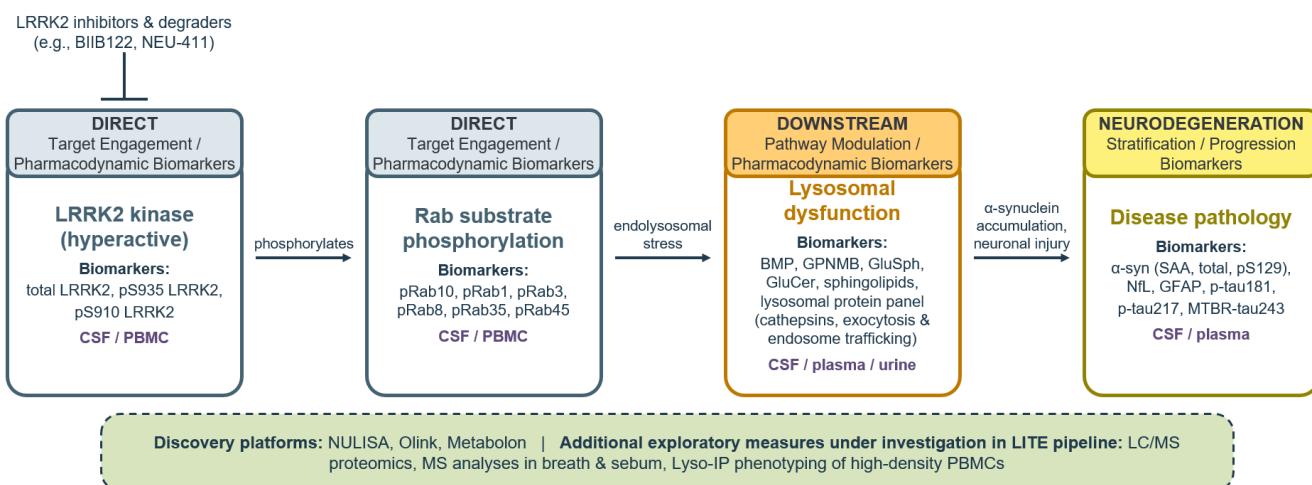


Biomarker Recommendations for LRRK2 Therapeutic Trials in Parkinson's Disease

This document provides biomarker guidance for sponsors and investigators designing clinical trials targeting LRRK2 (both direct kinase inhibitors and LRRK2-lowering modalities) in Parkinson's Disease (PD). Although not necessarily meant to be prescriptive, this document reflects emerging clinical trial data, published literature and recommendations from experts including those from the LITE Consortium. Biomarkers are organized by mechanistic proximity to LRRK2: direct pharmacodynamic or target engagement markers, downstream pathway engagement markers (not specific to LRRK2 pathway activation but often used as target engagement / pharmacodynamic markers), neurodegeneration / disease pathology biomarkers and discovery / exploratory biomarkers for Phase 1 and Phase 2 clinical trials. Predictive markers or those with enrichment potential include presence of a pathogenic LRRK2 genetic variant (i.e. G2019S) or evidence of elevated LRRK2 pathway activity (e.g. elevated urinary BMP or pRab10).

LRRK2 Pathway Biomarkers in Parkinson's Disease Trials



Biomarker Reference Table

Category	Biomarker/Compartment	Platform (Source)	Assay Status / Findings
Direct measures	LRRK2 (total), pRab10 / CSF	IP-mass spectrometry (Biognosys)	Duplex assay in optimization (Biogen protocol)
Direct measures	pRab12 / CSF	Mass spectrometry (Biognosys)	Assay in development
Direct measures	pS935-LRRK2, LRRK2 (total) / PBMC, CSF	Proprietary	MJFF conducting diligence
Direct measures	LRRK2 (total), pS935-LRRK2, pS910-LRRK2, Rab (total), pRab1, pRab3, pRab8, pRab10, pRab12, pRab35, pRab43 / PBMC	Rab PRM mass spectrometry (University of Dundee)	Provides a multiplexed readout of LRRK2 kinase activity and substrate phosphorylation, planning assay transfer to CRO

Direct measures	LRRK2 (total), pS1292-LRRK2, Rab10 (total), Rab12 (total), pRab12 / CSF, plasma, serum	NULISAqpcr (Alamar)	Assays in development
Downstream measures	BMP (multiple species-18:0_16:0, 18:0_18:0, 18:1_16:0, 18:1_16:1, 18:1_18:1, 18:1_18:2, 18:1_20:1, 18:1_20:2, 18:1_20:3, 18:1_20:4, 18:1_22:6, 18:2_16:0, 18:2_18:0, 20:1_22:6, 20:4_16:0, 20:4_18:0, 20:4_20:4, 20:4_22:6, 22:6_22:6) / plasma, urine	Mass spectrometry (Nextcea, Lipotype)	Urinary BMP elevated 3-7x in LRRK2 variant carriers in PPMI ^{1,2,3} ; reduced up to ~90% by NEU-411 in urine for Ph1 ⁴ . Prognostic use did not qualify; use as predictive/ pharmacodynamic marker only ² .
Downstream measures	Lysosomal protein panel (CTSB/D/F/L/S, GM2A, GPNMB, LAMP1/2, LC3, ubiquitin, GCase) / CSF, plasma	Mass spectrometry (Biogen; broader panel including other endolysosomal markers at Inoviv, Biognosys, University of Gothenburg)	GPNMB is lysosomal dysfunction marker secreted via LRRK2-modulated exocytosis. ⁵ Biogen CSF data available in PPMI at LONI ⁶ , identifying a lysosomal PD signature relevant for subtyping & patient stratification. CSF pRab10 reductions with BIIB122 correlated modestly with changes in select lysosomal proteins (e.g. CTSS) ⁷ .
Downstream measures	Targeted lipid panels (GluSph/GalSph, BMP, ceramides, gangliosides, GluCer/GalCer, Cer-1, sphingosines, Lyso-Gb3) / CSF, plasma, urine	Mass spectrometry (Nextcea, Lipotype)	PPMI data generation ongoing (expected Q1 2027). CSF testing in PPMI contingent on plasma/urine assessments.
Neurodegeneration	α -Syn (SAA/total/pS129) / CSF	SAA (Amprion), Total/pS129: Immunoassay (MSD, SIMOA (Quanterix), Elecsys (Roche))	SAA+ LRRK2-PD associated with younger onset ⁸ . SAA recommended for cohort stratification, not as a pharmacodynamic readout. Total & pS129 levels recommended as exploratory readouts (no evidence yet of pharmacodynamic response).
Neurodegeneration	A β 42/40 / CSF, plasma	CSF: Lumipulse (Fujirebio), Plasma: Precivity (C2N, NCRAD)	PPMI data available in LONI ⁶ . Alzheimer's co-pathology marker for cognitive stratification.
Neurodegeneration	p-tau181 / CSF, plasma	CSF (Fujirebio), Plasma (NCRAD)	PPMI data available in LONI ⁶ . Baseline levels are a prognostic marker for future cognitive decline.



Neurodegeneration	p-tau217 / plasma	Precivity (C2N, Lilly)	PPMI data available in LONI ⁶ . Baseline levels are a prognostic marker for future cognitive decline.
Neurodegeneration	MTBR-tau243 / CSF	Precivity (C2N)	PPMI data available in LONI ⁶ . Baseline levels are a prognostic marker for future cognitive decline.
Neurodegeneration	GFAP / plasma	SIMOA (Quanterix, NCRAD)	PPMI data available in LONI ⁶ . Astroglial exploratory marker in LRRK2 trials.
Neurodegeneration	NfL / CSF, plasma	SIMOA (Quanterix, NCRAD)	PPMI data available in LONI ⁶ . Slower NfL rise in LRRK2-PD vs idiopathic PD; higher NfL linked to faster cognitive decline ^{9,10} . Disease progression marker used as exploratory in LRRK2 trials.
Discovery platform	Proteomics / CSF, plasma	NULISA (Alamar), Olink	PPMI data available via LONI, data analysis ongoing ⁶
Discovery platform	Metabolomics / CSF, plasma, urine	Metabolon	PPMI data available Q4 2026 via LONI ⁶

Additional notes

- MDS-UPDRS remains the standard clinical outcome measure; the LUMA primary endpoint was time to confirmed worsening in MDS-UPDRS Parts II–III³. Digital measures are also emerging: the NEULARK Phase 2 trial of NEU-411 uses a Roche smartphone-based digital biomarker as its primary endpoint¹¹. Include MDS-UPDRS Parts I–III in all trials to contextualize biomarker changes.
- Baseline levels of pS935-LRRK2 are lower in manifesting G2019S carriers, indicating this readout may only be used as a pharmacodynamic/target engagement marker, not a disease-state marker¹².
- Urine BMP should be normalized to creatinine, is a stratification/pharmacodynamic marker and does not predict progression².
- CSF pRab10 shows a modest dynamic range centrally (~30–40% reduction at doses achieving >90% peripheral inhibition)^{7,13}; therefore, studies incorporating this marker should be powered accordingly.
- MSD and NULISA (Alamar) are recommended for multiplexing. Biognosys, Nextcea and Lipotype for mass-spectrometry assays; the Dundee (Alessi/Sammler) PRM assay for PBMC Rab phosphorylation. All assays should be performed in a CLIA-certified or equivalent lab with pre-defined QC criteria.
- Assays utilizing PBMCs are especially sensitive to sample processing time and may require fresh samples in some cases; ensure standardized collection protocols and collection-to-freezing intervals across sites.
- Exploratory biomarkers being tested in LITE for potential inclusion in Phase 2 LRRK2 trial design:
 - MS analyses in breath & sebum being tested as part of LITE pipeline- protocol available through LITE upon request
 - Lyso-IP phenotyping of high-density PBMCs being tested as part of LITE pipeline- protocol available through LITE upon request
- Assays in development (no clinical trial data yet; initial validation data expected 2026–2027):
 - Multiple total & phospho-LRRK2 & Rab assays in early development/validation (Alamar, Biognosys, MSD)
 - LRRK2 PET tracer in due diligence/early development



LITE collaboration opportunities

MJFF welcomes collaboration from each participating company's in-house assays to support validation in LITE/MJFF cohorts. The Foundation urges broad data sharing on potential target and pathway engagement as well as disease biomarkers across the LITE Consortium and encourages inclusion of the assays outlined above in Phase 1 and Phase 2 samples.

Phase 2 (preferred collaboration) Comparison of placebo to active arms may provide insights into target and pathway engagement in the desired patient population as well as downstream disease state markers, which could inform decisions on further investment in registration trials.
Phase 1 In healthy controls (HC), data from active arms could facilitate validation of target/pathway engagement endpoints. In individuals with Parkinson's disease (PD), integration of biomarker responses with data from larger cohorts such as PPMI could inform disease-relevant pharmacodynamic endpoints for Phase 2 trials.

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This document was prepared by the Michael J. Fox Foundation for Parkinson's Research. It is intended for use by clinical trial sponsors and investigators to guide, rather than dictate, biomarker selection and reflects the current state of evidence as of August 2026. Recommendations will be updated as new data emerge. For questions, contact the MJFF Biomarker Team at biomarkers@michaelfox.org.

