Parkinson's Precision Medicine Initiative

PPMI Groups and Subgroups Guidance Document for Statistical Analysis

Rationale:

PPMI enrollment cohorts are not considered as uniform as participants are recruited with a range of inclusion criteria. PPMI participants within an enrollment cohort may differ at baseline presentation or in longitudinal progression in some outcome measures due to biological characteristics utilized as group and subgroup enrollment or analytic group assignment criteria. Furthermore, these group and subgroup assignments have changed over the course of the study. Group and subgroup assignments utilize key variables such as genetic characteristics, smell function, and REM sleep behavior disorder. Statistical analysis plans should consider these variables to ensure that heterogeneity in outcomes is not due to enrollment criteria or differences in participant characteristics at baseline captured in group and subgroup assignments. This guidance document is meant to offer clarity on **suggested analysis cohorts and subgroups**. How this guideline applies to each future analysis will depend on the investigators reasoning, the study design, and data availability.

Enrollment groups:

- Parkinson's Disease
- Prodromal
- Healthy Control

Enrollment Subgroups:

Parkinson's Disease

- Sporadic, *GBA*, *LRRK2*, *GBA*/*LRRK2*, *SNCA*, *PRKN*, Other rare genetic
- Definitions:
    - Sporadic: Negative for *GBA*, *LRRK2*, *SNCA*, *PRKN* variants tested
    - *GBA*: Positive for *GBA* variant
    - *LRRK2*: Positive for *LRRK2* variant
    - *GBA/LRRK2*: Positive for a *GBA* and a *LRRK2* variant
    - *SNCA*: Positive for *SNCA* variant
    - *PRKN*: Positive for *PRKN* variant
    - Other rare genetic variant: Positive for a rare variant
    - Other genes tested for all groups:

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Prodromal

- Non-manifest carriers of PD risk genes (GBA, LRRK2, SNCA, PRKN, Other rare genetic variants)
- Hyposmia
- REM Sleep behavior disorder

Healthy Control

Analytic Subgroups

Parkinson's Disease: (definitions same as enrollment)

Prodromal:

- Post-2020: (A1, A2, B, C groups)
    - **Definitions**:
        - **A1:** Enrolled at a clinical site with PSG confirmed RBD **WITH** hyposmia (defined by an UPSIT percentile of <15 at the time of enrollment), with or without low DAT.
        - **A2:** Enrolled at a clinical site with PSG confirmed RBD **WITHOUT** hyposmia (defined by an UPSIT percentile of >15), with or without low DAT.
        - **B:** Hyposmia (defined by an UPSIT percentile of <15) enrolled thought clinical site or through PPMI Remote **WITH** possible RBD (self-reported PSG confirmed RBD or a clinical RBD diagnosis without PSG or who endorse RBD or dream enactment behavior on the self-reported high interest questionnaire), with low DAT.
        - **C:** Hyposmia (defined by an UPSIT percentile of <15) enrolled through clinical site or PPMI Remote **WITHOUT** possible RBD (>=6 on the RBDSQ, no endorsement of RBD/DEB on HIQ, or did not complete HIQ).
- Pre-2020 prodromal pilot do not align with the above definitions and should be considered as different for analysis plans.

Healthy (No subgroups- consider excluding NSD+ in across-enrollment comparisons)
Note: Pre-2020 HC had a MoCA requirement of score >/=27 at baseline, which was removed for post-2020 HC enrollment.

NSD Subgroups: (These are applied to each of the above enrollment subgroups as sub columns):

NSD+ v NSD-

- **Definition**: NSD+ is defined by the presence of aSyn detected by an abnormal neuronal a-syn test (current standard is the CSF aSyn-SAA). NSD- is defined by the absence of aSyn assigned to a negative neuronal aSyn test (current standard is the CSF aSyn-SAA).

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How to incorporate groups and subgroups:

Preliminary comparisons may be conducted utilizing Group and subgroup designations. These analyses should consider the following:

1) Comparison between enrollment cohort (PD*, Prodromal*, HC)
2) Comparison within enrollment group (PD, Prodromal, or HC) by analytic subgroup (PD: sporadic, GBA, LRRK2, GBA/LRRK2, PRKN, SNCA, rare), Prodromal (A1, A2, B, C), Healthy
3) Comparison within each analytic subgroup by NSD subgroup (NSD+, NSD-)

Additional comparisons should be hypothesis driven and in accordance with the proposed statistical analysis plan.

*It may be appropriate to consider genetic groups separately for PD and Prodromal cohorts (ie: comparison of PD GBA and Prodromal GBA carriers)

Example baseline tables to be made available with relevant comparisons.

Table 1. Between Enrollment Cohort

	Cohort		
	PD (N =X)	**Prodromal** (N = X)	**HC** (N = X)
Outcome A, n(%) or Med(IQR) or Mean(SD)			

Table 2. Prodromal By Analytic Subgroup

	Prodromal			
	A1 (N =X)	**A2** (N = X)	**B** (N = X)	**C** (N = X)
Outcome A, n(%) or Med(IQR) or Mean(SD)				

Table 3. Prodromal By Analytic Subgroup By NSD Status

	A1		A2		B		C	
Variable	**NSD -** (N =X)	**NSD +** (N = X)	**NSD -** (N = X)	**NSD +** (N = X)	**NSD -** (N = X)	**NSD +** (N = X)	**NSD -** (N = X)	**NSD +** (N = X)
Outcome A, n(%) or Med(IQR) or Mean(SD)								

Table 4. PD By Analytic Subgroup

	Sporadic PD (N = X)	**Genetic PD** (N = X)				
		GBA (N = X)	**LRRK2** (N = X)	**GBA/LRRK2** (N = X)	**SNCA** (N = X)	**PRKN** (N = X)
Outcome A, n(%) or Med(IQR) or Mean(SD)						

Table 5. PD By Analytic Subgroup By NSD Status

	Sporadic PD		**Genetic PD**					
			GBA		**LRRK2**		**PRKN**	
	NSD- (N = X)	**NSD+** (N = X)	**NSD-** (N = X)	**NSD+** (N = X)	**NSD-** (N = X)	**NSD+** (N = X)	**NSD-** (N = X)	**NSD+** (N = X)
Outcome A, n(%) or Med(IQR) or Mean(SD)								