

MSAC Application 1795

Positron emission tomography/computed tomography (PET/CT) dopaminergic imaging for evaluating Parkinsonism

Applicant: Australasian Association of Nuclear Medicine Specialists

PICO Confirmation

Summary of PICO/PPICO criteria to define question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Table 1 PICO Set Positron emission tomography/computed tomography dopaminergic Imaging in patients who are not responding as expected from initial standard therapy for Parkinson's disease

Component	Description
Population	Patients who are not responding (improvement of $\leq 30\%$ on the UPDRS III)¹ to standard treatments for PD after 12 weeks of therapy optimisation, but not greater than 24 months post treatment initiation. Notes: 1. The International Parkinson and Movement Disorder Unified Parkinson's Disease Rating Scale (UPDRS) is used to gauge the severity and progression of Parkinson's disease in patients. Part III of the UPDRS pertains to motor assessments.
Prior tests	The MDS-PD Diagnostic Criteria require a positive response ($>30\%$) to initial optimised dopaminergic medications, to support a diagnosis of probable PD. Other tests typically performed in Australia that could assist in diagnosing PD for patients with significant diagnostic uncertainty include genetic testing and neuroimaging.
Intervention	[18F]fluorodopa positron emission tomography/computed tomography (FDOPA PET/CT) dopaminergic imaging.
Comparator/s	Standard of care including any changes in patient management post-test scan. There are no comparative imaging modalities or tests available in Australia.
Reference Standard and Clinical utility standard	The reference standard is postmortem neuropathology. The clinical utility standard is FDOPA PET/CT.

Component	Description
Outcomes	Efficacy outcomes • Test accuracy ○ Including sensitivity, specificity, positive and negative predictive value ○ Area under the curve (AUC) for time-dependent receiver operating characteristics (ROC) ○ Inter-observer reliability • Clinical validity ○ Dopaminergic denervation – loss of nigral dopamine neurons ○ Semiquantification – parameters expressing loss of presynaptic dopaminergic neurons Change in management outcomes • Change in proportion of patients correctly diagnosed • Change in proportion of patients prescribed appropriate or medically necessary therapies, including L-DOPA • Other changes in clinical management (e.g. further investigations/monitoring)Change in patient-reported health status ○ Parkinson's Disease Quality of Life Questionnaire (PDQ-8) for patients with parkinsonism, including atypical parkinsonism ○ Quality of life in Essential Tremor (QUEST) for relevant patients ○ Dementia quality of life (DEMQOL) for patients with DLB Change in health outcomes (e.g. disease progression) Safety outcomes • Exposure to radiation (measured in millisieverts, mSv) • Harms (psychological health risks) associated with imaging • Harms associated with false positive and negative results Healthcare system outcomes • Cost effectiveness of FDOPA PET/CT testing • Costs of treatments received/cost offsets from avoidance of unnecessary therapies • Costs associated with managing FDOPA intolerance and other AEs • Financial implications
Assessment questions	What is the safety, effectiveness and cost-effectiveness of FDOPA PET/CT imaging in the differential diagnosis of people who have not responded as expected (0%-30% UPDRS III) to initial standard treatment for PD after 12 weeks of therapy optimisation but not greater than 24 months post treatment initiation? What are the net health benefits of FDOPA PET/CT imaging on health outcomes (QoL, disease management and progression) in people who have not responded as expected (0%-30% UPDRS III) to initial standard treatment for PD after 12 weeks of therapy optimisation but not greater than 24 months post treatment initiation?

AD = Alzheimer's Disease; AE = adverse event; APD = atypical Parkinson's disease; AUC = area under the curve; CPI = Caudate-Putamen Index; DLB = dementia with Lewy bodies; DDC = DOPA decarboxylase; DOPA = dopaminergic; FDOPA = [¹⁸F]fluorodopa; MDS = Movement Disorder Society; MSA = multiple system atrophy; PD = Parkinson's disease; PET/CT = positron emission tomography/computed tomography; PSP = progressive supranuclear palsy; QoL = quality of life; ROC = receiver operating characteristics; ROI = region of interest; SPECT = single-photon emission computed tomography; UPDRS III = Unified Parkinson's Disease Rating Scale Part III.

1. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. *Movement disorders*. 2015;30(12):1591-1601. doi:10.1002/mds.26424

Purpose of application

An application requesting MBS listing of positron emission tomography/computed tomography (PET/CT) dopaminergic imaging (FDOPA PET/CT) for evaluating parkinsonism was received from the Australasian Association of Nuclear Medicine Specialists by the Department of Health.

The test is designed to differentiate parkinsonian syndromes from other movement disorders.

The applicant claims the use of the proposed technology will result in more accurate diagnoses of parkinsonian syndromes which in turn enables superior health outcomes, while current standard practices in Australia do not include radiopharmaceutical PET imaging. The Applicant further claims that receiving a more accurate diagnosis of parkinsonism enables:

- earlier access to appropriate medications and more targeted allied health support;
- earlier exclusion of misdiagnosed PD for patients who are refractory to standard PD therapies; and
- potentially earlier access to more invasive therapies, such as deep brain stimulation (DBS) for patients who are refractory to standard therapies and with a confirmed diagnosis of PD post FDOPA PET.

The Applicant has indicated that they may seek Therapeutic Goods Administration (TGA) approval should MSAC provide support for the public funding of FDOPA PET imaging for evaluating parkinsonism. It is currently made available on request via Category B of the TGA's application pathway of their Special Access Scheme (SAS) for unapproved products for individual patients. Currently, the radioligand is produced by 3 public entities and one private entity:

- Austin Hospital;
- Royal Brisbane Hospital;
- South Australian Health and Medical Research Institute; and
- Cyclotek, Victoria (personal communication, pre-PASC teleconference, 21 February 2025).

FDOPA PET imaging involves the use of a radiopharmaceutical that is labelled with fluorine-18, a positron-emitting isotope with a relatively short half-life of approximately 110 minutes (Stormezand et al. 2024). This short half-life imposes logistical constraints on its transportation and use across different centres. In practice, FDOPA is produced in a cyclotron at or near a PET imaging facility due to its rapid decay. Transporting FDOPA to other centres is challenging. Cyclotek has TGA approved manufacturing facilities in New South Wales, Victoria, and Queensland with an established logistics and supply chain to reach centres in capital cities, and potentially regional cities, including Adelaide, Cairns, Rockhampton, and Perth. However, it is not clear whether they currently manufacture [¹⁸F] Fluorodopa (Cyclotek 2025).

PICO criteria

Population

PICO Set

PASC noted the population for PICO Set 1 as proposed in the application form consisted of patients with Parkinsonism, which is a diverse group, including both neurodegenerative and non-neurodegenerative conditions. PASC queried whether, in these circumstances, the test has the potential to become a frontline diagnostic test, rather than focussed on patients with significant diagnostic uncertainty. PASC considered that it would be difficult to clearly define the eligibility criteria for focussed patient groups and therefore

there was the potential for all patients with Parkinsonism to receive the FDOPA PET/CT whether there was diagnostic uncertainty or not. Therefore, PASC considered that PICO Set 1 should be removed from the population.

As per PASC comments, the proposed population therefore only covers PICO Set 2 in the Application form which pertains to an evaluation of patients with a diagnosis of PD, who are not responding as expected to standard therapy, early in their treatment course (Application form, p. 5 of the PICO Set 2). FDOPA PET/CT examination is proposed to evaluate patients who have not achieved the expected response to standard PD therapies. The Applicant estimates that approximately 10% of patients with a PD diagnosis referred to a movement disorder clinic may be deemed appropriate candidates for this imaging study (Application form, p. 5 of the PICO Set 1).

The targeted population proposed for assessment is defined as patients who have symptoms unresponsive to optimised standard treatment for PD according to the International Movement Disorder Society Unified Parkinson's Disease Rating Scale (UPDRS Part III), which is a response in the range, 0% to 30% of improvement in PD symptoms (Postuma et al. 2015). This response must be experienced by the patient after 12 weeks of therapy optimisation but not greater than 24 months post treatment initiation.

This definition describes patients with equivocal parkinsonism with a diagnosis of probable PD and who have symptoms unresponsive to initial dopaminergic medications (Postuma et al. 2015).

Symptoms unresponsive to dopaminergic medication

In patients with PD misdiagnosis rates may be high, ranging from 14% in specialist environments to 29% in community practice (Waller et al. 2021; Yeow et al. 2025). Coupled with patients with PD showing symptoms unresponsive to dopaminergic medication (0%-30% UPDRS), a differential diagnosis is required to rule out potential non-PD conditions (Morbelli et al. 2020). Table 2 summarises clinical factors affecting responses to dopaminergic medication and their clinical implications, describing essential tremor (ET), dementia with Lewy bodies (DLB), atypical parkinsonian syndromes (MSA, PSP), vascular parkinsonism, and PD-specific issues (advanced non-dopaminergic features).

Table 2 Aetiologies of patients with symptoms unresponsive to dopaminergic medication (0%-30%)

Aetiology	Mechanism of unresponsiveness (0%-30% UPDRS III)	Clinical Implications
Other diseases		
Misdiagnosis Essential Tremor (ET)	No nigrostriatal dopamine deficiency tremor arises from cerebellar-thalamic dysfunction rather than basal ganglia pathology	Normal FDOPA PET, lack of bradykinesia/rigidity, re-diagnosis as ET, trial beta-blockers (propranolol) instead of levodopa.
Misdiagnosis Dementia with Lewy Bodies (DLB)	Dopamine deficiency present, but parkinsonism overshadowed by cortical Lewy body pathology; levodopa response limited by non-motor dominance (hallucinations).	Reduced FDOPA PET uptake, early cognitive decline/hallucinations, shift to cholinesterase inhibitors, reconsider PD diagnosis.
Misdiagnosis Atypical parkinsonian syndromes	Conditions such as MSA, PSP, or CBD lack significant nigrostriatal dopamine deficiency or have postsynaptic dopamine receptor loss Lewy body pathology minimal or absent	Reassess for atypical features (early falls in PSP, autonomic dysfunction in MSA) MRI may show specific signs ("hot cross bun" in MSA) FDOPA PET abnormal but levodopa response poor

Aetiology	Mechanism of unresponsiveness (0%-30% UPDRS III)	Clinical Implications
Vascular parkinsonism	Symptoms due to cerebrovascular lesions (basal ganglia infarcts) rather than nigrostriatal degeneration Dopamine pathways variably affected or intact	MRI shows white matter changes or infarcts Lower-body predominant symptoms, poor levodopa response. History of stroke or vascular risk factors
Drug-induced parkinsonism	Dopamine receptor blockade (from antipsychotics) persists or unmasks PD-like symptoms without true dopamine deficiency Reversible if drug-related, but may coexist with PD	Review medication history, haloperidol, metoclopramide Normal FDOPA PET if purely drug-induced Symptoms may persist post-withdrawal if PD is revealed
Psychogenic parkinsonism	Functional (non-organic) aetiology; no dopaminergic deficit Symptoms driven by psychological factors rather than neurodegeneration	Inconsistent symptoms, distractibility on exam Normal FDOPA PET and MRI. No progression or response to levodopa.
Medication related		
Advanced PD with non-dopaminergic features	Late-stage PD involves non-dopaminergic symptoms (postural instability, freezing of gait, dementia) unresponsive to levodopa Loss of postsynaptic dopamine receptors or widespread pathology.	History of initial levodopa response that wanes Prominent axial symptoms or cognitive decline Consider adjunctive therapies (PT, DBS evaluation)
Suboptimal dosing or absorption	Inadequate levodopa dose, poor absorption (due to gastric emptying issues), or protein interference with transport across blood-brain barrier	Review dosing regimen and timing with meals Test higher doses or formulations (carbidopa-levodopa extended-release) Assess for GI issues
Medication tolerance or resistance	Long-term levodopa use may lead to receptor desensitization or downregulation in some patients Rare intrinsic resistance to dopaminergic therapy	History of prolonged exposure with diminishing returns Trial of dopamine agonists or MAO-B inhibitors Consider DBS if refractory motor symptoms persist
Coexisting or overlapping conditions		
Coexisting conditions	Comorbidities (arthritis, neuropathy) may mimic some aspects of parkinsonism or limit motor improvement Depression or apathy may mask perceived benefit	Evaluate for joint stiffness, sensory deficits, or psychiatric overlay Treat comorbidities (SSRIs for depression) Reassess PD-specific response with optimized management.
Pd with significant tremor dominance	Resting tremor in PD may respond less robustly to levodopa than bradykinesia or rigidity Tremor-dominant PD subtype less dopamine-responsive	Prominent tremor with minimal bradykinesia/rigidity Trial of adjunctive therapies (anticholinergics, DBS) Reassess tremor type (ET overlap)

Abbreviations: AD = Alzheimer's disease, CBD = Corticobasal degeneration, DBS = Deep brain stimulation, ET = Essential tremor, GI = Gastrointestinal, MAO-B = Monoamine oxidase B, MRI = Magnetic resonance imaging, MSA = Multiple system atrophy, PD = Parkinson's disease, PSP = Progressive supranuclear palsy, PT = Physical therapy, SSRIs = Selective serotonin reuptake inhibitors, UPDRS = Unified Parkinson's Disease Rating Scale.

Source: Adapted from (Deloitte Access Economics 2014; di Biase, Pecoraro & Di Lazzaro 2025; Dijk et al. 2020; Kobylecki 2020)

Table 2 identified possible aetiologies for symptoms unresponsive to treatment in patients with PD. ET lacks a dopaminergic deficit and DLB involves cortical pathology, leading to misdiagnosis compared with PD's nigrostriatal dopamine deficiency (Dijk et al. 2020; Kobylecki 2020). Re-diagnosis has significant clinical implications—ET should be treated with beta-blockers and DLB with cholinesterase inhibitors—while confirmed PD cases may require management changes such as anticholinergics or dose adjustments

(Kobylecki 2020). Conditions mimicking PD, such as psychogenic and vascular disorders, call for non-dopaminergic treatments (Ali & Morris 2015; Dijk et al. 2020).

Standard of care, comparators and outcomes

For patients with PD showing symptoms unresponsive to dopaminergic medication, as well as a misdiagnosis rate of 14%-29%—often involving ET and DLB—highlights the complexities involved in differentiating parkinsonism (di Biase, Pecoraro & Di Lazzaro 2025). This table summarises the standard of care, potential comparators, and possible outcomes for patients with symptoms unresponsive to dopaminergic medication, incorporating clinical re-assessment, advanced imaging FDOPA PET, and interventions to address misdiagnoses as well as PD-specific factors such as advanced non-dopaminergic features, and suboptimal dosing (Chin, Teodorczuk & Watson 2019; Dijk et al. 2020; Kobylecki 2020).

Table 3 Standard clinical practice, potential comparators and outcomes for patients with symptoms unresponsive to initial optimised PD therapies

Patient (Aetiology)	Standard clinical practice	Potential differential diagnoses	Outcomes
Misdiagnosis (ET)	- Clinical reassessment: Tremor type/history - FDOPA PET - Trial beta-blockers (propranolol)	- ET: Postural/kinetic tremor, alcohol-responsive vs. - PD: Resting tremor, levodopa responsive	Normal FDOPA PET, good response to beta-blockers, re-diagnosis as ET, no PD progression
Misdiagnosis (DLB)	- Cognitive/motor assessment - FDOPA PET, FDG-PET - Trial cholinesterase inhibitors	- DLB: Early hallucinations, parkinsonism vs. - PD: Later cognitive decline (PDD), motor primacy.	Reduced FDOPA PET uptake, occipital hypometabolism, symptom management with cholinesterase inhibitors, not PD
Misdiagnosis (Atypical Parkinsonian Syndromes, e.g., MSA, PSP, CBD)	- Neurological reassessment for atypical features - MRI and FDOPA PET - Discontinue levodopa if ineffective	- MSA: Autonomic failure, cerebellar signs - PSP: Vertical gaze palsy - CBD: Asymmetric rigidity vs. - PD: Motor symptoms	- Abnormal FDOPA PET, specific MRI findings (“hot cross bun” in MSA) - poor levodopa response - progressive decline
Vascular Parkinsonism**	- MRI for cerebrovascular evidence - Vascular risk management - Trial levodopa with reassessment	- Vascular: Lower-body symptoms, stepwise progression vs. - PD: Asymmetric, resting tremor.	- MRI shows infarcts - poor levodopa response - focus on vascular prevention.
Drug-Induced Parkinsonism	- Medication history review - Withdraw offending drug (antipsychotics) - FDOPA PET test if persistent	- Drug-induced: Symmetric, reversible vs. - PD: Asymmetric, persistent.	- Normal FDOPA PET - resolution post-withdrawal - persistent symptoms suggest unmasked PD.
Psychogenic Parkinsonism	- Neurological exam with distractibility tests - Psychiatric evaluation - FDOPA PET/MRI	- Psychogenic: Inconsistent, distractible vs. - PD: Consistent motor signs	- Normal FDOPA PET /MRI - no levodopa response - symptom variability with psychotherapy
Advanced PD with Non-Dopaminergic Features	- Assess disease stage, non-motor symptoms - Adjunctive therapies (e.g., PT, DBS) - Multidisciplinary care	- Advanced PD: Axial symptoms, cognitive decline vs. - Early PD: Responsive bradykinesia/rigidity.	- Waning levodopa benefit - focus on non-dopaminergic management - potential DBS candidacy

Patient (Aetiology)	Standard clinical practice	Potential differential diagnoses	Outcomes
Suboptimal Dosing or Absorption	- Review levodopa dose/timing - Trial higher doses/formulations - Assess GI function	- Suboptimal: Poor response due to dose/absorption vs. - Adequate dosing: Motor improvement	- Improved response with optimized dosing - resolution of absorption barriers
Coexisting Conditions	- Evaluate comorbidities (arthritis, depression) - Treat underlying conditions (SSRIs) - Reassess levodopa	- Coexisting: Comorbidity masks benefit vs. - Established PD: Clear motor response	- Improved motor assessment post-comorbidity treatment - clarified levodopa efficacy.
Medication Tolerance or Resistance	- Review treatment history - Trial adjunctive agents (e.g., MAO-B inhibitors) - Consider DBS	- Tolerance: Diminished response over time vs. - Early PD: Satisfactory initial response	- Partial benefit from adjunctive therapies - DBS for refractory cases - limited levodopa efficacy.
PD with Significant Tremor Dominance	- Assess tremor vs. other features - Trial anticholinergics or DBS - Reassess for ET overlap	- Tremor-dominant PD: Prominent tremor, less bradykinesia vs. - PD: Balanced motor response	- Variable levodopa response for tremor - improved control with anticholinergics/DBS - possible ET-PD syndrome

Abbreviations: CBD = Corticobasal degeneration, DBS = Deep brain stimulation, DLB = Dementia with Lewy Bodies, ET = Essential tremor, FDG-PET = Fluorodeoxyglucose positron emission tomography, FDOPA PET = Fluorodopa positron emission tomography, GI = Gastrointestinal, MAO-B = Monoamine oxidase B, MRI = Magnetic resonance imaging, MSA = Multiple system atrophy, PD = Parkinson's disease, PDD = Parkinson's disease dementia, PSP = Progressive supranuclear palsy, PT = Physical therapy, SSRIs = Selective serotonin reuptake inhibitors.

Source: Adapted from (Chin, Teodorczuk & Watson 2019; Dijk et al. 2020; Kobylecki 2020).

Table 3 summarises standard clinical practice, potential comparators, and outcomes for patients with symptoms unresponsive to dopaminergic medications, highlighting standard care from tremor reassessment in ET to cognitive evaluation in DLB. It contrasts the motor focus in patients with PD with postural tremor in patients with ET, and early hallucinations in DLB versus later decline in PD dementia (Ali & Morris 2015). Outcomes depend on accurate diagnoses—redirecting patients with ET to beta-blockers and patients with DLB to cholinesterase inhibitors—while confirmed cases of PD with tremor dominance or patients with advanced stages shift to anticholinergics or deep brain stimulation (DBS). Patients with PD mimics such as vascular or psychogenic disorders receive non-dopaminergic care, supported by imaging evidence (Ali & Morris 2015; Waller et al. 2021).

PASC noted that regarding the proposed population (from PICO set 2 of the Application form), the majority of patients on long-term dopaminergic medication for PD will eventually have a poor response to the medication as time progresses and that this lack of response was not indicative of diagnostic uncertainty. PASC therefore considered that it was important to specify the period of treatment after which the patient should be assessed for treatment response, to ensure that the group of patients who had been on long-term dopaminergic medication are excluded from being eligible for FDOPA PET/CT.

PASC proposed to restrict the population to patients who have received a trial of dopaminergic medication and have not responded as expected after 12 weeks of treatment but not greater than 24 months. Lack of response is to be defined as 0%-30% improvement in PD symptoms, according to the Unified Parkinson's Disease Rating Scale (UPDRS), Part III.

Background

The clinical differential diagnosis of parkinsonism is often straightforward, but dopaminergic imaging may enhance diagnostic accuracy in cases where the diagnosis is uncertain. FDOPA PET imaging is especially

useful for patients with incomplete or atypical syndromes, unsatisfactory response to therapy, overlapping symptoms (such as resting tremor and cogwheel rigidity seen in some patients with ET), or early/mild symptoms (Morbelli et al. 2020).

Parkinson's disease is defined by the gradual degeneration of dopaminergic neurons and the presence of Lewy bodies in the affected brain regions (di Biase, Pecoraro & Di Lazzaro 2025). Dopamine is a brain hormone that is synthesised by dopaminergic neurons in the substantia nigra that project into the striatum. As a neurotransmitter, dopamine is released from the presynaptic membrane into the synaptic cleft, where it binds to and activates dopamine receptors on the postsynaptic membrane, enabling signal transmission (Zhou et al. 2023). Progressive degeneration of dopaminergic neurons reduces dopamine levels in the substantia nigra and striatum, which leads to the onset of clinical symptoms associated with parkinsonism, including tremors, postural instability, bradykinesia, and muscle rigidity (Zhou et al. 2023).

Nuclear medicine investigations can evaluate both presynaptic and postsynaptic dopaminergic function (Morbelli et al. 2020; Stormezand et al. 2024). Presynaptic imaging aids in distinguishing between neurodegenerative parkinsonian syndromes and non-dopamine deficiency causes of parkinsonism through radiopharmaceutical uptake tracers of dopamine (such as 18fluorodopa (FDOPA) PET/CT) while postsynaptic imaging aids in distinguishing between neurodegenerative parkinsonian syndromes including idiopathic PD and atypical PD such as corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) through radiopharmaceutical tracers of dopamine glucose release (such as fluorodeoxyglucose (FDG) PET) (Morbelli et al. 2020; Stormezand et al. 2024).

The relevant populations associated with the diagnostic yield of FDOPA PET/CT were identified in an Australian study into the clinical utility of FDOPA PET/CT (Yeow et al. 2025). These are consistent with the population subsets identified in international guidelines and diagnostic flowcharts (Morbelli et al. 2020; Peralta et al. 2022). In a retrospective chart review comprised of 105 patients who were referred for FDOPA PET/CT due to significant diagnostic uncertainty, the results were reported according to the following patient characteristics associated with FDOPA uptake (Yeow et al. 2025):

1. Consistent with PD;
2. Normal FDOPA uptake;
3. Atypical reduction of FDOPA; and
4. Equivocal FDOPA reduction-subtle but not definite (Yeow et al. 2025).

Atypical reduction of FDOPA means there was a definite reduction in striatal FDOPA uptake, but the observed pattern was not typical for PD (Yeow et al. 2025). The reduction might occur in brain regions not typically affected in PD, such as areas outside the striatum (cortex or cerebellum), or it might spare regions usually affected. It may be unusually symmetric or involve an unexpected asymmetry not aligned with clinical symptoms (Yeow et al. 2025).

Equivocal FDOPA reduction-subtle but not definite, means there was an observation of a subtle, but not definite decrease in FDOPA uptake sufficient to confirm a diagnosis.

The FDOPA PET/CT results stratified by scan indication are reported in Table 4.

Table 4 FDOPA PET/CT results stratified by scan indication

Scan indication (N=105)	Number of patients per FDOPA PET/CT result (%)			
	Consistent with iPD	Normal	Atypical FDOPA reduction	Equivocal FDOPA reduction
Parkinsonism assessment (n=47)	24 (51.1)	21 (44.7)	1 (2.1)	1 (2.1)
Tremor assessment (n=43)	8 (18.6)	34 (79.1)	0 (0.0)	1 (2.1)
Drug effect determination (n=10)	1 (10.0)	9 (90.0)	0 (0.0)	0 (0.0)
APD assessment (n=5)	1 (20.0)	2 (40.0)	2 (40.0)	0 (0.0)
Total (N=105)	34 (32.4%)	66 (62.8%)	3 (2.8%)	2 (1.9%)

Abbreviations: APD = atypical (neurodegenerative) parkinsonian disorders, FDOPA PET = 18F-fluorodopa positron emission tomography, iPD =, idiopathic Parkinson disease.

Source: (Yeow et al. 2025)

The assessment of parkinsonism was to differentiate neurodegenerative (PD, DLB, PSP, MSA) from non-neurodegenerative causes (vascular parkinsonism, NPH, FND) in patients with parkinsonian symptoms including symptoms unresponsive to PD therapies (Yeow et al. 2025). Tremor assessments distinguished neurodegenerative from non-neurodegenerative aetiologies (Essential Tremor, Dystonic Tremor, and FND) in patients presenting predominantly with tremor. Drug effects were evaluated to determine whether parkinsonism or tremors were induced by antipsychotics in patients without PD, and to identify cases where PD symptoms may have been masked. Atypical PD assessments characterised striatal dopaminergic deficits in patients suspected of atypical parkinsonism (Yeow et al. 2025).

Pathology of parkinsonian syndromes

While PD was thought to be a disorder affecting movement only, it is now well understood that PD also encompasses non-motor signs and symptoms, including cognitive, neuropsychiatric, autonomic, gastrointestinal and others (di Biase, Pecoraro & Di Lazzaro 2025; Mellick 2024a; Waller et al. 2021).

The cluster of motor symptoms that are characterised in parkinsonism result from the disruption of specific neurological pathways in the nigrostriatal tract within the mid-brain. There are many causes for degeneration in this tract, leading to many causes for the symptoms of parkinsonism. The chronic and selective degeneration of specific dopamine-producing neurons within the substantia nigra, combined with the accumulation of alpha-synuclein proteins, results in a pathological diagnosis of primary or iPD which typically includes a significant response to initial dopaminergic medication, greater than 30% (Mellick 2024a; Postuma et al. 2015).

Presynaptic dopaminergic function involves the production of dopamine from 2 amino acids. L-tyrosine is first hydroxylated to L-dopa, which is then decarboxylated to dopamine by aromatic L-amino-acid decarboxylase (AADC). Dopamine is subsequently transported into vesicles by vesicular monoamine transporter 2 (VMAT2). Upon neuronal depolarisation, these vesicles release dopamine into the synaptic cleft, where it interacts with postsynaptic dopamine receptors. Excess dopamine can be reabsorbed into the presynaptic neuron by the dopamine transporter (DAT) (Morbelli et al. 2020; Peralta et al. 2022).

Presynaptic dopaminergic imaging can confirm a presynaptic degenerative dopaminergic deficit, aiding in the differential diagnosis between neurodegenerative and non-neurodegenerative causes of parkinsonism (Stormezand et al. 2024). Non-neurodegenerative causes of parkinsonism do not exhibit dopaminergic deficits, and present with a normal clinical response to the radiopharmaceutical tracer (Yeow et al. 2025)

Clinical indications

PD is highly heterogeneous with a complex array of motor and non-motor symptoms. This variability in clinical presentations of parkinsonism, including PD, leads to the classification of disease as either primary (idiopathic PD, iPD) followed by secondary parkinsonism and other parkinsonian syndromes (Mellick 2024a; Waller et al. 2021). Secondary parkinsonism includes non-neurodegenerative causes that do not respond to dopaminergic medication such as ET, vascular parkinsonism, psychogenic parkinsonism, and drug-induced parkinsonism (Stormezand et al. 2024).

iPD is marked by the loss of dopaminergic neurons in the substantia nigra that project to the striatum. Other conditions with presynaptic loss of striatal dopaminergic neurons include DLB, MSA, and tauopathies like CBD and PSP (Stormezand et al. 2024). While the other parkinsonian syndromes may experience a temporary improvement in their symptoms with dopaminergic medication, the response is not significant and is unsatisfying (di Biase, Pecoraro & Di Lazzaro 2025; Postuma et al. 2015). The European Association of Nuclear Medicine (EANM)/Society of Nuclear Medicine and Molecular Imaging (SNMMI) guidelines recommend presynaptic dopaminergic imaging to confirm degenerative deficits, aiding in the differentiation of neurodegenerative from non-neurodegenerative causes of parkinsonism (Stormezand et al. 2024).

The [¹⁸F] fluorodopa (FDOPA) PET/CT imaging in the proposed population is intended to enhance clinical decision-making for people with atypical presentation of parkinsonism, defined as patients who are unresponsive to standard treatment for PD within 12 weeks to 24 months post treatment initiation, by enabling a differential diagnosis of PD, or by excluding PD (Yeow et al. 2025).

The intent of FDOPA PET/CT imaging for the purposes of this application is to detect loss of nigrostriatal dopaminergic neuron terminals of patients with parkinsonian syndromes and especially to:

- support the differential diagnosis between ET and neurodegenerative parkinsonian syndromes;
- help distinguish between diseases with a similar symptomology, such as DLB and other dementias, in particular AD, by identifying the degree of loss of dopamine-producing neurons in the substantia nigra and striatum, particularly in the putamen for PD;
- support the differential diagnosis between parkinsonism due to presynaptic degenerative dopamine deficiency and other forms of parkinsonism (iPD and drug-induced, psychogenic or vascular parkinsonism); and
- detect early presynaptic parkinsonian syndromes (Morbelli et al. 2020).

Note: Postsynaptic dopaminergic imaging is useful for distinguishing typical from atypical parkinsonian syndromes, primarily to differentiate iPD from other neurodegenerative disorders such as MSA and PSP that involve D2 receptor loss. However, the clinical application of SPECT or PET tracers for this imaging is currently limited, and many centres internationally are now using other molecular imaging targets (Morbelli et al. 2020).

This is the population clinically indicated for this test according to the Guidelines (Morbelli et al. 2020).

Rationale for the proposed population

In many cases, diagnosing parkinsonism is straightforward, but dopaminergic imaging may enhance accuracy, especially in patients with poor therapy response. Despite updates to diagnostic criteria and numerous studies, the clinical diagnosis of PD remains uncertain (di Biase, Pecoraro & Di Lazzaro 2025). Clinical criteria for definitive diagnosis are still not met, necessitating post-mortem pathological confirmation. The gold standard is post-mortem examination, which reveals the loss of dopaminergic

neurons in the substantia nigra and the presence of Lewy bodies, known as Lewy pathology (di Biase, Pecoraro & Di Lazzaro 2025).

In a recently published retrospective case-control study comparing alive diagnosis at the time and post-mortem results at the UK Brain Bank, 4,571 participants were enrolled, comprising 1,048 Parkinson's patients and 1,242 healthy controls for the clinical diagnosis group, and 996 Parkinson's patients and 1,288 individuals without post-mortem abnormalities for the pathology diagnosis group (di Biase, Pecoraro & Di Lazzaro 2025). The high rates of false positive results (n=196 (14%) in the living PD group) and false negative results (n=151 (15.21%) in the post-mortem PD group) highlight the need for improved differential diagnosis, especially for non-neurodegenerative disorders, atypical parkinsonism, and dementias (di Biase, Pecoraro & Di Lazzaro 2025).

Using neuropathological post-mortem diagnosis as the gold standard, the clinical diagnosis of PD demonstrated 99% sensitivity, 86% specificity, 90.96% accuracy, an F1-Score of 0.89¹, and a ROC AUC of 0.925 (SE 0.006; 95% CI: 0.913, 0.937; p<0.001) (di Biase, Pecoraro & Di Lazzaro 2025). The most common pathological misdiagnosis among false positives was DLB (19.4%), while the most prevalent missed diagnosis in false negatives was Alzheimer's disease (18.5%) (di Biase, Pecoraro & Di Lazzaro 2025). The clinical PD diagnosis shows high sensitivity but lower specificity, suggesting a tendency to over-diagnose in the presence of parkinsonian symptoms. In false positives, the most frequent isolated neuropathological findings were DLB (19.4%), MSA (9.2%) and AD (7.6%), with 37.2% showing dual pathology and 9.2% triple pathology. For false negatives, the most common misdiagnosis was AD (18.5%), followed by other dementias (11.2%), PSP (6.6%), VE (5.9%) and MSA (4.6%). Many cases had dual (9.2%) or triple (2.6%) clinical diagnoses. These results indicate that AD and related dementias are confounding alive diagnoses, as cognitive issues often overshadow motor symptoms, highlighting the challenge in distinguishing PD dementia from DLB (di Biase, Pecoraro & Di Lazzaro 2025).

Dopamine synthesis involves converting L-tyrosine to L-dopa and then to dopamine, which is packed in vesicles and released into the synaptic cleft, specifically in the striatum, which is a key component of the basal ganglia involved in motor control, where it diffuses across the gap to interact with postsynaptic D2 receptors on striatal neurons, modulating movement and other functions (Morbelli et al. 2020). Recent advancements in nuclear medical imaging include semi-quantification methods, improved acquisition protocols and new fluorinated tracers for PET imaging. In 2020, the EANM and SNMMI published their guidelines on the use of FDOPA PET/CT as described in Table 5 (Morbelli et al. 2020).

Differential diagnosis of PD, atypical PD and non-neurodegenerative disorders

Nuclear medicine currently assesses both presynaptic and postsynaptic dopaminergic functions. Presynaptic imaging distinguishes between neurodegenerative parkinsonism and non-dopaminergic causes and is the subject of this application (Morbelli et al. 2020).

FDOPA PET/CT can assist in differentiating between PD and atypical parkinsonian syndromes, including multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and dementia with Lewy bodies (DLB) as described in (Morbelli et al. 2020) FDOPA assesses dopamine

¹ An F1-score is a statistical metric commonly used in nuclear medicine and machine learning to evaluate the performance of a classification model. It is the harmonic mean of precision (positive predictive value) and recall (sensitivity), providing a single score that balances the trade-off between correctly identifying positive cases and minimising false positives. The range is from 0 to 1, where 1 is perfect and 0 is failed. An F1-score of 0.89 indicates relatively high performance (Hicks et al. 2022)

synthesis and storage capacity in the nigrostriatal pathway, offering insights into neurodegenerative patterns (Saeed, Lang & Masellis 2020).

Table 5 How FDOPA PET/CT results differentiate between PD and atypical parkinsonian syndromes

Aspect	PD	MSA	PSP	CBD	DLB	Nondegenerative parkinsonism
Findings	Asymmetric putamen reduction, caudate spared	Symmetric striatal reduction, $\pm$ cerebellar loss (MSA-C)	Symmetric striatal reduction, caudate hit, $\pm$ midbrain loss	Asymmetric striatal reduction, $\pm$ cortical loss	Asymmetric putamen reduction, like PD	Normal striatal uptake, no dopaminergic deficit
Different from PD	NA	More uniform striatal loss, cerebellar clue	More caudate/mid brain loss	Cortical loss added to asymmetry	Similar to PD due to Lewy Bodies but slight difference in uptake	No reduction in uptake, unlike PD deficit
Limits	Overlap with APS	Early overlap; cerebellar not always seen	Mimics PD/MSA; midbrain subtle	Overlap with PD; cortical variable	Clinical reliance + imaging	Normal findings nonspecific; clinical cause varies

Abbreviations: APS = Atypical parkinsonian syndromes, CBD = Corticobasal degeneration, DLB = Dementia with Lewy bodies, MSA = Multiple system atrophy, MSA-C = Multiple system atrophy cerebellar type, PD = Parkinson's disease, PSP = Progressive supranuclear palsy, Nondegenerative Parkinsonism = Parkinsonism without neurodegenerative dopaminergic loss (drug-induced, vascular)
Source: adapted from (Saeed, Lang & Masellis 2020; Yang et al. 2025)

The differences between pre-synaptic and post-synaptic dopaminergic imaging are described in Table 6. These imaging techniques are primarily used in nuclear medicine (PET or SPECT) to assess the dopaminergic system, particularly in the context of movement disorders like PD and other parkinsonian syndromes. The table aims to clarify when each type is most applicable (Saeed, Lang & Masellis 2020; Yang et al. 2025).

Table 6 Differences between pre-synaptic and post-synaptic dopaminergic imaging

Aspect	Presynaptic dopaminergic imaging (imaging technique applicable to application 1795)	Postsynaptic dopaminergic imaging
Definition	Assesses the integrity and function of dopamine-producing neurons (pre-synaptic terminals)	Evaluates the dopamine receptors on the receiving neurons (post-synaptic sites)
Common Tracers	FDOPA (PET/CT) ^{123}I -FP-CIT (DATSCAN) (SPECT)	^{11}C -Raclopride (PET) ^{123}I -IBZM (SPECT)
Biological Target	Dopamine transporter (DAT) or dopamine synthesis capacity in pre-synaptic neurons	D2/D3 dopamine receptors on post-synaptic neurons
Primary Clinical Use	Differentiates neurodegenerative PD from non-degenerative causes (essential tremor, drug-induced parkinsonism)	Assesses receptor density and function, useful in atypical parkinsonism or research settings
Key Indications	Suspected PD or parkinsonian syndromes Distinguishing PD from mimics (essential tremor) Early diagnosis of dopamine neuron loss	Differentiating PD from atypical parkinsonian syndromes (MSA, PSP, CBD) Evaluating receptor status in psychiatric or drug-related studies

Aspect	Presynaptic dopaminergic imaging (imaging technique applicable to application 1795)	Postsynaptic dopaminergic imaging
Findings in PD	Reduced uptake in striatum (asymmetric in early PD), reflecting loss of dopaminergic neurons	Typically, normal or upregulated D2 receptors in early PD due to compensatory mechanisms
Findings in Atypical Parkinsonism	Reduced uptake (similar to PD), but pattern may vary (more symmetric in MSA)	Often reduced receptor binding (in MSA, PSP), reflecting post-synaptic damage
When to Use	Equivocal PD or when neurodegeneration needs confirmation Rule out non-degenerative causes of tremor or parkinsonism	When PD diagnosis is uncertain and atypical parkinsonism is suspected Research or advanced diagnostics (less routine clinically)
Limitations	Cannot distinguish PD from all atypical parkinsonism (MSA, PSP) alone	Less commonly used in routine clinical practice; more complex interpretation
Clinical Availability	FDA- and EU Mark approved and routine in many centres, though not approved by the TGA	Often limited to specialised centres or research

11C-Raclopride = Carbon-11-labeled raclopride (a postsynaptic PET tracer for D2 receptors), FDOPA = Fluorine-18-labeled L-DOPA (a presynaptic PET tracer), CBD = Corticobasal degeneration, DAT = Dopamine transporter, DATSCAN = Dopamine transporter scan (using loflupane I-123), IBZM = Iodobenzamide (123I-IBZM, a D2 receptor tracer), MSA = Multiple system atrophy, PD = Parkinson's disease, PET = Positron emission tomography, PSP = Progressive supranuclear palsy, SPECT = Single-photon emission computed tomography
Source: adapted from (Saeed, Lang & Masellis 2020; Yang et al. 2025)

The proposed population aligns with the practice guideline and procedure standards for dopaminergic imaging in parkinsonian syndromes published by the EANM and the SNMMI (Morbelli et al. 2020). It also aligns well with earlier guidelines for nuclear medical imaging, consistent with published guidelines by statutory health technology assessment (HTA) bodies (Grimes et al. 2019; NICE 2017). If FDOPA PET/CT was listed on the MBS, local practice would align with international standards (Morbelli et al. 2020).

A summary of the key recommendations and standards from the guidelines appear in Table 7 (Morbelli et al. 2020).

Table 7 EANM/SNMMI practice guidelines and procedure standards for dopaminergic imaging in parkinsonian syndromes

Section	Key recommendations and Standards
Purpose	Assist nuclear medicine practitioners in recommending, performing, interpreting, and reporting dopaminergic imaging for parkinsonian syndromes
Scope	Covers presynaptic (DOPA, DAT) and postsynaptic (D2 receptors) dopaminergic imaging using SPECT and PET/CT
Indications	Differentiate neurodegenerative parkinsonism (PD, MSA, PSP) from nondegenerative causes (essential tremor, drug-induced). Assess disease progression, treatment effects (D2 receptor blockade by neuroleptics), or rare conditions (Wilson's disease)
Contraindications	Pregnancy/breastfeeding (relative weigh risks vs benefits)
Tracer	Presynaptic: 123I-FP-CIT (DAT SPECT), 18F-FDOPA (PET for dopamine synthesis/storage) Postsynaptic: 123I-IBZM (D2 SPECT), 11C-raclopride (D2 PET)
Patient preparation	Discontinue interfering medications (SSRIs) if safe to do so Thyroid blocking (potassium iodide) for iodine-based tracers like 123I-FP-CIT, 1-4 hrs before injection
Acquisition protocols	PET/CT: 60–90 min post-injection (FDOPA), dynamic or static imaging, attenuation correction required SPECT: 15–45 min post-injection (123I-FP-CIT), 128x128 matrix, 30–45 min scan duration
Processing	Use filtered back-projection or iterative reconstruction (OSEM)

Section	Key recommendations and Standards
Interpretation	Visual: Assess striatal uptake symmetry, intensity (putamen vs caudate) Semiquantitative: Calculate specific binding ratios (SBR) using reference regions (occipital cortex, cerebellum)
Normal vs abnormal	Normal: Symmetrical striatal uptake, clear putamen/caudate definition Abnormal: Reduced uptake (asymmetric in PD, more uniform in APS), loss of comma-shaped striatum
Reporting	Include clinical indication, tracer used, acquisition details, findings (visual and quantitative), and interpretation (PD vs normal)
Quality control	Regular camera calibration, phantom testing for PET/CT and SPECT Ensure tracer radiochemical purity (>95%)
Limitations	Presynaptic imaging (FDOPA) cannot reliably distinguish PD from all APS due to overlapping deficits (DLB can be differentiated with careful clinical assessment)
Emerging issues	Semiquantification, harmonisation with normal database, and longitudinal analyses are advancing diagnostic precision.

¹¹C-raclopride = Carbon-11-labeled raclopride (a postsynaptic PET tracer for D2 receptors), ¹²³I-FP-CIT = Iodine-123-labeled N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)tropane (DAT SPECT tracer), ¹²³I-IBZM = Iodine-123-labeled iodobenzamide (D2 SPECT tracer), ¹⁸F-FDOPA = Fluorine-18-labeled L-DOPA (a presynaptic PET tracer), APS = Atypical parkinsonian syndromes, DAT = Dopamine transporter, DOPA = Dihydroxyphenylalanine (related to dopamine synthesis), EANM = European Association of Nuclear Medicine, MSA = Multiple system atrophy, OSEM = Ordered subset expectation maximization (reconstruction method), PD = Parkinson's disease, PET = Positron emission tomography, PSP = Progressive supranuclear palsy, SBR = Specific binding ratio, SNMMI = Society of Nuclear Medicine and Molecular Imaging, SPECT = Single-photon emission computed tomography, SSRIs = Selective serotonin reuptake inhibitors.

Source: adapted from (Morbelli et al. 2020)

Diagnosis and progression

There are no specific tests for parkinsonism, but it can be diagnosed using the Movement Disorder Society Parkinson's disease (MDS-PD) clinical diagnostic criteria (Grimes et al. 2019). The MDS-PD recommends diagnosis by a specialist physician based on clinical presentation to distinguish between primary and secondary parkinsonian syndromes, which include other neurodegenerative diseases sometimes referred to as Parkinson-plus syndromes (Mellick 2024a; Waller et al. 2021). However, diagnostic certainty is sometimes difficult and is based on patient history, examination and the exclusion of the signs and symptoms—known as red flags—of an alternative medical condition. Definitive diagnosis requires pathological confirmation post-mortem (di Biase, Pecoraro & Di Lazzaro 2025; Mellick 2024a).

The MDS-PD criteria is a stepwise process of assessment over time, which starts broadly and becomes more refined as the clinician becomes aware of the signs and symptoms and nearer to a diagnosis.

The MDS-PD criteria include 2 distinct levels of diagnostic certainty (Postuma et al. 2015). These are:

1. Clinically Established PD: Maximising specificity, the category is anchored with the goal that the large majority (i.e. at least 90%) will have PD. It is presumed that many true PD cases will not meet this certainty level; and
2. Clinically Probable PD: Balancing sensitivity and specificity, the category is anchored with the goal that at least 80% of patients diagnosed as probable PD truly have PD, but also that 80% of true PD cases are identified.

A summary of the MDS-PD diagnostic criteria for PD is presented in Table 8.

Table 8 Summary of the MDS-PD diagnostic criteria for PD

Component	Description
Prerequisite	Parkinsonism defined as bradykinesia (slowness of movement with decrement in amplitude or speed) + at least one of rest tremor or rigidity Must be assessed per MDS-UPDRS guidelines; not attributable to confounding factors (trauma)
Diagnostic categories	Clinically established PD Absence of absolute exclusion criteria At least 2 supportive criteria No red flags Maximises specificity of 90% (fewer false positives) Clinically probable PD Absence of absolute exclusion criteria Red flags (maximum 2) counterbalanced by supportive criteria (1 red flag = 1 supportive criterion needed) Balances sensitivity and specificity (80%)
Supportive criteria	Positive features increasing likelihood of PD Clear, sustained significant L-Dopa response (>30% improvement is required) L-Dopa induced dyskinesia Rest tremor in a limb (documented clinically) Positive olfactory loss or cardiac MIBG scintigraphy showing sympathetic denervation
Absolute exclusion criteria	Features ruling out PD Cerebellar abnormalities (ataxia, cerebellar gait) Downward vertical supranuclear gaze palsy or slowing Frontotemporal dementia or primary progressive aphasia diagnosis within 5 years Parkinsonism limited to lower limbs for >3 years Drug-induced parkinsonism (neuroleptics) Absence of L-DOPA response in severe cases Cortical sensory loss or apraxia Normal dopaminergic imaging (FDOPA PET/CT, DAT SPECT) Alternative condition clearly causing parkinsonism (stroke)
Red flags	Features suggesting alternative diagnoses but allowable in PD if outweighed Rapid gait impairment requiring a wheelchair within 5 years No progression of motor symptoms over 5+ years Early bulbar dysfunction (severe dysarthria) Inspiratory respiratory dysfunction Severe autonomic failure within 5 years (orthostatic hypotension) Recurrent falls (>1/year) within 3 years Disproportionate anterocollis or contractures within 10 years Absence of non-motor features (hyposmia) after 5 years Pyramidal signs (damage or dysfunction in the pyramidal tract) Bilateral symmetric parkinsonism

Abbreviations: DAT = Dopamine transporter, L-DOPA = Levodopa (L-3,4-dihydroxyphenylalanine), MDS-PD = Movement Disorder Society Clinical Diagnostic Criteria for Parkinson's Disease, MDS-UPDRS = Movement Disorder Society-Unified Parkinson's Disease Rating Scale, MIBG = Metaiodobenzylguanidine (used in cardiac scintigraphy), PD = Parkinson's disease, SPECT = Single-photon emission computed tomography. Source: Adapted from (Postuma et al. 2015)

Having established that the patient has parkinsonism, the MDS-PD criteria will be applied to determine whether the patient meets criteria for PD as the cause of this parkinsonism. Diagnosis of clinically established PD requires (Postuma et al. 2015):

1. Absence of absolute exclusion criteria;
2. At least 2 supportive criteria; and
3. No red flags.

Diagnosis of clinically probable PD can be made in:

1. Absence of absolute exclusion criteria; and
2. Presence of red flags counterbalanced by supportive criteria; that is, if one red flag is present there must also be at least one supportive criterion; if 2 red flags, at least 2 supportive criteria are needed. If there are more than 2 red flags, clinically probable PD cannot be diagnosed (Postuma et al. 2015).

The supportive criteria include (Postuma et al. 2015):

1. Clear and significant response to dopaminergic therapy is required. Patients should return to normal or near-normal function during initial treatment. If initial responses are unclear, a dramatic response can be indicated by:
 - a. Marked improvement with increased doses or notable deterioration with decreased doses, documented objectively (>30% change in UPDRS III) or subjectively by reliable reports from patients or caregivers;
 - b. Clear and significant on/off fluctuations, including predictable end-of-dose wearing off;

Note: A mere beneficial response is inadequate; the response must be strong. Predictable end-of-dose wearing off is essential to distinguish true dopaminergic fluctuations from daily variability, and can be documented retrospectively;

2. Presence of levodopa-induced dyskinesia;
3. Documented rest tremor in a limb, either currently or historically, primarily because rest tremor is less common in other conditions and may respond poorly to therapy, complicating criterion 1 in tremor-predominant PD; and
4. Positive results from at least one ancillary diagnostic test with over 80% specificity for distinguishing PD from other parkinsonian conditions, including:
 - Olfactory loss (anosmic or significantly hyposmic, age and sex-adjusted); and
 - Metaiodobenzylguanidine scintigraphy showing cardiac sympathetic denervation.

Note: The test must demonstrate >80% specificity across at least 3 studies from different centres (Postuma et al. 2015).

Absolute exclusion criteria and red flags imply the criterion is unmet due to unrelated factors. For example, cerebellar abnormalities from a stroke or wheelchair use due to spinal cord injury are not exclusionary for PD. The following features define the absolute exclusion criteria and exclude a PD diagnosis:

1. Clear cerebellar abnormalities like cerebellar gait, limb ataxia, or oculomotor issues (persistent gaze-evoked nystagmus, macro square wave jerks);
2. Downward vertical gaze palsy or slowing of downward saccades;

3. Diagnosis of probable behavioural variant frontotemporal dementia or primary progressive aphasia within 5 years;
4. Parkinsonian features limited to the lower limbs for over 3 years;
5. Treatment with dopamine receptor blockers or depleting agents consistent with drug-induced parkinsonism;
6. No response to high-dose levodopa (≥ 600 mg/day) despite moderate disease severity;
7. Clear cortical sensory loss, ideomotor apraxia or progressive aphasia;
8. Normal functional neuroimaging of the presynaptic dopaminergic system; this does not necessitate imaging for diagnosis; and
9. Documentation of an alternative condition likely causing parkinsonism or expert belief in an alternative diagnosis over PD.

Note: DLB is not considered an alternative parkinsonian syndrome according to this criterion (Postuma et al. 2015).

The Royal Australian College of General Practitioners (RACGP) published guidance for general practitioners, including identifying red flags suggesting a diagnosis other than PD should be suspected:

- Objective limb weakness (PD patients often report subjective weakness)
- Rapidly neurological decline over weeks to months
- Early, recurrent falls
- Absence of typical non-motor features (constipation, anosmia, rapid eye movement sleep disorder, daytime urinary urgency)
- Use of dopamine-blocking medications, such as prochlorperazine, metoclopramide or antipsychotics
- Severe orthostatic hypotension (>30 mmHg)
- Early cognitive impairment
- Urinary incontinence
- Lack of levodopa responsiveness (Waller et al. 2021).

When patients present with one or more red flags PD mimics should be considered. In Waller et al. (2021), the authors state that while ancillary tests such as neuroimaging can be helpful to lend support to the diagnosis and exclude mimics, PD remains a clinical diagnosis and a careful history and examination are crucial in determining the diagnosis (Waller et al. 2021). When to consider disease mimics are described in Table 9.

Table 9 Parkinson's disease mimics and when to consider

Essential or dystonic tremor	Tremor is absent at rest but becomes apparent with posture (with the arms outstretched) or when using the hands. Handwriting is usually large and shaky, rather than the micrographia typical of PD. Tremor can also affect the head, neck and voice. Other motor and non-motor signs of PD are typically absent.
Medication-induced parkinsonism	Recent or prolonged exposure to dopamine-blocking medications (prochlorperazine, metoclopramide, antipsychotic medications). Typically, bilateral, and symmetrical parkinsonism; however, can mimic typical PD.
Normal pressure hydrocephalus	Prominent gait freezing with broad-based gait and ventriculomegaly on neuroimaging (computed tomography or magnetic resonance imaging), particularly if combined with urinary incontinence and cognitive impairment.
Progressive supranuclear palsy	Early falls (particularly backwards) with postural instability. Early cognitive slowing or personality change. Poor levodopa response.

Multiple system atrophy	Early, severe autonomic signs, especially urinary incontinence, erectile dysfunction, and orthostatic hypotension. Cerebellar signs (broad-based gait, limb incoordination, action tremor). Poor levodopa response.
Dementia with Lewy bodies	Fluctuating cognition. Early, well-formed visual hallucinations. Dementia occurring concurrently with, or preceding, motor symptoms.

PD = Parkinson's disease
Source: (Waller et al. 2021)

The Canadian guideline for PD (2019) supports findings and recommendations from the Scottish Intercollegiate Guidelines Network (SIGN) and the UK National Institute for Health and Care Excellence (NICE). They recommend the use of ¹²³I ioflupane (¹²³I FP-CIT) SPECT scanning as an aid to clinical diagnosis in patients where there is uncertainty between PD and nondegenerative parkinsonism or tremor disorders (Grimes et al. 2019).

These recommendations were made prior to the release of the EANM practice guideline and the SNMMI procedure standard for dopaminergic imaging in parkinsonian syndromes (Morbelli et al. 2020).

Validation of the MDS-PD criteria

A retrospective review of medical records for consecutive patients with parkinsonism at the Queen Square Brain Bank was conducted from 2009 to 2019. Clinical diagnoses captured at early (within 5 years of symptom onset) and final stages were assessed by movement disorder experts and clinicians, applying the MDS-PD criteria retrospectively. Diagnostic accuracy parameters—including sensitivity, specificity and predictive values—were calculated using neuropathological diagnoses as the gold standard (Virameteekul et al. 2023).

In total, 267 patients (141 with PD and 126 with non-PD parkinsonism) were analysed. Clinical diagnostic accuracy was 97.2% for experts, 92.5% for MDS clinically probable PD criteria, and 90.3% for clinicians, with early-stage accuracies of 91.5%, 89.5%, and 84.2%, respectively. The MDS clinically established early PD criteria exhibited high specificity (98.4%) at early stages (Virameteekul et al. 2023).

The MDS Unified Parkinson's Disease Rating Scale

The MDS has published the Unified Parkinson's Disease Rating Scale (MDS-UPDRS), which is designed to assess non-motor and motor experiences of people with PD in daily living, as well as motor complications. It features a motor evaluation that characterises the extent and impact of the disease across diverse populations. This scale is applicable in both clinical and research settings (Jankovic & Tan 2020).

Part I addresses non-motor experiences, Part II focuses on motor experiences, Part III is the motor examination, and Part IV covers motor complications. Parts I and II include questions suitable for patient/caregiver completion without investigator input, while complex behaviour questions in Part I and motor fluctuation questions in Part IV require investigator interviews. Part III maintains objective assessments of parkinsonism with specific instructions for each task. The estimated rater time for administering the MDS-UPDRS is under 10 minutes for Part I, 15 minutes for Part III, and 5 minutes for Part IV, achieving the target of 30 minutes in total. Other questionnaire items are answered by patients or caregivers with minimal rater involvement. While comprehensive assessments emphasise motor aspects of PD, screening questions on non-motor elements focus on identifying the presence and severity of relevant issues (Goetz et al. 2008).

Each question has five responses linked to clinical terms: 0 normal, 1 slight, 2 mild, 3 moderate and 4 severe. Each descriptor includes criteria for the respective response. The progression of disability is

consistent: slight (1) indicates low-frequency symptoms with no functional impact; mild (2) indicates modestly impacting symptoms; moderate (3) entails significant but not complete functional impact; and severe (4) denotes symptoms that prevent function. The MDS-UPDRS includes 65 items across 4 parts: Part I (13 items), Part II (13 items), Part III (33 scores from 18 items with variations for body distribution) and Part IV (6 items) (Goetz et al. 2008).

Treatment options for PD

There is no cure for PD, and no therapies are effective for slowing or stopping brain degeneration in PD (Grimes et al. 2019). Dopaminergic therapy effectively addresses these deficits by alleviating bradykinesia, rigidity and tremor, with levodopa—combined with carbidopa or benserazide—being the most effective option for controlling motor symptoms in PD (Waller et al. 2021). Treatment initiation depends on patient preference, severity of motor and non-motor disabilities, and quality of life impact. Additional factors include occupation, age and comorbidities (Deloitte Access Economics 2014). Identifying symptoms that affect the patient's quality of life is crucial during consultations. For instance, in some patients, hand tremors may lead to motor disability, while other patients may primarily experience slowness. Even mild symptoms in a dominant hand can cause significant functional impairment and should inform the treatment plan. (Deloitte Access Economics 2014; Waller et al. 2021).

Delaying levodopa therapy for older patients with more than mild disability may inhibit effective early treatment. Withholding levodopa will not postpone motor fluctuations, such as peak dose dyskinesia, and may be detrimental (Waller et al. 2021). For mild PD, MAO-B inhibitors are well tolerated and can be taken once daily. Dopamine agonists (oral or patch) are also effective, but patients must be informed about the potential side effects of impulse control disorders, excessive daytime sleepiness, and hallucinations. Treatment with dopamine agonists should start gradually due to the potential for nausea and dizziness. If initial treatments fail, levodopa can be added. An overview of these treatments is presented in Table 10. (Jankovic & Tan 2020; Mellick 2024a; Waller et al. 2021).

Table 10 Commonly prescribed medications for Parkinson's disease and their side effects

Class	Common formulations	Typical dose ranges	Main side effects	Additional considerations
Levodopa + dopa decarboxylase inhibitor	Levodopa/carbidopa	300–1000 mg levodopa per day, administered 3–5 times/day	Nausea Orthostatic dizziness Somnolence	First-line therapy in most patients
	Levodopa/benserazide	300–1000 mg levodopa per day, administered 3–5 times/day	Nausea Orthostatic dizziness Somnolence	First-line therapy in most patients
Levodopa + dopa decarboxylase inhibitor + COMT inhibitor	Levodopa/carbidopa/entacapone*	300–1000 mg levodopa per day, administered 3–5 times/day	Nausea Orthostatic dizziness Somnolence	Initiation by specialist (neurologist or another PD specialist) advised
MAO-B inhibitor	Rasagiline Safinamide	1 mg daily 50–100 mg daily	Usually well tolerated Nausea Orthostatic dizziness Potential serotonin toxicity when combined with other serotonergic medications	Rasagiline can be first-line treatment for milder symptoms
	Selegiline	2.5–10 mg daily (in 2 divided doses, morning and midday)	Confusion Other side effects as above, (nausea, etc)	
Dopamine agonist	Pramipexole	Controlled release: 0.375–3 mg daily Immediate release: 0.125–1 mg 3 times daily	Nausea Orthostatic dizziness Hallucinations Impulse control disorders Peripheral oedema Withdrawal syndrome if rapidly tapered/ceased	Use with caution in elderly and those at risk of impulse control disorders (gambling, alcohol use disorder, hypersexual behaviour)
	Rotigotine patch	2–8 mg patch daily	Application site reactions Nausea Orthostatic dizziness Hallucinations Impulse control disorders Peripheral oedema Withdrawal syndrome if rapidly tapered/ceased	Use with caution in elderly and those at risk of impulse control disorders (gambling, alcohol use disorder, hypersexual behaviour)
Anticholinergic	Benzotropine	0.5–5 mg daily (in up to 3 or 4 divided doses)	Confusion Urinary retention Constipation Dry mouth Dry eyes	Useful occasionally for prominent rest tremor. Use with caution in elderly and those with cognitive frailty
	Trihexyphenidyl	0.5–5 mg daily (in up to 3 or 4 divided doses)	Confusion Urinary retention Constipation Dry mouth Dry eyes	Useful occasionally for prominent rest tremor. Use with caution in elderly and those with cognitive frailty

Class	Common formulations	Typical dose ranges	Main side effects	Additional considerations
NMDA receptor antagonist	Amantadine	100 mg 1–3 times daily	Hallucinations Peripheral oedema Insomnia Livedo reticularis	Useful for management of dyskinesia. Avoid late afternoon or evening administration to reduce risk of insomnia. Use with caution in patients with cardiac failure Initiation by specialist (neurologist or another PD specialist) advised

COMT = catechol-O-methyltransferase; MAO-B = monoamine oxidase B; NMDA = N-methyl-D-aspartate; PD = Parkinson's disease

Entacapone is a COMT inhibitor and works to prolong the action of levodopa. This can be particularly useful for patients whose PD symptoms reappear before their next medication dose is due.

Source: Waller et al. 2021

Most patients with moderate parkinsonism respond well with initial doses of between 100 mg to 200 mg of levodopa administered 3 times per day. Elderly patients may need slower titration due to potential side effects like nausea, and a starting dose of 50 mg/day is recommended, increasing in 50 mg increments every 3–7 days, aiming for an initial target dose of 100 mg 3 times daily, with up-titration to 450–600 mg, depending on symptoms. Patients not responding to levodopa should be referred to a neurologist for re-evaluation of the diagnosis (Waller et al. 2021).

Exercise and physical therapy are recommended as adjunct treatment in early parkinsonism. Patients are encouraged to engage in activities that they find enjoyable, combining aerobic, resistance, balance, and, if possible, high-intensity interval training. Complex activities like dance and agility training may improve motor function as well as cardiovascular health, cognition, mood and sleep. Early referrals to physiotherapy and occupational therapy could help sustain these activities. Physiotherapy is particularly beneficial in the early stages, enhancing functional ability and reducing risks of inactivity. While neurologists are important, GPs often serve as the first contact for patients with early symptoms or established diagnoses. An effective approach involves promptly identifying core symptoms, clearly explaining the diagnosis, addressing patient questions and initiating first-line therapy, all while maintaining open communication among the GP, patient and neurologist (Waller et al. 2021).

An overview of medications for non-motor symptoms appears in Table 11.

Table 11 Commonly prescribed interventions for non-motor symptoms

Symptom	Intervention	Typical dose ranges	Common side effects
Rapid eye movement sleep behaviour disorder	Clonazepam	0.5–1 mg at night	Somnolence
Insomnia	Sleep hygiene		
	Amitriptyline	5–25 mg approximately 2 hours pre-bedtime	Dry eyes Dry mouth Constipation Morning sedation Urinary retention (first exclude bladder outlet obstruction in men)
	Note: Ensure good nocturnal motor control—‘off’ symptoms (stiffness, cramping) may prevent/disturb sleep		
Constipation	Fibre supplement	1–2 teaspoons 3 times per day	Flatulence Bloating Abdominal discomfort
	Macrogol	1–2 sachets twice per day	Nausea Abdominal discomfort Diarrhoea
	Note: Avoid using anthranoid laxatives (senna) for >2 weeks, as there is a risk of bowel dependency and potentiation of constipation		
Psychosis	Quetiapine	12.5–75 mg in divided doses	Somnolence
Depression	Paroxetine	20 mg	Gastrointestinal upset Sedation Sexual dysfunction Anorexia
	Venlafaxine XR	75–150 mg	Gastrointestinal upset Insomnia Sedation Hyperhidrosis
Restless legs syndrome	Pramipexole	125–750 µg at night	Nausea Orthostatic dizziness Hallucinations Impulse control disorders Peripheral oedema Withdrawal syndrome if rapidly tapered/ceased Sleep attacks/somnolence
Orthostatic hypotension	Increase fluid (at least 1.5 L/day) and salt intake		Monitor for supine/nocturnal hypertension
	Fludrocortisone	100–300 µg in divided doses (morning, midday)	Oedema Hypertension Hypokalaemia

Source: Waller et al. 2021

The approach to managing PD based on current EBM findings for each stage and motor symptom is illustrated in Figure 1 (Fox et al. 2018).

Figure 1 Evidence-based medicine review of treatment options for motor symptoms of PD

(a) EARLY PD	
Early PD to prevent/delay disease progression	• Clinically useful: None to date • Not useful: Pramipexole; Co Q10; Creatine • Investigational: Selegiline, rasagiline, ropinirole, vitamin D, exercise
Early PD requiring symptomatic therapy	• Clinically useful: Non-ergot DA (piribedil, pramipexole IR and ER, ropinirole IR, rotigotine, Ergot DA (cabergoline, pergolide); Levodopa preparations (IR, CR, ER), MAO-B inhibitors (selegiline and rasagiline); anticholinergics • Possibly useful: Non-ergot DA (ropinirole PR), Ergot DA (bromocriptine); amantadine
Early or stable PD requiring adjunct therapy to levodopa	• Clinically useful: Non-ergot DA (piribedil, pramipexole IR and ER, ropinirole IR, rotigotine); rasagiline, zonisamide; anticholinergics • Possibly useful: Ergot DA (bromocriptine); amantadine • Investigational: selegiline; "early" (up to 4 years) bilateral STN DBS • Unlikely useful: Tolcapone • Not useful: Entacapone; safinamide
(b) TREATED PD: OPTIONS TO ADD IN TO OPTIMISED ORAL LEVODOPA	
Treating motor fluctuations	• Clinically useful: Non-ergot DA (pramipexole; ropinirole; rotigotine; apomorphine intermittent injections, pergolide); levodopa ER; COMT inhibitors (entacapone; opicapone); MAO-B inhibitors (rasagiline, safinamide; zonisamide); LCIG; bilateral DBS surgery (STN or GPI) • Possibly useful: Ergot DA (bromocriptine, cabergoline); istradefylline; tolcapone; Non-ergot DA (apomorphine infusion)
Treating dyskinesia	• Clinically useful: Amantadine; clozapine; LCIG; bilateral DBS surgery (STN or GPI); unilateral pallidotomy
Treating specific/general motor symptoms	• Clinically useful: Physiotherapy • Possibly useful: Rivastigmine (gait and balance); Exercise-based movement strategy training (gait and balance); formalized patterned exercises (gait and balance); speech therapy (speech and swallowing); occupational therapy; thalamic surgery (DBS or thalamotomy) (tremor) • Investigational: Donepezil (gait and balance); methylphenidate (gait and balance); memantine (gait and balance); cannabidiol; technology-based movement strategies; acupuncture; rTMS; tDCS

Boxes to the left define the type of patient (a) early PD (upper figure) and (b) treated PD optimised on levodopa (lower figure). Boxes to the right summarise the EBM conclusions for interventions (see text for definitions).

Source: Fox et al. 2018

Advanced therapies

When the beneficial effects of oral dopaminergic medication for treating PD reduce, patients may experience their motor response to each levodopa dose shorten and patients may notice re-emergence of their motor symptoms ('wearing off') alternating with dyskinesia. These fluctuations stem from a decline in dopamine neuron buffering, gastroparesis, microbiome effects and postsynaptic changes (Dijk et al. 2020; Waller et al. 2021). To mitigate these fluctuations, strategies include reducing levodopa dose intervals, adding a long-acting dopamine agonist, or using medications like iMAO-B or COMT inhibitors to lower levodopa metabolism. If standard dopamine replacement therapy (DRT) is inadequate, advanced therapies such as deep brain stimulation (DBS), continuous levodopa-carbidopa intestinal gel (LCIG), or continuous subcutaneous apomorphine infusion (CAI) are available (Dijk et al. 2020).

Indications for advanced therapies

Advanced therapies for PD aim to reduce motor fluctuations by providing continuous dopaminergic stimulation through levodopa infusion (LCIG) or apomorphine (CAI), or by addressing wearing off (OFF) symptoms via DBS. These treatments are considered when motor fluctuations become unmanageable with oral medications or when standard DRT leads to troublesome symptoms like dyskinesia and impulse control disorders. While motor symptoms primarily indicate advanced treatments, non-motor symptoms can also influence therapy selection. Although these therapies can improve on-drug states achieved with standard DRT, they do not impact disease progression. Exceptions include cases of gastrointestinal absorption issues and medication-resistant tremor, where DBS may be beneficial. Patients with significant differences in disability between OFF and ON periods often experience greater benefits, and a subset of patients with absorption problems may need advanced treatments (Dijk et al. 2020).

Deep brain stimulation

DBS has been in use for 25 years, with efficacy shown in large RCTs, though not against a blinded control group. It is approved by the TGA and is available on the MBS (MBS item numbers: 40850, 40851, 40852, 40854, 40856, 40860, 40862, 40863) (MSAC 2025). A neurosurgeon implants 2 electrodes in the subthalamic nucleus (STN) or globus pallidus internus (GPi), connected to a pulse generator beneath the clavicle. Post-surgery, DBS parameters are optimised, often necessitating adjustments in DRT, particularly after STN DBS. While patients still require DRT, the dose can be reduced by an average of 60% following STN DBS. Both GPi and STN DBS significantly decrease daily OFF time and increase ON time without troublesome dyskinesias, either through direct anti-dyskinetic effects (GPi) or reduced DRT (STN). Adverse effects may include dysarthria, balance issues and a slight risk of intracerebral haemorrhage. Some patients may need revision surgery for device issues. Recent advancements include rechargeable pulse generators, MRI-compatible hardware, multiple independent current pulse generators, and an upgrade from constant-voltage to constant-current stimulation. Newer electrodes feature steering capabilities for more precise current field shaping, minimising side effects and battery drainage. Improved imaging techniques allow for direct visualisation of the DBS target, facilitating electrode implantation under general anaesthesia (Dijk et al. 2020).

Levodopa-carbidopa intestinal gel

Levodopa-carbidopa intestinal gel (LCIG) delivers continuous levodopa via an intrajejunal tube connected to an external pump, enabling safe titration to high doses exceeding 2,000 mg/day and stabilising plasma levels. It is approved by the TGA and is listed on the Pharmaceutical Benefits Scheme (PBS) as a highly specialised drug. LCIG significantly reduces OFF time and increases ON time without troublesome dyskinesia, effectively replacing standard DRT. Common complications include device failures, infections, tube kinking and peritonitis. Medical complications include weight loss, abdominal pain and, variably,

peripheral neuropathy, in part related to levodopa metabolism. About 15% of patients may develop diphasic dyskinesia, characterised by leg-predominant ballistic choreiform movements. Diphasic dyskinesia can worsen at night after pump cessation. Increasing LCIG doses or adding dopaminergic medications may alleviate this. Preliminary evidence suggests that continuous 24-hour infusion can improve sleep, nocturnal akinesia, and daytime dyskinesia (Dijk et al. 2020).

Continuous apomorphine infusion

Apomorphine is a rapid-onset, subcutaneous dopamine agonist that targets all dopamine receptor subtypes, as well as serotonergic and adrenergic receptors. It is approved by the TGA and is available on the PBS. Despite its name, it lacks the pharmacological properties of morphine. When used continuously with a mini pump, it significantly reduces daily OFF time and increases daily ON time without causing troublesome dyskinesia. Daytime oral levodopa dose is reduced, and some patients may not need additional DRT. It can also alleviate nocturnal OFF symptoms with 24-hour use. Adverse effects may include skin changes, nausea, somnolence, neuropsychiatric issues and a small risk of immune haemolytic anaemia. After initial dose adjustments, patients who tolerate the treatment well can maintain stable doses, sometimes for years. The subcutaneous delivery system is non-surgical and easily reversible (Dijk et al. 2020).

Comparative effectiveness of DBS, LCIG and CAI

No head-to-head RCTs have compared DBS, LCIG and CAI, so only cautious indirect comparisons are possible. DBS increases ON time without troublesome dyskinesia by 3.3 hours per day, compared to 1.9 hours for LCIG and 2.0 hours for CAI. Quality-of-life improvements have been demonstrated for both DBS and LCIG, with long-term benefits for STN DBS lasting up to 10 years, albeit with some decline. In LCIG, 34% of patients discontinued treatment after a mean of 4.1 years due to adverse events, while in CAI, 50% of patients stopped after 15 months, mainly due to side effects. CAI is easier to initiate and discontinue than surgical treatments like DBS due to the need for physical removal of implanted devices. Advanced PD therapies are costly, with LCIG generally associated with higher costs for quality-adjusted life years (QALY), followed by DBS, which is more expensive in the first year. CAI tends to be the least costly when offered by generic companies (Dijk et al. 2020).

A proportion of patients are restricted to only one advanced treatment option due to absolute contraindications for others, while some may benefit more from a specific therapy, such as DBS for medication-refractory tremor. However, most patients are eligible for multiple advanced treatments due to similar indications related to motor fluctuations. Selecting a therapy involves considering local availability, treatment centre nuances, reimbursement, regulations, and limited clinical trial data on efficacy and side effects. Factors like non-motor symptom effects, device characteristics and cosmetic concerns also play a role. The decision should ideally be made collaboratively between the physician and patient, weighing the advantages and disadvantages of each option, alongside caregiver support. Without robust comparative evidence, the complexity of these considerations makes selection difficult (Dijk et al. 2020).

Treatment characteristics of available therapies and current perspectives on potential symptoms and contraindications are shown in Table 12 and Table 13.

Table 12 Treatment characteristics of available advanced therapies

	Deep brain stimulation (DBS) Administration of electrical pulses into a target area of the brain	Continuous apomorphine infusion (CAI) Administration of medication through a subcutaneously placed needle	Levodopa–carbidopa intestinal gel (LCIG) Administration of medication to the duodenum through a PEG tube)
Mono- or combination therapy	DBS is combined with oral medication	Apomorphine generally used with oral medications, sometimes as monotherapy	LCIG can be used as monotherapy or with oral medications
Possible side effects and risks	Infections due to surgery Speech problems Delirium Cognitive problems Behavioural changes Technical problems or empty battery leading to re-operation Balance and gait problems Brain haemorrhage	Subcutaneous nodules and erythema at the insertion site are common; severe local reactions are uncommon Nausea Hypotension Ankle oedema Somnolence Hallucinations Dopamine dysregulation syndrome and impulse control disorders Drug-induced haemolytic anaemia	Obstruction, pump malfunction Nausea Inflammation around the PEG tube entry site Leakage around the opening in the abdominal wall Displacement of the tube Weight loss Biphasic dyskinesia Constipation Peritonitis
Possible disadvantages	Risks inherent to a neurosurgical procedure Some systems are not MRI-compatible Can be problematic for passing of a metal detector Battery needs to be replaced every 5–9 years in case of a non-rechargeable battery	Patient must carry the pump during the day Every day, placing the subcutaneous needle and connecting the pump, care for the skin at the insertion site Possible problems/malfunctions of the pump Loss of efficacy may occur, partly due to skin changes interfering with drug absorption	Patient must carry the pump during the day Every day, connecting and disconnecting the pump, cleaning the tube and care for the skin at the insertion site An operation is needed for placement of the tube Possible problems/malfunctions of the pump
Possible advantages	In comparison with CAI and LCIG, there are no daily limitations, not having to carry an external pump	No surgery is required Many patients are eligible Possibility of testing the treatment, easily reversible	Many patients are eligible Possibility of testing treatment

CAI = continuous apomorphine infusion; DBS = deep brain stimulation; LCIG = levodopa–carbidopa intestinal gel; PEG = percutaneous endoscopic gastrostomy

Source: Djik et al. 2020.

Table 13 Current perspectives on potential symptom improvement and contraindications for the available advanced therapies

	Deep brain stimulation (DBS)		Continuous apomorphine infusion(CAI)		Levodopa–carbidopa intestinal gel (LCIG)	
	Potential symptom improvement	Contra-indication	Potential symptom improvement	Contra-indication	Potential symptom improvement	Contra-indication
Patient characteristic Lack of caregiver/nurse support	NA	–	NA	+	NA	+
Older age (>70)	NA	+	NA	–	NA	–
Symptom Motor fluctuations	++	–	++	–	++	–
Dyskinesia	++	–	+	–	+	–
Levodopa-resistant tremor	++	–	–	–	–	–
Nighttime motor symptoms	+	–	+ [¶]	–	+ [¶]	–
Drug-related hallucinations/delusions	+	–	+/-	+/-	+	–
Slight non-drug-related hallucinations	+/-	+/-	+/-	+/-	+/-	+/-
Troublesome non-drug-related hallucinations/psychosis	–	++	–	++	–	++
Impulse control disorders	+	+/-	+/-	+	+	+/-
Severe therapy-refractive depression	+/-	++	+/-	–	+/-	–
Apathy	–	+	+/-	–	+/-	–
Drug-related daytime somnolence	+	–	–	+	+/-	+/-
Restless legs	+/-	–	+	–	+	–
Postural instability	+ [‡]	+	+ [‡]	–	+ [‡]	–
Dysarthria	–	+	–	–	–	–
Peripheral neuropathy	–	–	–	–	–	+
Orthostatic hypotension	+/-	–	–	+	+/-	–
Non-motor fluctuations*	+	–	+	–	+	–
Mild cognitive impairment	–	–	–	–	–	–
Dementia	–	++	–	+	–	+/-

Legend: NA = not applicable. Potential symptom improvement: ++very likely; +probable; +/- unclear; – probably not; very unlikely. Contra-indication: ++absolute contra-indication; +relative contra-indication; +/- unclear; – no contra-indication. *e.g. anxiety, pain, clouded thinking, apathy; [‡]if levodopa responsive; continuation of therapy during the night.

This information is based largely upon clinical experience and expert opinion in the absence of robust evidence from comparative studies.

Source: Dijk et al. 2020.

In the past two decades, DBS, LCIG and CAI have expanded therapy options for PD, particularly when standard DRT fails. These treatments should ideally be initiated before disability arises. Treatment choice relies on device characteristics, comparative linked evidence, availability, individual risk factors, patient preferences and caregiver support. Early guidance from a specialist physician in movement disorders who is knowledgeable about advanced treatments is necessary (Dijk et al. 2020).

PASC noted that there are no disease modifying or curative therapies available for people with Parkinsonism (as with other neurodegenerative diseases), and available treatments consist of symptomatic and supportive care only.

Patient management for ET

Essential tremor generally presents as a postural or action tremor, occurring when the affected limb or body part is positioned against gravity or during voluntary movements, such as writing or drinking. The severity of the tremor can vary, ranging from mild shaking that is scarcely perceptible to more pronounced tremors that may substantially impact daily activities and overall quality of life (Ali & Morris 2015).

Relationship to PD

While the precise cause of essential tremor remains unclear, it is thought to involve abnormal electrical activity in the brain that affects the pathways responsible for movement control. Some patients exhibit a rest component, leading to diagnostic difficulties and misdiagnosis with PD (Ali & Morris 2015).

Essential tremor (ET) is a common movement disorder, with an estimated prevalence of 1.8% in Australia and its incidence rises with age and can develop at any stage, especially earlier for those with a family history (Louis & McCreary 2021). Tremors primarily affect the upper limbs, and can be postural or kinetic, however ET may also impact the head, lower limbs, voice, tongue, face, and trunk (Louis & McCreary 2021). Over time, tremor amplitude may increase, complicating tasks like writing, eating, and speaking (MSAC 2022). Although ET does not typically affect life expectancy, it can lead to significant psychosocial issues, exacerbated by anxiety and stress, especially in those with head and voice tremors, which may cause embarrassment and depression. Assessing functional and psychosocial impairments guide treatment decisions (MSAC 2022).

Clinical management of ET

Pharmacological treatments supported by the American Academy of Neurology include propranolol and primidone which remain established as effective for the treatment of ET (Zesiewicz et al. 2011). These medications are the most frequently and successfully used to treat ET, with propranolol being the only medication approved by the US Food and Drug Administration for this indication (Zesiewicz et al. 2011). However, it is important to note that 30% to 50% of patients will not respond to either primidone or propranolol. Other drug treatments exist although their levels of evidence were lower, reflected as probably or possibly effective (Zesiewicz et al. 2011), and are not listed here.

Deep brain stimulation (DBS) is a primary surgical treatment for medically refractory essential tremor (ET), but not all patients are suitable candidates or wish to undergo surgery (MSAC 2022). Magnetic resonance-guided focused ultrasound (MRgFUS) is a non-invasive alternative that targets and destroys the brain area responsible for tremors. While direct comparisons of MRgFUS and DBS are limited, MRgFUS meets the need for non-invasive options. The Medical Services Advisory Committee (MSAC) evaluated the safety, effectiveness, and cost-effectiveness of MRgFUS when compared with DBS. They acknowledged the clinical demand for a non-invasive intervention for those unsuitable for or unwilling to undergo DBS (MSAC 2022). Essential tremor, marked by involuntary, rhythmic tremors that affect daily life, may benefit from MRgFUS, which is accepted in other jurisdictions including the NHS in England (MSAC 2022).

Patient management for DLB

Dementia with Lewy bodies represents the second most prevalent type of neurodegenerative dementia among older adults however, it is frequently under-identified and misdiagnosed (Chin, Teodorczuk &

Watson 2019). It is estimated that DLB accounts for approximately 2.2% of hospitalisations due to dementia, with more than 100,000 Australians living with the condition (Chin, Teodorczuk & Watson 2019). DLB is characterised by intricate visual hallucinations, spontaneous motor parkinsonism, notable cognitive fluctuations, and Rapid Eye Movement sleep behaviour disorder. Neuropsychiatric symptoms and autonomic dysfunction are also frequently observed (Chin, Teodorczuk & Watson 2019). New diagnostic criteria and the introduction of specific biomarkers has improved detection rates and diagnostic precision, facilitating appropriate management strategies (Chin, Teodorczuk & Watson 2019). The clinical management of DLB presents challenges and necessitates an individualised, multidisciplinary approach involving specialist input (Chin, Teodorczuk & Watson 2019).

Relationship to PD

Lewy body diseases (LBDs), including PD, Parkinson's disease dementia (PDD), and dementia with Lewy bodies (DLB), are characterised by abnormal alpha-synuclein accumulation. Cognitive impairment affects 30%-40% of PD patients, rising to 80% after 20 years (Chin, Teodorczuk & Watson 2019). DLB and PDD share significant clinical and pathological features. DLB is diagnosed when dementia onset coincides with or precedes motor symptoms, while PDD is diagnosed when cognitive decline occurs at least one year after PD symptom onset. While the '1-year rule' aids research comparisons, it may be less practical in clinical settings, where broader terms like Lewy body disease or Lewy body dementia may be more appropriate (Chin, Teodorczuk & Watson 2019).

Clinical management of DLB

The recommended clinical management of DLB is presented in Table 14. Managing DLB is complex, requiring a patient-centred multidisciplinary approach due to disease heterogeneity. There are few RCTs on specific treatments for DLB (Chin, Teodorczuk & Watson 2019).

Table 14 Recommended clinical management of DLB

General:	• Patient and caregiver education • Physical exercise • Medication rationalisation • Advance care planning • (Resources: Dementia Australia, Lewy Body Society)
Cognitive symptoms:	• Cholinesterase inhibitors, donepezil, rivastigmine, galantamine • Memantine
Neuropsychiatric features:	• Non-pharmacologic interventions (psychoeducation, social stimulation, environmental modification) • Identification of potentially reversible triggers • Antipsychotics should be avoided • Antidepressants for depression and/or anxiety • Cholinesterase inhibitors, particularly for visual hallucinations and/or delusions • (Resource: Dementia Support Australia)
Motor symptoms:	• Physical exercise • Fall risk minimisation • Levodopa Dopamine agonists should be avoided
Sleep disturbance:	• Melatonin • Cholinesterase inhibitors • Memantine • Clonazepam (with caution)

Source: (Chin, Teodorczuk & Watson 2019)

Non-pharmacologic interventions like caregiver psycho-education, physical exercise, and cognitive training are recommended for all dementia types, with physical exercise shown to enhance cognition, motor skills, and mood (Chin, Teodorczuk & Watson 2019). Rationalising medications, particularly reducing

anticholinergic drugs like oxybutynin, should be a priority. In addition, fall risk reduction and advance care planning form the components of comprehensive DLB care (Chin, Teodorczuk & Watson 2019).

Disease burden

PD is characterised as a chronic and progressive condition and can lead to significant disability. The severity of PD can be classified using the Hoehn and Yahr (H&Y) scale, as shown in Table 15. Other scales have been developed to supplement the H&Y scale, including the Unified Parkinson Disease Rating Scale (UPDRS) and the Non-Motor Symptoms Scale (NMSS), which include measures such as behaviour, mood, activities of daily living (ADL) and the severity and burden due to non-motor symptoms of PD (Deloitte Access Economics 2014). For ease of presentation, the H&Y stages are included here.

Table 15 Hoehn and Yahr stages of PD severity

Stage	Characteristics
I	Unilateral involvement only, usually minimal or no functional impairment. Symptoms include tremor of one limb, changes in posture, locomotion and facial expression.
II	Bilateral or midline involvement without impairment of balance. Posture and gait affected.
III	First signs of postural instability; significant slowing of body movements, individual has some restriction of activities but can lead an independent life; disability is mild to moderate.
IV	Severe symptoms: walking limited, rigidity and bradykinesia. Severely disabling disease; individual is markedly incapacitated and is unable to live alone.
V	Cachectic stage. Individual is restricted to bed or a wheelchair unless aided.

Source: (Deloitte Access Economics 2014).

People with PD may not follow a linear progression through the stages of the disease. They may regress to an earlier stage during treatment or may experience an accelerated progression (Deloitte Access Economics 2014).

In Yeow et al., (2025) the mean age at the time of FDOPA PET was age 57.6 years (range 22-84 years) and the median symptom duration at the time of FDOPA PET was four years (range 0-45 years, based on 98 patients for whom symptom duration was known).

A longitudinal study conducted in Australia by Hely et al. (2008) tracked 130 people with PD over a 20-year period. The study reported:

- About 10% of participants experienced delayed progression, where symptoms did not advance beyond Stage II for a duration of 10 years but subsequently progressed during the following 5 years;
- Of the people diagnosed with Stage I or II at their baseline assessment, 73% progressed to at least Stage III, 41% advanced to at least Stage IV, and 13% moved to at least Stage V after 15 years, with median times from the start of the study being 3.5 years, 7 years and 6 years, respectively; and
- For people initially diagnosed with Stage III, 74% progressed to at least Stage IV, and 21% advanced to at least Stage V after 15 years, with median times from the start of the study being 4.5 years and 6.5 years, respectively.
- Thirty patients (15 men and 15 women) survived to the 20-year follow-up, which ranged from 19.8 to 22 years. Their average age was 74 years (SD 7.9), compared with 54 years at presentation and 62 years for patients initially diagnosed with Stage III PD.
- The median time from disease onset to death was 12.4 years (Deloitte Access Economics 2014; Hely et al. 2008).

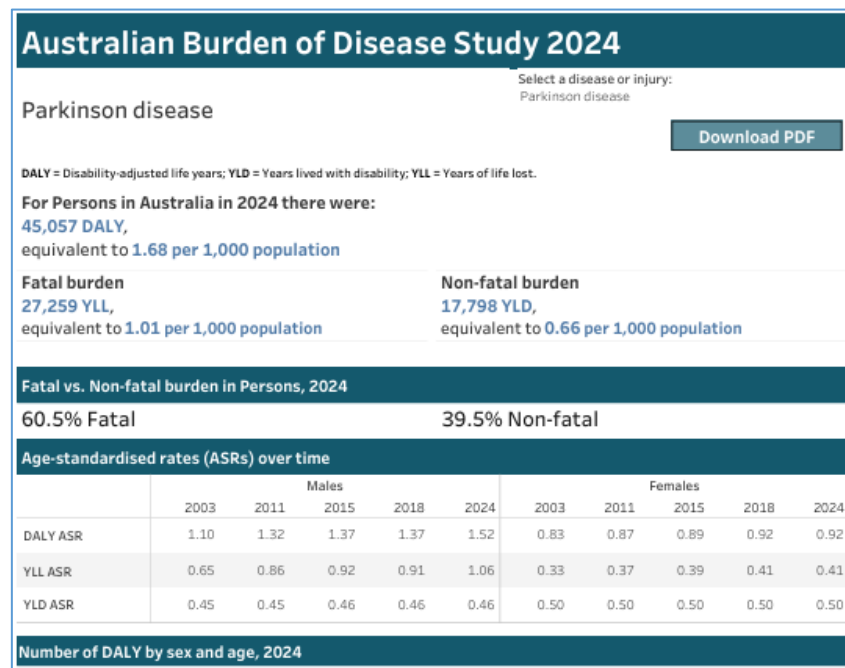
The mean pre-study disease duration was 23.5 months, which translates to approximately 5.5 years spent in Stage I and Stage II (45%), around 4 years in Stage III (33%), 2 years in Stage IV (16%), and the remaining 0.7 years in Stage V (6%) prior to death. This indicates that patients with PD can remain in the earlier stages of the disease for an extended period before progressing to later stages or death (Hely et al. 2008).

Overall, Hely et al. (2008) reported that patients with PD were about 2.5 times more likely to die post diagnosis from 3 to 20 years, with PD accounting for 54% of deaths. Pneumonia was identified as the most common cause of death, responsible for 25%, particularly in the later stages. However, due to mortality from various comorbid conditions, many individuals did not progress to Stages IV and V (Deloitte Access Economics 2014; Hely et al. 2008).

Deloitte's burden of disease study (2014) estimated the disability-adjusted life years (DALYs) of people with PD. In calculating the years of healthy life lost due to disability (YLD), the disability weights for PD were estimated to range from 0.48 for Stages I to III, 0.79 for Stage IV, and 0.92 for Stage V. Years of life lost due to premature death (YLLs) were based on the number of deaths estimated from PD and years of remaining expected life at the age of death from the Standard Life Expectancy Table (with a discount rate of 3% and no age weighting).

The Australian Institute of Health and Welfare publishes burden of disease studies for 220 diseases and injuries. They produce an interactive website from which PDF figures can be obtained, as shown in Figure 2 (AIHW 2024a).

Figure 2 Australian Burden of Disease Study



Source: (AIHW 2024b)

Overall, people with PD experienced 45,057 DALYs, equivalent to 1.68 per 1,000 population. The DALY age-standardised rates have steadily increased from 1.10 in 2003 to 1.52 in 2024 (AIHW 2024b).

Estimated size of the eligible population

PD is the second most common neurological condition globally but remains one of the least understood (Mellick 2024b). It is estimated that up to 150,000 people in Australia have PD and up to 19,500 new cases are diagnosed every year (Mellick 2024b).

Atypical parkinsonian syndromes were estimated to comprise about 5–7% of all types of parkinsonism (Lo 2022), while it was reported that about 10% of pathologically confirmed PD cases were unresponsive to levodopa treatment, and an additional 12% had a modest response (Pitz et al. 2020). The misdiagnosis rates for PD are reported to range from 14% (di Biase, Pecoraro & Di Lazzaro 2025) to 29% (Yeow et al. 2025).

Based on the estimated annual incidence and assuming a misdiagnosis proportion of 20%, about 3,900 patients per year are identified. As a prior test is required to prevent potential leakage, introducing a 24-month maximum period of treatment for scan eligibility effectively doubles the potential annual population. As a result, about 7,800 patients represents the eligible patient population. This estimate is comprised of patients presenting with symptoms unresponsive to dopaminergic medication consistent with the MDS-PD diagnostic criteria which requires a response (0% to 30% UPDRS III) to treatment to be eligible for the scan. This estimate is also evidenced by the relatively high false positive and false negative diagnosis proportions reported in the literature (di Biase, Pecoraro & Di Lazzaro 2025; Postuma et al. 2015; Waller et al. 2021).

The estimated size of the eligible population is represented in Table 16.

Table 16 Estimated size of the eligible population plus estimated leakage

Prevalent population		150,000
Annual incidence		19,500
Misdiagnosed (% annual incidence))	20%	3,900
Misdiagnosed (% annual incidence in the second year))	20%	3,900
Total potential annual population		7,800

Abbreviations: APD = atypical Parkinson's disease, PD = Parkinson's disease,
Source: Adapted from (di Biase, Pecoraro & Di Lazzaro 2025; Mellick 2024a; Yeow et al. 2025)

PASC noted potential issues of accessibility to testing for the population in rural and remote areas given that FDOPA PET/CT is not universally available across Australia. At the same time PASC noted that there is some evidence that the prevalence of Parkinson's Disease may be higher in regional, rural and remote areas of Australia than in urban localities, meaning that equity of access may be even more of an issue than usual, and may result in even higher costs to patients, families, travel and accommodation subsidy schemes and volunteer organisations.

Intervention

Description of FDOPA PET/CT

FDOPA is a PET radioligand that can be used to demonstrate the presence and pattern of striatal presynaptic dopaminergic deficit and can therefore assist in the diagnosis of iPD and related disorders. Functional imaging of nigrostriatal dopaminergic terminals via PET or SPECT evaluates the nigrostriatal dopaminergic system's integrity, aiding in the diagnosis of parkinsonian disorders. When compared with SPECT, PET has superior spatial resolution, which enables detailed analysis of dopaminergic terminal loss (Yeow et al. 2025). The radioligand FDOPA is converted by DOPA decarboxylase (DDC) into 18F-fluorodopamine, which is stored in presynaptic vesicles, enabling the assessment of presynaptic projection density. When compared with healthy controls, patients with iPD show reduced striatal FDOPA uptake, which is asymmetric and with an anteroposterior gradient (Yeow et al. 2025).

FDOPA PET/CT distinguishes PD from atypical parkinsonism by highlighting asymmetric dopaminergic loss in the posterior putamen with relative sparing of the caudate, unlike symmetric striatal reduction in MSA or caudate involvement in PSP (Morbelli et al. 2020; Yeow et al. 2025). Non-neurodegenerative conditions, such as essential tremor and drug-induced parkinsonism, show normal uptake. Presynaptic imaging, like FDOPA, can assist in identifying dopaminergic degeneration in iPD and atypical parkinsonian syndromes, while postsynaptic imaging (D2 receptor scans) helps differentiate iPD (preserved receptors) from atypical parkinsonian syndromes (reduced receptors), however, it is not available in clinical practice in Australia. FDOPA PET/CT supports targeted therapies, rules out non-neurodegenerative conditions to prevent unnecessary treatment, and enhances prognosis and symptom management (Morbelli et al. 2020; Yeow et al. 2025).

Proposed use of FDOPA PET/CT

Eligibility

The proposal for public funding is for use of the FDOPA PET/CT scan in patients with symptoms unresponsive to initial standard PD therapies defined as 0%-30% response (UPDRS, part III) after 12 weeks of therapy optimisation but not greater than 24 months post treatment initiation.

FDOPA is not yet an approved product for commercialisation in Australia. Regulatory approval is contingent upon a supportive finding for public funding and MBS listing by the Medical Services Advisory Committee (personal communication, pre-PASC teleconference, 21 February 2025).

Clinical involvement

- **Physician:** PET examinations must be conducted by or under the supervision of a certified nuclear medicine physician.
- **Technologist:** PET scans should be performed by registered/certified nuclear medicine technologists.
- **Physicist:** A certified medical physics expert (MPE) oversees the quality assurance of clinical PET systems, addresses malfunctions and ensures compliance with national and international radiation safety standards for both patients and staff (Morbelli et al. 2020).

Image reconstruction

To achieve high-quality images of the caudate and putamen, the standard approach involves iterative reconstruction using the Ordered-Subsets Expectation Maximisation (OSEM) method. However, the exact parameters may vary based on the specific scanner and scanning conditions. Small voxel sizes of 2–3 mm are necessary to effectively visualise the caudate and putamen.

The goal is to achieve sub-6 mm resolution while maintaining image sharpness. Spatial filters can be beneficial, but it is important to select the appropriate filter based on the characteristics of the available data. Additionally, since motion can affect image quality, implementation of motion correction might be required. This can be performed either during or after the scanning process, with the option to either correct the affected data or discard it. The priority is to maintain precise imaging throughout the process. (Morbelli et al. 2020).

Interpretation

The initial 90 minutes of FDOPA PET imaging primarily indicate the uptake and conversion of the tracer to [18F]fluorodopamine within the striatum. Visual analysis of these images adheres to principles used in [123]FP-CIT SPECT. Key steps include using a computer with an appropriate colour scale to identify the

maximum striatal voxel, ensuring accurate three-dimensional alignment to assess uptake symmetry, and reviewing all relevant slices to identify both striatal and extra-striatal uptake. In healthy individuals, striatal FDOPA uptake is typically homogeneous and symmetrical, with the putamen demonstrating the highest uptake levels (Morbelli et al. 2020).

Patients with PD exhibit a characteristic asymmetric reduction in putamen uptake, often with relative sparing of the caudate. This reduction generally begins in the posterior region and creates a gradient that shifts the maximum uptake towards the caudate. Increased midbrain extra-striatal uptake, which may resemble a 'Mickey Mouse' appearance, is also observed in cases of nigrostriatal degeneration. Atypical parkinsonian syndromes may present with different uptake patterns, such as the absence of caudate sparing in CBD and PSP, or localised defects in vascular parkinsonism. ET, psychogenic parkinsonism and drug-induced parkinsonism usually exhibit normal FDOPA uptake (Morbelli et al. 2020).

Semiquantification

A simple method for quantifying tracer uptake involves comparing the striatal signal to that in the occipital (striatal/occipital ratio (SOR)) or cerebellar cortex, where decarboxylation is minimal. This method has been shown to detect asymmetric putamen FDOPA reductions in iPD, with SOR reductions correlating with disability ratings (Morbelli et al. 2020).

Dynamic acquisition enables computation of FDOPA influx constants (K_i) from brain time-activity curves (TACs) and the creation of K_i maps at the voxel level using an occipital cortex reference input function. K_i represents the product of the free brain volume of distribution (V_d) of FDOPA at equilibrium and the decarboxylation rate constant (k_3). K_i indicates FDOPA transport from arterial plasma into dopaminergic neurons and its decarboxylation to FDOPA. Ideally, this method requires a metabolite-corrected plasma input function. However, using regions like the occipital cortex, where minimal specific FDOPA metabolites are present, allows for estimation of the plasma free signal without blood sampling. The influx constant K_i derived from brain uptake over 30–90 minutes equals k_3 times the ratio of free brain FDOPA to the sum of FDOPA and [^{18}F]fluoromethyldopa V_d (Morbelli et al. 2020).

K_i derived from the reference region approach and striatal/occipital fluorine-18 ratios at 90 minutes are highly correlated, and both effectively distinguish early PD from healthy controls. Both methods can quantify K_i , though few studies have simplified the K_i method with complete kinetic analysis. The K_i offers a more direct measure of the FDOPA decarboxylation rate constant than the ratio approach (Morbelli et al. 2020).

Part of [^{18}F]fluorodopamine is metabolised into [^{18}F]6-fluorohomovanillic acid (FHVA) and [^{18}F]6-fluoro-3,4-dihydroxyphenylacetic acid (FDOPAC). A dynamic PET scan at 3–4 hours post-FDOPA administration shows signal washout after 90 minutes due to monoamine oxidase B (MAO-B) and central catechol-O-methyltransferase (COMT) activity. PET can measure dopamine turnover in the striatum as the ratio of signal loss (k_{loss}) to influx (K_i). This method may be more sensitive than isolated K_i or SOR ratios but requires scans at both 90 minutes and 3–4 hours (Morbelli et al. 2020).

Quality control and inter-institutional PET system performance harmonisation

The guidelines focus on dopaminergic imaging in parkinsonian syndromes. However, there are technical and imaging-physics-related uncertainties that affect all PET exams. The recommendations in the guidelines should be considered for the use of brain PET examinations in multicentre studies or when data are compared with a reference database or disease patterns (Morbelli et al. 2020).

To ensure adequate image quality, quantitative performance and harmonisation, regular quality control (QC) checks of the PET system must be conducted, as outlined in previous EANM and joint EANM/SNMMI guidelines. PET(/CT) systems must be cross-calibrated with the local dose calibrator for accurate patient-specific radiotracer activity, following EARL recommendations (Morbelli et al. 2020).

Interpretation and conclusions

The report by the physician supervising the test must state whether a presynaptic dopaminergic deficit is present. Abnormal results indicate a deficit that may suggest diagnoses such as iPD, PSP, MSA, CBD or DLB. Loss of caudate sparing in iPD may indicate CBD or PSP, particularly with [¹⁸F]fluorodopa, which offers higher resolution.

Normal findings may suggest ET, drug-induced parkinsonism, psychogenic parkinsonism, AD or general good health. Descriptors like mild, moderate or severe can characterise deficits. A detailed diagnostic comment may incorporate results from other molecular ([¹⁸F]FDG PET, [¹²³I]mIBG) or structural imaging (MRI) when relevant. Follow-up or additional studies, such as [¹⁸F]FDG PET, perfusion SPECT, cardiac [¹²³I]mIBG scintigraphy, or D2 imaging, can be recommended to clarify the diagnosis (Morbelli et al. 2020).

Sources of error and artifacts include artifacts from patient movement, camera issues, improper processing, or tracer extravasation. Medication interference may affect overall tracer uptake but typically does not alter the asymmetrical pattern of reduced uptake (Morbelli et al. 2020).

Radiation safety

Radiation protection relies on 3 key principles: justification, optimisation and dose limits.

Justification for an examination at the individual level is implicit in this guideline. The acquisition parameters optimise dose for standard equipment, with further local optimisation possible for more sensitive devices. For patient medical exposure, dose limits do not apply; protection relies solely on justification and optimisation. For biomedical research, ICRP, WHO and EC guidance emphasises balancing societal value against effective dose, which ethics committees consider (Morbelli et al. 2020).

Dose constraints also extend to caregivers, relatives and non-radiation staff, dependent on local factors, and are managed by medical physics experts. The effective dose of FDOPA is 0.025 mSv/MBq and the organs receiving the highest absorbed doses are the urinary bladder wall and kidneys. Following this guideline typically results in effective doses under 5 mSv per examination. For CT scans used for attenuation correction, exposure settings should minimise effective doses to under 0.1 mSv (Morbelli et al. 2020).

Extra caution is necessary for foetuses and breastfeeding infants due to heightened radiosensitivity. Local protocols for assessing pregnancy status must be established. While pregnancy and breastfeeding are not contraindications for ionising imaging, careful justification is essential. Clinical decisions must evaluate benefits versus hypothetical harm, and in static scans, reducing activity may be feasible to lower doses without compromising image quality (Morbelli et al. 2020).

PASC noted that the risks of radiation for patients with multiple morbidities were low and acceptable as the dose is only fractionally higher than the dose from a standard CT. In addition, PASC noted that the patient population is typically older, which means that the effects of longer term radiation exposure may not have significant impact on the remainder of their lifetimes.

Claimed benefits

While ^{18}F -FDG PET reveals distinct hypometabolism patterns in parkinsonian disorders, presynaptic dopaminergic imaging convincingly demonstrates impaired dopaminergic function but is not routinely used to differentiate iPD from atypical PD. Presynaptic dopaminergic imaging, primarily using ^{123}I -FP-CIT DAT SPECT, highlights impaired dopaminergic function but is also not commonly used to differentiate iPD from atypical PD. Presynaptic dysfunction is a primary cause of iPD, whereas in atypical PD, it may result from postsynaptic cell loss. Visual and quantitative assessments can differentiate parkinsonism from conditions like ET that lack presynaptic defects. Although substriatal analysis shows differences among parkinsonian conditions, substantial overlap complicates accurate differentiation. PET ligands like ^{18}F DOPA might offer better differentiation between iPD and atypical PD due to enhanced quantification and spatial resolution when compared with SPECT. SOR are used clinically for diagnosing iPD, even in early stages (Comte et al. 2022).

Clinical management changed for 52.4% of patients after reviewing FDOPA scan results. Changes were more common after a normal FDOPA PET scan (53.0%) compared to scans indicating iPD (32.4%) and were more likely in patients with symptoms lasting over 15 years. Notable trends in changes to clinical management included increasing dopaminergic medications in 69.6% of patients with iPD results, reducing them in 38.7% in patients with normal scans, and suggesting antipsychotic medication weaning in 42.9% of patients where the scan was intended to differentiate drug-induced parkinsonism from iPD (Yeow et al. 2025).

PASC noted that epidemiological evidence regarding the sensitivity, specificity and predictive values of the diagnostic test should be made available and queried if this evidence was available from the Applicant. The applicant acknowledged that there is clinical evidence from Australia that can inform these metrics for the diagnostic test.

Specifications for PET/CT systems

The following specifications are relevant to the proposal for MBS listing:

- The PET/CT scan would be used up to 2 times in a patient's lifetime.
- Advanced 3D PET/CT systems that enable data acquisition for attenuation and scatter correction should be used.
- Dedicated brain PET systems can use transmission sources for effective attenuation maps.
- Equipment must have an axial field of view greater than 15 cm to cover the entire brain, including the cerebellum and brain stem.
- PET cameras should acquire both static and dynamic emission data in 3D mode, using frame or list mode (Morbelli et al. 2020).

Generalisability and applicability considerations

The radioligand has been made for PET/CT imaging in Australia for more than 10 years and used in patients across the demographic spectrum (personal communication, applicant, 21 February 2025). Published articles have not articulated patient demographics beyond age and sex. However, trial participants with iPD and atypical PD have been included in studies reported in this PICO. The sampling frames of the identified studies in the PICO are small yet their designs yield appropriate levels of evidence with respect to specificity, sensitivity and associated measures of association, relevant to the differentiation of iPD with other forms of parkinsonism (personal communication, pre-PASC teleconference, 21 February 2025). The radioligand is applicable for indicated patients in Australia who can tolerate it.

FDOPA PET/CT is not universally available across Australia. The Australian Government Department of Health and Aged Care lists PET units primarily in major cities (Queensland X-Ray in Brisbane, I-MED Radiology in Melbourne). No data confirms routine FDOPA use at all sites. Rural and remote Australians face significant disparities. For example, patients in outback Northern Territory or western Queensland may need to travel vast distances (Alice Springs to Adelaide, ~1,300 km), with one PET unit in the NT and limited regional options. This urban concentration delays diagnosis and treatment for iPD (Australian Department of Health and Aged Care 2025).

FDOPA must be produced via cyclotron at Australian urban hubs like Adelaide and used within hours. Transport from urban cyclotrons to rural sites is impractical rendering FDOPA unavailable outside metropolitan areas with on-site production (Personal communication, pre-PASC teleconference, 21 February 2025). The number of accredited PET units appears in Table 17.

Table 17 Number of PET units in Australia by State

State/Territory	Number of PET Units
ACT	4 (Regional = 0)
NSW	40 (Regional = 16)
NT	1
QLD	34 (Regional = 18)
SA	6 (Regional = 0)
Tas	3 (Regional = 1)
Vic	24 (Regional = 6)
WA	11 (Regional = 2)

Source: (Australian Department of Health and Aged Care 2025)

PASC considered that the DCAR should include a careful review of whether the more “commonplace” 18F-FDG metabolic PET could be an alternative to the proposed FDOPA PET/CT for some patients. PASC noted the applicant’s comments that while FDG PET is useful in identifying Lewy Body Dementia, it has lower accuracy in diagnosing Parkinson’s Disease and would not be useful in replacing FDOPA PET/CT in this application.

Comparator(s)

In the absence of publicly funded neuroimaging to support the differential diagnosis of parkinsonism, clinicians must rely on the clinical presentation of the patient. In addition to clinical assessment, potential tests that could assist in diagnosing PD include genetic testing, autonomic function testing, olfactory tests, drug challenge tests, neurophysiological and neuropsychological tests, and neuroimaging (Deloitte Access Economics 2014). While postsynaptic FDG PET imaging is available in Australia and listed on the MBS, it is not indicated for parkinsonism, therefore neuroimaging is a limited option in Australia for people with parkinsonism.

Dopamine transporter imaging with single-photon emission computed tomography (DAT SPECT) is used in other countries (particularly in Europe) for the differential diagnosis of parkinsonian disorders, however this diagnostic test is not available in Australia and cannot be used as a comparator for this application.

PASC noted that while postsynaptic FDG PET imaging is available in Australia and listed on the MBS, it is not indicated for Parkinsonism. PASC also noted the applicant’s comments that FDG PET has low accuracy in diagnosing Parkinson’s Disease. Therefore, PASC considered that FDG PET is not a comparator for this application

PASC noted that standard of care in treating symptoms for the presenting conditions, including changes in patient management, is the appropriate comparator.

Clinical utility standard (for investigative technologies only)

It is proposed that the clinical utility standard should be applied to FDOPA PET/CT imaging because it generates direct from test to health outcomes evidence, which establishes the clinical utility of the test.

The intervention section of this PICO describes the test platform, the specific parameters being tested, the body part scanned, the tracer utilised, the semi-quantitative interpretation of the image, and the criteria for defining the scan threshold results that support different clinical management actions (MSAC 2021).

In a key retrospective cohort study at the Royal Brisbane and Women's Hospital (Yeow et al. 2025) the clinical utility of FDOPA PET scans were assessed. The net health benefit derived from the scans were defined as normal presynaptic dopaminergic neuron uptake, presynaptic dopaminergic neuron loss consistent with iPD, atypical PD (with definite yet atypical striatal reduction), or equivocal PD (subtle, non-definite reduction); from which, scan threshold results supported different clinical management actions (Yeow et al. 2025)

Where FDOPA PET scans were used in cases of significant diagnostic uncertainty, changes in provisional diagnosis and management occurred. Changes in diagnosis and management were more frequent after a normal FDOPA PET scan (42.4% and 53.0%, respectively) than after a scan indicating iPD (23.5% and 32.4%, respectively) (Yeow et al. 2025).

Patient demographics (age and sex) and clinical data (symptom duration, reasons for the scan, provisional diagnoses pre- and post-scan, and management changes) were extracted and categorised by a single investigator. Indications for FDOPA scans included tremor assessment (differentiating parkinsonian/non-neurodegenerative causes), parkinsonism assessment (distinguishing neurodegenerative/non-degenerative causes), drug effect evaluation (assessing antipsychotic-induced symptoms) and APD assessment (characterising striatal deficits in suspected APD cases). Unclear provisional diagnoses or multiple competing diagnoses were recorded as 'uncertain' (Yeow et al. 2025). The indicated populations were consistent with the indicated populations described in the international guidelines (Morbelli et al. 2020).

PASC noted that the gold standard is postmortem neuropathology, and the clinical utility standard is appropriate.

Outcomes

Effectiveness outcomes

- Test accuracy:
 - Including sensitivity, specificity, positive and negative predictive value;
 - Area under the curve (AUC) for time-dependent receiver operating characteristics (ROC);
 - Inter-observer reliability;
- Clinical validity;
 - Dopaminergic denervation – loss of nigral dopamine neurons;
 - Semiquantification – parameters expressing loss of presynaptic dopaminergic neurons;

Change in management outcomes

- Change in proportion of patients correctly diagnosed
- Change in proportion of patients prescribed appropriate or medically necessary therapies, including L-DOPA
- Other changes in clinical management (e.g. further investigations/monitoring)
- Change in patient-reported health status
 - Parkinson's Disease Quality of Life Questionnaire (PDQ-8) for patients with parkinsonism, including atypical parkinsonism
 - Quality of life in Essential Tremor (QUEST) for relevant patients
 - Dementia quality of life (DEMQOL) for patients with DLB
- Change in health outcomes (disease progression)

Safety outcomes

- Exposure to radiation (measured in millisieverts, mSv);
- Harms (psychological health risks) associated with imaging; and
- Harms associated with false positive and negative results.

Healthcare system outcomes

- Cost effectiveness of FDOPA PET/CT testing;
- Costs of treatments received/cost offsets from avoidance of unnecessary therapies;
- Costs associated with managing FDOPA intolerance and other AEs; and
- Financial implications.

Rationale for selected outcomes

The International Consortium for Health Outcomes Measurement (ICHOM) has developed a standard set of patient-centred health outcome measures for evaluation PD (de Roos et al. 2017). The health outcome measures proposed for the PICO capture those proposed by ICHOM, including motor and non-motor symptoms, and patient-reported health status via the Parkinson's disease Quality of Life-8 (PDQ-8). The motor and non-motor symptoms include:

- Cognitive impairment, hallucinations and psychosis, depressed mood, anxious mood, apathy, and features of dopamine dysregulation syndrome. Collected with Part 1A of the MDS-UPDRS;
- Sleep problems, daytime sleepiness, pain and other sensations, urinary problems, constipation problems, light-headedness on standing, fatigue, sweating, and sexual function. Collected with Part 1 of the MDS-UPDRS; and
- Speech, saliva and drooling, chewing and swallowing, eating tasks, dressing, hygiene, handwriting, doing hobbies and other activities, turning in bed, tremor, getting out of a bed, a car, or a deep chair, walking and balance, and freezing. Collected with Part 2 of the MDS-UPDRS (de Roos et al. 2017)

Clinical validity parameters were derived from the development and validation of a radiomic model for the diagnosis of dopaminergic denervation on FDOPA PET/CT. These textural features are image biomarkers that could potentially improve early diagnosis and monitoring of neurodegenerative parkinsonian syndromes (Comte et al. 2022).

Clinical utility measures were derived from the study by Yeow et al. (2025). FDOPA PET interpretation and reporting were carried out by nuclear medicine physicians based on visual assessment and semi-quantitative analysis of striatal FDOPA uptake (Yeow et al. 2025). Changes in patient management and treatments were reported.

PASC noted that evidence for test accuracy and clinical validity is required and queried if this evidence was available from the Applicant. The Applicant advised that this evidence is available.

PASC queried the availability of high-quality peer reviewed published evidence and noted that changes in treatment and patient management were highly relevant outcomes of interest, rather than changes in imaging supported diagnoses alone.

PASC noted the applicant's comments that they are currently undertaking research at the South Australian Health and Medical Research Institute, called the MAP-DOPA study, to further understand the impact of FDOPA PET/CT on the change in diagnosis in patients with Parkinsonian symptoms. They envision that the study results will be ready in 1 year's time.

Value of knowing

While arriving at a diagnosis of PD is clinically complex, communicating the diagnosis to the patient may also be complex. As a chronic, progressive condition, patients should be referred to a specialist neurology service. The timing of this referral depends on many factors, including patient preference, GP resources and local specialist availability. If possible, early referral to a specialist PD nurse could be helpful. However, referring to specialist services should not of itself cause delay to treatment initiation. The decision to start treatment depends on patient preference, the severity of motor and non-motor disabilities, and impacts on quality of life (Waller et al. 2021).

PASC noted the importance of counselling as to the value of knowing, where there is sometimes an associated stigma attached to a confirmation of a disease or condition, and the counterpoint that some patients may be disappointed that their diagnosis is not clarified.

Assessment framework (for investigative technologies)

As the application has made a claim of superiority, the assessment must show an improvement in health outcomes.

In the proposed population results of the FDOPA PET/CT could lead to changes in clinical diagnosis and patient management such as patients with ET, or DLB were misdiagnosed with PD, or where patients with atypical PD have their condition confirmed, ruling out PD. There are potentially two comparator sets in this population. Set 1:

- confirmed PD compared with misdiagnosed PD

As the test can support the differentiation of parkinsonism in the misdiagnosed group, the following set describes the likely comparators for subset 2, such as to:

- support the differential diagnosis between ET and neurodegenerative parkinsonian syndromes;
- help distinguish between diseases such as DLB and other dementias, in particular AD; and
- support the differential diagnosis between parkinsonism due to presynaptic degenerative dopamine deficiency and other forms of parkinsonism (iPD) and drug-induced, psychogenic, or vascular parkinsonism).

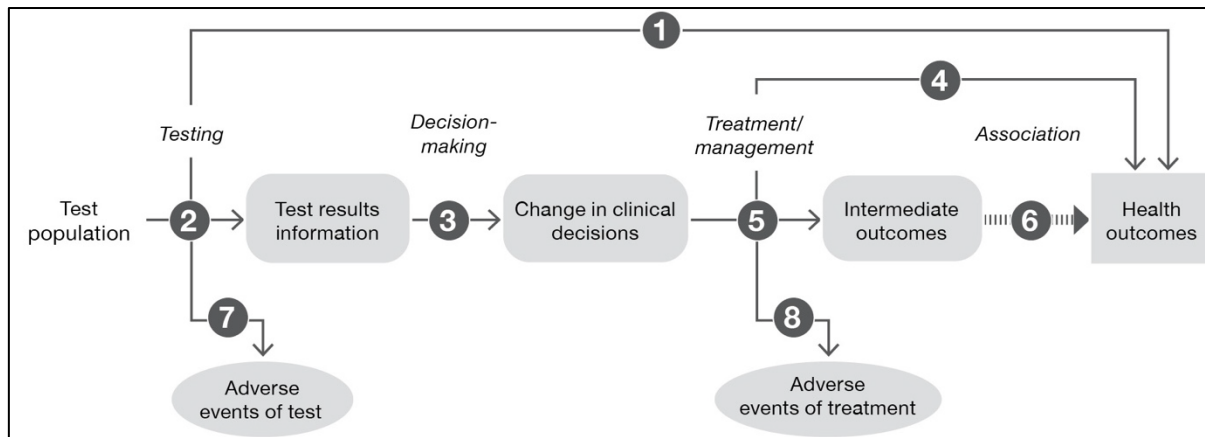
Changes also include treatment options for patients likely to benefit or not benefit, which would impact health and clinical outcomes for the patient.

The scan may also impact value of knowing outcomes for patients.

In circumstances where direct evidence is unavailable, evidence must be provided at each step of the assessment framework. Figure 3 shows the research questions that need assessing at each step to assess

FDOPA PET/CT imaging. Each number within the framework corresponds to one or more research questions that must be answered to support the clinical claim.

Figure 3 Assessment framework



1: direct from test to health outcomes evidence; 2: test accuracy; 3: change in diagnosis/treatment/management; 4: influence of the change in management on health outcomes; 5: influence of the change in management on intermediate outcomes; 6: association of intermediate outcomes with health outcomes; 7: adverse events due to testing; 8: adverse events due to treatment

Direct evidence

1. Does the additional use of the FDOPA PET/CT versus no FDOPA PET/CT in patients presenting with parkinsonian syndromes result in superior improvements in health outcomes (differential diagnosis of iPD or atypical PD, changes in treatment options) and better patient QoL?

Indirect evidence

2. How does the information provided by the FDOPA PET/CT differ from that provided by standard care?
3. What is the diagnostic accuracy of the FDOPA PET/CT against a clinical utility standard compared to clinical examination by specialist physicians currently applied in Australia?
4. Does the availability of the information provided by the FDOPA PET/CT lead to a change in patient management when compared to information gained from standard care?
5. What are the physical and psychological health risks associated with the addition of the FDOPA PET/CT as an add-on test compared to standard care?
6. What benefits (or harms) does the availability of information provided by the FDOPA PET/CT have on non-health outcomes related to the value of knowing, compared to information provided by standard care?

In the absence of RCT evidence demonstrating predictive value, are the following parameters met?

- An appropriate regulatory and quality assurance framework;
- An appropriate nomination of clinical place aligned with sufficiently robust clinical evidence of incremental prognostic value;
- An adequate justification of cost per test; and
- An acceptable total net financial cost to government.

Clinical management algorithms

Current clinical management for targeted population

There is no standard treatment for PD, and each option can effectively manage symptoms based on patient needs. Factors influencing appropriate treatment include the duration of PD, age, disease severity, comorbidities and individual characteristics, particularly for those with young-onset PD (Deloitte Access Economics 2014). Choosing the appropriate intervention for an individual patient can be guided by evidence-based medicine (EBM) recommendations. However, EBM is just one strategy, with other considerations including drug availability, cost, side effects, tolerability and patient preference (Fox et al. 2018).

A simplified version of the clinical management algorithm appears as follows:

- **Diagnosis made of PD:**
 - Consider impact of symptoms on QoL and ADL;
 - Discussion with patient regarding treatment options;
- **Initial medication** options for early disease (each group can be used as monotherapy);
- Medication options for **advancing disease; and**
- **Motor complications** unresponsive to medication changes: Consider non-oral therapy.

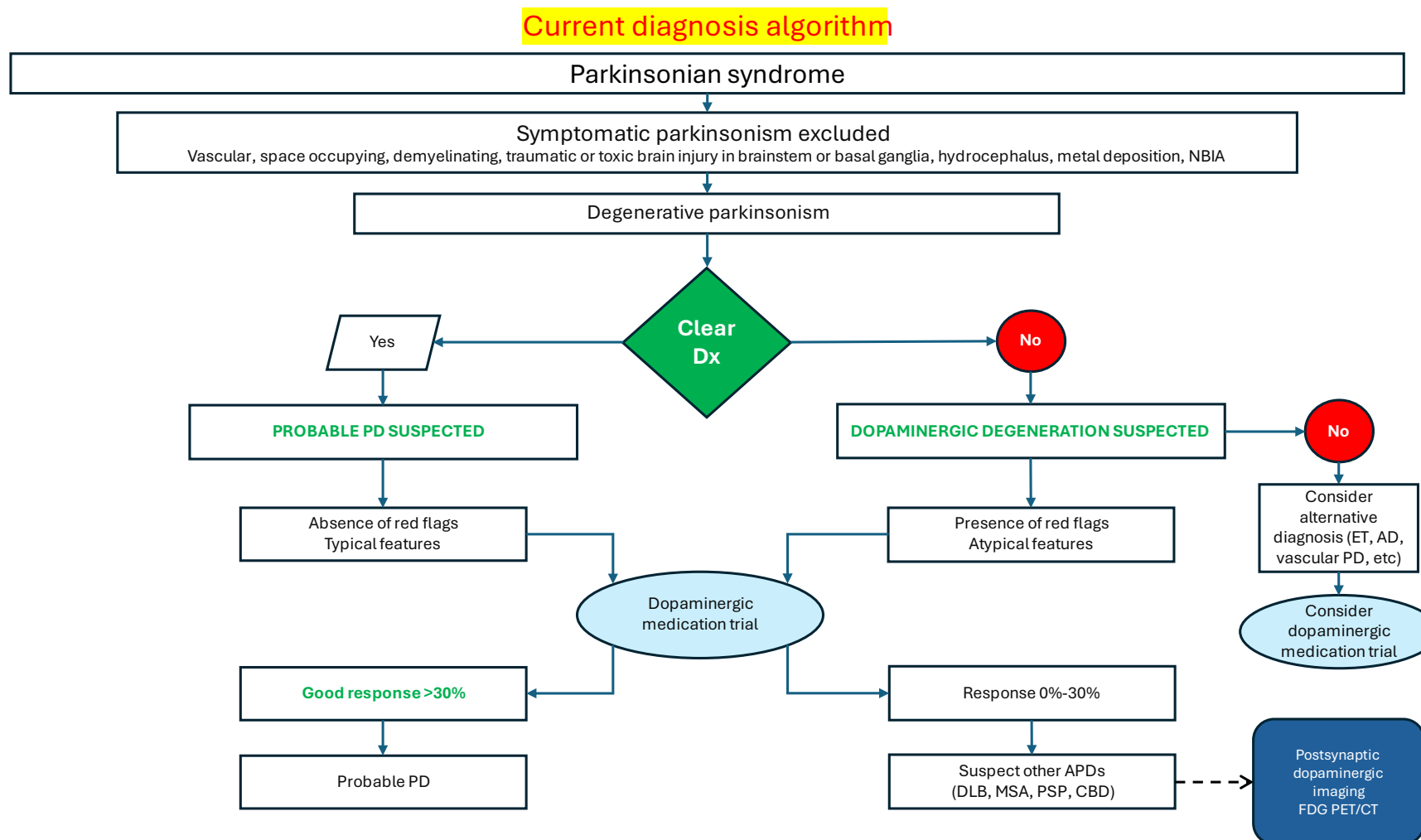
When a patient presents with atypical Parkinsonian symptoms, it is common practice for clinicians to initiate dopaminergic medication if there is a reasonable suspicion of a diagnosis for PD. However, if FDOPA PET/CT imaging was available, these patients would typically wait to begin medical therapy until after the imaging has been conducted (Personal communication, Applicant 21 March 2025).

The current diagnosis algorithm and proposed intervention are presented in Figure 4 and Figure 5.

PASC advised that while FDG PET is not listed on the MBS for Parkinsonism, it should still be included in the clinical algorithm. PASC noted that even when patients are identified as having uncertain PD, they are typically prescribed a trial of dopaminergic medication, even after the results of the diagnostic test, and this should be reflected in the proposed clinical algorithm. PASC advised that the clinical algorithm will need to be revised as per the discussed change in population.

The algorithms have been amended as per PASC advice.

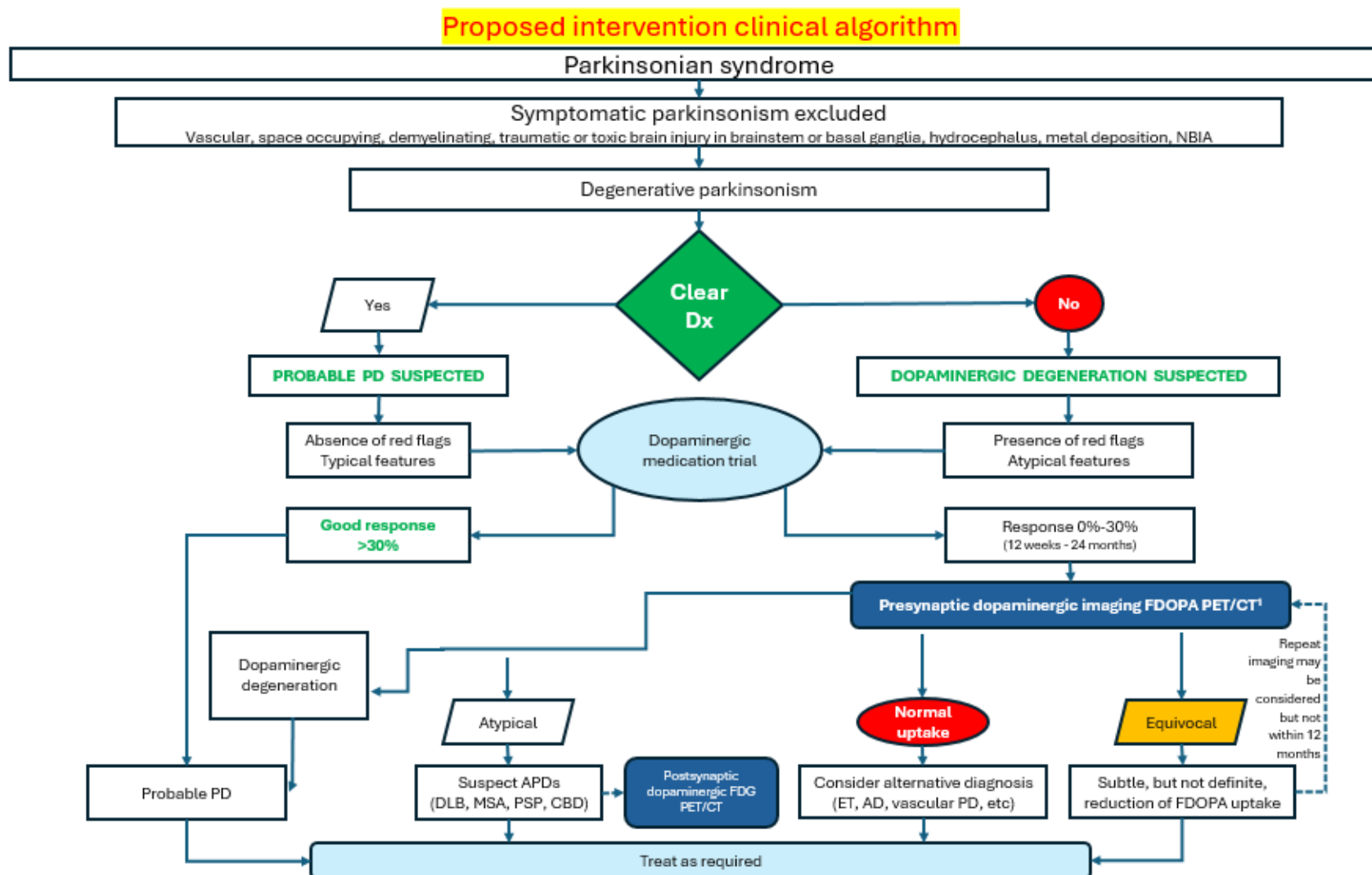
Figure 4 Current clinical management algorithm



AD = Alzheimer's disease, APDs = atypical parkinsonian disorders, CBD = corticobasal degeneration, DLB = dementia with Lewy bodies, Dx = diagnosis, MSA = multiple system atrophy, PD = Parkinson's disease, PET/CT = positron emission tomography/computed tomography, PSP = progressive supranuclear palsy, SPECT = single-photon emission computed tomography, NBIA = Neurodegeneration with Brain Iron Accumulation.

Source: Adapted from (Peralta et al. 2022) and (Yeow et al. 2025).

Figure 5 PET imaging diagnosis algorithm



AD = Alzheimer's disease, APDs = atypical parkinsonian disorders, CBD = corticobasal degeneration, DLB = dementia with Lewy bodies, Dx = diagnosis, MSA = multiple system atrophy, PD = Parkinson's disease, PET/CT = positron emission tomography/computed tomography, PSP = progressive supranuclear palsy, SPECT = single-photon emission computed tomography, NBIA = Neurodegeneration with Brain Iron Accumulation.

Source: Adapted from (Peralta et al. 2022) and (Yeow et al. 2025).

Note: 1. Maximum two tests per lifetime.

Change in clinical management

In an Australian study, clinician feedback indicated that earlier access to scans could enhance diagnostic certainty, optimise resource use and improve long-term outcomes. Following scan implementation, 90% of neurologists reported increased diagnostic certainty, with 21% of patients receiving a change in diagnosis. This reduced unnecessary medication trials for those without PD while allowing earlier therapy and invasive options for those diagnosed with PD, leading to better clinical outcomes and quality of life (Application form, p. 6 of the PICO Set).

In Yeow et al., (2025) 105 patients referred from the movement disorder clinic of three hospitals, representing cases where there was significant diagnostic uncertainty, were included, and symptom duration before FDOPA PET recorded for 98 patients, with a median of 4 years and the majority (62.2%, 61/98) had symptoms for 0-5 years. The primary indications for FDOPA PET were to differentiate neurodegenerative from non-neurodegenerative causes of parkinsonism (44.8%) and to distinguish parkinsonian tremor from other tremor causes (41.0%) (Yeow et al. 2025).

A change in diagnosis occurred in 36.2% of the 105 cases between pre-scan and post-scan, consistent across symptom duration groups. A normal FDOPA PET led to more changes than those consistent with PD (42.4% vs. 23.5%) (Yeow et al. 2025). All 34 FDOPA PET scans deemed consistent with PD resulted in post-scan diagnoses of degenerative parkinsonian disorders (27 PD, 2 DLB, 2 PSP, 1 MSA, 1 CBD, 1 unspecified APD (7/34, 20.6%) (Yeow et al. 2025).

PASC noted that the change in diagnosis rate reported in Yeow et al. was based on a denominator of the number of patients where there was significant diagnostic uncertainty. The true denominator of the number of patients who had a F-DOPA PET was unknown because while Yeow et al. stated that the study population was derived from a list of patients who underwent F-DOPA PET for movement disorder indications between 1 January 2011 and 23 June 2021 they did not report on the number of patients on this list.

Manual re-review showed no qualitative differences in FDOPA PET scans between APD and PD. Of 14 patients with an 'uncertain' pre-scan diagnosis, 12 received a definitive post-scan diagnosis, while 2 remained 'uncertain.' In contrast, five patients with a definitive pre-scan diagnosis became 'uncertain' post-scan (7/105, 6%) (Yeow et al. 2025).

Management changes were noted in specific clinical scenarios:

- patients with FDOPA PET results indicating PD, had dopaminergic medications initiated or increased (16/23, 69.6%);
- patients with normal FDOPA PET results, had their dopaminergic medications reduced (12/31, (38.7%); and
- patients with normal FDOPA PET results, were recommended to consider stopping antipsychotics due to potential drug-induced parkinsonism (3/7, 42.9%) (Yeow et al. 2025).

Among patients with management changes, eight (14.5%) involved surgical decisions:

- in five cases (5/55, 9%), DBS workup for PD was initiated or continued after a positive FDOPA PET;
- one case (1/55, 2%) avoided DBS workup after a normal FDOPA PET, with a revised diagnosis of functional neurological disorder (FND);

- one case (1/55, 2%) pursued gamma knife workup for dystonic tremor post normal FDOPA PET; and
- one case (1/55, 2%) initiated ventriculoperitoneal shunt workup for normal pressure hydrocephalus (NPH) following a normal FDOPA PET (Yeow et al. 2025).

Proposed economic evaluation

PICO Set

The application claimed that for patients presenting with symptoms unresponsive to dopaminergic medication for PD, FDOPA PET/CT can differentiate between iPD, DLB, and non-parkinsonian movement disorders, and is thereby superior in terms of health outcomes relative to current clinical practice (Application form, p. 5 of PICO Set 2). The claims advanced in the applications were that use of FDOPA PET/CT for the proposed population may improve the accuracy of clinical diagnosis and safety for patients with uncertain parkinsonism, thereby avoiding the negative consequences of treatment and minimising unnecessary treatment costs in patients unlikely to benefit.

The most appropriate economic evaluation is a cost-effectiveness or cost-utility analysis to determine costs relative to the test's effectiveness in improving patient-centred health outcomes as described in Table 18.

PASC noted the most appropriate economic evaluation for this application is a cost-utility analysis.

Table 18 Classification of comparative effectiveness and safety of the proposed intervention, compared with its main comparator, and guide to the suitable type of economic evaluation

Comparative safety-	Comparative effectiveness			
	Inferior	Uncertain ^a	Noninferior ^b	Superior
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain ^a	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Noninferior ^b	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

CEA = cost-effectiveness analysis; CMA = cost-minimisation analysis; CUA = cost-utility analysis

? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis.

a = 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations.

b = An adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence.

Proposal for public funding

The application proposed a new MBS item for FDOPA PET/CT.

The FDOPA PET/CT is not yet listed on the ARTG.

The draft MBS item descriptor, adapted from the proposed item descriptor in the application (application form, p. 23 of the PICO Set) and associated explanatory note are shown in Table 19.

Table 19 Proposed MBS item descriptor and explanatory note

Category 5 – DIAGNOSTIC IMAGING SERVICES
MBS Item XXXX FDOPA PET study of the brain, performed for the investigation of parkinsonian syndromes, where following the clinical evaluation of the patient by a specialist, or in consultation with a specialist, the request for the scan indicates that: - the patient has been initially treated for Parkinson's disease but has symptoms which are unresponsive to dopaminergic medication defined as 0%-30% response (Unified Parkinson's Disease Rating Scale) after 12 weeks of treatment optimisation but not greater than 24 months post treatment initiation; and - further investigation is required to confirm the diagnosis and inform subsequent treatment. Applicable once in any 12-month period. Applicable not more than twice per lifetime (R) Bulk bill incentive
Fee: \$1,200
Source: Draft MBS item descriptor based on discussions at the pre-PASC meeting
Draft Explanatory Note
Clinical notes for Item XXXX For Item XXXX, the service includes a semi-quantitative comparison of the results of the study, with the results of an FDOPA PET study of a normal brain from a reference database.

PASC discussed the frequency of the test and acknowledged that the test should be performed no more frequently than once every 12 months and considered that a twice per lifetime restriction may be appropriate

PASC noted that the item descriptor includes wording to restrict the test to patients who have had a trial of dopaminergic medication, with a lack of response, defined as 0% to 30% according to the Unified Parkinson's Disease Rating Scale, assessed after 12 weeks of treatment but not greater than 24 months post initiation of treatment.

Proposed fee

The proposed fee suggested in the application was \$950. This proposal will be confirmed during the assessment phase and determined based on the HTA economic evaluation.

The initial proposed fee was informed by pricing of other PET scans (personal communication, applicant, 21 February 2025).

The applicant advised that the fee covers the cost of producing the radioligand and may in fact be less than the costs incurred as manufacturing costs are expected to increase in the short term (personal communication, applicant, 21 February 2025).

PASC noted the proposed fee should be increased to \$1,200 to reflect increases in the costs of the radioisotope.

To ensure access to testing in rural and remote areas but also reduce the risk of leakage to patients who may not have diagnostic uncertainty, PASC considered the clinicians best placed to request the scan are consultant physicians, specialists, or General Practitioner in consultation with a consultant physician or specialist.

Summary of public consultation input

PASC noted and welcomed consultation input from 7 organisations and 42 individuals, 19 of whom were consumers and 23 health professionals. The 7 organisations that submitted input were:

- Australia and New Zealand Association of Neurologists
- Movement Disorder Society of Australia and New Zealand (MDSANZ)
- Royal Brisbane & Women's Hospital Department of Neurology - Movement Disorders Service
- Australasian Association of Nuclear Medicine Specialists (AANMS)
- Australian and New Zealand Society of Nuclear Medicine (ANZSNM)
- Royal Australian and New Zealand College of Radiologists (RANZCR)
- Parkinson's Australia

All of the consultation input received was supportive of public funding for FDOPA PET/CT for evaluating Parkinsonism. The consultation input raised concerns in relation to access and cost of the radiotracer.

Consumer Input

Most consumers who provided consultation input had been diagnosed with PD, were a carer for someone diagnosed with PD or were being investigated for PD. Individual consumers stated that the FDOPA PET/CT allowed a diagnosis and could change the treatments and management being offered, and provided some certainty during a challenging time.

Parkinson's Australia stated that FDOPA PET/CT can provide a quick and accurate diagnosis for PD, reducing the anxiety that comes with an uncertain diagnosis for patients, family and carers. An accurate diagnosis allows patients to choose evidence based interventions that can improve and/or slow progression of their condition.

Benefits and Disadvantages

The main benefits of public funding received in the consultation input included an accurate diagnosis for PD and Parkinsonian mimics, more time and labour efficient than a medication challenge, certainty of diagnosis allowing earlier use of effective treatments and less anxiety for patients and their family. RANZCR and MDSANZ stated that FDOPA PET/CT is the gold standard for helping to diagnose PD and other Parkinsonian syndromes. Input also stated that public funding would increase equity of access as FDOPA PET/CT is currently only available through clinical trials or by private funding.

There were no disadvantages of public funding received in the consultation input.

Population, Comparator (current management) and Delivery

The consultation input broadly agreed with the proposed populations. Input noted the importance of including all people where a clinical assessment still has diagnostic uncertainty. The Royal Brisbane & Women's Hospital Department of Neurology and AANMS proposed including an additional population for patients when the clinician is suspecting a diagnosis of Lewy body dementia to assess for neurodegeneration.

The consultation input largely agreed with the comparator, with all organisations agreeing that there is no comparator available in Australia. Individual health professionals and AANMS stated that the only potential comparator is dopamine transporter SPECT imaging, which is not available in Australia. Some of the input from individual health professionals proposed other MRI or CT scans, including nigrosome-1 MRI scans at 3

Tesla, as comparators. Other health professionals and the Royal Brisbane & Women's Hospital Department of Neurology stated that MRI markers are not sufficiently validated to distinguish PD from other Parkinsonian conditions and are not as accurate, particularly in the early stages of PD.

Individual consumers stated that counselling should be included in the services delivered before or after the intervention.

MBS Item Descriptor and Fee

The health professional and organisation input broadly agreed with the proposed service descriptor with most input highlighting the importance of patients having had a review by a specialist that was inconclusive or equivocal for a diagnosis. Input on the repeat frequency interval ranged from 1 to 3 years, with RANZCR stating that for some borderline cases patients may need to be monitored and would ideally be able to receive more than 2 scans in their lifetime.

The consultation input on the proposed item fee ranged from agreeing to proposing an increase in the fee to approximately \$1,200. RANCR, ANZSNM and AANMS all expressed concern over the increasing cost of the radiotracer and its supply, and recommending that the MBS fee covers the cost appropriately to ensure patients do not have an out of pocket cost for the service.

PASC noted that most feedback was mostly positive around the clinical utility of the proposed test.

PASC noted that there was less consistency in responses with respect to the proposed population of interest for the test. Some professional bodies suggested all patients with a movement disorder should be included to confirm diagnosis and direct therapy. Some feedback suggested the test should only include patients where the clinical assessment still has diagnostic uncertainty. Others said it should only include patients with a diagnosis of PD who do not have a typical response to standard therapy. There were also suggestions to include patients with Parkinsonian syndrome and Parkinson like syndrome, and others suggested including the following indications where FDOPA PET/CT may be helpful to differentiate between: idiopathic PD versus atypical PD; essential tremor versus tremor predominant PD; functional tremor disorder versus predominant PD; multisystem degeneration versus corticobasal degeneration and drug induced Parkinsonism versus neurodegenerative Parkinsonism.

PASC noted that these different populations would have substantially different costs and access implications.

PASC noted that the frequency of testing was also raised in the feedback suggesting limited clinical utility in conducting the test multiple times per patient.

PASC noted the potential variation in the prevalence and incidence of PD in rural and regional areas of Australia, highlighting the large distances travelled for people to receive care and treatment, and were interested in the opinion of an organisation such as the Rural Health Alliance about the best practice approach for rolling out this test to rural areas. PASC noted that the tracer can be flown to most regional centres that have a PET scanner.

Next steps

PASC noted that the application and the PICO need to be simplified and focused on patient groups that could be clearly identified and were supported by evidence.

PASC noted that there is a need for test accuracy values related to sensitivity, specificity and predictive values of the intervention that are evidence based in the population of interest, in order to progress to the

next steps. PASC queried if evidence from the Applicant could be made available to support a Department Contracted Assessment Report.

PASC noted applicant advice that other clinical evidence from South Australia has been collected, but the formal publication from the relevant clinical trial is yet to be published in peer-reviewed journals. While the availability of the clinical data is sufficient for the DCAR to proceed, PASC flagged that the Applicant may need to acknowledge the use of unpublished data.

Applicant Comments on Ratified PICO

We believe that this application provides an overview regarding the requirement for inclusion on the Medicare schedule.

We acknowledge that the PASC outcomes “*considered that the DCAR should include a careful review of whether the more “commonplace” 18F-FDG metabolic PET could be an alternative to the proposed FDOPA PET/CT for some patients.*” Of note, 18F is the same radionuclide used for DOPA and FDG imaging. This means that the decay characteristics are the same for both. From a logistical point of view regarding transport of the radiopharmaceutical, both would be able to be transported to the same locations as currently possible.

References

AIHW 2024a, *Australian Burden of Disease Study 2024*, Australian Institute of Health and Welfare, Canberra.

— 2024b, *Burden of Disease Summary*, Australian Institute of Health and Welfare, Canberra.

Ali, K & Morris, HR 2015, 'Parkinson's disease: chameleons and mimics', *Pract Neurol*, vol. 15, no. 1, pp. 14-25.

Australian Department of Health and Aged Care 2025, *PET Units in Australia*, DOHAC, viewed 15 March 2025.

Chin, KS, Teodorczuk, A & Watson, R 2019, 'Dementia with Lewy bodies: Challenges in the diagnosis and management', *Australian & New Zealand Journal of Psychiatry*, vol. 53, no. 4, pp. 291-303.

Comte, V, Schmutz, H, Chardin, D, Orlhac, F, Darcourt, J & Humbert, O 2022, 'Development and validation of a radiomic model for the diagnosis of dopaminergic denervation on [18F]FDOPA PET/CT', *Eur J Nucl Med Mol Imaging*, vol. 49, no. 11, pp. 3787-96.

Cyclotek 2025, *Cyclotek Logistics*, Cyclotek, viewed 21 March 2025.

de Roos, P, Bloem, BR, Kelley, TA, Antonini, A, Dodel, R, Hagell, P, Marras, C, Martinez-Martin, P, Mehta, SH, Odin, P, Chaudhuri, KR, Weintraub, D, Wilson, B & Uitti, RJ 2017, 'A Consensus Set of Outcomes for Parkinson's Disease from the International Consortium for Health Outcomes Measurement', *J Parkinsons Dis*, vol. 7, no. 3, pp. 533-43.

Deloitte Access Economics 2014, *Living with Parkinsons Disease*, Sydney.

di Biase, L, Pecoraro, PM & Di Lazzaro, V 2025, 'Validating the Accuracy of Parkinson's Disease Clinical Diagnosis: A UK Brain Bank Case-Control Study', *Ann Neurol*.

Dijk, JM, Espay, AJ, Katzenschlager, R & de Bie, RMA 2020, 'The Choice Between Advanced Therapies for Parkinson's Disease Patients: Why, What, and When?', *J Parkinsons Dis*, vol. 10, no. s1, pp. S65-S73.

Fox, SH, Katzenschlager, R, Lim, SY, Barton, B, de Bie, RMA, Seppi, K, Coelho, M & Sampaio, C 2018, 'International Parkinson and movement disorder society evidence-based medicine review: Update on treatments for the motor symptoms of Parkinson's disease', *Movement Disorders*, vol. 33, no. 8, pp. 1248-66.

Goetz, CG, Tilley, BC, Shaftman, SR, Stebbins, GT, Fahn, S, Martinez-Martin, P, Poewe, W, Sampaio, C, Stern, MB, Dodel, R, Dubois, B, Holloway, R, Jankovic, J, Kulisevsky, J, Lang, AE, Lees, A, Leurgans, S, LeWitt, PA, Nyenhuis, D, Olanow, CW, Rascol, O, Schrag, A, Teresi, JA, van Hilten, JJ, LaPelle, N & Movement Disorder Society, URTF 2008, 'Movement Disorder Society-sponsored revision of the Unified Parkinson's

Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results', *Mov Disord*, vol. 23, no. 15, pp. 2129-70.

Grimes, D, Fitzpatrick, M, Gordon, J, Miyasaki, J, Fon, EA, Schlossmacher, M, Suchowersky, O, Rajput, A, Lafontaine, AL, Mestre, T, Appel-Cresswell, S, Kalia, SK, Schoffer, K, Zurowski, M, Postuma, RB, Udow, S, Fox, S, Barbeau, P & Hutton, B 2019, 'Canadian guideline for Parkinson disease', *CMAJ*, vol. 191, no. 36, pp. E989-E1004.

Hely, MA, Reid, WG, Adena, MA, Halliday, GM & Morris, JG 2008, 'The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years', *Mov Disord*, vol. 23, no. 6, pp. 837-44.

Hicks, SA, Strumke, I, Thambawita, V, Hammou, M, Riegler, MA, Halvorsen, P & Parasa, S 2022, 'On evaluation metrics for medical applications of artificial intelligence', *Sci Rep*, vol. 12, no. 1, p. 5979.

Jankovic, J & Tan, EK 2020, 'Parkinson's disease: etiopathogenesis and treatment', *J Neurol Neurosurg Psychiatry*, vol. 91, no. 8, pp. 795-808.

Kobylecki, C 2020, 'Update on the diagnosis and management of Parkinson's disease', *Clin Med (Lond)*, vol. 20, no. 4, pp. 393-8.

Lo, RY 2022, 'Epidemiology of atypical parkinsonian syndromes', *Tzu Chi Med J*, vol. 34, no. 2, pp. 169-81.

Louis, ED & McCreary, M 2021, 'How Common is Essential Tremor? Update on the Worldwide Prevalence of Essential Tremor', *Tremor Other Hyperkinet Mov (N Y)*, vol. 11, p. 28.

Mellick, GD 2024a, *Ecosystem of Parkinson's in Australia Project Part 2: Systematic Review*, Parkinson's Australia, Canberra.

— 2024b, *Ecosystem of Parkinson's in Australia Project Part 3: Modelling geographic distributions & future*.

— 2024a, *Ecosystem of Parkinson's Part 1: Scoping Study*.

Morbelli, S, Esposito, G, Arbizu, J, Barthel, H, Boellaard, R, Bohnen, NI, Brooks, DJ, Darcourt, J, Dickson, JC, Douglas, D, Drzezga, A, Dubroff, J, Ekmekcioglu, O, Garibotto, V, Herscovitch, P, Kuo, P, Lammertsma, A, Pappata, S, Penuelas, I, Seibyl, J, Semah, F, Tossici-Bolt, L, Van de Giessen, E, Van Laere, K, Varrone, A, Wanner, M, Zubal, G & Law, I 2020, 'EANM practice guideline/SNMMI procedure standard for dopaminergic imaging in Parkinsonian syndromes 1.0', *Eur J Nucl Med Mol Imaging*, vol. 47, no. 8, pp. 1885-912.

MSAC 2021, *Guidelines for preparing assessments for the Medical Services Advisory Committee*, by MSAC, Department of Health and Aged Care.

— 2022, *Essential Tremor MSAC PSD*, Canberra.

— 2025, *MBS Online*, Commonwealth Department of Health and Aged Care, viewed 15 March 2025.

NICE 2017, *Parkinson's disease in adults*, National Institute for Health and Care Excellence, London.

Peralta, C, Strafella, AP, van Eimeren, T, Ceravolo, R, Seppi, K, Kaasinen, V, Arena, JE, Lehericy, S & International Parkinson Movement Disorders Society-Neuroimaging Study, G 2022, 'Pragmatic Approach on Neuroimaging Techniques for the Differential Diagnosis of Parkinsonisms', *Mov Disord Clin Pract*, vol. 9, no. 1, pp. 6-19.

Pitz, V, Malek, N, Tobias, ES, Grosset, KA, Gentleman, S & Grosset, DG 2020, 'The Levodopa Response Varies in Pathologically Confirmed Parkinson's Disease: A Systematic Review', *Mov Disord Clin Pract*, vol. 7, no. 2, pp. 218-22.

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 2015, 'MDS clinical diagnostic criteria for Parkinson's disease', *Mov Disord*, vol. 30, no. 12, pp. 1591-601.

Saeed, U, Lang, AE & Masellis, M 2020, 'Neuroimaging Advances in Parkinson's Disease and Atypical Parkinsonian Syndromes', *Front Neurol*, vol. 11, p. 572976.

Stormezand, GN, de Meyer, E, Koopmans, KP, Brouwers, AH, Luurtsema, G & Dierckx, R 2024, 'Update on the Role of [(18)F]FDOPA PET/CT', *Semin Nucl Med*, vol. 54, no. 6, pp. 845-55.

Virameteekul, S, Revesz, T, Jaunmuktane, Z, Warner, TT & De Pablo-Fernandez, E 2023, 'Clinical Diagnostic Accuracy of Parkinson's Disease: Where Do We Stand?', *Mov Disord*, vol. 38, no. 4, pp. 558-66.

Waller, S, Williams, L, Morales-Briceno, H & Fung, VS 2021, 'The initial diagnosis and management of Parkinson's disease', *Australian Journal of General Practice*, vol. 50, no. 11.

Yang, Y, Li, X, Lu, J, Ge, J, Chen, M, Yao, R, Tian, M, Wang, J, Liu, F & Zuo, C 2025, 'Recent progress in the applications of presynaptic dopaminergic positron emission tomography imaging in parkinsonism', *Neural Regen Res*, vol. 20, no. 1, pp. 93-106.

Yeow, D, Fielder, M, Hynard, S, Adam, R, Katz, M, Lehn, A, Thomas, P & O'Sullivan, JD 2025, 'Clinical utility of (18)F-fluorodopa positron emission tomography in the movement disorder clinic: an Australian experience', *Intern Med J*, vol. 55, no. 2, pp. 207-15.

Zesiewicz, TA, Elble, RJ, Louis, ED, Gronseth, GS, Ondo, WG, Dewey, RB, Okun, MS, Sullivan, KL & Weiner, WJ 2011, 'Evidence-based guideline update treatment of essential tremor', *Neurology*, vol. 77, pp. 1752-5.

Zhou, ZD, Yi, LX, Wang, DQ, Lim, TM & Tan, EK 2023, 'Role of dopamine in the pathophysiology of Parkinson's disease', *Transl Neurodegener*, vol. 12, no. 1, p. 44.