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Biomarkers

in Parkinson´s Disease

Final Report

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1 Background and research question

1.1 Description of disease

PD: second most common neurogenerative disease

Parkinson's disease (PD) is the second most common neurogenerative disease, affecting approximately 1% of people over the age of 65 [1, 2]. It primarily results from dopamine deficiency in the brain, leading to both motor symptoms like bradykinesia, muscular rigidity, postural instability, and rest tremor, and non-motor symptoms such as mood disorders, cognitive dysfunction, autonomic dysfunction, and sleep abnormalities [3, 4]. The motor symptoms, especially resting tremors, rigidity, and postural disabilities are directly related to this dopamine loss [2]. PD shows considerable variation in its motor and non-motor symptoms and progression rate. Current treatments focus on replacing or boosting dopamine, but have limited effect on disease progression. This is because by the time symptoms become noticeable, about 60%–80% of nigral dopamine neurons are already lost, typically over a period of five to 15 years [2]. Identifying patients between the presumed start of dopaminergic cell loss and the onset of clinical symptoms is crucial for developing effective neuroprotective treatments. PD's progression can be categorized into six neuropathological stages, with cognitive status correlating with the stage of the disease [3].

significant variability in symptoms and progression rate

1.2 Current (and future) treatment options

focus of current treatment: symptom control, disease-modifying treatment is needed

Currently there is no cure for PD. Treatment primarily aims at symptom control through medications, rehabilitation, and surgery, without altering the course of the disease. There is a need for *disease-modifying treatments* that can slow down or halt disease progression [3].

Available medications for *symptom control* include [5]:

medications for symptom control:

levodopa: 1st line in various formulations

- **Levodopa**, paired with carbidopa, or benserazide, is considered a first-line drug for improving movement symptoms, such as tremor and slowness. It can be delivered in a variety of formulations (pill, inhaled form, or infusion). As the disease progresses, there might be a "wearing off" effect, meaning that the benefit of the drug becomes shorter, and it needs to be taken more frequently.
  - **In** patients with motor fluctuations, a pro-drug[1] is available for subcutaneous infusion: **Foslevodopa/foscarbidopa** ABBV-951 (EMA approved).
  - **Inhaled levodopa** has been approved by EMA as an on-demand medication; it is currently not marketed in Austria.

[1] a biologically inactive compound which can be metabolized in the body to produce a drug

- Extended release (ER) **oral levodopa** IPX066 has a pharmacokinetic profile that provides a more continuous levodopa serum concentration; It is marketed as Rytary in the US and as Numient in a few other countries and will likely not be marketed in the EU.

MAO-B inhibitors

- **Monoamine oxidase-B (MAO-B) inhibitors** for improving movement symptoms. They help prevent the breakdown of brain dopamine by inhibiting the brain enzyme MAO-B. These include rasagiline, selegiline and safinamide.

Dopamine agonists

- **Dopamine agonists** stimulate the parts of the brain influenced by dopamine. Dopamine agonists aren't as effective as levodopa in treating symptoms. However, they last longer and may be used with levodopa to smooth the off-and-on effect of levodopa. These include apomorphine, pramipexole, pramipexole ER, ropinirole, ropinirole XL and transdermal rotigotine.
  - **Apomorphine**: injection therapy for fast improvement of OFF[2] symptoms (on-demand) as subcutaneous infusion to deliver under-the-skin dopamine agonists. The infusion is submitted to the FDA for drug approval and is also available in Europe. Sublingual apomorphine for fast improvement of OFF symptoms (on-demand) is approved by the FDA and EMA and will be marketed in Austria.

COMT inhibitors

- **Catechol-O-methyl transferase (COMT) inhibitors** help with changes in the ability to move as levodopa "wears off". Entacapone and opicapone are the primary medicines from this class, tolcapone is rarely prescribed due to its safety profile. Carbidopa-**levodopa**-entacapone is available as a combined pill.

Antiglutamatergics

- **Antiglutamatergic** medication amantadine can be taken alone to provide short-term relief of symptoms of mild, early-stage PD or given with carbidopa-levodopa during the later stages of PD to control dyskinesia induced by levodopa and to reduce OFF time.
  - ER amantadine will likely not be marketed in the EU.

Anticholinergics

- **Anticholinergics** such as biperiden have modest effects on parkinsonian symptoms with a possible slightly greater effect on tremor. However, their modest benefits are often offset by side effects such as impaired memory, confusion, hallucinations, and constipation.

new medications for symptom control in the pipeline

The drug development pipeline contains several new options for *symptomatic therapies*. Newer formulations that further improve and extend drug delivery promise to minimise motor fluctuations and "wearing off" symptoms [5]:

- A second continuous levodopa infusion therapy has been developed:
  - **ND0612** (NeuroDerm) (submitted for EMA approval)
- **P2B001** (Pharma Two B Ltd.): a low-dose, extended-release formulation of pramipexole and rasagiline in development for the treatment of movement symptoms for people newly diagnosed with PD.
- **IPX203** (Amneal Pharmaceuticals): an extended-release carbidopa-levodopa pill designed to extend PD symptom control while minimising motor fluctuations

[2] During an ON episode, the levodopa is working well and symptoms improve. During an OFF episode, the levodopa isn't working and symptoms return or get worse.

- **Tavapadon** (Cerevel Therapeutics): a once-daily pill in development, but further from the approval process. It aims to target and activate certain dopamine receptors to improve PD motor symptoms while minimising side effects.

The landscape of trials focused on *disease-modifying therapies* is expanding.

disease-modifying therapies in the pipeline:

Several experimental therapies are in early development stages, aiming to reduce alpha-synuclein production or to minimise the formation of alpha-synuclein (aSyn) clumps, known as Lewy bodies, in the brain. However, some frontrunners in research targeting aSyn have recently shown mixed results in slowing of PD progression [5, 6]:

aiming at alpha-synuclein:

prasinezumab, buntanetap

- **Prasinezumab** (Roche/Prothena): a monoclonal antibody administered as an intravenous infusion, is currently being studied in a multicenter, double-blind, placebo-controlled RCT called PASADENA (NCT03100149), consisting of three parts. It will evaluate the efficacy of prasinezumab against placebo over 52 weeks in participants with early PD. Part two of PASADENA did not meet its primary endpoint of reducing motor and non-motor symptoms in early-stage PD. However, it provided enough signs of efficacy in secondary outcome measures and had a good safety profile, leading the company to advance it into a further global Phase 2b study called PADOVA (NCT04777331), with a primary completion date of July 2024.
- **Buntanetap** (Annovis Bio): a phase 3 RCT (NCT05357989), investigating the efficacy, safety, and tolerability of buntanetap in early PD patients, a translation inhibitor: phase 3 study completed, results expected in 2024 [7].
- Oligomer-modulator anle138b (TEV-56286, **emrusolmin**): a phase 1b study to investigate safety, tolerability, pharmacokinetics and pharmacodynamics in 70 patients. Emrusolmin was well tolerated [8].

other potential drugs approved for another disease being evaluated in trials:

Several drugs, initially approved for other diseases, are being investigated – as re-purposed drugs - for their potential in slowing the progression of PD [9]:

exenatide, cancer therapies transdermal nicotine treatment

- **Exenatide**: a therapeutic agent approved to treat type 2 diabetes, currently in phase 3 clinical trials [5]. A recent study of a GLP-1 receptor agonist was negative overall with some indication of effect in a subgroup(younger patients) [10]. Further GLP1 agonists are being investigated [11]. A one-year, phase 2 trial (LixiPark) of Type 2 diabetes drug **lixisenatide** has reported positive early results, which indicate that the treatment may slow the progression of motor (or movement) symptoms [12].
- **Some novel cancer therapies** are in the early stages of testing for potential effectiveness in PD [5].
- **Transdermal nicotine treatment** showed negative results [13].

personalised medicine: genetic targeting of PD-related genes (GBA, LRRK2)

Every person with PD experiences symptoms differently. Developing therapies to target the biology of PD in a particular individual is known as *personalised medicine*. Genetic targeting is the most advanced way to subtype drug development for people with PD. Researchers are investigating possible therapeutic (esp. interventions for two PD-related genes [5], [9]):

- **Glucocerebrosidase (GBA)**, the most common Parkinson's-related gene mutation, carried by up to 10-15% of people who live with the disease [14].

- **Ambroxol** (GCase enhancer), licensed drug for the treatment of respiratory conditions, is tested in PD patients for increasing the levels of the protein GCase (glucocerebrosidase) [15]. In the AMBITIOUS STUDY (NCT05287503, EudraCT 2021-004565-13) ambroxol is tested in PD-patients with heterozygote GBA1-Mutation (phase 2) [16]. In the ASPro-PD STUDY (NCT05778617) ambroxol is tested in a phase 3 trial.

- **Leucine-rich repeat kinase 2 (LRRK2)**: variants of this gene are associated with an increased risk of Parkinson's disease. The gene variants are involved in about 1% of all PD diagnoses and 5% of those for people with a family history.
  - **LRRK2-inhibitors** are tested in PD patients with or without mutations [17]: in preclinical models, **the drug** inhibited LRRK2 kinase activity and in a phase 1/1b it was well tolerated. In the phase 2b LUMA trial (NCT05348785) of BIIB122, a small molecule inhibitor is tested in 640 patients [18].

It is critical to determine whether patients are potential candidates for gene-targeted medicine clinical trials. Knowledge of genetic status can also be important for therapeutic decision-making and for understanding individual disease progression [5].

1.3 Potential role of biomarkers

classes of biomarkers:

The Biomarkers Definitions Working Group has defined a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention" [19].

Biomarkers can be classified according to the "Biomarkers, Endpoints and other Tools (BEST)" resource from the FDA [20]:

diagnostic biomarker

monitoring pharmacodynamic/ response biomarker

predictive biomarker

- **Diagnostic biomarker**: detects or confirms the presence of a disease or condition of interest or identifies an individual with a subtype of the disease.
- **Monitoring biomarker**: is measured serially to assess the status of a disease or medical condition for evidence of exposure to a medical product or environmental agent, or to detect an effect of a medical product or biological agent.
- **Pharmacodynamic/ response biomarker**: when the level of a biomarker changes in response to exposure to a medical product or an environmental agent.
- **Predictive biomarker**: is defined by the finding that the presence or change in the biomarker predicts an individual (or group of individuals) more likely to experience a favourable or unfavourable effect from the exposure to a medical product or environmental agent.

- **Prognostic biomarker**: is used to identify the likelihood of a clinical event, disease recurrence, or disease progression in patients with a disease or medical condition of interest.
- **Safety biomarker**: is measured before or after an exposure to a medical intervention or environmental agent to indicate the likelihood, presence, or extent of a toxicity as an adverse event.
- **Susceptibility/ risk biomarker** indicates the potential for developing a disease or medical condition in an individual who does not currently have clinically apparent disease or the medical condition.

prognostic biomarker

safety biomarker

susceptibility/ risk biomarker

Despite the range of biomarkers, no presently available biomarker can predict the onset of PD or constitutes a definite diagnostic test. Misdiagnosis often occurs early in the disease due to similar signs and symptoms associated with PD and other neurodegenerative disorders such as PD with dementia (PDD), dementia with Lewy bodies (DLB) and multiple system atrophy (MSA). Often, an autopsy is required for confirmation, as clinical diagnosis usually occurs after substantial degeneration of substantia nigra neurons. Hence, there's a pressing need for reliable PD biomarkers to detect the disease in its prodromal, preclinical, or premotor stages, assess risk or susceptibility, and monitor motor stages. These biomarkers are crucial for early intervention and monitoring therapeutic interventions [2].

no definitive biomarker to detect or predict PD

pressing need for reliable PD biomarkers

1.4 Questions to be answered in this report

What is the current status of biomarkers in neurology with a focus on Parkinson's Disease (PD)?

- Question **(Q)1**: Which biomarkers (tests) are (commercially) available?
- **Q2**: What is the sensitivity and specificity of these biomarker tests? Specifically, what is the diagnostic accuracy of blood biomarker tests?
- **Q3**: For which drugs would the respective biomarkers be relevant?
- **Q4**: Are there any standardisation initiatives for biomarkers (in Europe)?

questions in this report:

available and validated biomarker in PD

standardisation initiatives

2 Methods

methods:

To answer **Q1-4**, a hand search for relevant review publications was performed in dedicated databases such as PubMed and through internet search.

handsearch for all questions

Regarding **Q2**: The information about sensitivity and specificity of respective biomarker tests was extracted/referenced from review publications and sources without assessing (and critically appraising the risk of bias of) the included diagnostic accuracy studies, since this was not in the scope of this rapid review – results are summarized in Table 1. Additionally, results from systematic reviews on diagnostic accuracy of blood biomarkers including a reference standard (standard diagnostic procedures) that differentiated patients with PD from patients with other dementia subtypes or from cognitively healthy controls were searched for.

primarily for systematic reviews

clinical guidelines

A supplementary hand search for **clinical guidelines** was performed. Inclusion criteria was that the guideline addresses Parkinson's Disease, and related diagnostics.

3 Results

routine-diagnostic work-up (now):

clinical investigation

The diagnosis of Parkinson's disease (PD) still rests on medical history and clinical examination with the cardinal symptoms bradykinesia, rigidity and resting tremor as most important pointers towards PD. Olfactory tests and cognitive can assist in differential diagnosis. However, even in highly specialized clinics complying to strict criteria, the accuracy of clinical diagnostics is only around 90% [14] and between 74% und 83% in less experienced centers [21]. Important clinical features supporting a diagnosis of PD are unilateral or asymmetric onset, classical pill rolling resting tremor and non-motor symptoms such as a reduced sense of smell and REM sleep behaviour disorder.

cMRI, cCT
DAT SPECT
FDG PET

Every patient with a parkinsonian syndrome (PS) should undergo structural imaging, preferentially cranial magnetic resonance imaging (cMRI), or cranial computed tomography(cCT) if there is a contraindication for MRI. Dopamin-Transporter single-photon emission computed tomography (DAT SPECT) is an additional tool for differentiating degenerative from non-degenerative parkinsonian syndromes and is indicated in unclear cases. In the differential diagnosis of degenerative PS and in the diagnosis of complex parkinsonian syndromes such as corticobasal syndrome, cranial fludeoxyglucose-18 (FDG) positron emission tomography (PET) plays a relevant role. In individual cases, other nuclear medicine procedures (e.g. meta-iodo-benzyl-guanidine, MiBG scan) are conducted. These approaches are non-invasive, but expensive, limiting their usefulness in standard diagnostics [1, 2, 22].

3.1 (Commercially) Available biomarkers for Parkinson ´s Disease

The future of diagnostics lies in the rapidly developing seeding techniques such as the **real-time quaking-induced conversion (RT-QuIC)** and **protein misfolding cyclic amplification (PMCA)** [23]. With these techniques,

future diagnostics:

RT-QuIC
PMCA

in CSF or blood

- **Cerebrospinal fluid (CSF)-based** differentiation of parkinsoian syndromes is already possible with a sensitivity and specificity of 95% [24]. However, the establishment of these techniques in individual laboratories is very time-consuming and still in its infancy (e.g. **αSyn RT-QuIC diagnostics from CSF** is under research).
- Further developments that could aid the seeding technique to achieve a breakthrough in diagnostics would be **α-synuclein diagnostics in blood exosomes** or the establishment of immuno- RT-QuIC. With these methods, reliable α-synuclein detection would bealso possible in blood.

In future, Parkinson's diagnostics will be biomarker-based [21]: a three-component classification acknowledges the complexity and heterogeneity of the disease by use of (SynNeurGe) [25]:

3 component classification of PD

1. presence or absence of **pathological α-synuclein** (S) in tissues or CSF;
2. evidence of underlying **neurodegeneration** (N) defined by neuroimaging procedures; and
3. documentation of **pathogenic gene variants** (G) that cause or strongly predispose to Parkinson's disease.

Several different PD biomarkers were identified in the literature, which can be categorised in **biochemical and genetic markers** [26].

biochemical and genetic biomarkers

1. **Biochemical** markers can be investigated either in the cerebrospinal fluid (CSF), in blood (plasma or serum), in other biofluids (saliva, tears) or in tissues like skin, olfactory mucosa, submandibular glands, and the colon [21, 27].
2. **Genetic** biomarkers: single genes leading to the heritable forms of PD have yet to be identified. Analysis for mutations in SNCA/ α -synuclein, PARK2/parkin, PINK1, PARK7/DJ1, LRRK2/dardarin and GBA are under research [14, 22, 27, 28].

Table 1, titled “Overview of Biomarkers in Parkinson’s Disease” presents the two main categories and types of biomarkers. However, this list may not be exhaustive. The identified biomarker types and their respective quantities are as follows:

identified PD biomarker types:
CSF,
blood-based,
other biofluids,
biopsy-based,
genetic,
imaging and
other

- CSF biomarkers (n=5)
- Blood-based biomarkers (n=3)
- Biomarkers from other biofluids (n=1)
- Biopsy-based (peripheral tissue samples) biomarkers (n=1)
- Genetic biomarkers (n= 5)
- “Other” category (n=2).

For related further information on each biomarker and individual products, see Table 1**.**

3.2 Sensitivity and specificity of biomarker for Parkinson´s disease

information on sensitivity and specificity (if available) of different biomarkers are to be considered with caution

Table 1 presents the information about diagnostic accuracy of the identified biomarker categories. Where information was available, values for **sensitivity and specificity** were indicated, or at least the link to the source(s) were stated. Also, further diagnostic **performance parameters** (apart from **sensitivity and specificity, e.g. positive predicted value, negative predicted value** etc.) were reported. For some biomarkers, the provided values differed to some minor extent according to the source. Respective diagnostic accuracy studies were neither reviewed nor critically appraised. Results should be considered with caution.

no systematic review on diagnostic accuracy of biomarkers

We could not identify any systematic review on the diagnostic performance of **biomarkers** including a reference standard (standard diagnostic procedures) differentiating patients with PD from patients with other dementia subtypes or from healthy controls.

Information on regulatory status of specific products

regulatory status

Where information on the **regulatory status** of the biomarkers could be identified, respective notes were made in Table 1. However, this information could not be gathered for all individual products.

3.3 Companion biomarker for drug selection

biomarker qualification for clinical trials

Biomarkers in clinical trials are usually chosen through confidential discussions between regulators and sponsors, or through a public, formal biomarker qualification process to expedite tool adoption. This qualification offers a standardised method for biomarker use in drug development, providing clarity and consistency. Once a biomarker is qualified for a specific use, it typically doesn't need further review for sponsor use in drug development [29].

biomarker to guide the differential diagnosis and treatment

The use of biomarkers in trials serves multiple purposes. One aim is to aid the differential diagnosis between essential tremor (or drug-induced parkinsonism; not a licensed indication but useful in clinical practice) and neurodegenerative parkinsonian disorders (like progressive supranuclear palsy, multiple system atrophy (MSA), corticobasal degeneration (CBD), or vascular parkinsonism). Biomarkers also act as surrogates for tracking disease progression (DAT scan not used for this purpose) and help identify patient subtypes with similar clinical phenotypes but differing etiopathogenesis. For instance, genotyping can reveal multiple independent genotypes linked to PD development [30].

limitations of using DAT imaging for stratification of patients

Imaging (such as DAT) has several limitations: Firstly, it cannot distinguish between various forms of degenerative parkinsonism Secondly, it's not suitable for measuring target engagement in PD trials, as decreased DAT levels don't directly correlate with synuclein pathology [29]. Given the challenges in accurately identifying PD pathology, especially in early stages, new biomarkers are crucial for selecting appropriate trial participants. Advances in imaging and novel biomarker discovery are vital. Continued refinement of this tool is necessary, particularly for future trials in the prodromal and premotor stages of PD. Utilising longitudinal data from past and ongoing studies, like the **Parkinson's Progression Markers Initiative (PPMI)** and PRECEPT, will likely enhance future trial success. This approach is in line with strategies for precision medicine in PD, emphasising the importance on biomarker-driven phenotypes [29]. To foster collaboration across centres the **Global Parkinson´s Genetics Program (GP2)** was established to develop and test therapies for genetic variations [31].

new biomarkers are crucial for the selection of trial participants in the future

CSF, tissue samples, genetic testing, SPECT imaging, and functional MRI as biomarker outcomes in novel drug studies

Some of the disease-modifying therapy drugs in the research pipeline are already utilising biomarkers in their clinical trials. For instance, risvodetinib (IkT-148009) [19], exenatide [20], buntanetap [21], prasinezumab (PRX002) [60] and memantine [32] studies included CSF, tissue samples, genetic testing, SPECT imaging and functional MRI as biomarker outcomes (see details in Table 1).

clinical guidelines

Only a limited number of **clinical guidelines** with respect to PD and its diagnosis were identified - see Table 2**.** Clinical guidelines in the field of Parkinson´s Disease and related diagnostics". So far, none of the identified clinical guidelines recommend (or even mention) genetic testing, but mostly clinical investigation and imaging (and olfactory testing). However, EMA recommends assessing outcomes and biomarkers for validation of associations [33].

Table 1: Overview of biomarkers in Parkinson´s Disease

Type of biomarker	Name of biomarker	Trademark name of test/assay/device	Further information on test/assay/device	Regulatory approval status of test/assay/device	Sensitivity/Specificity of the biomarker	Biomarker relevant for medication (if applicable)	Austria-relevant information based on expert input	References
Biochemical markers								
CSF	Alpha-synuclein (α Syn)	SYNTap (Amprion)	Qualitative laboratory developed test (LDT) in the U.S., aSyn-seeding amplification assay (aSyn-SAA)	FDA breakthrough device designation, no CE mark [34].	Sensitivity range from 78.7% to 87.3%, specificity from 89.5% to 97.2%, positive predictive value (PPV) is 88.9%, negative predictive value (NPV) is 79.7% [35].	Risvodetinib (IkT-148009) [36], Exenatide [37], Buntanetap [38]	Research only	Coughlin [27]
CSF	total-aSyn (t-aSyn), oligomeric aSyn (o-aSyn), phosphorylated aSyn (p-aSyn)	LEGEND MAX™ Human α-Synuclein ELISA Kit (Biolegend) Mesoscale (Mesoscale Discovery) MagQu α-Synuclein and Phosphorylated-α -Synuclein S129 tests (MagQu) Simoa Alpha-Synuclein Discovery Kit (Quanterix)	Enzyme-linked immunosorbent assay (ELISA) Electrochemiluminescence (ECL) Immunomagnetic reduction (IMR) assay LTD, single molecule array (SiMoA)	Research-only [39]. Research-only [40] Research-only [41] Research-only [42].	In a study, assays measuring t-aSyn had 61–94% sensitivity and 25–64% specificity for distinguishing PD from controls [43]. In a meta-analysis, the pooled sensitivity and specificity of t-aSyn were 85% (95% CI 0.77–0.90) and 74% (95% CI 0.67–0.80), with an area under the receiver operating characteristic curve (AUC) of 0.85 (95% CI 0.82–0.88) [44].	Risvodetinib (IkT-148009) [36], Exenatide [37], Buntanetap [38]	Research only	Coughlin, Parnetti [27, 45]

Type of biomarker	Name of biomarker	Trademark name of test/assay/device	Further information on test/assay/device	Regulatory approval status of test/assay/device	Sensitivity/Specificity of the biomarker	Biomarker relevant for medication (if applicable)	Austria-relevant information based on expert input	References
CSF	Alzheimer-like markers: amyloid-beta (Aβ)42, Aβ40, total-tau (t-tau), phosphorylated-tau (p-tau)	Lumipulse (Fujirebio): G β-Amyloid 1-42, G β-Amyloid 1-40, G Total Tau and G pTau181 Inno-bia AlzBio3 (Innogenetics) MagQu Amyloid β1-40, Amyloid β1-42, Tau, and Phosphorylated Tau tests (MagQu)	Enzym-linked immunosorbent assay (ELISA) xMAP bead-based assay IMR assay	FDA approval, CE marked [46-49]. Research-only [50] No FDA approval, CE-marked [51-53].	"Conflicting results of CSF Aβ42 diagnostic accuracy in PD patients compared to controls (AUC 0.64). The diagnostic accuracy is higher (AUC 0.81) in differentiating dementia in PD patients (PDD) compared to AD patients. Diagnsotic accuracy is low for differentiating PD and PDD from dementia with Lewy bodies (AUC 0.64). Studies on CSF t-tau and p-tau have not identified a distinct PD profile" [45].	Buntanetap [38]	Research only	Coughlin, Parnetti [27, 45]
CSF	Neuroimflammation markers: YkL-40, MCP-1, CRP, IL6	-	-	-	"YkL-40 and MCP-1 are increased in atypical parkinsonian patients compared to PD thus can discriminate tauopathies from synucleinopathies, though this is best achieved by combining them with non-inflammatory CSF markers (AUC 0.95)" [54].	Buntanetap [38]	Research only	Vijiaratnam [54], Yamashita [55]

Type of biomarker	Name of biomarker	Trademark name of test/assay/device	Further information on test/assay/device	Regulatory approval status of test/assay/device	Sensitivity/Specificity of the biomarker	Biomarker relevant for medication (if applicable)	Austria-relevant information based on expert input	References
CSF	Neurofilament light chain (NFL)	Lumipulse G NfL CSF (Fujirebio) NF-light ELISA (TECAN/IBL International)	ELISA ELISA	Research-only [56] CE-marked [57]	A meta-analyis showed a pooled sensitivity of 98% (95% CI 0.89–1.00) and specificity of 84% (95% CI 0.74–0.91), with AUC 0.94 (95% CI 0.92–0.96) to discriminate PD from MSA [44].	Buntanetap [38]	Research only	Coughlin [27], Tönges [30]
Blood/plasma	aSyn: t-aSyn, o-aSyn, p-aSyn	Simoa Alpha-Synuclein Discovery Kit (Quanterix) Alpha synuclein tests (Invitrogen) Meso Scale Discovery (MSD) Luminex xMAP (Luminex) MagQu α-Synuclein and Phosphorylated-α -Synuclein S129 tests (MagQu) LEGEND MAX™ Human α-Synuclein ELISA Kit (Biolegend)	SiMoA ELISA ECL xMAP bead-based assay IMR ELISA	Research-only [42] Research-only [58] Research-only [40] Research-only [59] Research-only [41] Research-only [39]	Several conflicting results for the measurement of t-aSyn in plasma using ELISA, ECL, mass spectrometry and immunoassays [27, 45]. In a single study, the combination of red blood cell (RBC) o-aSyn with RBC t-aSyn, RBC heteroaggregates of α-synuclein with Aβ42, and RBC t-tau and p-tau has been reported to have an excellent diagnostic accuracy (AUC 0·98) in distinguishing patients with PD from controls. Similar to o-aSyn, plasma p-aSyn is higher in patients with PD compared with controls (AUC 0·71) [45]	-	Now: Research only Near future; rapidly developing seeding techniques such as RT-QuIC and PMCA	Coughlin, Parnetti, Zubelzu, Okuzumi [27, 45, 60, 61]

Type of biomarker	Name of biomarker	Trademark name of test/assay/device	Further information on test/assay/device	Regulatory approval status of test/assay/device	Sensitivity/Specificity of the biomarker	Biomarker relevant for medication (if applicable)	Austria-relevant information based on expert input	References
Blood/plasma	Aβ42, Aß40, t-tau, p-tau	Amyloid Beta 42 Assay (Aβ42), Aβ40 Assay, pTau181 Assay (Quanterix) Lumipulse G β-Amyloid 1-40 Plasma, G β-Amyloid 1-42 Plasma, G pTau 181 Plasma (Fujirebio)	SiMoA ELISA	Research-only [62, 63]. Research-only [64-66]	Only a few studies have assessed Aβ42 in PD blood, reporting inconsistent findings regarding blood level or correlation with cognitive functions. Evidence on tau protein level in PD blood is even more limited [30].	-	Research only	Coughlin, Parnetti [27, 45], Tönges [30]
Blood/plasma	NfL	Lumipulse G NfL Blood	ELISA	Research-only [67].	In a recent review, the authors cite a study reporting that plasma NfL assays could distinguish between PD patients and patients with MSA and PSP each, along with PSS, with a sensitivity and specificity of about 90 %, which was comparable to results derived from CSF NfL [55].	-	Research only	Tönges [30], Yamashita [55], Vijiaratnam [54]
Other biofluids (e.g. tears, saliva)	t-aSyn, o-aSyn	-	To differentiate PD from healthy controls.	-	-	-	Research only	Coughlin, Parnetti [27, 45]
Biopsy-based (peripheral tissue samples)	p-aSyn	Syn-One Test (CND Life Sciences)	LDT in the U.S., aSyn-SAA.	LDT, no FDA approval, no CE mark [68].	In patients with diagnosed synucleinopathy, the sensitivity was 95.5% and specificity was 96.7%. The specific sensitivity rate was 92.7% for PD [69].	Risvodetinib (IkT-148009) [36]	Research only Skin biopsies: role in clinical practice is still unclear, even if less invasive	Coughlin, Parnetti [27, 45]
Genetic biomarkers								
Genetic testing	SNCA	-	Identifies point mutations and gene multiplications in multiple affected families in >1 generation.	-	-	Exenatide [37]	Rapid changes are expected:	Gasser, Pal [28, 70]

Type of biomarker	Name of biomarker	Trademark name of test/assay/device	Further information on test/assay/device	Regulatory approval status of test/assay/device	Sensitivity/Specificity of the biomarker	Biomarker relevant for medication (if applicable)	Austria-relevant information based on expert input	References
Genetic testing	LRRK2	-	For known pathogenic variants in patients with a clinical picture of typical PD and a positive family history or for known LRRK2 founder mutations in high mutation frequency populations.	-	-	-	young patients and patients with a positive family history should already be offered genetic clarification if they are interested, with a view to study participation and possibly positive results from ongoing studies.	Gasser, Pal [28, 70]
Genetic testing	GBA1	-	For patients with typical PD limited to the known founder mutations of established pathogenic role in high mutation frequency populations.	-	-	-		Gasser, Pal [28, 70]
Genetic testing	PRKN, PINK1, DJ-1	-	For patients with typical PD, particularly when the disease onset is <50 years or when onset is very early and if consanguinity is present in the family.	-	-	-		Gasser, Pal [28, 70]
Genetic testing	ATP13A2, PLA2G6, FBXO7, DNAJC6, SYNJ1, VPS13C, PTRHD1	-	Test when onset is very early (<40 years) if no mutation in PRKN, PINK1, and DJ-1 genes is found.	-	-	-		Gasser, Pal [28, 70]

Abbreviations: AD: Alzheimer's disease, Aß: amyloid beta, aSyn-SAA alpha-synuclein seeding amplification assay, AUC: area under the curve, CSF – cerebrospinal fluid, DAT: dopamine transporter, DLB: dementia with Lewy bodies, EMA: European Medicines Agency, EPAR: European Public Assessment Report, FDA: Food and Drug Administration, IF immunofluorescence, MSA: multiple system atrophy, NPV: negative predictive value, PD: Parkinson's disease, PDD: Parkinson's disease dementia, PPV: positive predictive value, PS: parkinsonian syndromes, PSP: progressive supranuclear palsy, p-tau: phosphorylated tau, t-tau: total tau, t- α-Syn: total alpha-synuclein, o- α-Syn oligomeric alpha-synuclein, p- α-Syn phosphorylated alpha-synuclein,

Table 2: Clinical guidelines in the field of Parkinson´s Disease and related diagnostics

Author/ Year	National Institute for Health and Care Excellence (NICE) (2017) [71]	Deutsche Gesellschaft für Neurologie e.V. (DGN) (2023) [72]	European Medicines Agency (EMA)/ Committee for Medicinal Products for Human Use (CHMP) (2012)[73]	Grimes et al. (2019) [74] + Scottish Intercollegiate Guidelines Network (SIGN) (2010) [75]
Title	Parkinson's disease in adults	Parkinson's Disease (original title: S2-Leitlinie Parkinson-Krankheit) (published at AWMF online).	Guideline on clinical investigation of medicinal products in the treatment of Parkinson's disease	Canadian guideline for Parkinson disease + Diagnosis and pharmacological management of Parkinson's disease (SIGN)
Language	English	German	English	English
Statements/recommendations regarding biomarker(s)	**PET imaging** and **SPECT** can be intuitively good biomarker for the disease. They may improve diagnostic accuracy at the start of trials and may be more sensitive than clinical outcomes and have a role in clinical practice. **Recommendations:** Do not use **PET** in the differential diagnosis of parkinsonian syndromes, except in the context of clinical trials. Consider **123I-FP-CIT SPECT** for people with tremor if essential tremor or non-neurodegenerative parkinsonism (such as drug-induced) cannot be clinically differentiated from parkinsonism. 123I-FP-CIT SPECT should be available to specialists with expertise in its use and interpretation. Do not use **structural MRI** to diagnose Parkinson's disease. Structural MRI may be considered in the differential diagnosis of other parkinsonian syndromes. Do not use **magnetic resonance volumetry** in the differential diagnosis of parkinsonian syndromes, except in the context of clinical trials.	**Olfactory testing**, for example with the Sniffin' Sticks test, increases the positive predictive value to ≥80% and the diagnostic certainty of PD after ruling out common alternative causes for hyposmia at the time of diagnosis. Therefore, it is recommended as complementary diagnostic due to its low invasiveness. However, the presence of normosmia does not rule out PD. **CT scans** should not be used for the differential diagnosis of parkinsonian syndromes. CT scans should only be used for the exclusion of symptomatic causes if an individual in case an MRI is contraindicated. **Cranial MRI (cMRI)** should be performed early in the course of the disease for differential diagnosis in clinical parkinsonian syndrome. **Transcranial brain parenchyma sonography (TCS)** performed by a qualified examiner can be considered to support the differential diagnosis of PD versus atypical and secondary parkinsonian syndromes. The predictive value of TCS alone in an individual is limited. A **FDG PET scan** may be considered when there are sufficient clinical indications of an atypical parkinsonian syndrome, and the findings have clinical consequences (e.g., regarding diagnosis, prognosis, therapy). Postsynaptic SPECT of the Striatum (IBZM-SPECT) should not be used in the differential diagnosis. **Cardiac MIBG** scintigraphy or SPECT may be considered for distinguishing Parkinson's disease from multiple system atrophy (MSA), especially when FDG PET is not available.	Biomarkers measuring the cerebral dopamine uptake (**123I-FP-CIT SPECT**) or dopamine-receptor density (**PET-F-dopa**) cannot be considered sufficient surrogate biomarkers. Although these are biomarkers for nigrostriatal function, it is not established that they correlate to a meaningful, measurable and persistent changes in clinical function. Simultaneous assessment of **clinical outcome and biomarkers** is recommended in order to evaluate whether both are causally associated and to assess the potential predictive value of a biomarker for clinical outcome. Of note, current imaging techniques are not predictive for non-dopaminergic related symptoms. **Genetic assessments** are not mentioned.	Routine use of **functional imaging** is not recommended for the differential diagnosis of PD and Parkinson plus disorders such as progressive supranuclear palsy and multiple system atrophy (grade: C; source: SIGN). **PET** scanning is not recommended as part of the diagnostic work-up of parkinsonian syndromes, except within a research framework (grade: good practice point; source: SIGN). **123I-FP-CIT SPECT** scanning should be considered as an aid to clinical diagnosis in patients where there is uncertainty between PD and nondegenerative parkinsonism or tremor disorders (grade: B; source: SIGN). **CT** or **MRI** brain scanning should not be routinely applied in the diagnosis of idiopathic PD (grade: C; source: SIGN), **but to exclude other causes.** Imaging modalities have been extensively researched over the years for a more accurate diagnosis of PD, in the differential diagnosis of parkinsonian disorders, as well as in the consideration of a possible progression marker for typical PD. However, to date, no single test has been shown to have sufficient sensitivity and specificity to accomplish all 3 objectives. **Genetic testing** for monogenic parkinsonism is not yet recommended in routine clinical practice (grade: good practice point; source: SIGN).

	Do not use **magnetic resonance spectroscopy** in the differential diagnosis of parkinsonian syndromes. Do not use **acute levodopa and apomorphine challenge tests** in the differential diagnosis of parkinsonian syndromes. Do not use **objective smell testing** in the differential diagnosis of parkinsonian syndromes, except in the context of clinical trials. **Genetic assessments** are not mentioned.	**Neurofilament Light Chain (NFL)**, whether obtained from cerebrospinal fluid or blood, is not suitable as a diagnostic biomarker for PD due to its lack of specificity. However, it can be helpful in distinguishing PD from atypical parkinsonian syndromes. Genetic assessments in the **GBA1 gene** should not yet be conducted routinely. Various biomarkers are currently in development aiming to enable early, reliable, and precise diagnosis of parkinsonian syndromes in living patients. Particularly, **PET tracers** for imaging alpha-synuclein (aSyn) aggregates in the human brain and **seeding assays** (such as the RT-QuIC assay), which can detect pathological aSyn aggregates in biological fluids like blood or cerebrospinal fluid—potentially specific to certain disease entities (e.g., Lewy body disease vs. multisystem atrophy)—are attractive and promising methods. Before such biomarkers can become a diagnostic standard in routine diagnostics for parkinsonian syndromes, further research and studies are still necessary.		
Level of recommendation	-	All with high consensus (over 90%).	-	Good practice point: best practice based on the clinical experience of the guideline development group. Grade B: the body of evidence includes high quality systematic reviews (SR) or high quality case control or cohort studies, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from high quality meta-analyses, SR of RCTs, or RCTs with a very low or low risk of bias. Grade C: the body of evidence incluides well conducted case control or cohort studies with a low risk of bias and a moderate probability that the relationship is causal, directly applicable to the target population and demonstrating overall consistency of results.

3.4 Standardisation initiatives in Europe

standardisation and validation of biomarkers/ diagnostic tests is necessary

There are **several initiatives** focusing on standardisation and validation of biomarkers/diagnostic tests:

several initiatives are ongoing:

Image Biomarker Standardization Initiative

The **Image Biomarker Standardization Initiative** focuses on standardizing quantitative radiomics for high-throughput image-based phenotyping. The field of radiomics deals with extraction of large numbers of features from medical images that quantify its phenotypic characteristics in an automated, high-throughput manner. This initiative aims to establish a common language and definitions for radiomics features, develop a general image processing scheme, provide datasets with reference values for software verification and calibration, and offer reporting guidelines for radiomic analyses. This has led to the production of validated reference values for radiomics features to enhance software verification and study reproducibility [76].

Innovative Medicines Initiative (IMI) project

There is an ongoing **Innovative Medicines Initiative (IMI) project called European Platform for Neurodegenerative Diseases (EPND)** that aims to accelerate biomarker discovery for neurodegenerative diseases by creating a collaborative platform between existing European research infrastructures [77]. The EPND catalogue offers an extensive list of international cohorts with neurodegenerative diseases/biomarker studies [78].

recommendations for validation of biomarker as IVD/ companion diagnostics from

MedTech Europe,

EMA and

FDA

MedTech Europe proposed a fit-for-purpose approach for validating predictive biomarker assays used in early clinical trials. This approach accommodates the variability in assay use and development stages, often leading to the co-development of assays with drugs [79].

The EMA reviewed approved medicinal products and found varying levels of detail in biomarker and diagnostic test documentation in the European Public Assessment Report (EPAR) and the Summary of Product Characteristics (SmPCs). The new Regulation (EU) 2017/746 on in vitro diagnostic medical devices requires manufacturers to consult with regulatory authorities, offering an opportunity for more consistent and transparent documentation [80].

Shared Data and Specimen Biorepositories: Recent efforts have focused on standardizing protocols for sample acquisition, storage, analysis, and distribution in biorepositories. Harmonization efforts, such as the Biospecimen Review Access Committee, streamline biomarker discovery. The European Union's BIOMARKAPD consortium has developed standard operating procedures for sample collection and analysis in neurodegenerative diseases, with a focus on Alzheimer's and Parkinson's diseases [81].

Assay Standardization and Reference Samples: Standardizing assays and developing reference samples, like those created by the Parkinson's Disease Biomarkers Program (PDBP), are crucial for cross-laboratory comparisons and assay normalization. Reference standards are particularly important for biomarkers beyond the discovery phase [81].

Looking outside of Europe, in the U.S, the **FDA Biomarker Qualification Program** helps integrate biomarkers into drug development processes by guiding scientists on best practices for biomarker discovery and application in clinical trials [81].

4 Discussion and Conclusion

many different biomarkers are available but with limited application in clinical guidelines and practice

Despite significant research efforts, the clinical application of PD biomarkers remains limited, as many studies focus more on discovery rather than on the subsequent evaluation of these biomarkers [4]. The pressing need in the field is for biomarkers that are reliable, cost-effective, sensitive, reproducible, non-invasive, and thoroughly validated. These biomarkers should ideally integrate clinical assessments, laboratory findings, imaging data, and genetic information to enhance future PD diagnosis. However, due to PD's heterogeneous nature, no single biomarker can definitively describe the disease, predict its course, or distinctly classify its subtypes [2].

most recent guideline (S2k-Leitlinie) from 2023 highlights PET imaging and α-Syn seeding amplification assays as potential PD biomarkers in clinical practice

Amidst these challenges in PD biomarker research, recent developments in clinical guidelines offer a glimpse into the evolving landscape of PD diagnosis. The **German Society for Neurology's** latest clinical guideline on PD, titled "Parkinson's Disease" ("S2k-Leitlinie Parkinson-Krankheit"), reflects this progression. The guideline highlights that various biomarkers are currently in development aiming to enable early, reliable, and precise diagnosis of parkinsonian syndromes in living patients. Particularly, **PET tracers** for imaging α-Syn aggregates in the brain and **seeding assays**, which can detect pathological α -Syn aggregates in biological fluids like blood or CSF, are promising methods. Before such biomarkers can become a diagnostic standard in routine diagnostics for parkinsonian syndromes, further research and studies are still necessary [72]. To address the complexity of the disease, the studies should aim for multidimensional analyses involving large patient cohorts, using blood-based biomarkers, cerebrospinal fluid, and tissue samples.

only a few CSF and imaging biomarkers have CE mark/EMA approval

available evidence about diagnostic accuracy is scarce

key is harmonisation of the procedure and availability of certified reference materials and methods

At present, only a few CSF and imaging biomarkers have received CE mark or EMA approval and are commercially available in Europe. In contrast, the U.S. has seen two recent advancements: an alpha-synuclein (α-Syn)-seeding amplification assay has been designated as an FDA breakthrough device, and a tissue-based α -Syn test, which is not subject to FDA approval, received Clinical Laboratory Improvement Amendments (CLIA) approval in 2023. However, blood-based biomarkers have not yet received similar approvals in either Europe or the U.S. The diagnostic accuracy of most biomarkers is not well-established yet, highlighting the need for more research in this field. Harmonisation of procedures, certified reference materials, and methods are key for biomarker implementation, and ongoing efforts are aimed at standardisation and validation [82].

However, the developments towards a three-component classification of PD will have impact not only on the understanding of the disease, but also have implications on the definition of the disease.

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