Recommendations of the Global Multiple System Atrophy Research Roadmap Meeting

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Neurology® 2018;90:74-82. doi:10.1212/WNL.0000000000004798

Abstract

Multiple system atrophy (MSA) is a rare neurodegenerative disorder with substantial knowledge gaps despite recent gains in basic and clinical research. In order to make further advances, concerted international collaboration is vital. In 2014, an international meeting involving leaders in the field and MSA advocacy groups was convened in Las Vegas, Nevada, to identify critical research areas where consensus and progress was needed to improve understanding, diagnosis, and treatment of the disease. Eight topic areas were defined: pathogenesis, preclinical modeling, target identification, endophenotyping, clinical measures, imaging biomarkers, nonimaging biomarkers, treatments/trial designs, and patient advocacy. For each topic area, an expert served as a working group chair and each working group developed priority-ranked research recommendations with associated timelines and pathways to reach the intended goals. In this report, each groups' recommendations are provided.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

α-syn = α-synuclein; **MSA** = multiple system atrophy; **SWOT** = strengths, weaknesses, opportunities, and threats.

Multiple system atrophy (MSA) is a rare and devastating neurodegenerative disorder presenting clinically with severe autonomic failure, parkinsonism, cerebellar ataxia, and corticospinal tract signs in varying combinations.[1] MSA is considered an orphan disease with an annual incidence rate of 0.1–3 per 100,000 depending on age and geographic region.[2–5] The estimated prevalence rates range from 1.9 to 4.9.[4,6–9] MSA is a progressive and incurable disease leading to death typically within 9 years after symptom onset.[10–17] There are substantial knowledge gaps in the scientific understanding of and clinical approach to MSA. The pathophysiology underlying MSA is poorly understood, although abnormal forms of α-synuclein (α-syn) appear to play a key role in the pathogenic neurodegenerative cascade.[18] Diagnostic certainty can be challenging and symptomatic therapies are of limited and transient benefit in alleviating disease burden.[12,15] Because MSA is a rare disease, international collaboration is critical to generate cohorts of sufficient size for studying and advancing knowledge about this disorder; such global efforts can be difficult to implement.[19] In 2014, an international meeting involving leaders in the field and MSA advocacy groups was convened in Las Vegas, Nevada, to address these issues and develop a roadmap for MSA-related research. A summary of these recommendations is provided below.

Methods

Similar to the development of the 2013 NIH Alzheimer's Disease–Related Dementias Conference,[20] the overall process was divided into planning, preconference, conference, and postconference activities.

Planning

Planning efforts began in early 2014 when the meeting chairs defined the objectives of the meeting. The prespecified goals of the meeting are presented in the table. The 6 objectives were then incorporated into 7 topics, and for each topic a 5- to 6-member working group and chair were designated (see Results). Together with the working group chairs, the meeting chairs and advisory board recruited relevant researchers for each working group.

Preconference

Each working group was tasked with developing a prioritized list of up to 4 recommendations for their topic prior to the meeting. Conference calls were convened for each working group prior to the conference to develop draft recommendations. All recommendations were based on the working group's analysis of current strengths, weaknesses, opportunities, and threats (SWOT analysis) in their research area. The SWOT analysis was summarized and incorporated into a "need" describing the rationale for the recommendation. In addition, a "pathway" was developed to identify the essential items to achieve the recommended goal. Thus, all recommendations had the following predefined structure: recommendation (what?), need (why?), and pathway (how?). Complete full-text final recommendations from each working group are provided in appendix e-1 (links.lww.com/WNL/A22).

Conference

The Global MSA Research Roadmap Meeting was held on November 1–2, 2014, at the Keep Memory Alive Event Center on the campus of the Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas, Nevada. There were approximately 75 international conference participants representing academia, industry, advocacy groups, and the NIH. Working groups were first charged to discuss and finalize their premeeting working group recommendations during an in-person workshop at the conference. Subsequently, each working group presented their recommendations to the meeting participants, which was followed by an open discussion on the proposed recommendations, their priority levels, and the anticipated timelines.

Postconference

Each working group finalized their recommendations incorporating conference feedback and discussion. Subsequently, a manuscript was developed that included input from the conference chair and co-chairs, advisory panel, and working group chairs.

Results

The primary outcome of the conference is the prioritized MSA research roadmap recommendation list summarized in figures 1 and 2. Estimated timelines and pathways to reach the intended goals were also developed and are summarized in figures e-1 and e-2 (links.lww.com/WNL/A21). Research recommendations are presented by topic area and prioritized as per each working group, incorporating the meeting discussion. The complete working group documents are provided in appendix e-1 (links.lww.com/WNL/A22).

Key themes drawn from the research roadmap recommendations warrant consideration. Preclinical MSA research would benefit from improved understanding of pathogenesis, particularly the development of novel preclinical models that more faithfully reproduce MSA pathology, symptomatology, and progression. Such models would also enable standardized preclinical testing of potential therapies. Clinical research would benefit from improved diagnostic accuracy, particularly for early diagnosis through advances in clinical and biomarker research. Furthermore, and similar to the preclinical recommendations, coordinated and standardized diagnostic and therapeutic

Table Prespecified meeting objectives

1. To develop a roadmap for MSA-related research to provide a framework for therapeutic development from an expanded understanding of the following:
• Molecular pathogenesis
• Preclinical modeling
• Targeting of pathologic development and spread
• Understanding divergence of α-synucleinopathy vs PD
• Disease phenotypes and outcome measures, including global registry
• Disease onset, disease progression, and therapeutic response biomarkers
• Experimental therapeutic development
2. To identify critical needs/barriers to advance MSA research
3. To further acquaint funding agencies with MSA and unmet research/therapeutic needs
4. To further global coalitions and collaborative efforts to advance research in MSA
5. To engage pharmaceutical and biotechnology companies in discussions on MSA therapeutic development
• Including MSA as a potential model disease for neurodegenerative therapeutic development
• Including the commonality of α-synuclein in MSA and PD as integral to disease pathology
6. To elevate awareness of MSA through publicity, publication resultant from the meeting, and engagement of stakeholders for MSA advocacy

Abbreviations: α-syn = α-synuclein; MSA = multiple system atrophy; PD = Parkinson disease.

approaches were considered essential to facilitate future collaboration and develop and validate outcome measures for future clinical trials.

The Pathogenesis Working Group set 3 research priorities with elucidation of the relationship between oligodendroglial pathology and neuronal death viewed as the primary research area. It was also agreed that additional work on α-syn, through investigation of protein structure, assembly into filaments, and propagation of abnormal structure, would significantly advance the field. Finally, the panel thought that additional investigations in regional anatomic vulnerability to pathology, initiating factors, and changes that precede α-syn accumulation, aggregation, posttranslational modifications, and cell-to-cell transmission and their role in driving disease would be warranted. The initiation of projects providing insights into these research priorities were estimated to require at least 3 years and formative work would not be expected to be completed before 2020.

Current in vivo MSA models incompletely replicate the disease process,[21] which may contribute to their failure to predict clinical benefit from attempts at therapeutic intervention. The Preclinical Modeling Working Group ranked the development of novel rodent MSA models incorporating recent findings from nonvertebrate models, in vitro models, as well as human brain tissue studies as top priorities. Thus far, behavioral studies in MSA animal models mainly have focused on motor deficits whereas nonmotor endpoints have not been studied systematically. However, both motor and nonmotor outcomes are pertinent for drug discovery in MSA since patients experience motor impairment along with severe generalized autonomic failure, cognitive deficits, and other nonmotor symptoms. Therefore, the panel identified the characterization of existing transgenic MSA models using nonmotor endpoints, wet biomarkers, and multimodal neuroimaging as another important research priority. MSA genetics and underlying pathogenesis remain poorly understood and the generation of hypothesis-blind models of MSA (i.e., induced pluripotent stem cells) also was considered another top research priority.

The Preclinical Target Development Working Group identified α-syn as the most promising target for future interventional therapies. It was suggested that research should focus particularly on (1) measuring and reducing α-syn pathology in models of oligodendroglial α-syn overexpression for future translation into human trials and (2) identification/validation of biomarkers through bidirectional/iterative feedback with human studies. A close collaboration between preclinical and clinical researchers is critical to facilitate the development of reliable biomarkers; clinical studies often generate hypotheses regarding which biomarkers may hold promise, and preclinical testbeds can then be used to develop specific diagnostic tools. After clinical validation, these newly developed tools may facilitate therapeutic development and improve patient care.

The Clinical MSA Phenotype Working Group noted that it is essential, as with other neurodegenerative disorders, for any effective treatment to be started as early as possible in the disease course. However, the low sensitivity of early clinical diagnosis of MSA means that the disease is typically diagnosed at a time when the pathology is advanced.[22] Therefore, the clinical working group on MSA phenotype concluded that developing a patient-completed clinical questionnaire and physician-confirmed checklist should improve sensitivity of early clinical diagnosis and ranked this objective as their top research priority. The working group recommended developing a detailed operations manual to facilitate the diagnosis of MSA using the current consensus criteria including standardized wording of key clinical questions.[23] As a second step, the development of a clinical score–based aid to diagnose MSA without necessarily requiring sophisticated and costly investigations would be highly warranted.

Improvements in clinical measures were also identified as a research area that requires special attention. The Clinical Outcome Measures Working Group agreed that the development of a valid international rating scale based on the revision and improvement of the existing Unified MSA Rating Scale[24,25] should be the top research priority, which could be

Figure 1 Preclinical working groups and recommendations (priority-ranked)

	Committee members	Recommendations
Pathogenesis WG #1	Janice Holton (Chair) Thomas Gasser Matt Huentelman Poul H. Jensen Ronald Melki Shoji Tsuji	(1) Understand the relationship between oligodendroglial pathology and neuronal death and determine methods to influence these interactions. (2) Understand the role of α-syn in MSA by investigating protein structure, assembly into filaments and propagation of abnormal structure. (3) Understand regional vulnerability to pathology, initiating factors, early cellular and pathological changes that precede α-syn accumulation, aggregation, post-translational modifications, cell-to-cell transmission of α-syn and their role in driving disease.
Modelling WG #2	Gregor Wenning (Chair) Patrik Brundin Un Kang Vikram Khurana Woojin S. Kim Eliezer Masliah Wassilios Meissner	(1) Develop novel in vivo models of MSA for interventional target discovery. (2) Characterize existing tg MSA models using non-motor endpoints, wet biomarkers and multimodal neuroimaging. (3) Develop iPSC models of MSA for interventional target discovery and screening of candidate neuroprotective agents.
Target development WG #3	Glenda Halliday (Chair) Gal Bitan Dale Schenk Nadia Stefanova Patricia Walicke	(1) Develop biomarkers for and treatments to the increased alpha-synuclein in animal models overexpressing alpha-synuclein in oligodendroglia.

α-syn = α-synuclein; iPSC = induced pluripotent stem cell; MSA = multiple system atrophy.

achieved employing a model similar to what has recently been conducted by the International Parkinson and Movement Disorders Society to update the Unified Parkinson's Disease Rating Scale.[26–28] There was consensus that an international registry providing standardized and comprehensive phenotypic data linked to local biobanks/biomaterial collections as well as imaging data would advance the field. Thus, the clinical outcome measure working group defined the creation of a unified dataset for MSA and implementation of an international global registry as their second top research priority.

The Imaging Biomarkers Working Group recognizes that previous studies provide a rich MRI repertoire with potential to be used in diagnosis, natural history, and treatment studies.[29] There is, however, lack of consistent evidence for MRI-based changes in MSA at magnetic fields of 3.0T or higher, scarce evidence for early MRI-based changes, and limited comparability among studies given heterogeneous MRI protocols, study populations, and different segmentation techniques. The working group prioritized the development of standardized protocols for MRI-based diagnostics at current conventional field strengths with exploration of the sensitivity of a multimodal approach (e.g., PET/MRI, multimodal MRI) to disease progression and preclinical diagnosis as their top priority. Another focus area was the development and implementation of functional imaging protocols with currently available tracers to evaluate MSA-related brain networks and dopaminergic integrity using PET and SPECT. Finally, the imaging panel agreed that development of sensitive and reproducible imaging agents to assess molecular aspects of MSA pathology including α-syn aggregation is warranted.

The Non-Imaging Biomarkers Working Group noted that fluid and tissue biomarker data for MSA are sparse,[30] and there is a is a critical need to standardize and validate methods for both cross-sectional and longitudinal studies. The working group prioritized establishing an infrastructure for standardized collection of biofluids (CSF and blood-based) and tissues (standardized skin biopsy; central and autonomic nervous system at autopsy) their top research priority. Another recommendation was the exploitation of ongoing multicenter biomarker cohorts (both existing and future ones) in 2 ways: (1) to determine the profile of candidate, pathologic analytes in patients with MSA through validated testing platforms; and (2) to interrogate specimens in an unbiased manner through complementary strategies for the discovery of potential markers. Further research toward the development of a cutaneous biomarker for MSA by measuring the degree of deposition for pathologic variants of α-syn deposition in cutaneous autonomic nerves was also considered important.

Similar to other group recommendations, the Clinical Treatments and Trials Working Group prioritized the need for developing tools to facilitate earlier diagnosis and for creating biobanking infrastructure dedicated to MSA. In addition, prospective cohort studies to characterize progression rates and sensitivity to change over time of clinical, imaging, and other biofluid markers were ranked as top research priority. Additional recommendations were focused on the development of

Figure 2 Clinical working groups and recommendations (priority-ranked)

	Committee members	Recommendations
Phenotype WG #4	Niall Quinn (Chair) Florian Krismer David Robertson Peter Lewitt Jeremy Schmahmann	(1) Develop a patient-completed clinical questionnaire and physician-confirmed check-list to aid early clinical diagnosis of MSA-P and MSA-C. (2) Write an "operations manual" on how to diagnose MSA and to develop a GLOBAL clinical score-based aid to diagnose MSA that can be used in all healthcare settings, and does not necessarily require, but can be supplemented by, special investigations.
Clinical outcome measures WG #5	Olivier Rascol (Chair) Art Hewitt Bill Holt Horacio Kaufmann Thomas Klockgether Glenn Stebbins	(1) Development of a valid international rating scale based on the revision and improvement of the existing UMSARS. (2) Creation of a unified dataset for MSA and implementation of an international global registry.
Biomarkers (Imaging) WG #6a	David Eidelberg (Chair) David Brooks Klaus Seppi Andrew Siderowf Ryan Walsh	(1) Develop standardized protocols for MRI-based diagnostics at conventional field strengths and explore sensitivity of multimodal approach (e.g PET/MRI) to disease progression and preclinical diagnosis. (2) Develop multicenter task force to explore, assess, and implement functional imaging protocols with currently available tracers to evaluate MSA-related brain networks and dopaminergic integrity using existing PET and SPECT tracers. (3) Develop sensitive and replicable imaging agents to assess molecular aspects of MSA pathology including synuclein aggregation and local CNS inflammatory activity in the brains of MSA patients.
Biomarkers (non-imaging) WG #6b	Leslie Shaw (Chair) Roy Freeman Andreas Jeromin Michael Schlossmacher Jing Zhang	(1) Identify and establish infrastructure needs including standardized procedures for biological biomarkers--both collection of fluids and tissues and the biomarker tests that will be recommended for use--in MSA multicenter studies. (2) Determine the "pathologic biomarker profiles" in MSA patients using pathology-based and "unbiased" validated biomarker tests in biofluids and CNS/ANS autopsy tissues in ongoing multicenter studies. (3) Develop a cutaneous biomarker for multiple system atrophy by measuring alpha-SYN deposition in cutaneous autonomic nerves.
Treatments and trials WG #7	Phillip Low (Chair) Victor Abler Hubert Fernandez Wendy Galpern Susanne Ostrowitzki Steven Piantadosi Werner Poewe	(1) Characterize and validate clinical markers of disease activity and progression through natural history studies to inform the design of clinical trials. (2) Develop sensitive outcomes to evaluate disease modifying therapies including validated biomarkers of disease activity, progression, and response to treatment. (3) Identify disease modifying therapies, and initiate exploratory and confirmatory randomized clinical trials (RCT). (4) Identify promising treatments to improve major symptoms and function in patients with MSA.
Patient advocacy WG #8	Pam Bower (Chair) Judy Biedenharn Philip Fortier Larry Kellerman (Co-Chair) Carol Langer Cyndi Roemer Lily Shih Sharon Sutton	(1) Increase knowledge about MSA among medical professionals by developing a continuing education program that emphasizes patient-centered care. Develop accredited MSA centers of excellence to serve as models. (2) Initiate a funded liaison who works with stakeholders to access funds, cultivate the development of innovative technologies, and nurture collaborative research programs. (3) Institute a public information structure to develop and disseminate information tailored for advocacy and awareness. (4) Develop a dynamic and collaborative network of partnerships among relevant organizations that will strengthen advocacy, raise awareness, support patient responsive research and government action.

ANS = autonomic nervous system; MSA = multiple system atrophy; SYN = synuclein; UMSARS = Unified MSA Rating Scale.

novel therapies for disease modification and promising symptomatic treatments. It was recognized that advances in preclinical and clinical research as outlined above are needed to facilitate the development of novel treatments.

The Patient Advocacy Working Group highlighted the importance of developing a continuing education program to inform medical and allied health professionals about MSA, along with establishing clinical centers of excellence, as the top

priorities. In addition, a funded liaison who works with stakeholders to access funds, cultivate the development of innovative technologies, and nurture collaborative research programs was considered another important goal. A public information structure to develop and disseminate information tailored for advocacy and awareness should be another focus area in the next years. Finally, a collaborative network of relevant, nonmedical organizations would be important to strengthen advocacy and support patient-responsive research.

Discussion

In the last decade, MSA has seen an encouraging increased interest among clinical and experimental scientists, along with improved international collaboration. In this spirit, a dedicated MSA research roadmap meeting that involved global leading MSA researchers was undertaken, with the overarching goal of helping to further coordinate thinking and efforts to enable progress toward clinically meaningful therapeutics. This report reflects the carefully considered recommendations developed collaboratively by a large group of leaders in the field and is intended to be an authoritative (but not the only) source for guiding future research efforts and priorities regarding MSA.

Each of the recommendations in this report provides important research goals on its own. During the conference, differing opinions about the current state and future directions were discussed and, upon agreement, incorporated into the final recommendation. Hence, the prioritized recommendations list reflects a thoughtful, collaborative, and efficient approach to ultimately prevent, stop, or cure MSA. It is important to mention that lower-ranked recommendations in this report do not reflect a lack of importance; inclusion suggests that the research objective is indeed among the top priority items in the field. In addition, these recommendations are not meant to be exclusive. It will be critical to continuously explore new research areas as they emerge, and modify the research roadmap accordingly. In addition, we recognize achievement of these research goals is ambitious and will require not only funding but also the continued commitment of established as well as new investigators in the MSA field. The present recommendations constitute an initial framework for future research efforts in MSA. These goals may be refined in the future, and it is recognized that an overall ranking irrespective of the different areas of research may be useful to the research community and cost-effectiveness is also an important consideration.

Although major knowledge gaps remain, the prerequisites for change are in place: (1) a passionate and committed research community to execute this research plan, (2) a growing international collaborative that encompasses preclinical work as well as clinical research, and (3) a fully dedicated and well-organized network of advocacy. The rate of progress is limited in part by the rarity of the illness and the available resources, highlighting the vital role of MSA advocacy and collaboration. Our sincere hope is that the Global MSA Research Roadmap recommendations will help to advance research in MSA, broaden the knowledge and awareness of MSA, recruit talented scientists from neighboring disciplines, further raise awareness, and thus allow us as a community to develop effective therapies as quickly as possible for this fatal disease.

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Acknowledgment

This article is in memory of MSA patient Kerry Simon and in acknowledgment of "Fight MSA," an initiative Kerry helped start that provided support to the Global MSA Research Roadmap Meeting. The authors also acknowledge the "Keep Memory Alive" organization that helped support and host the Global MSA Research Roadmap Meeting. Finally, the authors acknowledge Dale Schenk in memoriam, who spoke at and provided critical insight to the Global MSA Research Roadmap Meeting and whose pioneering efforts in immunotherapies for neurodegenerative disease continue to hold promise for those with MSA. In their honor and in honor of all those with MSA, we will Kerry On to Fight MSA. Meeting chairs, advisory board, and working groups: meeting chairs: Ryan R. Walsh (chair), Wendy Galpern, and Jeffrey Cummings (co-chairs); advisory board: Glenda Halliday, Walter Koroshetz, Phillip Low, and Gregor Wenning; working group members: Pathogenesis Working Group: Janice Holton (chair), Thomas Gasser (premeeting), Matt Huentelman, Poul Henning Jensen, Ronald Melki, Shoji Tsuji. Preclinical Modeling Working Group: Gregor K. Wenning (chair), Patrik Brundin, Un Kang, Vikram Khurana, Woojin Scott Kim, Eliezer Masliah, Wassilios Meissner. Preclinical Target Development Working Group: Glenda Halliday (chair), Gal Bitan, Dale Schenk, Nadia Stefanova, Patricia Walicke. Clinical

MSA Phenotype Working Group: Niall Quinn (chair), Florian Krismer, Peter Lewitt, David Robertson, Jeremy Schmahmann. Clinical Outcome Measures Working Group: Olivier Rascol (chair), Art Hewitt, William Holt, Horacio Kaufmann, Thomas Klockgether, Glenn Stebbins. Clinical Imaging Biomarker Working Group: David Eidelberg (chair), David Brooks, Klaus Seppi, Andrew Siderowf, Ryan Walsh. Clinical Non-Imaging Biomarker Working Group: Leslie M. Shaw (chair), Roy Freeman, Andreas Jeromin, Michael Schlossmacher, Jing Zhang. Treatment and Trials Working Group: Phillip Low (chair), Werner Poewe, Wendy Galpern, Steven Piantadosi, Hubert Fernandez, Victor Abler, Susanne Ostrowitzki.

Study funding

Study Funded by Fight MSA.

Disclosure

R.R. Walsh, F. Krismer, and W.R. Galpern report no disclosures relevant to the manuscript. G.K. Wenning: consulting and advisory board membership with honoraria from Astra Zeneca and Teva Pharmaceuticals. Grants and research: Austrian Science Fund, MSA Coalition. P.A. Low reports no disclosures relevant to the manuscript. G. Halliday is National Health and Medical Research Council Senior Principal Research Fellow (1079679). W.J. Koroshetz, J. Holton, N.P. Quinn, and O. Rascol report no disclosures relevant to the manuscript. L.M. Shaw receives support from the NIH/NIA, U19 AG024904, MJ Fox Foundation for Parkinson's Disease Research, Eli Lilly, and Roche; has provided quality control oversight for the Fujirebio AlzBio3 immunoassay; and provides quality control oversight for the Roche Elecsys CSF immunoassay platform for AD biomarkers as part of his responsibilities in the ADNI study. Dr. Shaw also provides consultation to Eli Lilly, Roche, and Novartis. D. Eidelberg and P. Bower report no disclosures relevant to the manuscript. J.L. Cummings acknowledges COBRE 1P20GM109025-01A1 and Keep Memory Alive. V. Abler is an employee of Teva Pharmaceuticals. J. Biedenharn, G. Bitan, and D.J. Brooks report no disclosures relevant to the manuscript. P. Brundin has received commercial support as a consultant from Renovo Neural, Inc., Roche, Teva Inc., Lundbeck A/S, AbbVie Inc., Neuroderm, Versant Ventures/Apollo, IOS Press Partners, and Cellular Dynamics Inc. H. Fernandez, P. Fortier, R. Freeman, T. Gasser, and A. Hewitt report no disclosures relevant to the manuscript. G.U. Höglinger has served on the advisory boards for AbbVie, Alzprotect, Asceneuron, Bristol-Myers Squibb, Novartis, Roche, Sellas Life Sciences Group, and UCB; has received honoraria for scientific presentations from AbbVie, Roche, Teva, and UCB; has received research support from CurePSP, the German Academic Exchange Service (DAAD), German Research Foundation (DFG), the German Ministry of Education and Research (BMBF), and the Sellas Life Sciences Group; and has received institutional support from the German Center for Neurodegenerative Diseases (DZNE). M.J. Huentelman: M.J.H. acknowledges R21NS093222 from the NIH, National Institutes of Neurological Disorders and Stroke. P.H. Jensen, A. Jeromin, U.J. Kang, H. Kaufmann, L. Kellerman, and V. Khurana report no disclosures relevant to the manuscript. T. Klockgether receives/has received research support from the Deutsche Forschungsgemeinschaft (DFG), the Bundesministerium für Bildung und Forschung (BMBF), the Bundesministerium für Gesundheit (BMG), the Robert Bosch Foundation, and the European Union (EU). He serves on the editorial board of *The Cerebellum* and the *Journal of Neurology*. He has received consulting fees from Biohaven, ICON Clinical Research, and Atheneum. W.S. Kim, C. Langer, P. LeWitt, E. Masliah, W. Meissner, and R. Melki report no disclosures relevant to the manuscript. S. Ostrowitzki is an employee of Genentech Inc., a Member of the Roche Group. S. Piantadosi reports no disclosures relevant to the manuscript. W. Poewe reports personal fees from AbbVie, Allergan, AstraZeneca, Boehringer-Ingelheim, Boston Scientific, Britannia, GlaxoSmithKline, Ipsen, Lundbeck, Medtronic, MSD, Merck-Serono, Merz Pharmaceuticals, Novartis, Orion Pharma, Teva, UCB, and Zambon (consultancy and lecture fees in relation to clinical drug development programs for PD). Royalties: Thieme, Wiley Blackwell, Oxford University Press, and Cambridge University Press. D. Robertson, C. Roemer, D. Schenk, M. Schlossmacher, J.D. Schmahmann, K. Seppi, L. Shih, and A. Siderowf report no disclosures relevant to the manuscript. G.T. Stebbins: consulting and advisory board membership with honoraria: Acadia Pharmaceuticals, Adamas Pharmaceuticals, Inc., Ceregene, Inc., CHDI Management, Inc., Ingenix Pharmaceutical Services (i3 Research), Neurocrine Biosciences, Inc., Pfizer, Inc., Ultragenyx Pharmaceutical. Grants and research: NIH, Michael J. Fox Foundation for Parkinson's Research, Dystonia Coalition, CHDI, International Parkinson and Movement Disorder Society, CBD Solutions. Honoraria: International Parkinson and Movement Disorder Society, American Academy of Neurology, Michael J. Fox Foundation for Parkinson's Research, Food and Drug Administration. Intellectual property rights: none. Ownership interests: none. Royalties: none. Expert testimony: none. Salary: Rush University Medical Center. N. Stefanova received research grants from the Austrian Science Fund (FWF), the MSA Coalition, AstraZeneca, and BioArctic Neuroscience AB. S. Tsuji, S. Sutton, and J. Zhang report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Received April 24, 2017. Accepted in final form September 29, 2017.

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