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Review

Advances in biomarkers for Parkinson's disease: from molecular pathology to precision diagnostics

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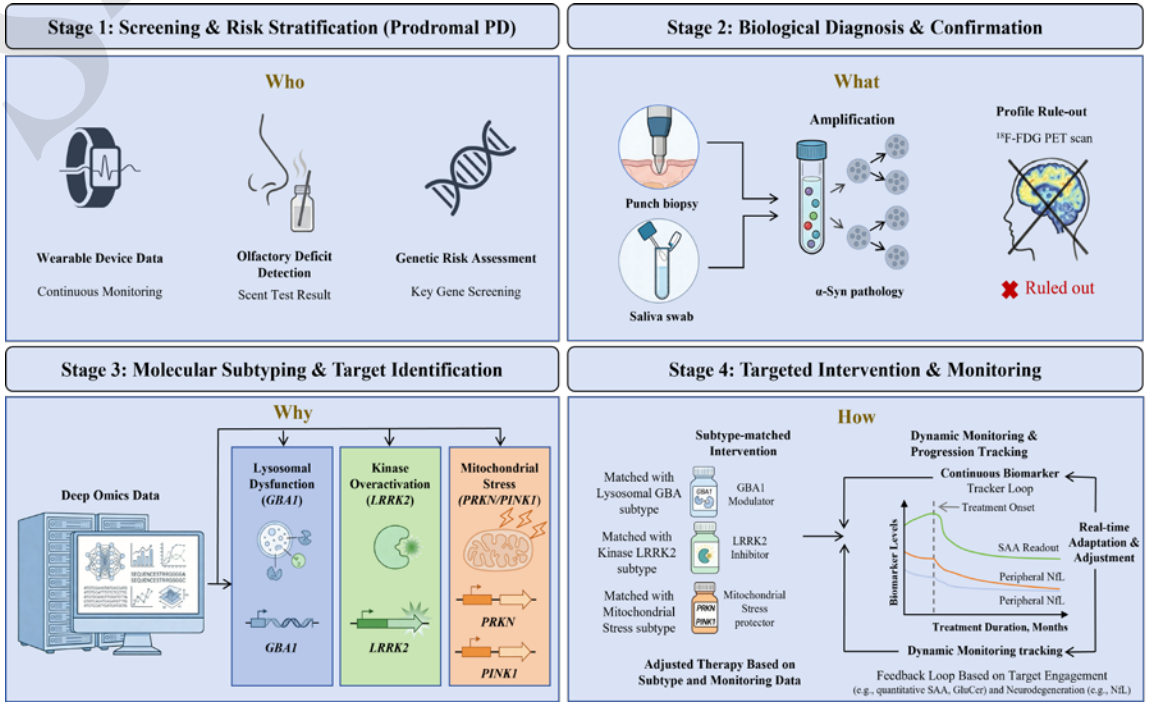
Background:

· **Parkinson's disease** (PD) is the second most common neurodegenerative disorder worldwide, facing significant challenges in early diagnosis and precise subtyping.

· Traditional diagnosis relies on motor symptoms, often missing the window for early intervention.

· Paradigm shift: from static concentration measurements to functional activity detection, ushering in a new era of precision diagnostics.



Proposed Clinical Workflow for Precision Medicine in PD.

1. α-Syn-SAA: A Disruptive Core Pathological Detection Technology

· **Principle:**

Using pathological α-synuclein as a "seed" to amplify in vitro and perform real-time fluorescence detection (RT-QuIC / PMCA).

· **Performance:**

Sensitivity >90% and specificity >96% for clinical PD diagnosis

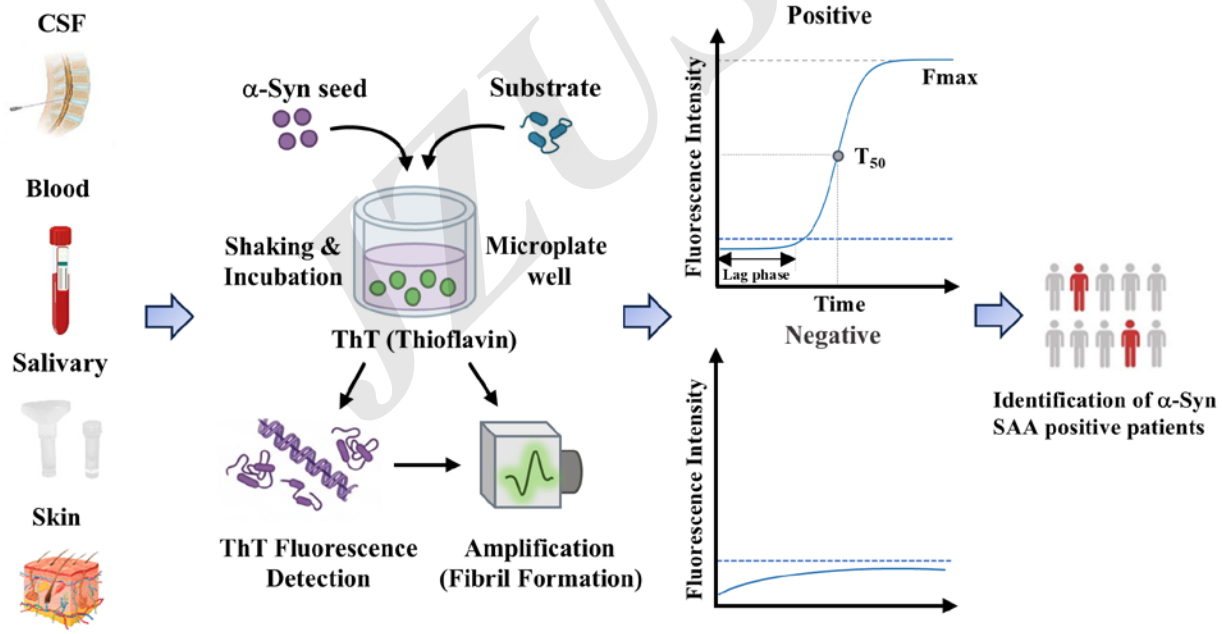
Detects pathological changes 10–20 years before the onset of motor symptoms

· **Diverse sample types:**

Cerebrospinal fluid (CSF), skin, saliva, and oral mucosa can all be tested, enabling minimally invasive or non-invasive detection.

· **Risk stratification:**

Based on kinetic parameters (T_{50}, TTT) to distinguish "fast amplifiers" from "slow amplifiers" and predict the risk of disease conversion.



Schematic illustration of the α-synuclein seed amplification assay (α-Syn-SAA) workflow.

2. Multi-omics Integration and AI: From Heterogeneity to Individualized Subtypes

•Multi-omics dimensions:

·Metabolomics: Abnormalities in the xanthine metabolism pathway (HPRT1-related)

· Proteomics: Novel CSF biomarkers such as Midkine and osteomodulin

· Epigenomics: Blood 5hmC signature enables early diagnosis (AUC 0.923)

•AI-enhanced diagnosis:

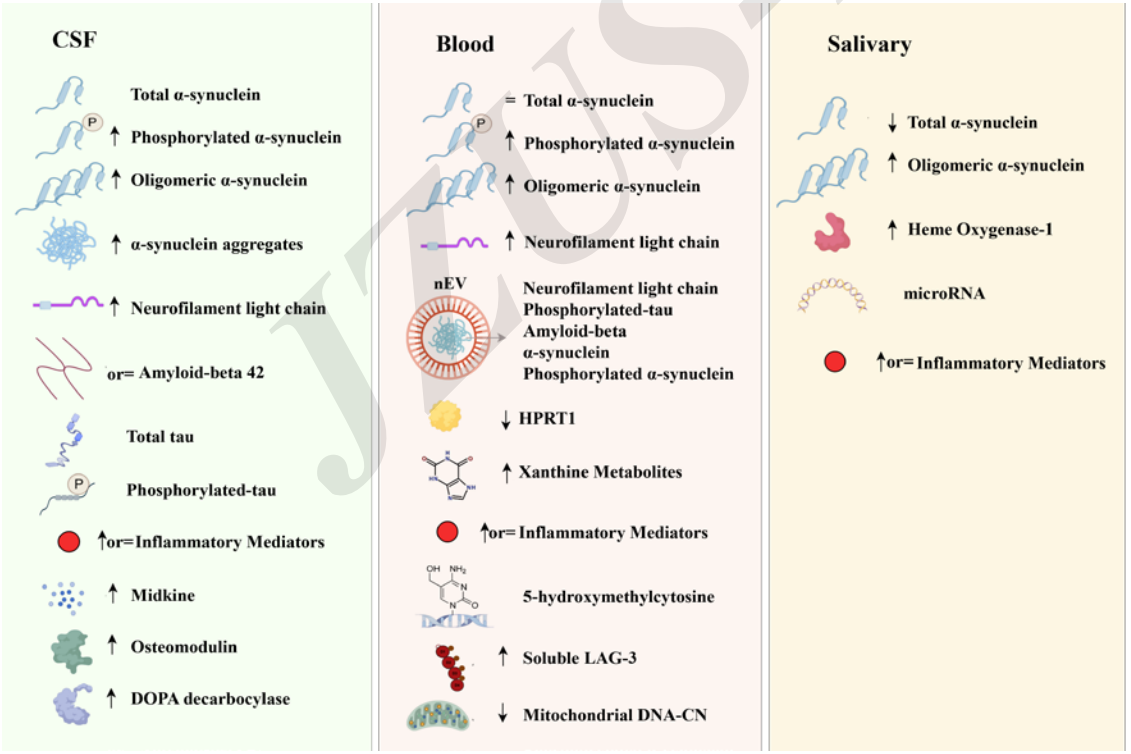
· Machine learning models (e.g., CRANK-MS) directly analyze full metabolomics data, AUC >0.995

· Integration of proteomics and metabolomics predicts cognitive impairment (AUC 0.981)

•Clinical value:

· Enables molecular subtyping (e.g., GBA1-driven, LRRK2-driven, PRKN-driven)

· Guides targeted therapy enrollment and pharmacodynamic monitoring



Biomarker profiles in cerebrospinal fluid, blood, and saliva in PD.

3. From Laboratory to Clinic – The Implementation Pathway for Precision Medicine: A Biomarker-Driven Clinical Workflow for PD

Four-stage implementation pathway:

- **Screening and stratification (community/primary care):** Digital biomarkers + olfactory testing + genetic risk
- **Biological confirmation (specialty care):** Peripheral α-Syn-SAA + blood NfL + ^{18}F-FDG PET
- **Molecular subtyping (deep phenotyping):** Whole-genome sequencing + multi-omics → identify the driving pathway
- **Targeted therapy and dynamic monitoring:**

  Target engagement markers (e.g., p-RAB12, GluCer)

  Longitudinal quantitative α-Syn-SAA + digital motor monitoring + neurofilament light chain

Biomarker Category	Core Technology / Target	Key Biomarkers	Clinical Value	Research Value	Info Value
α-Syn Pathology	SAA (RT-QuIC, PMCA), immuno-assays	α-Syn-SAA, p-α-Syn, o-α-Syn, T-α-Syn	+++	+++	+++
Genetic (*SNCA*)	DNA sequencing, genotyping, meth-ylation analysis	*SNCA* point mutations, multiplication, methylation levels (blood)	++	+++	+++
Genetic (GBA1)	DNA sequencing, genotyping	GBA1 mutations (e.g., N370S, L444P)	+++	+++	+++
Genetic (*LRRK2*)	DNA sequencing, genotyping	*LRRK2* mutations (e.g., G2019S)	++	+++	+++
Genetic (*PRKN/PINK1*)	DNA sequencing, genotyping	*PRKN, PINK1* mutations	++	+++	+++
Structural MRI (Nigrosome-1)	High-resolution SWI / QSM	Nigrosome-1 ("swallow tail" sign)	+++	++	++
Structural MRI (Neuromelanin)	Neuromelanin-sensitive MRI	NM-MRI signal, SN/LC volume	++	++	++
Molecular Imaging (Dopamine)	DAT-SPECT / PET	DAT-SPECT / PET binding ratio	+++	++	++
Molecular Imaging (Metabolism)	^{18}F-FDG PET	PD-related spatial covariance pattern (PDRP), APS-specific patterns	+++	+++	++
Fluid (CSF)	Immunoassays, mass spectrometry, SAA	α-Syn species, NfL, Aβ42, p-tau, DDC, sTREM2	+++	+++	+++
Fluid (Blood)	Immunoassays, exosome isolation, metabolomics	NfL, T-α-Syn, nEV-derived α-Syn/p-tau/Aβ, GluCer isoforms, metabolites	++	+++	++
Fluid (Peripheral)	Saliva/urine assays, skin biopsy	Salivary α-Syn-SAA, skin p-α-Syn, HO-1, mi-croRNAs; urinary aggregates	++	++	++
Multi-omics + AI	Metabolomics, proteomics, epige-nomics, machine learning	Metabolite panels, protein signatures, DNA meth-ylation/hydroxymethylation	+	+++	+++
Digital + Clinical	Wearables, olfactory tests, sleep studies	Gait/activity metrics, UPSIT, iRBD status	+++	++	++

Comparison of Research Methods for PD Biomarkers: Clinical, Scientific and Informational Value with Core Application Scenarios

4. Summary and Future Perspectives — PD Biomarkers Enter a New Era of Functional Detection and Precision Medicine

- **Three core driving forces:**
  - α-Syn-SAA enables direct detection of pathological activity
  - Multi-omics + AI reveal disease heterogeneity and novel pathways
  - Peripheral samples (blood, saliva, skin) promote minimally invasive / non-invasive testing
- **Key translational directions:**
  - Unify testing standards (global SOPs, commercial quality control materials)
  - Large-scale prospective multicenter validation
  - Integrate digital biomarkers to achieve continuous remote monitoring
- **Ultimate goal:**
  - Early warning → precise subtyping → targeted intervention → dynamic efficacy assessment, truly realizing individualized, whole-course management of PD.