID: 1913360.
[37] Jankovic J, Rajput AH, McDermott MP, Perl DP. The evolution of diagnosis in early Parkinson disease. Parkinson Study Group. Arch Neurol. 2000 Mar;57(3):369-72. doi: 10.1001/archneur.57.3.369. PMID: 10714663.

	(AZSAND), with autopsies performed						
Rajput 1991 [39]	Canadian movement disorder clinic (MDC). All Parkinsonian Syndrome cases seen between 1968 - 1990 with autopsies performed.	43	Initial visit Early-stage disease	Clinical 2/3 cardinal signs	Neurologist/ movement disorder specialist	Neuro-pathology	65%
Jankovic 2000[40]	A subset of patients that underwent autopsy in an ancillary study based on patients enrolled in DATATOP PD therapeutic study	13	Initial visit Early-stage disease (<5 y duration)	Not well-defined. Only those patients who the investigators believed had had idiopathic PD, mild disability, and symptoms for 5 years or less were considered candidates for the study.	Specialist (CT investigator)	Neuro-pathology	38%

Table 1. Summary of studies assessing diagnostic accuracy in early PD

Several additional factors may further suggest that the real-world results would be even lower than what was reported in the clinical studies in the meta-analysis. As mentioned above, when looking at the clinical accuracy of initial diagnosis in early-stage disease patients, with the same clinical signs, in which response to dopaminergic treatment (levodopa) was not demonstrated, the predictive value of the cardinal clinical signs of PD was even lowered further to 26%.[41] Excluding patients with a history of taking levodopa, information on the response to levodopa treatment would not be available, and the lower end of the values reported in literature are more likely to be indicative of actual performance.

Furthermore, as noted above, because tremors that are not PD related are challenging to distinguish from PD tremor, the existence of tremor further impacts estimates of accurate diagnosis. In one study, it was shown that removal of action tremor scores improved the sensitivity and specificity at 2 years before diagnosis.[42] Since only a subset of studies in the meta-analysis included patients with tremor,

[41] Adler CH, Beach TG, Hentz JG, Shill HA, Caviness JN, Driver-Dunckley E, Sabbagh MN, Sue LI, Jacobson SA, Belden CM, Dugger BN. Low clinical diagnostic accuracy of early vs advanced Parkinson disease: clinicopathologic study. Neurology. 2014 Jul 29;83(5):406-12. doi: 10.1212/WNL.0000000000000641. Epub 2014 Jun 27. PMID: 24975862; PMCID: PMC4132570.

[42] Postuma RB, Lang AE, Gagnon JF, Pelletier A, Montplaisir JY. How does Parkinsonism start? Prodromal Parkinsonism motor changes in idiopathic REM sleep behavior disorder. Brain. (2012) 135:1860–70. doi: 10.1093/brain/aws093

the actual results in clinical settings where tremor patients would be enrolled would be expected to be lower than the results in the meta-analysis.

Lastly, in majority of the meta-analysis studies, patients were typically evaluated in the clinic by neuromotor specialists. In the community setting as proposed for the NMP study, the performance would be expected to be even lower.

Taken together, the lower end of the performance values reported in literature are more likely to be indicative of the actual performance of SOC in similar clinical settings as proposed for the NMP study.

- **Sensitivity Performance**

In the meta-analysis by Rizzo et al., there was a wide range of sensitivity performance from 44.4% to 99.8%. Several studies had a sensitivity below 60% or the lower bound 95% CI 60%. These studies are summarized in the table below. As discussed above, these studies do not fully represent the use scenario for the proposed NMP study, which would be a community based study for the initial diagnosis of early stage PD in patients with uncertain diagnosis including tremor. The performance in the meta-analysis is likely to be an overestimation of the SOC performance in such setting. For example, overall performance was reported for Adler and Beach, 2014, [43] which would be higher than the performance for early stage PD only, as discussed above. Therefore, the studies summarized in the table below suggest NMP performance with sensitivity of 60% would be sufficient while NMP performance of sensitivity > 90 is exceeding the performance requirement. NMP aided SOC will improve the sensitivity for detecting in early Parkinson's.

[43] Adler CH, Beach TG, Hentz JG, Shill HA, Caviness JN, Driver-Dunckley E, Sabbagh MN, Sue LI, Jacobson SA, Belden CM, Dugger BN. Low clinical diagnostic accuracy of early vs advanced Parkinson disease: clinicopathologic study. Neurology. 2014 Jul 29;83(5):406-12. doi: 10.1212/WNL.0000000000000641. Epub 2014 Jun 27. PMID: 24975862; PMCID: PMC4132570.

Study	Patient Population	Setting	Clinical diagnosis	Gold standard diagnosis	Sensitivity
Bower JH et, Mov Disord 2002[44]	39 incident cases of parkinsonism in Olmsted County, MN, for the years 1976 to 1990 (Rochester Epidemiology Project)	Community-based	Clinical diagnosis based on revision of available medical records by a movement disorders expert	Pathological examination	44.4% [23.2%, 67.5%]
Bajaj NPS et al, JNNP 2010[45]	38 tremulous patients with clinical uncertain PD in early stages (demographic data not reported).	Clinic-based	Clinical diagnosis by two blinded reviewers (movement disorders experts) of video recording of all patients. UKPDSBRC criteria (with the exception of rigidity) were used	Working clinical diagnosis by an expert after a mean follow-up of 39.5 months, taking into account all clinical and imaging data	Reviewer 1: 53.4% [30.7%, 75.4%] Reviewer 2: 77.7% [54.5%, 92.7%]
Hughes AJ et al, Neurology 1992[46]	100 with clinical PD diagnosis (mean age at onset 64.5; range 31-85). Collected from 1987 to 1990.	Clinic-based	Clinical diagnosis plus these three best predictors derived from logistic regression analysis: no atypical features for PD, asymmetrical onset and no suggestion of a cause for another PS	Pathological examination	68.1% [57.3%, 77.8%]

[44] Bower JH, Dickson DW, Taylor L, et al. Clinical correlates of the pathology underlying parkinsonism: a population perspective. Mov Disord 2002;17:910–916.
[45] Bajaj NP, Gontu V, Birchall J, et al. Accuracy of clinical diagnosis in tremulous parkinsonian patients: a blinded video study. J Neurol Neurosurg Psychiatry 2010;81: 1223–1228.
[46] Hughes AJ, Ben-Shlomo Y, Daniel SE, Lees AJ. What features improve the accuracy of clinical diagnosis in Parkinson's disease: a clinicopathologic study. Neurology 1992;42:1142–1146.

Study	Patient Population	Setting	Clinical diagnosis	Gold standard diagnosis	Sensitivity
Litvan et al, Arch Neurol 1998[47]	105 patients with PS diagnosis (mean age at onset 60 y)	Clinic-based	Diagnosis of primary neurologists (from clinical practice) and diagnosis of six movement disorders expert (three senior and three junior) based on clinical vignettes. An initial (based only on the clinical judgment) and a final diagnosis (with all information including laboratory and imaging data; mean follow-up of 9 years) were provided. No specific diagnostic criteria were used	Pathological examination	Initial clinical diagnosis by expert 71.5% [48.1%, 89.0%] Clinical diagnosis mainly by nonexperts 89.7% [69.6%, 98.4%] Refined clinical diagnosis of by expert 77.5% [54.1%, 92.7%]

Table 2. Summary of studies with relevant sensitivity estimates

[47] Litvan I, MacIntyre A, Goetz CG, et al. Accuracy of the clinical diagnoses of Lewy body disease, Parkinson disease, and dementia with Lewy bodies: a clinicopathologic study. Arch Neurol 1998;55:969–978.

- **Specificity Performance**

Similar to sensitivity, there was a wide range of specificity performance in the Rizzo meta-analysis. Several studies had a specificity below 45% or the lower bound 95% CI below 45%. These studies are summarized in the table below. As discussed above, these studies do not represent the use scenario for the proposed NMP study, and would be an overestimation of the SOC performance. Therefore, the studies summarized in the table below suggest NMP performance with specificity of 45% would be sufficient while current NMP performance of specificity > 60% is exceeding the performance requirement. NMP aided SOC will improve the specificity for detecting early Parkinson's.

Study	Patient Population	Setting	Clinical diagnosis	Gold standard diagnosis	Specificity
Hughes AJ et al, jnnp 1992[48]	100 with clinical PD diagnosis (mean age at onset 64.5; range 31-85). Collected from 1987 to 1990.	Clinic-based	Clinical diagnosis performed by movement disorders specialist or general neurologist or geriatrician. All cases were also re-evaluated with the UKPDSBRC clinical criteria	Pathological examination	34.2% [17.8%, 53.3%]
Hughes AJ et al, Neurology 2001[49]	100 patients with clinical diagnosis of PD (mean age at onset 62.2; range 29 to 82). Collected between 1996 and 1998.	Clinic-based	Clinical diagnosis without specific criteria performed by neurologists in 86 subjects (movement disorders experts in 61), geriatricians in 7 and internal medicine specialists in 7. Re-evaluation of diagnosis according to: UKPDSBRC criteria Calne criteria (clinically definite) Gelb criteria (clinically possible and probable) Three selected clinical features (asymmetrical onset, no atypical features, no possible etiology for another parkinsonian syndrome)	Pathological examination	32.4% [10.9%, 61.3%]
Winter Y et al., Mov Disord 2010[50]	341 incident cases of PD and atypical parkinsonian syndromes recruited and followed up between 2006 and 2008 in the Northeast district of Moscow. Mean duration between onset and diagnosis 8.4±6 months	Community-based	Baseline clinical diagnosis by movement disorders experts according to UKPDSBRC clinical criteria	UKPDSBRC clinical criteria re-applied after at least 6 months of follow up	25.4% [13.0%, 40.9%]

[48] Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181–184.

[49] Hughes AJ, Daniel SE, Lees AJ. Improved accuracy of clinical diagnosis of Lewy body Parkinson's disease. Neurology 2001;57:1497–1499.

[50] Winter Y, Bezdolnyy Y, Katunina E, et al. Incidence of Parkinson's disease and atypical parkinsonism: Russian population-based study. Mov Disord 2010;25:349–356.

Study	Patient Population	Setting	Clinical diagnosis	Gold standard diagnosis	Specificity
Horvath J et al, Brain Pathol 2013[51]	261 patients with clinical diagnosis of PS collected between 1914 and 2010 (mean age at death 79.3 (32-98); age at onset not reported)	Clinic-based	Clinical diagnosis performed by neurologists, psychiatrics or specialists in internal medicine. Use of diagnostic criteria not specified.	Pathological examination	37.9% [28.9%, 47.6%]
Rajput AH et al, Can J Neurol Sci 1991[52]	59 with PS diagnosis (mean age at onset not reported). Collected from 1968 to 1990.	Clinic-based	Initial clinical diagnosis performed by a general neurologist or a movement disorder specialist.	Pathological examination	46.4% [29.1%, 64.4%]
Caslake R et al, jnnp 2008[53]	Incident cohort of 66 patients (over 18 months from November 2002) with PS and at least one year of follow up (mean age 74.4±10.1; median disease duration 12.7 months, interquartile range 6-8-24.2; mean age at diagnosis 75.0±10.5 yrs and mean age at onset 73.5±9.01).	Community-based	Referral by general practitioners. Baseline clinical diagnosis by movement disorders specialists. No diagnostic criteria used.	Latest clinical diagnosis by experts (at least one year after baseline clinical evaluation). Latest diagnosis on UKPDSBRC criteria (in five patients pathological examination)	Clinical diagnosis at baseline 55.1% [37.5%, 71.8%] Baseline PD clinical vs latest PD diagnosis on UKPDSBRC criteria (or autopsy) 45.7% [30.1%, 62.0%]
Marshall VL et al, Mov Disord 2009[54]	99 patients with tremor and/or parkinsonism with initial uncertain diagnosis (mean age 60.8; mean H&Y 1.5; age at onset not reported). Collected between 1999 and 2005	Clinic-based	Clinical diagnosis at baseline performed by movement disorders specialists from multiple centers. UKPDSBRC criteria step 1 were used.	Video gold standard diagnosis after 36 months of follow-up (consensus of 2 experts on patients' video and available clinical data)	46.6% [29.6%, 63.9%]

[51] Horvath J, Burkhard PR, Bouras C, Kövari E. Etiologies of parkinsonism in a century-long autopsy-based cohort. Brain Pathol 2013;23:28–33.
[52] Rajput AH, Rozdilsky B, Rajput A. Accuracy of clinical diagnosis in parkinsonism: a prospective study. Can J Neurol Sci 1991;18:275–278.
[53] Caslake R, Taylor K, Scott N, et al. Age-, gender-, and socioeconomic status-specific incidence of Parkinson's disease and parkinsonism in northeast Scotland: the PINE study. Parkinsonism Relat Disord 2013;19:515–521.
[54] Marshall VL, Reininger CB, Marquardt M, et al. Parkinson's disease is overdiagnosed clinically at baseline in diagnostically uncertain cases: a 3-year European multicenter study with repeat [123I]FP-CIT SPECT. Mov Disord 2009;24:500–508.

Study	Patient Population	Setting	Clinical diagnosis	Gold standard diagnosis	Specificity
Joutsa J et al, Parkinsonism Relat Disord 2014[55]	111 patients with clinical diagnosis of PS collected between 2000 and 2012 (mean age at death 75 (48-89); mean age at diagnosis 70 years)	Clinic-based	Clinical diagnosis performed by general neurologists	Pathological examination	57.5% [42.8%, 71.5%]

Table 3. Summary of studies with relevant specificity estimates

[55] Joutsa J, Gardberg M, Röyttä M, Kaasinen V. Diagnostic accuracy of parkinsonism syndromes by general neurologists. Parkinsonism Relat Disord 2014;20:840–844.

Conclusion

Although critical for achieving better clinical outcomes, early diagnosis of PD is extremely challenging. The sensitivity and specificity of current SOC for the early diagnosis of PD are suboptimal, and any diagnostic tool that could help improve the performance would have meaningful clinical impact.

Based on the review of literature on SOC, expressed in terms of sensitivity and specificity, it can be concluded that the current SOC aided with NMP performance goals would need to reach 60% sensitivity and 45% specificity. This was already proven in Europe.

The next step in the US will be validating the sensitivity and specificity with the same performance goals of 60% sensitivity and 45% specificity. A study protocol is agreed with FDA and the proposed clinical study will be executed with Prof Irene Litvan at UCSD.