Advisory Board for Toxic Substances and Worker Health

Parkinsonian Disorders in the Energy Employees Occupational Illness Compensation Program

In 2018, the Department of Labor requested that the Board assist in evaluating aspects of the recognition and causation of Parkinsonian disorders in the Energy Employees Occupational Illness Compensation Program. We list below the questions and our responses and recommendations.

A.   <u>Diagnosis and Terminology in Parkinson's-related Disorders</u>

1.   What are the appropriate aliases of Parkinson's disease?

2.   Should Parkinsonism and/or Manganism be treated the same as Parkinson's disease? What are the criteria for a finding that the diagnosis is appropriate? (For example, many claimants are symptomatic for "the shakes," but what medical evidence allows for the diagnosis of Parkinsonism or other related diagnoses?) Inclusion of ICD-10 codes would be ideal for ascertaining coverage under such policy.

Recommendation:

The Board recommends that the clinical diagnosis of Parkinsonism, as established primarily but not exclusively by a neurologist, is treated the same as the diagnosis of Parkinson disease throughout the EEOICP claim adjudication process, with respective entries of both terms and aliases recommended in the DOL's Site Exposure Matrix (SEM). The Board has identified the following aliases that are in use for both terms with corresponding ICD 9 and ICD 10 codes

ICD 9 332	-	Parkinson's Disease
ICD 9 332.0	-	Paralysis agitans, Parkinsonism or Parkinson's Disease NOS – not otherwise specified, idiopathic, primary
ICD 9 332.1	-	Secondary parkinsonism
ICD 10 G20	-	Parkinson's Disease, Hemiparkinsonism, Idiopathic Parkinsonism, Paralysis Agitans, Primary Parkinsonism
ICD 10 G21	-	Secondary parkinsonism

Rationale:

Parkinsonism is a general term that refers to a group of related neurodegenerative movement disorders or syndromes affecting the extrapyramidal system. Impairment of motor function is a common clinical characteristic in these disorders which include several neurological entities with broad spectrum of clinical symptomatology, risk factors, pathological features, and rates of progression. As there are no biomarkers or clinically valid diagnostic tests to clearly

differentiate between these disorders, the Board recommends combining these under a common diagnosis of Parkinsonism.

The earliest and typically the most prominent symptom of motor function impairment in Parkinsonism is bradykinesia, a slowness in initiation and carrying out of movements. Often progressive, it may be accompanied by other motor symptoms, including muscle rigidity with involvement of individual or entire muscle groups, frequently asymmetric; resting "pill rolling" tremor, and postural instability, all presenting in any combination, and with varying degree of intensity over time (Postuma et al., 2015; Rizek et al., 2016).

Parkinsonian syndromes are classified based on clinical presentation with response/or lack thereof to known therapeutic agents (dopamine replacement therapy) as well potential risk factors. Medications (neuroleptics, antipsychotic, metoclopramide), drugs (synthetic meperidine, MPTP); infections (syphilis, post-encephalitis); metabolic (parathyroid, post-anoxic) and vascular abnormalities (strokes, i.e., lower body parkinsonism); as well as pathologic growth of, and/or injury to brain structures, have been known to result in parkinsonian symptoms (Rizek et al., 2016) and are classified as secondary parkinsonisms.

Inhalational exposures to toxic agents, including manganese (Mn) and carbon monoxide (CO), have also been known to present with motor abnormalities consistent with Parkinsonian symptomatology, and are classified under toxic effects of each exposure respectively, i.e., carbon monoxide poisoning (ICD-10 T58.94 vs ICD-9 332.1); manganese, manganism (ICD-10 T57.2X1 vs ICD-9 332.1). These disorders may occur at any age, with motor function impairment typically within days to weeks following the exposures (Choi and Cheon, 1999; Choi, 2002). A longer latency, up to a decade or more, associated with low, chronic exposures is not uncommon in their pathogenesis (Huang et al. 1993; Huang et al., 1998).

No biomarkers have been found to date to confirm the individual diagnoses of parkinsonism. Functional testing, including brain imaging techniques such as Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) have been increasingly used to assess neurochemical changes in the brain and differentiate among different types of parkinsonian disorders. Their clinical validity, however, is still under study (Loane and Politis, 2011; Politis, 2014; Rizek et al., 2016). The diagnostic gold standard is the post-mortem pathology.

Parkinson disease (PD) is the most common of all Parkinsonisms with estimates of up to 80% of all cases, (Schwartz and Henchcliffe, 2009). Frequently referred to in earlier literature as Parkinson's disease, paralysis agitans, primary parkinsonism, idiopathic parkinsonism, or hemiparkinsonism, Parkinson disease affects individuals primarily over the age of 50 with risk increasing with age and males predominantly over females with a 2:1 ratio. Early onset of this disease (<50 years) is rare, estimated at less than 5% of cases (Van Den Eeden et al., 2003; Ferguson et al., 2016). Genetic mutations have been identified in the etiology of Parkinson but are estimated to account for less than 15% of all PD cases, mostly early onset (Tanner et al., 1999; Martin et al., 2011), A combination of genetic, environmental and occupational factors are thought to play a role in the etiology of the remainder 85% of cases of this disease (Caudle et al. 2012; Caudle, 2015).

The clinical onset of motor function impairment in Parkinson Disease is typically over the age of 50. Studies have shown that motor deficits may be preceded, up-to 20 years or more, by a prodromal stage of non-specific impairment in a sense of smell, chronic constipation, depression, and sleep disorders (Kalia and Lang, 2015). Research is underway to identify and evaluate clinical tests and biomarkers in this prodromal stage of the disease (Politis, 2014; Berg et al., 2015; Heinzel et al.,2019).

The diagnostic gold standard in Parkinson disease is post-mortem pathology with degeneration of dopaminergic nerve cells in the basal ganglia, substantia nigra part of the mid-brain and abnormal protein, α-synuclein depositions leading to impairment in the production of dopamine neurotransmitter (Dickson, 2012).

Sets of diagnostic criteria have been developed including UK's Parkinson Disease Society Brain Bank Clinical Diagnostic Criteria (Hughes et al. 1992) and, more recently, the International Parkinson and Movement Disorder Society (MDS) Clinical/Research Diagnostic Criteria (Table 1), to assist in the clinical and research diagnosis and differentiation of Parkinsonisms (Postuma et al., 2015). The primary diagnosis of bradykinesia accompanied by at least one of three other motor symptoms and an unequivocal response to dopaminergic therapy is supportive of the diagnosis of Parkinson disease.

Parkinson-Plus syndromes are disorders that present with classical motor impairment symptoms of Parkinsonian syndromes but lack a response to dopamine substitute therapies. These disorders are sporadic, have additional (''plus'') clinical features and diverse pathology with neurodegeneration typically more extensive and progressive than that seen in classical PD. Genetic mutations as well as other factors including brain injury have been shown to play a role in their pathogenesis (Wenning et al., 2011; Olfati et al., 2019; Armstrong and McFarland, 2019). Parkinson-Plus syndromes are also known as Atypical Parkinsonisms and are classified as Multiple Systems Atrophy (MSA) (ICD-10 G13.8 vs ICD 9 333.0), Progressive Supranuclear Palsy (PSP) (ICD-10 G23.9 vs ICD 9 333.0), Corticobasal Degeneration (CBD) (ICD -10 G31.85 vs ICD-9 331.6) and Lewy Body Dementia (LBD) (ICD -10 G31.83 vs ICD-9 331.82).

B.   Causation and Presumptions

1) What toxins are associated with each of the diagnosis? (Any input would require supporting medical health science literature from peer reviewed human studies to support any proffered associations)

2) Are there any presumptions that the Board could offer regarding worker exposure to these toxins? For example, if the committee finds the exposure to manganese as a causal connection to Parkinson's disease, are there certain labor categories or work processes that are associated with this exposure?

3) Are there any causation presumptions that can be made? For example, when an employee has a diagnosis of X, exposure to Y, for a period of Q years, and a latency period of Z, DEEOIC should accept the claim.

Recommendation:

The Board recommends that in addition to carbon monoxide and steel/manganese products already included in the EEOICPA Procedure Manual and DOL Site Exposure Matrix, exposures to carbon disulfide (CS_2) and trichloroethylene (TCE) be presumed to cause, contribute, or aggravate Parkinsonism claims. These exposures were present in the DOE weapons complex and have been shown to be associated with increased risk of Parkinsonism in human studies. The Board also recommends, based on epidemiologic studies, a minimum exposure duration of eight (8) years for Part E causation in adjudicating Parkinsonism claims with exposures to carbon disulfide and trichloroethylene.

At present, the Board issues no recommendations for methanol, toluene, n-hexane, and polychlorinated biphenyls (PCBs), or other work–related exposures common throughout the DOE weapons complex. The Board also issues no recommendation for pesticides or specific pesticide products that may have been used on DOE installations. Current evidence is not sufficient to support a presumption of these additional agents with regard to Parkinsonism. As new research is emerging, the Board recommends a periodic review of human studies literature on risk factors for Parkinsonism for DOL to provide updates in this field.

Presumption of causation implies the judgment that the literature at the current time is sufficient to support the statement that the exposure can contribute to causation of the disease or aggravate the course of the disease in exposed populations, and the judgment that the degree of exposure in the individual is sufficient to have produced this contribution to causation in that individual. This use of presumptions is intended to identify the subset of people with the straightforward presentations to streamline the compensation process by eliminating the need for detailed causal evaluation by the physician and industrial hygienist. It must be emphasized that if an individual DOEs not meet the criteria for the presumption of causation, this DOEs not imply that there is not sufficient evidence of causation. It simply means that individuals who do not meet these presumptive criteria and would need to be evaluated through a fact-based process entailing industrial hygiene and medical review to make the judgment whether the exposure contributed to causation of the disease.

Rationale:

Inhalational exposures to carbon monoxide and manganese resulting in Parkinsonian type deficits have been well-documented in the literature and are included, along with related work processes, in the DOL's EEOICP Procedure Manual and Site Exposure Matrix (SEM). Recent studies and case reports provide description of parkinsonian symptomatology following inhalational and dermal occupational exposures to carbon disulfide (CS_2,) and trichloroethylene (TCE) solvents. There is also a growing body of epidemiological research showing exposures to

trichloroethylene (TCE) to increase the risk of Parkinson Disease (PD) in occupationally exposed populations. These exposures and studies are briefly reviewed herein.

Solvents have been used commonly throughout industry, as degreasing agents and varnishes, in cleaning parts and machining equipment, in dry cleaning, in construction and as substrates in paints and paint thinners (Sainio, 2015). Unpublished former DOE worker medical screenings' program data shows extensive use of organic (hydrocarbon) solvents in DOE weapons operations throughout the decades, primarily in degreasing and machining operations, with the highest exposed jobs including painters, equipment mechanics and production workers (BAECP FWP, 2011). A 2011 Bahr et al. study of DOE workers from Paducah Gaseous Diffusion Plant identified workers who worked in laboratory, in maintenance/electricians, in maintenance/lubrication, in waste or chemical operations as those with highest exposures to TCE. Solvents use has also been common in uranium and plutonium recovery processes in nuclear weapons programs (Todd, 2011). The DOE's Office of Health and Environmental Research Subsurface Science Program study identified TCE and toluene in most of soil, sediments and ground water samples collected from or near the disposal sites at eighteen (18) DOE facilities within the weapons complex around the country (Riley et al. 1992).

Main routes of exposure to solvents are through inhalation, skin and/or ingestion uptake. Liver, kidney damage, depression of bone marrow and cancers (In some) have been reported following exposure to many organic solvents solvents, with other effects including respiratory impairment, reproductive system abnormalities and dermatitis following low-level exposures (Dick, 2006). Organic solvents are also predominantly neurotoxic with acute, high concentration exposures leading to central nervous system suppression of respiration and long-term exposures associated with chronic solvent encephalopathy (Bale et al., 2011; van Valen et al.,2012; Sainio, 2015) and Parkinsonian type deficits following chronic solvents abuse (Uitti et al., 1994; Pezzolli et al., 1996). A possible dose-response relationship with duration of exposure to solvents and increased risk of death from PD has been reported in a mortality study of 20,256 Rolls-Royce plants workers from the UK (McDonnell et al., 2003). A recent meta-analysis of peer-reviewed epidemiological studies found an overall increase in risk for PD associated with exposure to solvents (OR=1.35 95%CI 1.09-1.67) (Pezzoli and Cereda, 2013).

Carbon disulfide (CS$_2$) has been used as a solvent for phosphorus, asphalt, resins, and rubber and as a building block for other substances in organic chemistry. Primarily used in textile, rubber and cellophane manufacture, this chemical has also been found in soils/sediments and ground water samples from DOE's nuclear weapons facilities across the country (Riley et al., 1992). According to Site Exposure Matrix, CS$_2$ has been used at DOE sites for activities associated with chemistry laboratories, isotope separation, laser research and development, and medical equipment sterilization. It is also used in paints, enamels, varnishes, paint removers, explosives, rocket fuel, putty preservatives, and rubber cement as well as a solvent for waxes, lacquers, camphor, resins, and vulcanized rubber. CS2 is also used as an insecticide for soil treatment and grain storage to control insects and nematodes and as an overall process solvent (DEEOIC SEM, 2020).

Cardiovascular, developmental and neurotoxic effects have been described following exposures to CS$_2$ with neurotoxicity involving both central and peripheral nervous system (ATSDR, 1996).

Case reports document four (4) cases of chronically exposed viscose rayon plants' workers with Parkinsonian symptoms following presumably inhalational exposures to CS_2. Each of those workers had 20 plus years of exposure with three of them working in jobs involving fiber cutting and cellulose production and one as a painter (Hageman et al 1999; Huang et al., 2004).

TCE has been widely used as a degreasing and cleaning agent, in metal fabrications, as an anesthetic and a building block for number of household chemicals (ATSDR, 2019). Its peak use occurred before 1970's and DOE's Subsurface Science Program reported TCE as the most commonly found solvent in ground water and soil samples collected from or near the disposal sites in the nuclear weapons facilities (Riley et al., 1992). SEM documents TCE's use at DOE sites for activities associated with boiler and pressure vessel erection, repair, and testing; chemistry laboratories; drum/box/container stenciling; dry cleaning; electrical maintenance; HVAC maintenance; machining; mechanical maintenance; metal degreasing; painting; plumbing/pipefitting; and sheet metal fabrication. Per SEM, Trichloroethylene has also been used as an extraction solvent for greases, oils, fats, waxes, and tars; by the textile processing industry to scour cotton, wool, and other fabrics; in dry cleaning operations; and as a component of adhesives, lubricants, paints, varnishes, paint strippers, pesticides, and cold metal cleaners (DEEOIC SEM, 2020)

A link between TCE exposure and Parkinson disease has been reported in case studies and epidemiologic observations (Guehl et al., 1999; Kochen et al., 2003). Gash et al. (2008) reported most recently on a cluster of thirty (30) chronically TCE-exposed workers, all from a small measuring instruments manufacturing plant, with Parkinsonian type deficits, three of whom were eventually diagnosed with PD. This group of workers ranged in age from 46 to 67 years, with exposure duration between 8 and 33 years and each of the three workers diagnosed with PD held jobs in degreasing metal parts involving daily work in TCE exposure for over 25 years.

The association between TCE exposure and increase in risk of PD has also been shown by Goldman et al. in their 2012 nested case - control study of twin pairs from the National Academy of Sciences/National Research Council World War II Veteran Twins Registry Cohort. Ninety-nine (99) twin pair participants in this study who were discordant for diagnosis of PD, and whose lifetime exposure to solvents was assessed based on self-reports and industrial hygiene guided interviews had greater than six-fold increase in risk for PD when exposed to TCE up to 2% of work time or one hour per week, compared to those never exposed to TCE (OR=6.1, 95% CI 1.2-33). The risk was also elevated for those exposed to either TCE or perchloroethylene (OR=8.9, 95% CI 1.7-47), as well as those with longer duration of TCE exposure (OR=3.2, 95% CI 1.1-10 for TCE and OR=4.1 95% CI 1.4-11.8 for either TCE or PERC) and highest cumulative exposure dose (OR=5.2, 95% CI 1.03-26). Electricians, dry cleaners, industrial machinery repairmen and health workers were identified as at risk for most frequent TCE exposure.

In addition, in their assessment of evidence for TCE and tetrachloroethylene (PCE) exposures as drinking water contaminants at Camp Lejeune, the ATSDR (2017) concluded, based on animal, mechanistic studies and epidemiological evidence from Goldman's 2012 twins study and Bove et al. (2014) study of mortality among Camp Lejeune workers, that the evidence for TCE is "equipoise and above for causation for TCE and Parkinson Disease".

Although not yet a presumption, a brief review of up-to-date literature on pesticides is presented below to serve as a basis for further review and future recommendations in this area.

Pesticides are a group of chemical compounds used widely in farming, agricultural and household applications to control crop health and eliminate rodents (rodenticides), fungus (fungicides), plants/weeds (herbicides) and insects (insecticides). Exposure to pesticides has been associated with various health outcomes, description of which is beyond the scope of this review. However, over the last two decades, a growing number of epidemiological studies have been conducted showing these compounds to be a potential risk factor for Parkinson Disease, with analyses of pooled data repeatedly showing increase in risk and incidence rates of this disease (Priyadarshi et al., 2000; Pezzoli and Cereda, 2013; Breckenridge et al.,2016; Ahmed et al., 2017; Gunnarson and Bodin, 2018), specifically with occupational exposures (van der Mark et al., 2012; Van Maele-Fabry et al., 2012). The systematic reviews also point to a potential dose-response relationship with duration of exposure (Yan et al, 2017). While these studies provide a wealth of information and identify jobs with highest exposure potential (farmers, pesticide applicators, workers in pesticide manufacturing, horticulturists, green house workers, and gardeners) the results demonstrate a high degree of variability in studies designs, exposure assessment methods, and/or case definitions. Additionally, most studied populations were exposed to numerous combinations of pesticides, making attribution of specific compounds problematic.

DOE Subsurface Science Research Program reported pesticides among the least commonly found compounds, shown in concentrations ranging from trace to parts per thousand in soil/sediment samples from two to five facilities and water samples from only one site under study (Riley et al. 1992). The use of pesticides throughout the DOE's weapons complex has been documented in DOL's SEM which provides listing of several products and chemical compounds. Some of these compounds, specifically in the insecticides and herbicides groups (paraquat, chlorpyriphos, rotenone, maneb, dieldrin, heptachlor and atrazine) have been shown previously in animal models to induce dopaminergic cell degeneration and α-synuclein deposition, consistent with Parkinsonian pathology (Betarbet et al., 2000; Caudle et al., 2005; Cichetti et al. 2005; Filipov et al. 2007; Hatcher et al. 2007; Cannon et al. 2009). These compounds have been further studied in human studies over the years and while the results indicate increase in risk of Parkinson Disease associated with exposures to chlorpyriphos OR= 2.0, 95% CI 1.02–3.8 (Dhilon et al. 2008); 2,4-dichlorophenoxyacetic acid OR=2.59, 95% CI 1.03-6.48 (Tanner et al. 2009); rotenone (OR= 2.5, 95% CI 1.3–4.7) and paraquat OR= 2.5, 95% CI 1.4–4.7 (Tanner et al. 2011), and the combination of paraquat and maneb OR=1.75, 95% CI 1.13-2.73 (Costello et al. 2009) the potential for co-exposures to additional pesticide compounds is present in most studies, making a conclusive link between any specific pesticide difficult to establish.

Table 1 MDS Clinical Diagnostic Criteria for PD—Executive Summary/Completion Form

The first essential criterion is parkinsonism, which is defined as bradykinesia, in combination with at least one of rest tremor or rigidity. Examination of all cardinal manifestations should be carried out as described in the MDS–Unified Parkinson Disease Rating Scale (Goetz, Tilley, Shaftman, et al., 2008). Once parkinsonism has been diagnosed:

Diagnosis of Clinically Established PD requires:

(1) absence of absolute exclusion criteria,
(2) at least two supportive criteria, and
(3) no red flags

Diagnosis of Clinically Probable PD requires:

(1) absence of absolute exclusion criteria
(2) presence of red flags counterbalanced by supportive criteria
    – If one red flag is present there must also be at least one supportive criterion.
    – If two red flags, at least two supportive criteria are needed.
    – No more than two red flags are allowed for this category.

Supportive criteria (Check box if criteria met)

☐ 1. Clear and dramatic beneficial response to dopaminergic therapy. During initial treatment, patient returned to normal or near-normal level of function. In the absence of clear documentation of initial response a dramatic response can be classified as:
    (a) Marked improvement with dose increases or marked worsening with dose decreases. Mild changes do not qualify. Document this either objectively (>30% in UPDRS III with change in treatment) or subjectively (clearly documented history of marked changes from a reliable patient or caregiver).
    (b) Unequivocal and marked on/off fluctuations, which must have at some point included predictable end-of-dose wearing off.

☐ 2. Presence of levodopa-induced dyskinesia.

☐ 3. Rest tremor of a limb, documented on clinical examination (in past, or on current exam)

☐ 4. The presence of either olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy

Absolute exclusion criteria: The presence of any of these features rules out PD:

☐ 1. Unequivocal cerebellar abnormalities, such as cerebellar gait, limb ataxia, or cerebellar oculomotor abnormalities (e.g., sustained gaze-evoked nystagmus, macro square wave jerks, hypermetric saccades).

☐ 2. Downward vertical supranuclear gaze palsy or selective slowing of downward vertical saccades.

Table 1 MDS Clinical Diagnostic Criteria for PD—Executive Summary/Completion Form—cont'd

☐ 3. Diagnosis of probable behavioral variant frontotemporal dementia or primary progressive aphasia, defined according to consensus criteria (Rascovsky et al., 2011) within the first 5 years of disease.

☐ 4. Parkinsonian features restricted to the lower limbs for more than 3 years.

☐ 5. Treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism.

☐ 6. Absence of observable response to high-dose levodopa despite at least moderate severity of disease.

☐ 7. Unequivocal cortical sensory loss (i.e., graphesthesia, stereognosis with intact primary sensory modalities), clear limb ideomotor apraxia, or progressive aphasia.

☐ 8. Normal functional neuroimaging of the presynaptic dopaminergic system.

☐ 9. Documentation of an alternative condition known to produce parkinsonism and plausibly connected to the patient's symptoms, or, the expert evaluating physician, based upon the full diagnostic assessment feels that an alternative syndrome is *more likely* than PD.

Red flags

☐ 1. Rapid progression of gait impairment requiring regular use of wheelchair within 5 years of onset.

☐ 2. A complete absence of progression of motor symptoms or signs over 5 or more years unless stability is related to treatment.

☐ 3. Early bulbar dysfunction: *severe* dysphonia/dysarthria (speech unintelligible most of the time) and/or severe dysphagia (requiring soft food, NG tube, or gastrostomy feeding) within first 5 years.

☐ 4. Inspiratory respiratory dysfunction: either diurnal or nocturnal inspiratory stridor and/or frequent inspiratory sighs.

☐ 5. Severe autonomic failure in the first 5 years of disease. This can include:
  (a) Orthostatic hypotension (Gilman et al., 2008)—orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic, in the absence of dehydration, medication, or other diseases that could plausibly explain autonomic dysfunction, or
  (b) Severe urinary retention or urinary incontinence in the first 5 years of disease (excluding long-standing or small amount stress incontinence in women), that is not simply functional incontinence. In men, urinary retention must not be due to prostate disease, and must be associated with erectile dysfunction.

Table 1 MDS Clinical Diagnostic Criteria for PD—Executive Summary/Completion Form—cont'd

☐ 6. Recurrent (>1/year) falls due to impaired balance within 3 years of onset.

☐ 7. Disproportionate anterocollis (dystonic) and/or contractures of hand or feet within the first 10 years.

☐ 8. Absence of any of the common nonmotor features of disease despite 5 years disease duration. These include sleep dysfunction (sleep-maintenance insomnia, excessive daytime somnolence, symptoms of REM sleep behavior disorder), autonomic dysfunction (constipation, daytime urinary urgency, symptomatic orthostasis), hyposmia, or psychiatric dysfunction (depression, anxiety, or hallucinations).

☐ 9. Otherwise unexplained pyramidal tract signs, defined as pyramidal weakness and/or clear pathologic hyperreflexia (excluding mild reflex asymmetry and isolated extensor plantar response).

☐ 10. Bilateral symmetric parkinsonism. The patient or caregiver reports bilateral symptom onset with no side predominance, *and* no side predominance is observed on objective examination.

Criteria Application:

1. Does the patient have parkinsonism, as defined by the MDS criteria?   Yes ☐ No ☐

   If no, *neither* probable PD nor clinically established PD can be diagnosed. *If yes*:

2. Are any absolute exclusion criteria present?   Yes ☐ No ☐

   If "yes," *neither* probable PD nor clinically established PD can be diagnosed. *If no*:

3. Number of red flags present   ____

4. Number of supportive criteria present   ____

5. Are there at least two supportive criteria *and* no red flags?   Yes ☐ No ☐

   If yes, patient meets criteira for *clinically established PD. If no*:

6. Are there more than two red flags?   Yes ☐ No ☐

   If "yes," probable PD *cannot* be diagnosed. *If no*:

7. Is the number of red flags equal to, or less than, the number of supportive criteria?   Yes ☐ No ☐

   If yes, patient meets criteria for *probable PD*

In: Postuma RB, Berg D, Stern M, et al. (2015) MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord; 12:1591-1601.

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