VIEWPOINT

# A Statement of the MDS on Biological Definition, Staging, and Classification of Parkinson's Disease

Francisco Cardoso, MD, PhD,[1*] Christopher G. Goetz, MD,[2] Tiago A. Mestre, MD, PhD,[3] Cristina Sampaio, MD, PhD,[4,5] Charles H. Adler, MD, PhD,[6] Daniela Berg, MD,[7] Bastiaan R. Bloem, MD, PhD,[8] David J. Burn, MD, FRCP,[9] Michael S. Fitts,[10] Thomas Gasser, MD,[11] Christine Klein, MD,[12] Marina A.J. de Tijssen, MD, PhD,[13] Anthony E. Lang, MD, FRCPC,[14] Shen-Yang Lim, MD, FRACP,[15] Irene Litvan, MD,[16] Wassilios G. Meissner, MD, PhD,[17,18,19] Brit Mollenhauer, MD,[20] Njideka Okubadejo, MBChB, FMDP,[21] Michael S. Okun, MD,[22] Ronald B. Postuma, MD,[23] Per Svenningsson, MD, PhD,[24] Louis C.S. Tan, MD, PhD,[25] Taiji Tsunemi, MD, PhD,[26] Sarah Wahlstrom-Helgren, PhD,[27] Oscar S. Gershanik, MD,[28,29] Victor S.C. Fung, PhD, FRACP,[30] and Claudia Trenkwalder, MD, PhD[31,32*]

[1]*Movement Disorders Unit, Neurology Service, Internal Medicine Department, The Federal University of Minas Gerais, Belo Horizonte, Brazil*
[2]*Department of Neurological Sciences, Rush University Medical Center, Chicago, Illinois, USA*
[3]*Ottawa Hospital Research Institute; University of Ottawa Brain and Mind Research Institute; Division of Neurology, Department of Medicine, University of Ottawa, The Ottawa Hospital Ottawa, Ottawa, Ontario, Canada*
[4]*CHDI Management/CHDI Foundation, Princeton, New Jersey, USA*
[5]*Laboratory of Clinical Pharmacology and Therapeutics, Faculty of Medicine, University of Lisbon, Lisbon, Portugal*
[6]*Department of Neurology, Mayo Clinic College of Medicine, Mayo Clinic Arizona, Phoenix, Arizona, USA*
[7]*Department of Neurology, University Hospital Schleswig-Holstein, Campus Kiel and Christian Albrechts-University of Kiel, Kiel, Germany*
[8]*Radboud University Medical Center, Donders Institute for Brain, Cognition, and Behavior, Department of Neurology, Center of Expertise for Parkinson and Movement Disorders, Nijmegen, The Netherlands*
[9]*Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, United Kingdom*
[10]*UAB Libraries, The University of Alabama at Birmingham, Birmingham, Alabama, USA*
[11]*Department of Neurodegeneration, Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany. German Center for Neurodegenerative Diseases, Tübingen, Germany*
[12]*Institute of Neurogenetics, University of Lübeck, Lübeck, Germany*
[13]*Department of Neurology, Expertise Centre Movement Disorders, University Medical Centre Groningen, Groningen, The Netherlands*
[14]*Edmond J. Safra Program in Parkinson's Disease, University Health Network and the University of Toronto, Toronto, Ontario, Canada*
[15]*Division of Neurology, Department of Medicine, and the Mah Pooi Soo and Tan Chin Nam Centre for Parkinson's and Related Disorders, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia*
[16]*Parkinson and Other Movement Disorders Center, Department of Neurosciences, University of California San Diego, La Jolla, California, USA*
[17]*CHU Bordeaux, Service de Neurologie des Maladies Neurodégénératives, Bordeaux, France*
[18]*Univ. Bordeaux, CNRS, IMN, Bordeaux, France*
[19]*Department of Medicine, University of Otago, Christchurch, and New Zealand Brain Research Institute, Christchurch, New Zealand*
[20]*Department of Neurology, University Medical Center, Kassel, Germany*
[21]*Neurology Unit, Department of Medicine, Faculty of Clinical Sciences, College of Medicine, University of Lagos, Lagos, Nigeria*
[22]*Adelaide Lackner Professor of Neurology, Norman Fixel Institute for Neurological Diseases, University of Florida Health, Gainsville, Florida, USA*
[23]*Department of Neurology, McGill University, Montreal Neurological Institute, Montreal, Quebec, Canada*
[24]*Section of Neurology, Karolinska Institutet, Stockholm, Sweden*
[25]*National Neuroscience Institute, Singapore*
[26]*Department of Neurology, Juntendo University Faculty of Medicine, Tokyo, Japan*
[27]*International Parkinson and Movement Disorder Society, Milwaukee, Wisconsin, USA*
[28]*Movement Disorders Unit, Institute of Neuroscience, Favaloro Foundation University Hospital, Buenos Aires, Argentina*
[29]*Cognitive Neuroscience Laboratory, Institute of Cognitive Neurology (INECO), Buenos Aires, Argentina*



**Key Words**: Parkinson's disease, parkinsonism, α-synuclein, diagnosis, staging

***Correspondence to:** Prof. Francisco Cardoso, The Federal University of Minas Gerais, Av Pasteur 89/1107, 30150-290 Belo, Horizonte, MG, Brazil. E-mail: fecardosoc@gmail.com; Prof. Claudia Trenkwalder, Paracelsus Elena Klinik, Klinikstr 16, 34128 Kassel, Germany. E-mail: ctrenkwalder@gmx.de

**Relevant conflicts of interest/financial disclosures**: A.E.L., C.H.A., C.K., D.B., and R.D.P. are part of the team responsible for one of the biological diagnosis proposals. B.M. is one of the co-authors of the biological staging proposal. The other co-authors do not report any conflict of interest related to this article.

**Funding agency**: Movement Disorder Society provided financial support for the organization of the Atlanta In-Person Meeting.

[Correction added on 26 December 2023, after first online publication: Reference 12 was updated]

**Received:** 15 August 2023; **Revised:** 16 November 2023; **Accepted:** 20 November 2023

**Published online 13 December 2023 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.29683**

[30]Movement Disorders Unit, Department of Neurology, Westmead Hospital and Sydney Medical School, University of Sydney, Sydney, New South Wales, Australia
[31]Paracelsus-Elena Klinik, Kassel, Germany
[32]Department of Neurosurgery, University Medical Center, Goettingen, Germany

Disease staging is an important tool in both clinical research and medical practice because it allows for an unequivocal allocation of individuals into groups of shared biomedical characteristics along a specific disease trajectory. The disease staging approach comes from the field of cancer, in which the disease's extent and chronological progression were systematically described as early as the 1930s.[1] In this case, a staging system was developed to describe—for each particular type of cancer—the primary tumor, nodes, and metastasis (TNM) at various sites.[2] Cancer staging is defined solely by anatomical and biological features, and the symptoms that the patient experiences are not included. The TNM system has been used for several decades and is well-validated in its ability to establish prognosis and direct treatment protocols. With the rapid expansion of new data and advances in the field of neurodegeneration, there has been a growing interest in developing a similar format for disease staging and/or classification in Parkinson's disease (PD).

As the primary global organization in the field of PD and related disorders, the International Parkinson and Movement Disorder Society (MDS) seeks to serve as an active voice in the conversation regarding the staging and/or classification of PD. MDS perceives a need for a wide international consensus in research aiming to stage or classify PD with the involvement of clinicians, basic science researchers, persons living with PD, and other stakeholders including regulatory agencies and pharmaceutical companies. Moreover, the development of biological diagnostic criteria and a staging or classification system must follow a rigorous methodological process. This article follows an MDS meeting held in April 2023 on staging in PD (Appendix A). The gathering included a diverse group of international experts, including a patient representative. We present here the summary and recommendations of the meeting with the aim of providing the foundational principles for the development of a biological definition and any staging or classification system for PD following a discussion among MDS leaders at a recent roundtable (Appendix A).

## Definitions of Disease, Staging, Classification, and Rating Scales

Terminology around disease definition, disease classification and staging are formally distinct, but often misused and mistakenly applied interchangeably. Table 1 provides a clarification of the terms and their intended use. Staging is based on key points within the natural history of a disease, allowing the prediction of future relevant disease milestones. We recognize that staging can also be pivotal in developing therapeutic approaches as it can partition individuals into groups with similar outcomes, and it allows for quick and effective communication with patients about disease severity and expected clinical outcomes including, in some instances, treatment responsivity. In the best-case scenario, a well-developed staging system will provide the framework to detect disease in the earliest stages, where disease progression could be slowed or prevented. Ideally, a staging system also aligns with the optimal management approach for the patient.[3,4]

**TABLE 1** *Core definitions of disease, staging, classification, and rating scales*

| Term | Definition |
|---|---|
| Disease | A disease is defined as a deviation or disorder in the normal functioning of a living organism, resulting in specific symptoms, physiological abnormalities, or pathological changes. The definition of the disease may be used differently in sets of criteria: etiologic, syndromic, pathologic, etc.[5] |
| Disease classification | Disease classification refers to the systematic categorization and organization of diseases based on various criteria. It involves grouping diseases into distinct categories or classes to facilitate understanding, diagnosis, treatment, research, and communication among healthcare professionals. Within a given disease, it is possible to define several subtypes.[6] |
| Disease staging | Disease staging refers to the process of categorizing and classifying the extent or progression of a particular disease. Each stage is identified by characteristics (biomarkers, clinical features) that are prognostic of future events or transition to a more advanced stage in the course of the disease.[7] |
| Rating scale | A rating scale is a standardized measurement instrument used in clinical practice and research to quantify or measure specific aspects of a patient's health, symptoms, functioning, or disease severity.[8] |

## Biological Definition and Diagnosis in PD and Other Neurodegenerative Diseases

Historically, the ability to measure neurodegeneration anatomically and biologically has been limited in vivo. Until recently, clinicians have only had the option of evaluating signs and symptoms. In PD, the careful expert assessment of clinical findings is still used to both diagnose the disease and measure the clinical severity. Recent advancements in the knowledge of the underlying biology of PD as well as in the fields of biomarkers and brain imaging have resulted in an improved understanding of the pathophysiology of PD. These advances have opened opportunities to explore whether disease definition may include clinical and biologically based components. The challenge of any biological and clinical diagnosis system is to apply it globally in a useful and practical way, as has been established for other diseases.

Before a biological staging system can be developed, a biological definition of the disease must be established. This construct presents a specific challenge in PD, which was first clinically defined by James Parkinson as "Shaking Palsy."[9] It was later termed Parkinson's disease by Jean-Martin Charcot.[10]

Although research supports the existence of multiple underlying disease-triggering mechanisms that likely contribute to PD,[11] there is ongoing debate regarding whether a common biological overlap exists that could be harnessed for the purpose of disease slowing or reversal. α-Synuclein (α-syn) aggregation is currently considered a possible prevailing biological event that is present in a majority of cases with the final pathologically confirmed diagnosis of PD. In vivo the aggregation of α-syn can be identified by a biophysical test, called seed amplification assay (SAA). This assay originates from the prion field and has in the past years successfully been developed for α-syn. Specific properties of the endogenous aggregated protein lead to the amplification of introduced recombinant monomeric (non-natively aggregated) protein, here α-syn. The α-syn SAA works most reliable for α-syn in cerebrospinal fluid (CSF), but recent studies indicate that also other fluids (saliva, blood) and tissue (colonic mucosa, skin) from PD patients can be applied. It is important to state that a positive α-syn seeding test occurs in PD. A proposal exists of a biological definition based, for the most part, on the documentation of a positive α-syn SAA in the spinal fluid.[12] Several other groups have documented the presence of α-syn in other tissues such as skin, salivary glands, and colonic mucosa. Nevertheless, it is important to recognize that SAA documents the existence of an abnormal α-syn via its laboratorial amplification at a supraphysiological level. The seeding test per se does not necessarily reflect any seeding or aggregation of α-syn in the brain or in neurons of this patient. In addition, there is no reliable way of predicting if, when, and which clinical syndrome, an α-syn SAA-positive individual will develop, and currently no quantification from SAA that measures an α-syn-targeted biological change over time. Even the contribution of α-syn to the disease may vary from patient to patient, with a sizeable subgroup of individuals not showing any contribution of α-syn at all. Consequently, these gaps in knowledge hamper any clinical designation anchored on SAA.

Further, genetic forms of the disease, such as leucine-rich repeat kinase 2 (LRRK2)-PD, Parkin (PRKN)-PD, and others pose a challenge to the concept of α-syn playing a central role in the pathogenesis of the disease because α-syn pathology is found in <50% of these individuals post-mortem,[13,14] and α-syn SAA is often negative in LRRK2-PD. Therefore, the genetic status needs to be appropriately addressed when defining a disease in which a classification or staging proposal is developed from.

For both Alzheimer's disease (AD) and Huntington's disease (HD), working groups established a biological definition before embarking on the creation of a staging/classification system. It is important to emphasize that staging always comes after classification, which is based on the definition of a disease entity. In AD, the classification system is grounded in biomarkers and disease progression data, the amyloid/tau/neurodegeneration (ATN) system.[15] Although debated, this disease is currently defined by a biological profile with three established biomarkers that were originally part of the diagnostic criteria and then integrated into the disease definition and classification. The AD classification/staging system reflects the biomarker profile, where more positive biomarkers correspond to advancing stages.[16] Very recently, the National Institute on Aging and the Alzheimer's Association have updated the ATN system, incorporating plasma biomarkers and taking into consideration that there are instances of nonequivalence between fluid and imaging biomarkers. Importantly, the authors also have included three new biomarkers categories: inflammatory and immune mechanisms, vascular brain injury, and synucleinopathy (for public comments @AAIC23). The classification/staging system development benefited from a stereotypical disease progression in AD.[17]

HD, in contrast, is a disease defined by an identifiable genetic cause—the triplet CAG expansion in the *HTT* gene with a recently developed evidence-based staging system.[18]

## Staging in PD

In an internationally diverse community, the need for a globally accessible, clinically, and biologically anchored staging system for PD is evident. This multidimensional tool requires a focus on clinical care to capture the progression of the disease's motor and non-motor aspects. Each domain should calibrate similarly for unified messaging and a balanced impact on overall patient function and be clinicometrically sound. The staging should

facilitate communication among clinicians and healthcare providers while also allowing clinicians to communicate with their patients about the status of their PD. The meeting attendees agreed that a comprehensive biological and clinical staging system will be helpful to advance the scientific field of PD both for basic research and clinical assessment. This tool would likely benefit from the rapidly expanding biomarker field and may improve the development of disease-modifying treatments by adding new selection/stratification criteria and endpoints for clinical trials, once adequately validated for its proposed use.

### Past Initiatives

The Hoehn and Yahr (H&Y)[19] clinical stages of PD are often referenced in the discussion of staging. This approach was developed after observing patients and ranking their parkinsonism (unilateral vs. bilateral), disability level, and presence or absence of balance impairment.[19] This clinical staging system is not anchored on a biological or pathological basis and thereby differs from the current staging approaches for AD and HD[20] or any cancer staging system. To be clear, the H&Y is not a staging system according to the current understanding of staging. The strength of the H&Y staging is that it is easy to implement in the clinic, giving it "international currency" and making it a preferred tool globally. However, in view of the current appreciation that PD is both a motor and non-motor illness, the H&Y stages do not capture the non-motor symptoms and fail to correlate with the patient's overall functional status.[20] In addition, it does not cover a pre-clinical phase of the disease, which can be considered a major limitation for its application in the development of therapies that delay disease progression. Initiatives to update the time-honored H&Y staging system with non-motor and biological integration are topics under discussion by the MDS. Modified versions using 0.5 designations have never been validated. H&Y is the most widely recognized staging system, used worldwide by clinicians, investigators, payors, and regulatory agencies. Program participants agreed that, although a new clinical and biological staging system is needed, we should learn from the H&Y experience and not prematurely abandon it for an unvalidated or impractical replacement.

### Current Initiatives

Unlike the H&Y scale, based solely on clinical observation of PD, there have been attempts to develop integrated clinical and biological PD diagnosis and staging systems based on a biological definition of PD.[12,21] One proposal for a new biological classification of the disease ("SynNeurGe") combines the presence or absence of pathological α-syn ("Syn") deposition in tissues (eg, skin) or positive seeding assays in tissue or CSF (with criteria designed to distinguish between PD from multiple system atrophy [MSA]); with evidence of underlying neurodegeneration ("Neur") as defined by selected neuroimaging procedures, including but not limited to presynaptic nigrostriatal dopamine scanning, and documentation of pathogenic gene variants ("Ge"), which cause or strongly predispose to PD, including those that may not be associated with underlying α-syn pathology. Clinical syndromes associated with the biological designations are also detailed.[21] It should be emphasized that this proposal in reality conforms more to a classification system rather than a definition, although they are entangled concepts. However, it is problematic to combine classification and staging because they involve distinct methodologies. In the final published version of the proposal, the authors took the approach of calling it a classification.[21] An alternative proposal starts with the conceptualization of a neuronal synuclein disease (NSD), which includes all conditions with a positive CSF-SAA plus documentation of dopaminergic deficit (currently using dopamine active transporter scan). These disorders would include PD, but also Lewy body dementia (LBD), rapid eye movement (REM) sleep behavior disorder (RBD), and even asymptomatic individuals with a positive SAA, but not MSA. Leveraging CSF-SAA as the unifying central biomarker to identify patients with elevated α-syn levels in CSF, researchers documented a diagnostic sensitivity of 87.7 for individuals with positive CSF-SAA and an abnormal dopamine transporter imaging.[14] Their consequent proposed staging system for PD combines this assay along with genetic markers, α-syn aggregation, dopamine dysfunction as measured by dopamine transporter imaging, and clinical features yet to be defined.[12] For reasons already discussed in the section above, many experts point out that CSF α-syn aggregation should not be the singular feature anchoring any staging system in PD. The landmarks that defined the proposed stages have not been proven to be predictive of future disease progression or events, as required by a valid staging system.[12] The AD experience, also reviewed above, supports this notion because the most recent update of AD classification incorporates a larger number of variables.

## Practical Considerations for a PD Classification and Staging System

When evaluating a staging system, many points must be considered. Below we highlight the discussion that took place during the MDS-sponsored meeting in April 2023 on this important topic.

### Staging System Development Methodology

The basis of a staging system can be biological, clinical, or a combination of the two. Given the strong motor and non-motor dimensions of PD and the growing developments in biomarker research, the participants agreed that the ideal formula would combine both approaches. A

staging system development requires a robust methodology with a prior definition of the population or disease to be staged. Currently, because there is no consensus on a unified biological definition based on α-syn and because staging systems follow established definition, we cannot logically move into even suggestions of biologically based staging criteria. Specifically, PD must be defined clinically for a clinical staging system and biologically for a biological one or defined in an integrated way embracing both biological and clinical anchors. Furthermore, an explicit indication of the system's intended use (and benefits as well as possible adverse consequences) for either clinical care, research, or both is necessary. Finally, a protocol, preferably an evidence-based consensus method, would need to be developed. Specifically, this protocol requires an accompanying validation process and analytic plan with prespecified strategies for longitudinal review and revision.[22] Scientifically, it is critical that the anchors defining each stage are clear and represent the progression of the disease. As such, stage 1, however defined, is milder and has a better prognosis than more advanced (or numerically or alphabetically higher) stages. As such, transition to stage 2 has more serious prognostic implications than stage 1, but would still have a better longitudinal prognosis than Stage 3. Moreover, patients should go through stages sequentially. In the absence of disease-modification treatments, subjects with PD are expected to relentlessly progress along stages, although the duration of each stage could vary between subjects.

### Biological and Biomarkers Issues

For a biological definition to be operationalized into a diagnosis, classification, and/or staging system, it must be measurable. In the case of assays involving α-syn, this criterion poses a specific challenge. α-Syn, a protein with a cellular function that is not fully understood,[23] can misfold and aggregate in the brain with local levels higher near the site of aggregation. This aggregation in the brain is, however, not reflected in any direct way by the SAA method. Current methods used by research groups to measure α-syn require a CSF sample, making testing for α-syn levels challenging for most PD patients worldwide at the present time.[14,24,25] Yet, this is a rapidly evolving field with the potential development of blood-based SAA. In addition, there is the possibility to document the presence of α-syn in other body fluids or tissues (eg, skin) either by SAA or other accepted techniques such as immunohistochemistry and immunohistofluorescence.[26]

The limitation to CSF or tissue biopsies may change with recent investigations documenting the ability to measure α-syn in peripheral blood using immunoprecipitation-based real-time quaking-induced conversion in the serum[27] or investigating seeding-competent α-syn within blood exosomes.[28] However, both methods have not been replicated by other groups yet. In addition, SAA is currently a qualitative method, and a quantitative assay would be needed to allow correlations with clinical severity measures or markers of disease progression to be incorporated into a staging system.

In addition to the challenge of sample collection, current methods also have limited precision, and therefore, can only be used as a binary output (present or absent) for disease identification. Currently, these approaches are unable to capture the extent of α-syn protein aggregation and its longitudinal change.[29] The quantification tools available continue to expand and develop; therefore, the prospect of a biologically valuable measurement tool of α-syn levels remains hopeful, but is not clinically applicable or tested worldwide at the present time. Given these challenges of biological complexity, genetic disease forms, measurement precision, and global validation, participants agreed that a greater consensus on a clinical and biological definition and staging of PD needs to be established. Future studies will test how well biomarkers correlate to the post-mortem pathology that currently still serves as the confirmatory diagnostic standard in PD.

We recognize that the advancement in biomarkers research has been the main impetus for the conversation on new biological definition, classification, and staging system proposals for PD. However, important considerations must be taken into account. This field is a rapidly advancing area of research, and any staging system must be prepared for the validation and expansion of tools on an ongoing basis. Even as these advances come to fruition, it is problematic and potentially counterproductive to anchor a staging system on an unstable set of criteria if the major goals of the process include worldwide use, a clear messaging vehicle for patients, and to be a rapid source of communication. Whereas a "working" or provisional set of criteria moves the field forward for field testing and may be considered strictly for research purposes, a final definition requires validation before adoption or official designation.

### Pathological Issues

Ideally, any biological staging biomarker must appropriately correlate to the pathology at post-mortem studies. This is critical for use in the disease definition. In contrast, if one wants to use a biomarker for staging, it must predict progression or a future disease event. It remains unclear if peripheral α-syn pathology precedes central nervous system α-syn pathology. Studies that include post-mortem pathology often highlight the prevalence of co-pathologies.[30-32] Knox et al[33] showed, for instance, that 50% of PD individuals with mild cognitive impairment, one of the pathologically validated clinical markers of late-stage progression, have AD pathology on post-mortem studies. Additionally, post-mortem studies confirm that there are pathological findings, including α-syn aggregation, in the absence of motor symptoms.

### Differential Diagnosis Issues

Meeting participants placed special emphasis on the point that a biological definition of a disease must be useful to distinguish it from conditions sharing clinical similarities. α-Syn aggregation disorders are clinically variable and include PD, DLB, and MSA and its common prodromal condition, RBD. Although in PD, the α-syn aggregation occurs predominantly in neurons; in MSA it takes place predominantly in oligodendrocytes. In most assays, SAA can identify α-syn aggregates in the CSF, but they do not distinguish between the different diseases, although one current assay identified different seeding kinetics between PD and MSA.[34,35]

There is controversy among experts, whether the current clinically defined PD and DLB are one biological entity or biologically different diseases with some overlap, whereas their clinical pictures and evolution are different. There are important gaps in knowledge for which answers need to be found to develop a valid biological definition probably followed by a staging system. New biological concepts of PD may impact on this discussion as well. Preclinical development of markers that differentiate conditions based on protein folding appear promising, but again need to be applicable to the issue of differential clinical diagnosis.[34]

### Genetic Issues

Genetic characteristics can be appropriately considered with definition and classification. It should be noted that the number of individuals with genes that are causal for PD (ie, Mendelian/monogenic forms) or carriers of risk variants such as in the *GBA1* gene, that may also modulate the disease course, is low. However, as these genes are important to understand the pathogenesis of PD and the number of these patients is still significant, these pathogenic variants should be considered as part of a biological definition, classification, or staging system. One challenge in incorporating genetics in the PD diagnosis and staging systems is the variability of pathogenic variant frequencies. It is well known that a same pathogenic variant can be protective or harmful depending on the population under consideration and, moreover, the same pathogenic variant can result in different pathologies depending on the ethnicity of the carrier. It must also be kept in mind that most genetic studies in PD have been limited to Caucasian individuals in Europe and North America.[36-38]

### Clinical Practice Issues and Global Implications

When considering any staging system for clinical practice, the considerations must focus on the patient's experience and the tools available in the clinic. The feasibility of running a test in an everyday clinical setting must be of primary concern. Highly invasive and technologically sophisticated tests are currently inaccessible to many patients globally, and the MDS is highly conscious of its international representation. In fact, considering the geographic location of centers performing dopamine transporter imaging[39] and SAA, it can be estimated that at best a small minority of the currently diagnosed PD population globally will have access to these tests. Of note, even a substantial number of individuals living in high-income areas currently have limited access to tests that could potentially be used in the proposed diagnosis and staging systems under development. This opens up the possibility of creating a highly undesirable, two-tiered diagnostic and staging system for PD, dictated by access to technology limited by geography and expense. The situation— as unfair and unequal as it is—is similar in the abovementioned field of cancer (or AD and even HD), where access to sophisticated tumor staging, imaging, and genotyping is also limited to patients in certain geographic areas and often based on financial resources available. Despite this inequality that needs to be overcome, these staging systems may be useful and improve treatment and prognosis of many patients. It is a true dilemma, and we need to do everything we can to help promote availability of the best diagnostic and staging tools as widely as possible. Any current proposals for definition, classification, or staging of PD must be clearly recognized as for research purpose only.

Furthermore, the prospect of a staging system for PD must be approached with caution. In the established healthcare systems, this shift in diagnosis would have a major impact on patients, governments, insurers, clinical trials, and other stakeholders within the field. For instance, in many areas of the world access to care is coupled with carrying a World Health Organization International Classification of Diseases (ICD) code. Some of the individuals meeting the proposed diagnosis and staging schema will not meet criteria for ICD codes. It is fair to predict that the epidemiological research of these conditions and, consequently, public health policies could undergo significant changes if the current proposals are incorporated into clinical practice. Ethical responsibility must be established for subjects who may receive a diagnosis before experiencing symptoms or those who have previously received a clinical PD diagnosis, but will not meet the biological diagnosis criteria. Conversely, healthy subjects, who may or may not ever develop clinical PD, may be labelled as having a disease by virtue of a biological definition. A change in diagnosis can significantly impact a patient's access to benefits and mental health. The management and counseling of these patients may be advised similarly to what is done for genetic counseling, for example, for patients with HD.[40-42] The proposed criteria for diagnosis and staging are primarily intended for research. Even if they are validated, they should be used for research alone until it is proved that people will benefit from the new criteria as part of regular clinical

care. One must be aware that in the AD field these tests have become available to the public outside the research and even clinical care context, generating undue confusion and uncertainty.[43]

### *Clinical Trial Issues*

In clinical trials, staging concerns focus on correctly identifying a group of patients with the same disease and quantifying the disease severity and progression. However, any measurement must be reproducible and correlate with the patient's daily function for the trial results to be clinically meaningful. For individuals in a pre-symptomatic stage, disease-defining biomarkers applicable to clinical trials must be sensitive to changes in the underlying biology. Currently, there is no such biomarker of change in PD. Specifically, there is no reliable way of predicting if, when and which clinical syndrome, a CSF-SAA-positive individual will develop, and currently no quantification from CSF-SAA that measures change over time. This limitation is a major drawback that will scientifically complicate applications of staging systems reliant on this assay for clinical trials of prodromal or pre-symptomatic PD. The proposed systems should include a scale for use in clinical trials to give specificity and to prevent over-generalization.

## Conclusions

MDS recognizes the value and efforts of current proposals for a biological diagnosis and staging or classification systems in PD. Notwithstanding the tremendous potential this paradigm shift holds for PD and development of novel therapies and the relevance of these studies, at the present time such an approach needs to be validated in terms of the biological basis as well as the ability to correlate with progression of the disease and the experience of individuals with clinically defined PD and related disorders. Therefore, the currently available proposals will need to be thoroughly scrutinized by MDS and the scientific community in general to assess their value, and steps for future development. At present, they cannot be viewed as the basis for any MDS-endorsed change in disease definition, classification, or staging.

Indeed, biological assays and disease markers are promising exploratory outcomes, but their adoption will depend on field testing across the gamut of PD. Accessibility to those tests for all those affected by PD worldwide is another practical concern that requires continuous attention. The MDS leadership draws attention to this well-established validation requirement in citing one of its prior large-scale programs, the development of the MDS-revision of the Unified Parkinson's Disease Rating Scale. The latter required full cognitive pre-testing and full field validation before it allowed publication and official presentation as a new assessment tool. A similar process could be applied to these new initiatives to introduce biological markers to help define, stage, or classify PD. The discoveries are of interest and have promise at the present time, but they will need to be fully tested and validated before any changes in official disease definition, categorization, or staging can be considered. MDS will continue to encourage discussions, engaging foundations, governments, regulatory agencies, and patient groups in the process so that science moves forward with neutrality and rigor. MDS awaits such developments and encourages others to have the same engagement and vigilance. ■

**Acknowledgment:** MDS provided financial support for the organization of the Atlanta In-Person Meeting.

## Data Availability Statement

This manuscript reflects discussions held a meeting convened by the MDS. As such it did not involve data collection.

## References

1. Dukes CE. The classification of cancer of the rectum. J Pathol Bacteriol 1932;35(3):323–332.
2. Greene FL, Sobin LH. The staging of cancer: a retrospective and prospective appraisal. CA Cancer J Clin 2008;58(3):180–190.
3. Ammar KA, Jacobsen SJ, Mahoney DW, et al. Prevalence and prognostic significance of heart failure stages: application of the American College of Cardiology/American Heart Association heart failure staging criteria in the community. Circulation 2007;115(12):1563–1570.
4. Severino P, Mather PJ, Pucci M, et al. Advanced heart failure and end-stage heart failure: does a difference exist. Diagnostics (Basel) 2019;9(4):170.
5. Bueter A. On illness, disease, and priority: a framework for more fruitful debates. Med Health Care Philos 2019;22(3):463–474.
6. Aggarwal R, Ringold S, Khanna D, et al. Distinctions between diagnostic and classification criteria? Arthritis Care Res (Hoboken) 2015;67(7):891–897.
7. Kufe D, Pollock R, Weichselbaum R, et al. Holland-Frei Cancer Medicine. 6th ed. Hamilton, ON: BC Decker; 2003.
8. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the unified Parkinson's disease rating scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord 2008;23(15):2129–2170.
9. Parkinson J. An Essay on the Shaking Palsy. London, UK: Whittingham and Rowland; 1817.
10. Charcot J. Lectures on the Diseases of the Nervous System Delivered at la Salpetriere (translated by G. Sigerson). London: New Sydenham Society; 1877.
11. Outeiro TF, Alcalay RN, Antonini A, et al. Defining the riddle in order to solve it: there is more than one "Parkinson's disease". Mov Disord 2023;38(7):1127–1142.
12. Simuni T, Chahine L, Poston K, et al. Biological definition of neuronal a- synuclein disease: towards an integrated staging system for research. Lancet Neurology. In press 2024.
13. Kalia LV, Lang AE, Hazrati LN, et al. Clinical correlations with Lewy body pathology in LRRK2-related Parkinson disease. JAMA Neurol 2015;72(1):100–105.
14. Siderowf A, Concha-Marambio L, Lafontant DE, et al. Assessment of heterogeneity among participants in the Parkinson's progression

markers initiative cohort using alpha-synuclein seed amplification: a cross-sectional study. Lancet Neurol 2023;22(5):407–417.

15. Jack CR Jr, Bennett DA, Blennow K, et al. A/T/N: an unbiased descriptive classification scheme for Alzheimer disease biomarkers. Neurology 2016;87(5):539–547.
16. Hampel H, Hardy J, Blennow K, et al. The amyloid-beta pathway in Alzheimer's disease. Mol Psychiatry 2021;26(10):5481–5503.
17. Jack CR Jr, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 2010;9(1):119–128.
18. Tabrizi SJ, Schobel S, Gantman EC, et al. A biological classification of Huntington's disease: the integrated staging system. Lancet Neurol 2022;21(7):632–644.
19. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology 1967;17(5):427–442.
20. Goetz CG, Poewe W, Rascol O, et al. Movement Disorder Society task force report on the Hoehn and Yahr staging scale: status and recommendations. Mov Disord 2004;19(9):1020–1028.
21. Höglinger GU, Adler CH, Berg D, et al. SynNeurGe: research criteria for a biological classification of Parkinson's disease In Press.
22. Mestre TA, Fereshtehnejad SM, Berg D, et al. Parkinson's disease subtypes: critical appraisal and recommendations. J Parkinsons Dis 2021;11(2):395–404.
23. Burre J, Sharma M, Sudhof TC. Cell biology and pathophysiology of alpha-Synuclein. Cold Spring Harb Perspect Med 2018;8(3):a024091.
24. Russo MJ, Orru CD, Concha-Marambio L, et al. High diagnostic performance of independent alpha-synuclein seed amplification assays for detection of early Parkinson's disease. Acta Neuropathol Commun 2021;9(1):179.
25. Majbour N, Aasly J, Abdi I, et al. Disease-associated alpha-Synuclein aggregates as biomarkers of Parkinson disease clinical stage. Neurology 2022;99(21):e2417–e2427.
26. Magalhaes P, Lashuel HA. Opportunities and challenges of alpha-synuclein as a potential biomarker for Parkinson's disease and other synucleinopathies. NPJ Parkinsons Dis 2022;8(1):93.
27. Okuzumi A, Hatano T, Matsumoto G, et al. Propagative alpha-synuclein seeds as serum biomarkers for synucleinopathies. Nat Med 2023;29(6):1448–1455.
28. Kluge A, Bunk J, Schaeffer E, et al. Detection of neuron-derived pathological alpha-synuclein in blood. Brain 2022;145(9):3058–3071.
29. Poggiolini I, Gupta V, Lawton M, et al. Diagnostic value of cerebrospinal fluid alpha-synuclein seed quantification in synucleinopathies. Brain 2022;145(2):584–595.
30. Irwin DJ, Hurtig HI. The contribution of tau, amyloid-Beta and Alpha-Synuclein pathology to dementia in Lewy body disorders. J Alzheimers Dis Parkinsonism 2018;8(4):444.
31. Chu Y, Hirst WD, Kordower JH. Mixed pathology as a rule, not exception: time to reconsider disease nosology. Handb Clin Neurol 2023;192:57–71.
32. Spotorno N, Coughlin DG, Olm CA, et al. Tau pathology associates with in vivo cortical thinning in Lewy body disorders. Ann Clin Transl Neurol 2020;7(12):2342–2355.
33. Knox MG, Adler CH, Shill HA, et al. Neuropathological findings in Parkinson's disease with mild cognitive impairment. Mov Disord 2020;35(5):845–850.
34. Shahnawaz M, Mukherjee A, Pritzkow S, et al. Discriminating α-synuclein strains in Parkinson's disease and multiple system atrophy. Nature 2020;578(7794):273–277.
35. Ozawa T, Paviour D, Quinn NP, et al. The spectrum of pathological involvement of the striatonigral and olivopontocerebellar systems in multiple system atrophy: clinicopathological correlations. Brain 2004;127(Pt 12):2657–2671.
36. Zhang Y, Shu L, Sun Q, et al. Integrated genetic analysis of racial differences of common GBA variants in Parkinson's disease: a meta-analysis. Front Mol Neurosci 2018;11:43.
37. Shu L, Zhang Y, Sun Q, Pan H, Tang B. A comprehensive analysis of population differences in LRRK2 variant distribution in Parkinson's disease. Front Aging Neurosci 2019;11:13.
38. Schumacher-Schuh AF, Bieger A, Okunoye O, et al. Underrepresented populations in Parkinson's genetics research: current landscape and future directions. Mov Disord 2022;37(8):1593–1604.
39. Lim SY, Tan AH, Ahmad-Annuar A, et al. Parkinson's disease in the Western Pacific region. Lancet Neurol 2019;18(9):865–879.
40. Crook A, Jacobs C, Newton-John T, O'Shea R, McEwen A. Genetic counseling and testing practices for late-onset neurodegenerative disease: a systematic review. J Neurol 2022;269(2):676–692.
41. Nance MA. Genetic counseling and testing for Huntington's disease: a historical review. Am J Med Genet B Neuropsychiatr Genet 2017;174(1):75–92.
42. Schaeffer E, Toedt I, Kohler S, Rogge A, Berg D. Risk disclosure in prodromal Parkinson's disease. Mov Disord 2021;36(12):2833–2839.
43. Rubin R. Consumers can now buy a blood test to evaluate their Alzheimer disease risk, but should they? JAMA 2023;330(13):1214–1216.

## Appendix

Meeting participants: Francisco Cardoso; Charles Adler; Daniela Berg; Bas Bloem; Michael S. Fitts; Thomas Gasser; Christopher G. Goetz; Clifford Jack; Anthony Lang; Shen-Yang Lim; Irene Litvan; Kenneth Marek; Tiago A. Mestre; Brit Mollenhauer; Njideka Okubadejo; Michael Okun; Ron Postuma; Cristina Sampaio; Tatyana Simuni; Per Svenningsson; Louis Tan; Taiji Tsunemi; and Claudia Trenkwalder.