



Published in final edited form as:

*Mov Disord.* 2017 March ; 32(3): 319–324. doi:10.1002/mds.26913.

## Biomarker-driven phenotyping in Parkinson disease: a translational missing link in disease-modifying clinical trials

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## Abstract

Past clinical trials of putative neuroprotective therapies have targeted Parkinson disease (PD) as a single pathogenic disease entity. From an Oslerian clinico-pathologic perspective, the wide complexity of PD converges into Lewy bodies and justifies a reductionist approach to PD: a single-mechanism therapy can affect most of those sharing the classic pathologic hallmark. From a systems-biology perspective, PD is a group of disorders that, while related by sharing the feature of nigral dopamine-neuron degeneration, exhibit unique genetic, biological and molecular abnormalities, which probably respond differentially to a given therapeutic approach, particularly for strategies aimed at neuroprotection. Under this model, only biomarker-defined, homogenous subtypes of PD are likely to respond optimally to therapies proven to affect the biological processes within each subtype. Therefore, we suggest that precision medicine applied to PD requires a reevaluation of the biomarker-discovery effort. This effort is currently centered on correlating biological measures to clinical features of PD and on identifying factors that predict whether various prodromal states will convert into the classical movement disorder. We suggest, instead, that subtyping of PD requires the reverse view, where abnormal biological signals (i.e., biomarkers) rather than clinical definitions are used to define disease phenotypes. Successful development of disease-modifying strategies will depend on how relevant the specific biological processes addressed by an intervention are to the pathogenetic mechanisms *in the subgroup of targeted patients*. This precision-medicine approach will likely yield smaller but well-defined subsets of PD amenable to successful neuroprotection.

## Keywords

Parkinson disease; biomarkers; neuroprotection; systems biology

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## Introduction

The elusive and highest priority therapeutic frontier in Parkinson disease (PD) remains the development of disease-modifying or neuroprotective interventions. Neuroprotection using a precision medicine paradigm would ideally occur (1) prior to or at the earliest stages of a diagnosable form of the disease, (2) with interventions targeting specific biological processes associated with disease progression, and (3) in a PD subgroup where such key abnormal processes have been confirmed through validated biomarkers. A perfect set of

biomarkers would not only serve to select appropriate patients for a specific disease-modifying intervention, but also reflect disease progression and response to therapy. Therapeutic progress for disease modification would be accelerated by focusing on disease subgroups sharing similar abnormal molecular and biological characteristics.<sup>1</sup>

Biomarker-validated populations have remained a missing link in the translational efforts of putative disease-modifying therapies over the past two decades. Ongoing biomarker-discovery efforts have been designed based on consensus clinical criteria for PD and its subtypes (e.g., tremor-dominant PD). We will here briefly review the pitfalls associated with anchoring the development of biomarkers on clinical criteria and suggest that devoting the next decade to the generation of unbiased biomarker-driven subtyping (rather than clinical phenotype-driven biomarker validation) will help identify possibly smaller, and biologically more homogenous, subsets of PD patients that are more likely to be amenable to specific molecular targeting.

### The short history of failures in neuroprotective efforts

Treating PD as a single disease has greatly served the development of symptomatic therapies based on dopaminergic enhancement, given the common denominator of all its variants: dopamine deficiency. This model, however, has consistently failed when testing potential disease-modifying interventions.<sup>2</sup> Indeed, drugs that have effectively targeted putative pathogenetic mechanisms in animal models of PD have consistently failed to accomplish disease modification in PD patients. The range of arguments justifying the translational failures range from inappropriate clinical trial designs, insufficiently sensitive endpoints, inadequate target engagement of putative neuroprotective interventions, patients recruited at an advanced disease stage, and, animal models (on which these interventions were developed) that do not “recapitulate the complexity of the human disease.”<sup>3</sup> But a critical step in the translational efforts deserves greater recognition: the same biological mechanisms identified as critical for the drugs shown to be neuroprotective in animal models must be critical in the group of PD patients targeted by the clinical trials of those drugs.

Two approaches to PD offer radically different outlooks for neuroprotection. On the one hand, the model of PD as a complex, heterogeneous disease assumes that all the clinical, genetic, and molecular variability can be traced to a unifying pathological core, namely aggregated  $\alpha$ -synuclein found in Lewy bodies and neurites. On the other hand, the very complexity of PD, which has led to the notion that there exist different Parkinson *diseases*<sup>4</sup> which represent unique pathophysiologic entities, even if Lewy bodies are a common pathologic end-product and there are sufficient clinical elements to group them under the same diagnostic umbrella. The former model assumes that a drug may act on most patients with PD if the mechanism of action is *sufficiently common* or *dominant* across all clinical subtypes. Dopamine replacement strategies have been well served by this model because dopamine deficiency, predominantly from nigrostriatal neurodegeneration, is a dominant feature in all subtypes of PD. However, alterations in basic underlying biological processes such as mitochondrial, proteostatic, lysosomal, and inflammatory mechanisms may differ substantially among PD subtypes. Under the PD-as-several-diseases model, selected mitochondrial enhancement strategies (e.g., to enhance mitophagy or restore electron

transport chain activity) would be expected to succeed only in the subgroup of PD patients where mitochondrial dysfunction is an upstream event rather than a downstream byproduct of other molecular abnormalities. Clinical trials of drugs enhancing mitochondrial function will continue to fail if they include a substantial number of patients for whom mitochondrial dysfunction is not central.

In conclusion, the prevailing one-disease approach to PD has unsuccessfully predicted that clinical trials targeting a single pathogenic mechanism will mitigate disease progression in patients who share a clinical diagnosis but are heterogeneous regarding underlying molecular pathogenesis. Conversely, in the emerging precision-medicine model of neuroprotection, therapies can best succeed in the select subgroup of patients that share the biological aberrations such therapies were demonstrated to mechanistically alter.

## The lessons from oncology

In the mirror-image field of oncology, where cells abnormally proliferate rather than degenerate, cancer was long viewed as a single, if heterogeneous disease. Breast cancer, for instance, was to be approached in a similarly aggressive fashion, with radical mastectomy, because it was equally malignant regardless of age or any other clinical variables.<sup>5</sup> In the 1950s and 1960s the application of breast-conserving surgery (“quadrantectomy” or “lumpectomy”) was widely believed as inappropriate compared to radical surgery. Only toward the late 1970s and early 1980s, after the first randomized clinical trial comparing these procedures demonstrated no difference in survival,<sup>6, 7</sup> breast cancer began to be reconsidered as a cluster of several diseases and a search for its biological subtypes was initiated.

The last three decades of cancer research redefined cancer entirely, using a systems-biology approach to guide its nosology and disease-modifying treatment. Under this paradigm in breast cancer, a combination of nine histological types (e.g., tubular, ductal, mucinous, etc. for invasive and in-situ carcinomas) with any combination of validated molecular markers (mainly, estrogen receptor [ER], progesterone receptor [PR], human epidermal growth factor receptor 2 (HER2), and others [e.g., ErbB2, p53, Ki67]) yields nearly 20 breast cancer subtypes, each with a distinct survival curve and response to therapy.<sup>8</sup> For example, the drug cocktail that is most effective for patients with HER2-positive breast cancer may be ineffective or harmful for patients with HER2-negative cancer.<sup>9</sup> Within this sophisticated layering of nosological data created to guide therapy, there still are subtypes of breast cancer that remain biologically difficult to characterize (e.g., the malignant “triple negative” [ER-negative, PR-negative, and HER2-negative] basal-like subtype).<sup>10</sup>

Unlike oncology, the field of neurodegenerative diseases does not have ready access to affected tissue for histopathology and this has contributed to the long dominance of clinical (and more recently, imaging) criteria for biomarker development. An oncologist examines several biomarkers in order to individualize a rational disease-modifying anti-cancer treatment: the specific histologic type, the plausible genetic mutations, the presence of ER/PR/HER2 receptors, and the anatomical spread. Only then is a rational therapeutic cocktail administered, addressing known mechanisms and preempting plausible alternative

mechanisms of cancer development for that specific patient. Neurologists involved in research of neurodegenerative diseases have remained committed to the reductionist model of PD (and, for that matter, Alzheimer disease (AD) and other disorders) as a single “but complex” disease, in the same manner as oncologists viewed cancer until the late 1970s.

### Clinical phenotype to biomarkers: Pitfalls in the current model

The success of future neuroprotective therapies in PD and other neurodegenerative disorders will depend on the extent to which biomarkers of disease subtypes and subtype-specific progression will help identify suitable populations for promising molecular interventions. The current model for biomarker development is anchored on a traditional definition of PD, as recently refined by the International Parkinson and Movement Disorders Society.<sup>11</sup> This phenotype-driven biomarker development program is based on the assumed existence of biological/molecular underpinnings for each diagnostic entity, as well as the corresponding prodromal state. The most important effort based on this premise is the Parkinson’s Progression Markers Initiative (PPMI), launched in 2011 by the Michael J. Fox Foundation for Parkinson’s Research.<sup>12</sup>

After a clinical diagnosis is made, the current approach to biomarker research (Figure 1A) evaluates how biological markers correlate with the clinical diagnosis (“state biomarkers”) or evolution (“rate biomarkers”). The most recent analysis of the PPMI CSF data found that PD subjects (n = 412) have lower alpha-synuclein ( $\alpha$ -syn), total tau (t-tau), and phosphorylated tau (p-tau), but not lower amyloid- $\beta$ 1–42 ( $A\beta$ 1–42) compared to healthy controls (n = 189).<sup>13</sup> As such,  $\alpha$ -syn, t-tau, and p-tau could be considered biomarkers of disease, even if their individual diagnostic value for PD diagnosis is limited due to the large overlap with healthy controls. Nevertheless, these may be considered for use at a population level if confirmed in other cohorts. However, in the *De Novo Parkinson* or DeNoPa cohort (n = 123 PD; 106 age-matched healthy controls) neither t-tau nor p-tau in CSF segregated PD from controls.<sup>14</sup> Only  $\alpha$ -syn was lower at baseline but it did not change over a 2-year period, suggesting it is not useful for monitoring disease progression.<sup>14</sup> Thus, CSF biomarkers from clinically defined phenotypes exhibit substantial signal overlap and the outcomes may vary between cohorts. Furthermore, this model has left unanswered the question of which biomarkers might help assist in individualizing molecular therapy in a precision-medicine future.

Extensively used clinical phenotypes include tremor-dominant (TD), postural instability-gait disorder (PIGD), non-motor mild cognitive impairment (PD-MCI), and dementia (PDD) subtypes.<sup>15</sup> In clinical epidemiologic studies, the motor PIGD phenotype is associated with greater likelihood of evolving into the PD-MCI and PDD phenotypes.<sup>16</sup> Segregating these clinical phenotypes based on Unified Parkinson Disease Rating Scale (UPDRS)<sup>17</sup> data collected in the PPMI, only low  $\alpha$ -syn, but not changes in this or other biomarkers, was associated with the PIGD phenotype and also with worse cognitive performance (e.g, PD-MCI/PDD).<sup>13</sup> In another PPMI analysis, however, the 2-year conversion to PD-MCI (n= 286 participants without MCI at baseline) was associated with lower mean baseline CSF  $\beta$ -amyloid 1–42 (343.8 vs. 380.4 pg/mL,  $p < 0.01$ ) but not  $\alpha$ -syn.<sup>18</sup> These conflicting data have been suggested to reflect “disease heterogeneity”, but have not yet forced a

reconsideration of the *clinical phenotype* → *biomarker* model for validating both the disease subtypes and the corresponding presumed biomarkers.

Importantly, the separation of PD from other disorders on clinical grounds is challenged by the finding that molecular elements traditionally considered a domain of other neurodegenerative disorders may “explain some of the variability in PD.” For example, amyloid as measured by CSF A $\beta$ 1–42 is present in 17% of dopamine transporter scan-positive PD patients within two years from diagnosis.<sup>19</sup> These patients are older, more cognitively impaired, and have more cortical atrophy in medial temporal, frontal and brainstem structures.<sup>19</sup> Thus, this small but significantly different group of patients exhibiting a PD-AD hybrid (two diseases or a defined molecular/pathology subtype?) defies the “neat” clinical separation between  $\alpha$ -syn and amyloid/tau pathologies, or between PD and AD clinical phenotypes.

Lastly, a major problem with biomarker discovery using clinical phenotypes as anchors is the “instability” of the clinical phenotypes themselves: Within a year of enrollment in the PPMI study, the mean values of the two common motor phenotypes, TD and PIGD, defined using the scoring of related sub-items from the UPDRS,<sup>20</sup> shifted by nearly 40% and 20%, respectively, regardless of dopaminergic treatment.<sup>21</sup> This cast further doubt on the relevance of any molecular/biological derangements presumed to be associated with each of these clinical phenotypes.

### **Biomarkers to clinical phenotype: Ideal model**

The desirable approach (Figure 1B), based on a systems-biology model, assumes that PD is a point-of-entry diagnosis encompassing patients with several genetic, biological and pathophysiologic abnormalities. The ideal biomarker discovery program is based on large, aging populations with or without a neurological diagnosis at baseline. Some of these individuals will be diagnosed with PD, some with AD, some with other neurodegenerative disorders, and some will remain neurologically healthy. The statistical analysis would not be dependent on the clinical diagnoses as the independent variable but, rather, on the biological and molecular abnormalities. Identification of abnormal biological processes would occur in an unbiased manner, detached from any preconceived notion of whether it correlates with a clinically defined disease. Abnormally high and low signals would then be used, in isolation or in combination, to determine the extent to which they correlate with specific clinical features and with the progression of motor or non-motor disability. While some biomarkers may correlate with previously defined PD subtypes (e.g., PD-MCI), others will most likely segregate with previously unrecognized phenotypes (e.g., prominent postural tremor and a non-neurological impairment, such as arthritis), for which we have no current consensus clinical criteria. Many will not be associated with a clearcut clinical phenotype. For example, biomarker pairs A&B and C&D may be associated with parkinsonism, and A&B may include early dementia in 50% and C&D may include early dementia in 30%. Even if distinct biomarker patterns were not to lead to distinctive clinical phenotypes (as it may be theoretically expected based on current evidence: for instance, patients with *GBA* mutations do indeed have more dementia and these mutations may be associated with the clinical picture of dementia with Lewy bodies but many patients behave no differently from those



without a clear disturbance of lysosomal function<sup>22</sup>), the biological homogeneity of these PD subtypes would represent suitable targets for the application of “personalized” disease-modifying therapies. A potentially powerful way to implement this *biomarker* → *clinical phenotype* model is through an exploratory, unbiased, non-hypothesis-driven approach to biomarker development, with a reverse analytic plan to that applied in the PPMI and other biomarker validation cohorts. An exponentially larger sample of aging adults than available in those cohorts would be required to have adequate power because an unbiased biomarker development program would concentrate on recognizing the phenotype of those whose biological signals represent unique patterns (rather than simple ‘positive-negative’ biomarkers based on a given cutoff of “positivity”) or are outliers in the measurement spectrum in order to discriminate subgroups ideal for potentially neuroprotective molecular therapies.

### Implications for clinical trials

It is critical for the biological action of therapies with promising neuroprotective potential, confirmed to engage relevant molecular targets, to be considered only in patients with the appropriate biomarker signatures. Without biomarkers of disease (for patient selection) and progression (for response monitoring), the chances for success in neuroprotection trials are limited. In the immediate future, clinical trials of drugs with neuroprotective properties may succeed, in the absence of biomarkers to assist in the selection of a suitable cohort, only if the mechanisms of action of the interventions are of sufficiently broad applicability in Lewy body PD. For instance, despite the lack of a biomarker for propagation of  $\alpha$ -syn pathology, it is conceivable that immunotherapies aimed at disrupting this mechanism of disease progression may be applicable to a large proportion of PD patients. Future clinical trials may also target selected genetic (e.g., at-risk or manifest *LRRK2* mutation carriers for initial trials of *LRRK2* kinase inhibition,<sup>23</sup> and *GBA* mutation carriers for trials of glucosylceramide synthase inhibitor to influence glucocerebrosidase activity<sup>24</sup>) or polysomnography-defined pre-motor REM sleep behavior disorder subtypes.<sup>25</sup> An ongoing example of the use of a biomarker to define a clinical trial cohort is the SURE-PD3 study, in which inosine, a precursor of urate, is only given to patients with low baseline urate, a molecular biomarker that predicts the rate of disease progression.<sup>26</sup>

There are several major challenges in ushering the era of precision medicine for PD through biomarker development programs. Besides assay variability, population heterogeneity, differing power to detect a range of biological effects, we will need to: (1) differentiate between specific *and early* biomarkers (linked to causative pathological mechanisms and therefore targetable for therapy development) vs. non-specific *or late* biomarkers (reflecting reactive plasticity or self-perpetuating neurodegenerative cycles and unwarranted for therapeutic targeting) vs. biomarkers reflecting a physiological response to injury; (2) understand the extent to which identifiable biomarkers may be “unstable” (transient) or constant throughout the course of the disease. This will require a ranking of biomarkers related to the phenotypic staging they represent and the early-versus-late relevance in the neurodegenerative processes: This may take many years to ascertain, particularly if our starting point, due to logistical and power issues, will need to be restricted to large PD cohorts (advanced as well as *de novo* and prodromal, as in PPMI) rather than even larger

population-based cohorts. Thus, we need to take a large, unbiased step back to invest the next decade laying the groundwork for biomarker-driven clinico-molecular phenotyping in PD to inform the development of clinical trials targeting smaller, but better defined, biologically homogeneous PD subtypes, one at a time. This will imply reconsidering the wisdom of further phenotype-based biomarker development programs and current clinical diagnostic criteria to select patients for disease-modifying clinical trials. Such an expensive, time consuming but transformational effort will require the engagement of the entire research community, with substantial investments from foundations, industry and government.

## Authors' roles

1. Research project: A. Conception, B. Organization, C. Execution
2. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique

AJE: 1A, 1B, 1C, 2A, 2B

AEL: 1A, 1B, 1C, 2B

MAS, CMT, HHF, DKS, JBL, AM, AC-P, PB, MAK, RE, KK, DW, EAM, DGS: 1B, 1C, 2B

## Appendix

**Financial disclosures related to research covered in this article:** None

## Financial disclosures

**Dr. Espay** has received grant support from NIH, Great Lakes Neurotechnologies and the Michael J Fox Foundation; personal compensation as a consultant/scientific advisory board member for Abbvie, TEVA, Impax, Merz, Acadia, Cynapsus, Lundbeck, and USWorldMeds; publishing royalties from Lippincott Williams & Wilkins, Cambridge University Press, and Springer; and honoraria from Abbvie, USWorldMeds, Lundbeck, Acadia, the American Academy of Neurology, and the Movement Disorders Society.

**Dr. Schwarzschild** receives grant support from the National Institutes of Health, Department of Defense, Michael J. Fox Foundation, Parkinson's Disease Foundation, Parkinson's Alliance, Target ALS, and ME & MO Hoffman Foundation. He serves on the scientific advisory board of CBD Solutions.

**Dr. Tanner** is an employee of the University of California-San Francisco and the San Francisco Veterans Affairs Medical Center and an intermittent employee of the Parkinson's Institute. She serves on the Scientific Advisory Boards of the Michael J. Fox Foundation and the National Spasmodic Dysphonia Association as a voluntary consultant, and has provided paid consulting services to Ultragenyx Pharmaceuticals, Neurocrine Biosciences, Cynapsus Therapeutics, Sage Biometrics and Adamas Pharmaceuticals. She has received compensation for serving on Data Monitoring Committees from Biotie Therapeutics, Voyager Therapeutics and Intec Pharma. She receives grant support from the Michael J. Fox



Foundation, the Parkinson's Disease Foundation, the Department of Defense and the National Institutes of Health.

**Dr. Fernandez** has received research support from Abbvie, Acadia, Auspex/Teva, Biotie Therapeutics, Civitas, Kyowa/Prostrakan, Michael J. Fox Foundation, Movement Disorders Society, NIH/NINDS, Parkinson Study Group, Rhythm, Synosia, but has no owner interest in any pharmaceutical company; honoraria from Biogen, GE Health Care, Lundbeck, Merz Pharmaceuticals, Pfizer Pharmaceuticals, Prime Education Inc., Carling Communications, Medscape; royalty payments from Demos Publishing for serving as a book author/editor. The Cleveland Clinic has contracts with Abbvie, Merz Pharmaceuticals, and Ausepx/Teva for Dr. Fernandez' role as a member of the Global Steering Committee for LCIG studies and as a consultant or speaker; Head Principal Investigator for the Xeomin Registry Study; and Co-Principal Investigator in SD-809 Tardive Dyskinesia global studies. Dr. Fernandez also serves as the Chair of the Publication Committee for Xeomin Studies (Merz Pharmaceuticals); a member of the Publication Committee for Dysport studies (Ipsen Pharmaceuticals) but he does not receive any personal compensation for these roles.

**Dr. Simon** has received funding for research from National Institutes of Health, the Micheal J. Fox Foudnation, the Weston Brain Institute, Edison Pharmaceuticals, and Lysosomal Therapeutics. He receives support for clinical programs for Parkinson's disease patients from the National Parkinson Foundation. He has served as a consultant for Lysosomal Therapeutics.

**Dr. Leverenz** has received compensation as a consultant for Axovant, GE Healthcare, Navidea Biopharmaceuticals, Piramal Healthcare, and Teva Pharmaceuticals. He receives grant funding from Alzheimer's Association, Alzheimer's Drug Discovery Foundation, Genzyme/Sanofi, Jane and Lee Seidman Fund, Michael J Fox Foundation, and the National Institute of Health.

**Dr. Merola** has received speaker honoraria from CSL Behring, Cynapsus Therapeutics, and UCB Pharma

**Dr. Chen-Plotkin** is supported by the NIH (P50 NS053488, UO1 NS082134, and RO1 NS082265), the Burroughs Wellcome Fund, the Benaroya Fund, the Pechenik Montague Award Fund, and the Biomarkers Across Neurodegenerative Disease initiative from the Alzheimer's Association/Weston Institute/Michael J. Fox Foundation.

**Dr. Brundin** has received commercial support as a consultant from Renovo Neural, Inc., Roche, Teva Pharmaceutical Industries, Lundbeck A/S, AbbVie Inc, IOS Press Partners and Versant Ventures. Additionally he has received commercial support for research from Renovo, Teva and Lundbeck. Dr. Brundin has ownership interests in Acousort AB and Parkcell AB.

**Dr. Kauffman** is an employee of the CONICET. He has received grant support from Ministry of Science and Technology of Argentina and Ministry of Health of Buenos Aires.

**Dr. Erro** received consultancies from Zambon.

**Dr. Kieburz** has received research support the National Institutes of Health (NINDS), Michael J Fox Foundation, and TEVA; and has acted as consultant for the US National Institutes of Health (NINDS), Acorda, Astellas Pharma, AstraZeneca, BioMarin Pharmaceutica, Biotie, Britannia, CHDI, Clearpoint Strategy Group, Clintrex, Corium International, Cynapsus, Forward Pharma, Genzyme, INC Research, Intec, Lundbeck, Medivation, Melior Discovery, Neuroderm, Neurmedix, Orion Pharma, Otsuka, Pfizer, Pharma2B, Prana Biotechnology, Prothena/Neotope/Elan Pharmaceutical, Raptor Pharmaceuticals, Remedy Pharmaceuticals, Roche/Genentech, Sage Bionetworks, Sanofi, Serina, Sunovion, Synagile, Titan, Upsher-Smith, US WorldMeds, Vaccinex, Vertex Pharmaceuticals, and Weston Brain Institute.

**Dr. Woo** has nothing to disclose.

**Dr. Macklin** serves on Data Monitoring Committees for Acorda Therapeutics and Shire Human Genetic Therapies, Inc. and receives grant funding from the Adolph Coors Foundation, ALS Association, Autism Speaks, Biotie Therapies, Michael J Fox Foundation, and the US Food and Drug Administration, Health Resources and Services Administration, and the National Institutes of Health.

**Dr. Standaert** is a member of the faculty of the University of Alabama at Birmingham and is supported by endowment and University funds. Dr. Standaert is an investigator in studies funded by Abbvie, the American Parkinson Disease Association, the Michael J. Fox Foundation for Parkinson Research, The Bachmann-Strauss Dystonia and Parkinson Foundation, the Dystonia Medical Research Foundation, Acerta Pharma, Ceregene, Inc. (now Sangamo Biosciences), Quintiles, Inc., Alabama Department of Commerce, and NIH grants P01NS087997, P20NS087997, R25NS079188, R01NS092122, and P2CHD086851. He has a clinical practice and is compensated for these activities through the University of Alabama Health Services Foundation. In addition, in the last three years he has served as a consultant for or received honoraria from, Auspex Inc., Teva Neurosciences, Serina Therapeutics, AstraZeneca, Abbvie, the Michael J. Fox Foundation for Parkinson Research, The International Parkinson Disease and Movement Disorder Society, the National Institutes of Health, Boston University, The American Institute for Biological Sciences, Huntsville Hospital, the American Academy of Neurology, Banner Sun Health, Viropharma (now Shire), the Kirchner Group, Georgia Regents University, the US Department of Justice, and he has received royalties for publications from McGraw Hill, Inc

**Dr. Lang** has served as an advisor for AbbVie, Allon Therapeutics, Avanir Pharmaceuticals, Biogen Idec, Boehringer Ingelheim, Bristol-Myers Squibb, Ceregene, Cipla, InteKrin, Lilly, Medtronic, Merck, Novartis, NeuroPhage Pharmaceuticals, Teva, and UCB; received honoraria from Medtronic, Teva, UCB, and AbbVie; received grants from Brain Canada, the Canadian Institutes of Health Research, the Edmond J. Safra Philanthropic Foundation, The Michael J. Fox Foundation, the Ontario Brain Institute, National Parkinson Foundation, Parkinson Society Canada, Physicians Services Incorporated (PSI), Tourette Syndrome Association, W. Garfield Weston Foundation; received publishing royalties from Saunders, Wiley-Blackwell, Johns Hopkins Press, and Cambridge University Press; and has served as an expert witness in cases related to the welding industry.

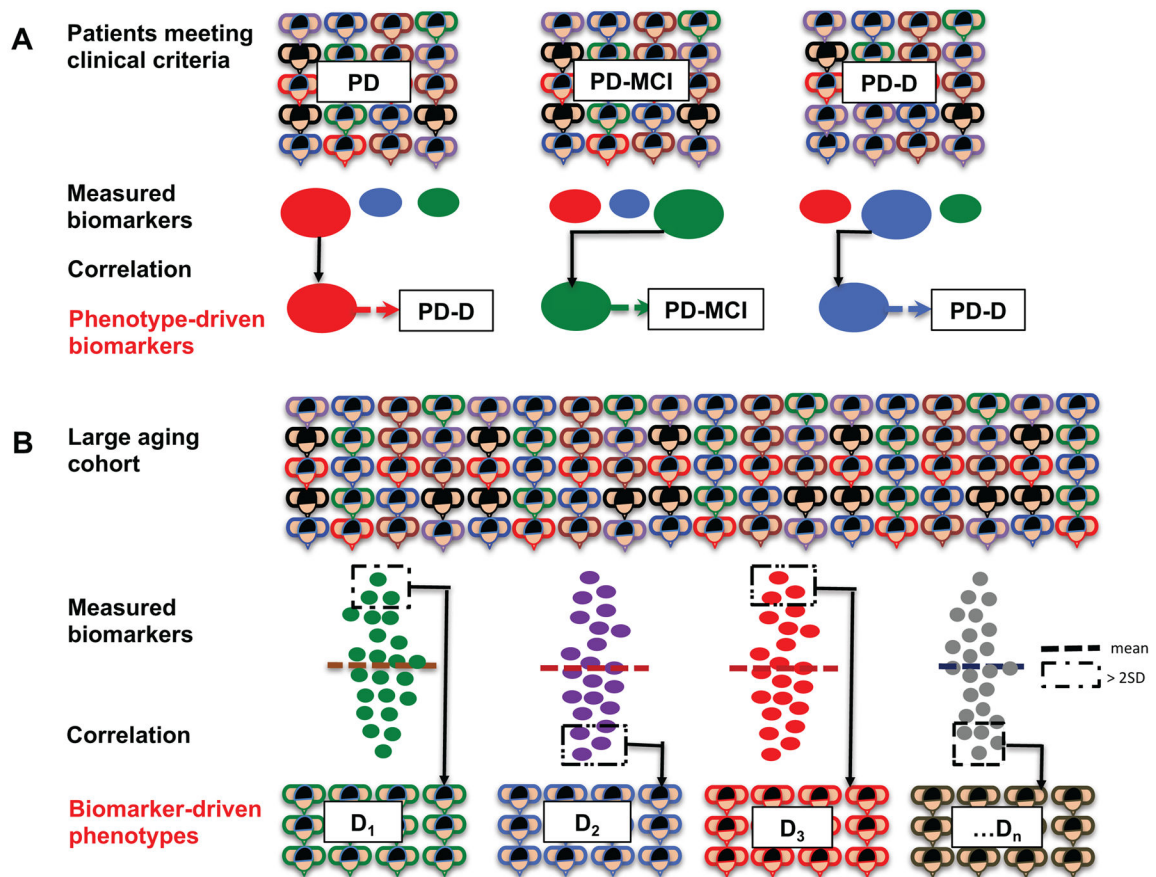
## Appendix

**Funding sources for manuscript:** none

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**Figure 1. Biomarker development models**

**A. Clinical phenotype → Biomarker validation.** Under this model, clinical phenotypes are established as the “truth” against which biomarkers are validated. After defining the clinical constructs (e.g., PD-MCI), statistical analyses determine the strength of correlation with a variety of abnormal biological signals. In this example, the “green” signal becomes a biomarker of PD-MCI. **B. Biological/molecular abnormalities → Biomarker-driven phenotypes.** Under this model, the “truth” is unknown and the analysis is non-hypothesis driven (exploratory). Biological/molecular signals are examined within a large cohort of individuals, including criteria-meeting “PD” but also individuals with other PD-like diagnoses and those aging without overt disease. The biomarker-driven phenotypes ( $D_1$ ,  $D_2$ ... $D_n$ , where D stands for “disease”) share strong biological homogeneity, even if not clinically, as they are generated based on abnormal biological signals (exemplified as >2 standard deviations above the mean for green and red signal; and >2 SD below the mean for purple and a theoretical gray “n” signal).