Journal of Parkinson's Disease 14 (2024) 623–636
DOI 10.3233/JPD-249002
IOS Press

Conference Title: Planning for Prevention of Parkinson's: A trial design forum

Organizing Committee: Grace Crotty, MD, Michael Schwarzschild, MD PHD, Daniela Berg, MD PhD, Tanya Simuni, MD, Caroline Tanner, MD PhD, Jessi Keavney, MBA, and Katherine Callahan

Sponsors (as of April 11, 2024): Planning for Prevention of Parkinson's: A trial design forum is hosted by Massachusetts General Hospital, with funding made possible in part by The Sergey Brin Family Foundation, Rita and Norton Reamer, The ABY Fund, Sanofi US, Biogen, Cerevel, Cure Parkinson's, Roche, American Parkinson Disease Association, LikeMinds Inc, Parkinson Canada, and Parkinson's UK.

Funding for this conference was made possible, in part, by the Food and Drug Administration through grant 1 R13 FD008015-01. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.

ABSTRACTS

Retromer stabilization using a pharmacological chaperone protects in an α-synuclein based mouse model of Parkinson's

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Background: We assessed the effects of a pharmacological approach to stabilize the retromer complex in a Parkinson's disease (PD) mouse model. Missense mutations in the VPS35 gene are a rare cause of familial PD. The VPS35 protein is a subunit of the retromer cargo recognition complex and regulates multiple pathways within neurons, some of which are potentially relevant for the pathophysiology of PD. Prior studies have revealed a role for the retromer complex in controlling accumulation and clearance of α-synuclein aggregates. We previously identified an aminoguanidine hydrazone, 1,3 phenyl bis guanylhydrazone (compound 2a), as a pharmacological stabilizer of the retromer complex that increases retromer subunit protein levels and function. Recent data emphasized that VPS35 is also a key regulator of αSynuclein degradation pathways.

Methods: Here, we assessed the efficacy of 2a in protecting against αSynuclein pathology and dopaminergic neuronal degeneration in a PD mouse model generated by unilateral injection of AAV-A53T-αSynuclein in the substantia nigra. Moreover, we analyzed the effect of 2a on αSyn degradation pathways in neuroblastoma cell lines.

Results: Daily intraperitoneal administration of 2a at 10 mg/Kg for 100 days, led to robust protection against behavioral deficits, dopaminergic neuronal loss and loss of striatal dopaminergic fibers and striatal monoamines in PD mouse model. Treatment with 2a activated αSynuclein degradation pathways in the SN and led to significant reductions in aggregates and pathological αSynuclein. We analyzed the effect of 2a administration on the main αSyn degradation pathways in SH-SY5Y neuroblastoma cells, and we found a significant impact of 2a on macroautophagy, CMA and the proteasomal system.

Conclusion: These data suggest retromer stabilization as a promising therapeutic intervention for PD leading to neuroprotection of dopaminergic neurons and attenuation of the accumulation of αSynuclein pathology. These data highlight 2a or other regulators of the retromer complex as potential clinical drug candidates for future testing in PD patients.

Promoting physical activity in people with Parkinson's disease through a smartphone-based intervention: a pilot study

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Background: Physical activity may be beneficial for secondary prevention of Parkinson's disease (PD). Increasing - and sustaining - a physically active lifestyle remains challenging, especially for people with PD. We investigated target engagement, usability, and symptomatic effects of a motivational smartphone application (STEPWISE app) for increasing physical activity in PD.

Methods: We performed a four-week, double-blind pilot trial. Thirty people with PD who were able to walk independently and did not take more than 7,000 steps per day at baseline were randomized to minimal, moderate, or large increases in step counts. The primary outcome was step count continuously collected with the participants' own smartphones. Secondary and exploratory outcomes were usability of

the app as assessed with a translated version of the System Usability Scale (SUS, range 0-100) and measures of physical fitness and motor- and non-motor functioning.

Results: Step counts per day increased over 4 weeks in a dose-dependent pattern (mean±SD: minimal=1064±1030, moderate=1689±2060, large= 2745±3817). Usability of the STEPWISE app was perceived as excellent (SUS 86.6±12.7). Movement Disorders Society-Unified Parkinson's Disease Rating Scale total scores declined significantly in all groups, without group differences.

Conclusion: This study provides preliminary evidence for target engagement of a remote, smartphone-based exercise intervention in people with PD. This motivates and supports further development of a smartphone application to increase physical activity in people with manifest PD. This approach could potentially motivate people with PD all over the world to become - and stay - physically active. We need trials studying the effectiveness of such an application for secondary prevention of PD, primary prevention of PD, and treatment and prevention of other neurodegenerative diseases.

Longitudinal Clinical Outcomes in Non-Manifest LRRK2 G2019S Carriers

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Background: LRRK2 G2019S is the most prevalent autosomal dominant genetic cause of Parkinson's disease (PD). PD-associated genetic variants, such as LRRK2 G2019S, provide a clear and easily identifiable method for identifying at-risk populations who may be ideally suited for PD prevention trials. However, a better understanding of progression in carriers is needed to inform the design of such trials.

Methods: In a remote, prospective, cohort study, 211 LRRK2 G2019S carriers without a PD diagnosis are completing annual study visits. Clinical outcome measures included the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS parts I-III), Scales for Outcomes in Parkinson's Disease-Autonomic (SCOPA-AUT), Epworth Sleepiness Scale (ESS), REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ), Beck Depression Inventory (BDI-II), Parkinson Anxiety Scale (PAS), Montreal Cognitive Assessment (MoCA), and the University of Pennsylvania Smell Identification Test (UPSIT). To examine change from baseline to year two in clinical outcome measures, we performed a mixed model repeated measures analysis. To model mean outcome measures over time in those with versus without hyposmia (≤20% percentile for age and sex on UPSIT) and with versus without REM sleep behavior disorder (RBDSQ ≥ 6) we used generalized estimating equations.

Results: 201 non-manifest carriers (mean age (SD) 53.9 (14.9), 59% female, 75% Ashkenazi Jewish) contributed longitudinal data. Over a two-year period, most clinical measures were stable (mean change from baseline, standardized effect size): MDS-UPDRS part I (-0.81, 0.25), part II (0.07, 0.03), part III (0.17, 0.06), MoCA (0.71, 0.43), SCOPA-AUT (-0.50, 0.13), ESS (-0.27, 0.13), RBDSQ (-0.32, 0.18), BDI-II (-0.11, 0.02), PAS (-0.94, 0.22). Participants with baseline hyposmia (n = 46) versus without hyposmia (n = 148) did not demonstrate any significant differences in any clinical measure over time. BDI-II scores improved over time in participants with baseline RBD (n = 27) versus without RBD (n = 182) (p-value=0.004).

Conclusion: In a large, remote cohort of non-manifest LRRK2 G2019S carriers we found that standard clinical measures were not sensitive to change over a two-year period. Those with RBD showed unexpected improvement in BDI-II scores over time compared to those without RBD. No differences were seen over time with regard to the presence or absence of hyposmia. Our results highlight the need for more sensitive measures and better predictors of disease progression in this population.

Prodromal Parkinson's Disease and Subsequent Risk of Parkinson's Disease and Mortality

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Background: Prodromal Parkinson's disease (PD) refers to the stage wherein early features of PD neurodegeneration are present. However, the association of individual and combined prodromal PD features with the subsequent risk of PD in the general population and the risk of mortality in individuals with PD warrant further investigation through large-scale prospective study.

Methods: We included 501,475 participants free of PD at baseline from the UK Biobank study. Eight prodromal features including depression, rapid eye movement sleep behavior disorder (RBD), urinary incontinence, erectile dysfunction, constipation, anxiety, orthostatic hypotension, and hyposmia were measured using self-reported diagnoses, hospital admission records, and primary care data. Incident PD cases were identified using linkages with hospital admission, death register, and self-report. Vital status and date of death were provided by the UK National Health Service (NHS) and the NHS Central Register. The associations of the number of prodromal PD features (categorized as 0, 1-2, and 3+) with the risk of developing PD and the risk of mortality were estimated using the Cox proportional hazard models.

Results: The prodromal PD features were associated with a higher risk of developing PD. For individuals with 3+ vs. 0 prodromal PD features, the multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were 3.12 (2.58-3.78) for men and 2.71 (2.11-3.47) for women, after adjusting for sociodemographic factors, lifestyle factors, health conditions, and standard polygenic risk score (PRS) for PD. Prodromal PD features predicted only PD onset occurred during the first six years of follow-up (adjusted HR for 3+ vs. 0 prodromal features=10.5; 95% CI: 8.60, 12.9), but not for PD onset after 6 years (adjusted HR =1.00; 95% CI: 0.76, 1.32). Presence of prodromal PD features, either before or after PD diagnosis, conferred high risk of mortality among participants with PD (P<0.05 for both).

Conclusions: Having prodromal PD features were associated with a higher probability of developing PD in the short-term and a higher risk of mortality among individuals with PD.

Innovating Clinical Trial Design to Accelerate Assessment of Disease Modifying Therapies for Parkinson's Disease: The EJS ACT-PD Initiative

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Background: Inefficiencies in the current clinical trials process cannot match the urgent pace required to identify effective treatments to modify PD progression. Long delays between clinical trial phases and running multiple sequential trials greatly increases the cost, time, and number of control participants needed to find answers. The repeated set-up and dismantling of site delivery infrastructure removes opportunities to build on delivery frameworks and expertise. Additionally, recruitment and retention strategies need improvement to target diverse populations and produce generalisable results. Multi-arm, multi-stage (MAMS) trials offer an innovative and cost-effective approach to address these challenges. Advantages include simultaneous assessment of multiple therapies against a shared placebo arm; early identification of futile therapies; and seamless addition of new interventions within the core trial infrastructure.

Methods: The Edmond J Safra Accelerating Clinical Trials in PD (EJS ACT-PD) initiative has designed a MAMS protocol to accelerate assessment of potential disease-modifying therapies (DMTs) for PD. >90 key UK stakeholders, including people with PD (PwP) and

care partners have addressed specific issues regarding trial design; outcome measures; therapy selection; infrastructure; funding and sustainability; and patient inclusion. Decisions have been further informed by an international advisory group; the MHRA; and a UK-wide Site Capability Survey assessing current PD research infrastructure. A Community Advisory Panel has provided input from under-served groups on improving accessibility and inclusivity.

Results: This trial will be an inclusive phase 3, multi-centre, MAMS trial for PwP on stable Parkinson's medication without dementia, severe disability or major comorbidities. Participants will be stratified by sex, centre, age, and Hoehn & Yahr stage and randomised to one of three active treatment arms or placebo for three years. Two futility analyses on the inverse variance weighted MDS-UPDRS parts 1, 2 and remote 3 will inform discontinuation of ineffective treatments. The primary outcome will be a 30% reduction in disease progression as assessed by parts 1 and 2 of the MDS-UPDRS. To encourage inclusivity the trial has broad inclusion criteria and allows for either in-person or remote visits to support participation of participants across the UK. Core trial staff and a tiered delivery model based on site capabilities will support the involvement and development of less experienced sites.

Conclusions: We have co-designed a MAMS trial protocol to assess potential DMTs for PD. Aiming to recruit from December 2024 across 40 UK sites, the trial will provide ongoing research opportunities, strengthen UK PD research infrastructure, and promote research inclusivity.

Lumbar Punctures in Parkinson's Research

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Background: Lumbar punctures for cerebrospinal fluid (CSF) analysis have become increasingly common in neurological research, providing valuable insights into various changes associated with conditions like Parkinson's disease (PD). However, the invasive nature of this procedure poses concerns among patients and impedes widespread adoption.

Methods: To address these challenges, efforts have been made to standardize procedures, improve informed consent processes, and explore less invasive methods for collecting biomarkers. Cure Parkinson's conducted a focus group involving individuals with Parkinson's (PwP) to understand their experiences and gather suggestions for enhancement.

Results: The focus group highlighted the importance of clear communication and standardized protocols in improving patient experiences and ensuring the efficacy of procedures. This underscores the significance of collaboration and innovation in refining techniques, prioritizing patient safety, and driving progress in PD research.

Conclusion: Moving forward, integrating technological advancements with clinical insights is essential for identifying novel biomarkers and developing effective treatments for Parkinson's disease. By doing so, the quality of life for individuals affected by PD can be significantly enhanced.

Impact of Lighting Therapy on Disordered Sleep in Parkinson's Disease (PD) Genetic Subgroups: A pilot single-arm intervention trial

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Objective: To characterize responses to a passive lighting intervention in LRRK2 and GBA carriers with PD.

Background: Sleep disturbances in PD are common and may precede the development of motor symptoms. (1) Light therapy has benefited sleep quality and mood outcomes in various populations of PD patients. (2) A proposed mechanism for the positive impact of light therapy is that circadian entrainment improves the processing of nocturnal synuclein. (3, 4). If light

therapy improves sleep in genetic PD subtypes, this low cost, minimal risk intervention could be utilized by carriers of mutations that increase PD risk well in advance of clinical PD symptoms.

Methods: In this single-arm, within-subject intervention study, baseline sleep quality and rest-activity metrics were evaluated using a wrist actigraph worn for 1 week. Lighting was then administered to participants through table/floor lamps or personal light therapy glasses for 2 hours every morning for 4 consecutive weeks. Post-intervention data for the same outcome measures were collected during the final week of the intervention period.

Results: Among 15 participants with genetic variants (8 women, 7 men; mean [SD] age 68.4 [11.8] years, disease duration 9.65 [5.95] years), 9 were LRRK2 carriers and 6 were GBA carriers. LRRK2 participants [75.19 (6.8)] were significantly older than GBA [58.3 (10.42) p = 0.002] and had a higher mean age of onset (LRRK2 66.2 (11.3) vs. GBA 49.8 (11.2), p = 0.023)]. Overall group change in sleep time for GBA was 16.8 minutes [51.6] and for LRRK2 was 9.6 minutes [43.52]. When stratified by response to lighting intervention, as indicated through an increase in total sleep time, in GBA, 4/6 (66.7%) participants responded positively, and in LRRK2, 5/9 (55.6%) responded positively. Within GBA carriers, baseline sleep time was lower among responders (306.8 [100.3] minutes) than non-responders (419.8 [27.5] minutes) (p = 0.13). Within LRRK2-PD, olfactory performance as indicated by UPSIT was worse among non-responders (24th [14.81] percentile) compared to responders (62nd [33.2] percentile, p = 0.082).

Conclusions: LRRK2-PD and GBA-PD subgroups may have heterogenous responses to light therapy. Better understanding these differences may allow for tailored prevention and treatment recommendations. Light therapy is a non-invasive, low-cost intervention that can be adopted by individuals at increased risk of developing PD years before clinical symptoms emerge.

A comparison of Parkinson's disease symptom profiles in LRRK2 G2019S and GBA N370S single and dual carriers

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Background: The most common monogenic forms of Parkinson's disease (PD) are linked to two founder variants: LRRK2 G2019S and GBA N370S. LRRK2-PD results in a milder clinical phenotype with lower rates of non-motor symptoms. GBA-PD appears to be more severe with higher rates of dementia. Clinical studies suggest dual LRRK2/GBA carriers may have less risk of developing more severe PD symptoms, which goes against the concept of a "dual hit" being more detrimental. Our aim was to explore the impact of pathogenic variants in the LRRK2 and GBA genes on PD symptom pathology.

Methods: We combined data from 23andMe's Research Cohort and the Fox Insight Study in a mega analysis of genotyped individuals with and without PD. Data were coalesced across self-report surveys to provide a lifetime incidence of symptoms (motor, autonomic, cognitive, sleep, olfaction) across longitudinal encounters. Demographics, age at diagnosis, lifestyle/risk factors, and family history of PD were also collected. Cumulative incidence of PD was estimated using an accelerated failure time model that adjusted for sex and education.

Results: We compared data from 27,046 non-carriers with (idiopathic) PD (n=6.8 million non-manifest), 452 LRRK2 G2019S PD carriers (n=7,427 non-manifest), 404 GBA N370S PD carriers (n=33,448 non-manifest), and 34 dual LRRK2 G2019S/GBA N370S carriers with PD (n=182 non-manifest). Relative to idiopathic PD, LRRK2-PD was associated with a milder phenotype with lower rates of bradykinesia (LRRK2: 76% vs. 82%), hallucinations (7% vs.15%), hyposmia (31% vs. 45%) and REM behavior disorder (RBD, 14% vs. 26%). GBA-PD was similar to idiopathic PD with high rates of bradykinesia (both 82%), hallucinations (both 15%), but higher rates of RBD (GBA: 34% vs. 26%), and hyposmia (54% vs. 45%). Dual carriers trended phenotypically towards LRRK2, but showed more variability. The predicted cumulative incidence of PD by age 80 was 4% for non-carriers, 9% for GBA carriers, 38% for LRRK2 carriers, and 62% for dual carriers.

Conclusion: GBA N370S carriers reported a higher burden of non-motor symptoms, suggesting pathology extending beyond the substantia nigra. Not all dual

carriers had this severe phenotype, which suggests that the presence of the LRRK2 G2019S variant may result in a more restricted pattern of neurodegeneration. It does appear, however, that the dual hit concept may prove to be true when it comes to developing PD, as dual carriers have the highest disease penetrance at any given age.

Skin Alpha-Synuclein Seed Amplification Assay (SAA) for the differential diagnosis of Parkinsonism

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Background: Alpha-synuclein (a-Syn) aggregates are the hallmark pathology of PD and MSA and can be detected through seed amplification assays (SAA) in CSF and other biospecimens, including skin. Distinguishing PD from MSA is a diagnostic challenge. In this study, we evaluated the diagnostic accuracy of skin SAA for detecting a-Syn aggregates and distinguishing between synucleinopathies.

Methods: Participants were recruited at the University Hospital of Würzburg (Germany) and Brigham and Women's Hospital (Boston, USA). We evaluated 41 PD, 30 MSA, 27 healthy controls (HC), and 16 patients with non-synucleinopathy neurodegenerative disorders. The diagnosis was made based on the latest MDS consensus criteria for each condition. The MSA group was further classified into the cerebellar and parkinsonian subtypes. Three 5 mm skin biopsies were obtained from each participant. Skin biopsies were obtained from the posterior neck (C7), lower back (Th10), thigh, and ankle. The 100-µl SAA reaction buffer included 1 mg/mL C-terminus 6xHis-tagged recombinant wild-type α-syn, 500 µM NaCl, 100 mM PIPES, 10 µM thioflavin T (ThT), and 2µl of 0.5% w/v skin biopsy lysate. Four replicates per sample were incubated at 37°C in a 96-well microplate for 48 hours. ThT fluorescence intensity was measured every 45 minutes in a BMG Fluostar Omega reader. Samples were considered positive if ≥75% of the replicates crossed a predefined fluorescence threshold. Participants were considered positive if at least one of the samples was positive.

Results: 35 (85%) patients with PD and 22 (73%) patients with MSA had at least one sample with positive a-Syn aggregation. A total of 295 samples were obtained and a-Syn was most frequently detected in the thigh (51/101) compared to other sites (75/194). The maximum ThT fluorescence (maxRFU) was significantly higher in the PD group than in the MSA group (mean maxRFU PD: 219013.72, MSA: 83074.72, p <0.0001). Among positive samples, a mean maxRFU >150,000 RFU was 84% sensitive and 88% specific for a PD diagnosis. Similarly, a value <50,000 RFU was 95% sensitive and 94% specific for an MSA diagnosis. aSyn aggregation was more frequently detected in MSA-P (16/18) than in MSA-C (6/12). At least one skin SAA sample was positive in 3 HCs and 5 cases with PSP (n = 12).

Conclusion: Our results show that skin SAA can detect α-syn aggregates across synucleinopathies with high diagnostic accuracy. Moreover, skin SAA can help in the differential diagnosis between MSA and PD based on maximal ThT fluorescence.

Participants with Early Parkinson Disease Seen in Teaching Hospitals: Are They Representative of the Overall Parkinson Disease Population?

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les, CA, USA.; [6]Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada

Background: Parkinson's Disease (PD) clinical studies, including disease modifying therapy trials, have historically enrolled participants from a narrow spectrum of the population. Consequently, the generalizability of trials findings remains limited. The extent of this phenomenon is understudied.

Methods: This retrospective cohort study examined health administrative data from Ontario, Canada (1995-2022). We identified persons newly diagnosed with PD aged ³ 40 and identified whether they had visited a neurologist associated with a teaching hospital within three years of diagnosis (early teaching hospital neurologist contact versus not). This classification was designed to partially replicate disease-modifying trial inclusion criteria. The study baseline date was 3 years following diagnosis date. We compared demographic characteristics of persons with PD by type of physician contact and examined subsequent time to onset of PD progression milestones including second antiparkinsonian drug, falls, dementia, advanced PD therapies, home care services, long-term care and death. Hazard ratios (HR) were derived from Cox Proportional-Hazards modeling. Individuals were censored upon death, healthcare coverage termination or December 31st, 2022.

Results: A total of 19,948 individuals with PD were identified, 4,386 (22.0%) with early teaching hospital neurologist contact and 15,562 (78.0%) without. Individuals were followed for 8.4 ± 5.1 years (mean ± SD). Compared to persons with no early contact, those with early contact were significantly younger (mean age 67.0 ± 10.5 versus 70.6 ± 10.4 years old, standardized mean difference (SMD)=0.348), belonged to higher income neighborhoods, had fewer comorbidities, and were taking fewer medications at baseline. There were no differences in sex, proportion of immigrants, and rural residents. Individuals with contact had earlier interventions: higher hazards of starting a second antiparkinsonian drug (hazard ratio (HR)=1.30; 95% confidence intervals (95% CI): (1.21, 1.38); initiating advanced PD therapies (HR: 2.350 (2.09, 2.64)), and receiving home care services (HR: 1.06 (1.02,1.10)). Additionally, those with contact had lower hazards of dementia (HR: 0.813 (0.77, 0.86)), admission to long-term care (HR: 0.62 (0.58,0.67)) and death (0.68; (0.64,0.72)). The hazard of falls was similar.

Conclusion: Individuals with PD seen by teaching hospital-based neurologists within the first 3 years of disease, and therefore likely candidates for disease-modifying therapy trials or other early PD studies, exhibit systematic differences from the broader Ontario PD population. They were younger, had fewer comorbidities, belonged to higher income neighborhoods, had access to earlier interventions, and had slower progression. Understanding these distinctions is crucial for understanding the generalizability of trial results and improving trial recruitment strategies.

B12 Status associated with LRRK2 variants and Parkinson disease

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Novel animal model data raise the potential utility for a physiologic form of vitamin B12 (adenosylcobalamin) as a disease modifying agent in carriers of variants in the leucine rich repeating kinase (LRRK2). While it is not required that B12 be low in LRRK2 variant carriers for such an agent to be efficacious, it is of interest to determine whether B12 levels are lower in LRRK2 G2019S variant carriers overall, and with and without PD. We thus examined B12, homocysteine (Hcy) and methylmalonic (MMA) levels in 87 idiopathic, LRRK2(G2019S) negative PD (IPD), 42 LRRK2(G2019S)-PD, 20 LRRK2(G2019S) carriers without PD (non-manifesting carriers, NMC), and 43 controls without PD or LRRK2(G2019S) variants. Sex distribution and age (mean [range]) were: IPD 73.6% male, 67.8 years [40-88]; LRRK2-PD 52.4% male, 70.0 years [53-86]; LRRK2-NMC 35% male, 55.9 years [22-76]; controls 25.6% male, 66.9 years [23-90]. B12 levels (pg/mL, mean±SD) were: IPD 620.8±344.4; LRRK2-PD 809.3±474.7; LRRK2-NMC 582.95±325.2, and controls 690.4±402.0 (p=0.0504). Neither MMA nor Hcy levels differed by group, though MMA was highest in IPD (p = 0.085).

Continuous B12 levels did not correlate with MoCA score; higher levels of MMA and Hcy levels were associated with lower MoCA scores (MMA r = -0.17, p = 0.027; Hcy r = -0.22, p = 0.006). Higher Hcy levels was also associated with higher (worse) UPDRS III (motor) scores (r = 0.18, p = 0.035), but B12 and MMA levels did not. It is of interest that LRRK2 G2019S carriers without PD, many of whom will never develop PD, had the lowest B12 levels, while LRRK2 PD had the highest levels of B12. This may be attributed to many of the LRRK2 PD having supratherapeutic levels that are suggestive of supplementation - and likely used to treat underlying deficiency. However, there are multiple levels of potential bias in reporting supplements, which may differ between PD and control groups. Thus while there is great potential to use B12, which is inexpensive, low-risk and well tolerated, and determining the clinical status of B12 in individuals with LRRK2 variants, particularly those who have not yet developed disease is informative, larger sample sizes may further elucidate these relationships. Further analysis in this dataset is planned to include adjusting for B12 supplementation to determine if supplementation positively affects cognitive and motor scores and can explain the higher levels of B12 found in the LRRK2 PD group.

Tracking the Progression of Parkinson's Disease Symptoms Using Consumer Wearable Devices

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Background: Recent advancements in wearable technology have shown promise in monitoring Parkinson's Disease (PD) symptoms, complementing traditional clinical assessments. While these digital mobility outcomes moderately correlate with established clinical scales like MDS-UPDRS, they offer unique insights into patients' functional behaviors in real-world settings. However, most attempts to measure progression with wearables rely on relatively small sample sizes, assess only a few points in time and rely on research devices. Here we assess symptom progression in a large cohort of PD patients.

Methods: In 1000+ subjects with Parkinson's disease with wearable data, we assessed long term trends in tremor, dyskinesia, gait, vitals, and sleep. For metrics with high daily variability, such as tremor and dyskinesia, we used windowing functions and statistical aggregation to assess changes across time. We applied an algorithm to identify statistical changes in metric trajectory, which we compared against known therapeutic interventions such as medication changes or deep brain stimulation programming updates. In a subcohort with data prior to disease diagnosis, we explored wearable data trends during the prodromal period.

Results: Along a subset of metrics, a subset of patients (80%) showed progression in mobility metrics as a result of a combination of age related changes and Parkinson's disease. In patients with worsening trends, decreases in walking speed and step length were observed. Patient reported outcomes were used to validate some of the progression metrics, patients with the steeper declines were four times more likely to have experienced a fall compared to other patients.

Conclusion: Worsening symptoms can be identified and characterized with consumer wearable devices, reflecting inadequate therapeutic maintenance and/or worsening disease. Conversely, subjects with improved metrics may indicate good symptom management. Data-driven approaches for assessing longitudinal symptom change and how individual patients deviate from one another in progression patterns may yield insights on disease progression phenotypes in large patient cohorts.

Evaluating Operating Characteristics Under Differences in Placebo Response for a Platform Trial in Parkinson's Disease

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Platform trials are an adaptive clinical trial design in which multiple experimental therapies can be evaluated within a single clinical trial. A master protocol governs the conduct of a platform trial, with regimen-specific subprotocols to detail the conduct of specific experimental therapies within the platform. Platform trials can increase efficiency in trial conduct by creating a shared infrastructure of study sites and procedures and allowing each experimental therapy to be evaluated against a shared control arm. The efficiency of a platform trial can expedite the identification of

effective therapies, which is particularly appealing in contexts where there are few to no existing treatment options, such as Parkinson's Disease (PD). In a platform trial, participants are often randomized in a two-stage fashion. First, participants are randomized to a regimen in the platform, with there being a regimen for each experimental therapy of interest. Secondly, they are randomized to either active treatment or matching placebo within a regimen. To maintain blinding, the matching placebo for a given regimen is designed to be as similar as possible to the active treatment, including consideration for the mode of administration. Under standard assumptions that the controls across regimens should behave similarly, the shared control arm appeals to patients because it ensures higher odds of receiving an active treatment. However, a challenge arises if experimental therapies have different modes of administration (e.g., oral, intravenous), with the potential of eliciting different "placebo effects". When controls from across regimens are combined to create the shared control arm, differences in placebo response rates according to different modes of placebos could impact the operating characteristics for comparing any active treatment to shared control. Historically, most therapies for PD have been orally administered, but in recent years, there has been more variety in the mode of administration of promising therapies. This variety leads to the potential for differential placebo responses in any current platform trial in PD, such as the Path To Prevention (P2P) Therapeutics Platform Trial. This work evaluates the impact of differences in placebo response on operating characteristics, specifically for an example in PD with a primary outcome measure of the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III. Various scenarios for the placebo response and treatment effects across treatment regimens will be considered, and the type 1 error rate and power will be assessed for individual evaluations of each active treatment in the platform.

Regulatory Science and Global Multistakeholder Collaborations Are Key To Enabling Biological Staging Of Neuronal Alpha-Synuclein Disease: Perspectives From Critical Path Institute

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Aims: Biological staging of disease represents a paradigm shift in catalyzing drug development by targeting earlier stages of the disease prior to onset of clinical symptoms. A novel biological staging framework for Neuron alpha-Synuclein Disease (NSD) grounded in innovative advances in biomarkers and genetics is highlighted.

Methods: Regulatory agencies recommend that public private partnerships comprised of multiple stakeholders are key to advancing data driven translational tools that focus on underlying pathophysiology of the disease. Examples of biological staging frameworks with profound impact on drug development focused on early intervention include Type 1 Diabetes and Huntington's disease. The experience of Critical Path Institute as a neutral convener was key in these examples. A data driven iterative path to advancing a biological staging framework for NSD was initiated by regulatory agency leaders in 2022.

Results: Critical success factors for ensuring efficient data driven advancement of biological staging of disease are the ability to appropriately stage the disease process through the integration of translational platforms, clinical outcome assessment tools, biomarkers, genetics and quantitative solutions to optimize trial design. A series of iterative multistakeholder meetings took place in 2022-2023 to review emerging scientific advances within the Parkinson's disease (PD) and dementia with Lewy bodies (DLB) fields aimed at establishing biological definitions of disease and a new biological staging paradigm for clinical trials. The role of public private partnerships has been key in all cases to advancing the evolution and adoption of biological staging that is inclusive to regulatory agencies and has emphasis on patient centricity.

Conclusions: The precompetitive global collaboration framework pioneered by multiple stakeholders is primed to catalyze the path to the generation of disease modifying therapies targeting neuronal synucleinopathies with true promise for prevention on the horizon.

Enrollment of Racial and Ethnic Minorities in Disease-modifying Drugs in Parkinson's Disease RCTs: Are We Doing It Right? A Systematic Review and Meta-Analysis

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Objectives: To perform a systematic review and meta-analysis comparing racial and ethnic recruitment in individuals with Parkinson's Disease (PD) enrolled in disease-modifying clinical trials.

Background: There is a historic underrepresentation of racial and ethnic minorities in clinical trials for PD, which might limit the generalizability of these studies.

Methods: We searched PubMed, Embase, and Cochrane Library for studies of patients enrolled in clinical trials for potential disease-modifying therapies for PD. Only multi-center double-blind, randomized, placebo-controlled clinical trials (DBRCT) evaluating pharmacological therapies were evaluated. The primary outcome was race and or ethnicity prevalence. Secondary outcomes were other social determinants of health, including gender, educational level, and income. We computed pooled prevalence of minority groups, with 95% confidence intervals (CIs). Statistical analysis was performed using R (version 4.3.1).

Results: A total of 6,383 patients from sixteen randomized clinical trials were included. Race and ethnicity were reported in thirteen studies (41.3% of all studies, or 4,965 participants). Among the studies that reported racial and ethnic data, the overall percentage of non-white patients was 3.69% (183), Hispanic/Latino 0.92% (46), Asian 0.48% (24), black/African American 0.36% (18), American Indian and more than one race 0.08%, and native Hawaiian 0.02% (1), unknown/not reported 1.67% (83) and other 0.18% (9). Gender was reported in all studies. Educational level was described in three RCTs (18.75% of all studies), and income in only two studies (12.5% of all studies).

Conclusions: There is an underrepresentation of racial and ethnic minorities in disease-modifying clinical trials for PD. Other social determinants of health, such as income and educational level are rarely reported in the clinical trials. This finding highlights the lack of racial and ethnic diversity in disease-modifying clinical trials for PD, which could represent an obstacle for the generalizability of future effective disease-modifying therapies in PD.

Diagnostic performance of plasma pTau181 and pTau217 as biomarkers of Alzheimer's disease co-pathology in Lewy Body disease

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Background: Lewy body disease (LBD) often co-occurs with Alzheimer's disease neuropathological change (ADNC), which can be detected using plasma pTau181 and pTau217. Few studies have investigated these biomarkers in LBD, and none have focused on alpha-synuclein (aSyn) positive participants. We aimed to determine whether there was a difference in the diagnostic performance of plasma pTau181 and pTau217 for detecting ADNC and amyloidosis (Aβ+) in LBD participants with and without cognitive impairment. We established LBD-specific cut-points for these biomarkers, and investigated their associations with CSF AD biomarkers in LBD. Finally, we conducted a sensitivity analysis in aSyn-positive participants.

Methods: We included 230 Stanford research participants: cognitively normal (CN=110), Parkinson's disease cognitively normal (LBD-CN=43), LBD with cognitive impairment (LBD-CI=41), and Alzheimer's disease (AD=36). Plasma pTau181 was measured with the Lumipulse G platform, and pTau217 with the ALZpath pTau217 assay. aSyn positivity was assessed in CSF with SYNTap®. Diagnostic performance of pTau181 and pTau271 in distinguishing ADNC (determined by CSF pTau181/Aβ42) and amyloidosis (determined by CSF Aβ42/Aβ40 or amyloid-β PET) were evaluated with receiver-operating characteristic (ROC) analyses. The Youden index determined the optimal cut-points, and the DeLong test compared model accuracy. Associations between plasma and CSF AD biomarkers were evaluated with Spearman's Rank-Order Correlations.

Results: In the LBD-CI group, plasma pTau181 and pTau217 had similar diagnostic performance in distinguishing ADNC+ from ADNC-. Additionally, in the LBD-CN and LBD-CI groups, both biomarkers had similar diagnostic performance in distinguishing Aβ+ from Aβ-. However, in the sensitivity analysis, pTau217 outperformed pTau181 for detecting Aβ+ in aSyn-positive participants (pTau217 AUC= 0.88, 95%-CI: 0.77-1 vs pTau181 AUC= 0.77, 95%-CI: 0.64-0.90, p=0.045). In both LBD groups, combining plasma biomarker levels with age and sex did not improve the models› prediction of ADNC or amyloidosis. Optimal cut-points for both plasma pTau181 and pTau217 in detecting ADNC and amyloidosis in LBD differed from those for AD. Within the LBD-CI group, plasma pTau181 and pTau217 were associated with CSF pTau181, Aβ42/Aβ40, and pTau181/Aβ42. Interestingly, only plasma pTau217 was associated with CSF Aβ42 in LBD-CI participants, and with CSF pTau181, Aβ42/Aβ40, and pTau181/Aβ42 in LBD-CN participants. Plasma pTau181 was not associated with CSF AD biomarkers in LBD-CN participants.

Conclusion: Our findings indicate that plasma pTau181 and pTau217 reliably detect concomitant ADNC and amyloidosis in LBD. Plasma pTau217 appears more sensitive for detecting amyloidosis in aSyn-positive participants. Moreover, we showed that these biomarkers have LBD-specific cut-points, and distinct associations with CSF AD biomarkers.

Impairment of REM Sleep Architecture: A Potential Biomarker for Parkinson's Progression

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Parkinson's disease (PD) is known to be correlated with a number of sleep conditions, including excessive daytime sleepiness (EDS), sleep apnea, insomnia, and REM Sleep Behavior Disorder (RBD). RBD, in particular, a condition characterized by a lack of muscular paralysis in Rapid Eye Movement (REM) sleep causing patients to move and act out dreams, is considered an early indicator of PD. Indeed, most patients who suffer from RBD eventually develop Parkinson's disease or another neurodegenerative disease.

Our study finds that the effects of Parkinson's disease on impairing normal REM sleep far surpass those of the RBD subpopulation alone. In fact, we show that the majority of Parkinson's patients in our cohort have impaired REM sleep architecture compared to age-matched controls. This impairment appears as a loss of REM cyclic structure as the disease progresses ($p<0.001$). We report the results of a longitudinal sleep study following a cohort of participants for up to one year. In total, we gathered over 10,000 nights of sleep data from 50 individuals, 25 of whom are at

varying stages of PD, 9 are LRKK2 carriers who have no PD diagnosis, and the rest are age-matched control individuals. Using a novel Expectation-Maximization algorithm, we analyze the REM sleep cyclic architecture over time for each individual.

Our results show that the REM cyclic architecture deteriorates significantly in individuals with PD compared to their age-matched controls. Individuals with LRKK2 mutation and no PD diagnosis exhibit a more consistent REM architecture than those with PD but less so than the control individuals. Interestingly, this impairment in the cyclic structure of REM sleep increases with PD disease duration (Pearson correlation is 0.64 with $p < 0.001$). Meanwhile, the control group had no significant correlation between REM cyclic architecture and age, showing further evidence that the destruction of REM architecture is beyond normal aging and is characteristic of individuals with Parkinson's disease. It is suspected that sleep problems in PD, specifically issues pertaining to REM such as RBD, are a result of neurodegeneration in the brainstem. Due to its anatomical proximity to the basal ganglia (the origin of PD-related neurodegeneration), REM impairment could provide an early indicator of PD and a progression marker of the disease. Further investigation of this relationship between REM architecture deterioration and disease progression within early diagnoses and prodromal populations is proposed to further assess the strength of this biomarker.