3. Martino D, Karnik V, Osland S, Barnes TRE, Pringsheim TM. Movement disorders associated with antipsychotic medication in people with schizophrenia: an overview of Cochrane reviews and meta-analysis. Can J Psychiatry 2018;63(11):706743718777392. https://doi.org/10.1177/0706743718777392

4. Loonen AJ, Doorschot CH, van Hemert DA, Oostelbos MC, Sijben AE. The schedule for the assessment of drug-induced movement disorders (SADIMoD): test-retest reliability and concurrent validity. Int J Neuropsychopharmacol 2000;3(4):285–296.

5. Loonen AJ, Doorschot CH, van Hemert DA, Oostelbos MC, Sijben AE. The schedule for the assessment of drug-induced movement disorders (SADIMoD): inter-rater reliability and construct validity. Int J Neuropsychopharmacol 2001;4(4):347–360.

6. Knol W, Keijsers CJ, Jansen PA, Belitser SV, Schobben AF, Egberts AC, van Marum RJ. Validity and reliability of the Simpson-Angus scale (SAS) in drug induced parkinsonism in the elderly. Int J Geriatr Psychiatry 2009;24:183–189.

# Disease Progression in Multiple System Atrophy: The Value of Clinical Cohorts with Long Follow-Up

In their recent publication, Kühnel et al[1] described the progression of multiple system atrophy (MSA) in the European MSA study group (EMSA-SG) cohort via an innovative disease progression model (DPM). DPMs are valuable longitudinal methods to describe MSA natural history while accounting for data uncertainty (delayed diagnosis, uncertain timing, heterogeneous staging).[2] The mean trajectories of clinical progression are described along the homogeneous disease continuum (Fig. 1C) rather than the observed time since diagnosis (Fig. 1A) thanks to a temporal recalibration of progression according to an individual latent disease time, anchored to MSA disease stage at inclusion.

The population characteristics and the length of individual follow-up are critical in natural history studies and DPMs. Kühnel's study relied on 121 patients with rather advanced stage, outdated diagnosis criteria, and short follow-up of 2 years.[1,3] We replicated Kühnel's analysis on repeated Unified MSA Rating Scale sum scores I (activities of daily living) and II (motor examination) from the French MSA cohort[4] (663 patients) with maximum follow-up of 11 years, consensus diagnosis criteria,[5] and early stages at entry (see Supplementary Material Data S1 for details). MSA progression spanned a larger period than in the original paper (Fig. 1C) with mean time gaps at inclusion estimated at 3.6 and 9.1 years for moderately-dependent and helpless patients at inclusion, respectively (Fig. 1B right panels); and significant inter-patient differences (SD = 2.14 years). When restricting the sample to 2.5-year follow-up, these differences were smaller, especially among the most aggressively affected patients at entry, with estimates of 2.5 and 6.6 years (Fig. 1B left panels) and smaller inter-patient differences (SD = 0.79 years). This suggests that studies restricted to short-term follow-up overestimate the progression rate and underestimate inter-patient differences.

When applying DPMs, differences across stages should be carefully interpreted. They do not quantify the expected amount of time spent in each stage by a patient, but the time gap between patients entering the study at different stages. Estimating the duration spent in each disability stage requires specific modeling of disability over time.

Furthermore, DPMs usually rely on strong assumptions that may impact the results:

1. Sigmoid shape: based on generalized logistic function, progression trajectories are restricted to sigmoids leading to suboptimal fit of the data compared to data-driven approaches (see Data S1);
2. Conditional markers' independence: individual recalibration requires the assumption that the latent disease time captures all the correlation between markers, which may be unlikely in practice;
3. Homogeneity of progression: DPMs assume a unique mean profile of progression when subphenotypes of clinical progression may exist[4];
4. Non-informative death: death is assumed to be predictable by the observed course of the markers when death caused by MSA may induce a more informative dropout to be jointly modeled.[6]

In conclusion, DPM constitutes a promising tool for disease study, but it needs to be interpreted with



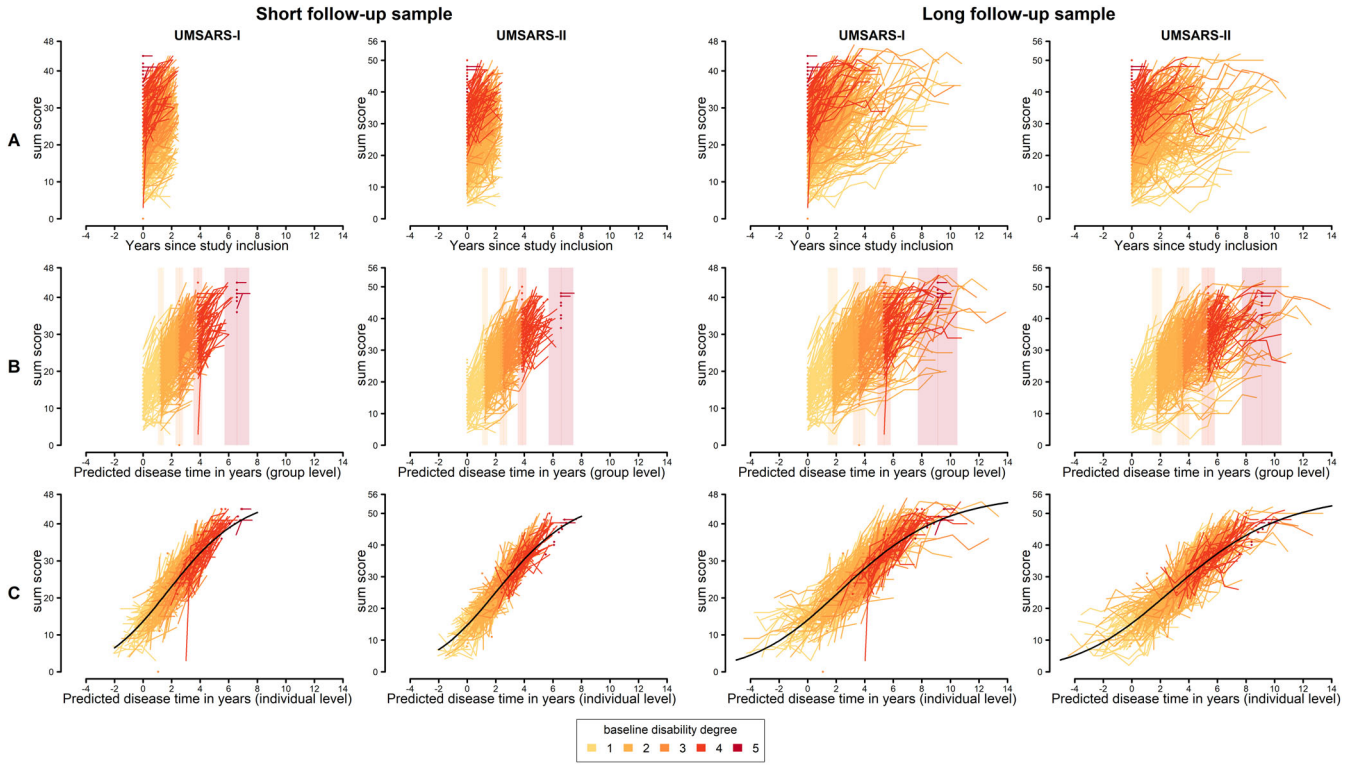
*Correspondence to: Alexandra Foubert-Samier, Univ. of Bordeaux—BPH Center, 146 rue Léo Saignat, 33076 Bordeaux, Cedex, France; E-mail: alexandra.samier-foubert@u-bordeaux.fr

Alexandra Foubert-Samier and Cécile Proust-Lima contributed equally to this work.

**Relevant conflict of interest/financial disclosures:** The authors report no conflict of interest in line with the content of the manuscript.
**Financial disclosures of all authors (for the preceding 12 months):** T.S., M.L., C.H., and C.P.-L. have nothing to disclose. M.F. received honoraria to speak from BIAL, AbbVie, Orkyn, Consultancies for Bial and LVL Médical. A.P.-L. received honoraria from Almylam and Biohaven. P.P. received honoraria from IKT Laboratory and grant from the French Research Agency. W.G.M. has received fees for editorial activities with Elsevier, and consultancy fees from Lundbeck, Biohaven, Roche, Alterity, Servier, Inhibikase, Takeda, and Teva. O.R. received honoraria for scientific advice from companies developing novel therapies of biomarkers for MSA, including Lundbeck, Neuralight, ONO Pharma, Servier, Takeda, UCB, and received scientific grants for MSA from the French Ministry of Health, the French MSA Association ARAMISE, the MSA coalition, Lundbeck, ONO Pharma, Servier, Takeda. A.F.-S. received honoraria from Aguettant Laboratory.
**Funding agencies:** This work was funded by the French National Research Agency (Project DyMES—ANR-18-C36-0004-01) and the region Nouvelle-Aquitaine as part of the ESR project call 2021.

**Received:** 6 February 2023; **Revised:** 15 May 2023; **Accepted:** 17 May 2023

**Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.29534**




*Footnote :* **Panel B** Time 0 for the predicted disease years at the group level corresponds to the entry time in the cohort among those entered with a disability level of 1 (completely independent).
**Panel C** Time 0 for the predicted disease years at the individual level corresponds to the mean entry time in the cohort among those entered with a disability level of 1 (completely independent).

**FIG. 1.** Progression of UMSARS-I and II in the French multiple system atrophy (MSA) cohort when considering the entire cohort follow-up (right panels) or when restricting the analysis to the first 2.5 years (left panels). Are reported the individual trajectories of UMSARS-I and II sum scores according to (**A**) the observed time since cohort entry, (**B**) to the predicted disease time after recalibration according to the disability stage at entry, and (**C**) to the individual predicted disease time. [Color figure can be viewed at wileyonlinelibrary.com]

caution and calls for less stringent assumptions. The replication on the French MSA cohort highlights the importance of describing MSA progression based on long-term follow-up data and large cohorts to prevent too pessimistic projections and underestimation of sample sizes.

**Acknowledgments:** We would like to thank the French National Research Agency (Project DyMES-ANR-18-C36-0004-01) and the Nouvelle-Aquitaine region (Project AAPR2021A-2020-11937310) for their financial support that made this work possible. Several authors of this publication are members of the European Reference Network for Rare Neurological Diseases—Project ID no: 739510.

## Data Availability Statement

Research data are not shared.

Tiphaine Saulnier, MS,[1] Margherita Fabbri, MD, PhD,[2,3] Anne Pavy-Le Traon, MD, PhD,[2,3] Mélanie Le Goff, MS,[1] Catherine Helmer, PhD,[1,4] Patrice Péran, PhD,[5] Wassilios G. Meissner, MD, PhD,[6,7,8] Olivier Rascol, MD, PhD,[2,3] Alexandra Foubert-Samier, MD, PhD,[1,4,6,7*] and Cécile Proust-Lima, PhD[1,4]

*[1]Univ. Bordeaux, Bordeaux Population Health Research Center, Inserm U1219, Bordeaux, France, [2]MSA French Reference Center, Univ. Hospital Toulouse, Toulouse, France, [3]Univ. Toulouse, CIC-1436, Departments of Clinical Pharmacology and Neurosciences, NeuroToul COEN Center, NS-Park/FCRIN Network, Toulouse University Hospital,InsermU1048/1214, Toulouse, France, [4]Inserm, CIC1401-EC, Bordeaux, France, [5]ToNIC, Toulouse NeuroImaging Center, Univ Toulouse, Inserm, UPS, Toulouse, France, [6]CHU Bordeaux, Service de Neurologie des Maladies Neurodégénératives, IMNc,CRMRAMS, NS-Park/FCRIN Network, Bordeaux, France, [7]Univ. Bordeaux, CNRS, IMN, Bordeaux, France, and [8]Department Medicine, University of Otago, Christchurch, and New Zealand Brain Research Institute, Christchurch, New Zealand*

## References

1. Kühnel L, Raket LL, Åström DO, et al. Disease progression in multiple system atrophy—novel modeling framework and predictive factors. Mov Disord 2022;37:1719–1727.
2. Li D, Iddi S, Thompson WK, Donohue MC. Alzheimer's disease Neuroimaging initiative. Bayesian latent time joint mixed effect models for multicohort longitudinal data. Stat Methods Med Res 2019;28:835–845.
3. Geser F, Seppi K, Stampfer-Kountchev M, et al. The European multiple system atrophy-study group (EMSA-SG). J Neural Transm 2005; 112:1677–1686.
4. Foubert-Samier A, Pavy-Le Traon A, Guillet F, et al. Disease progression and prognostic factors in multiple system atrophy: a prospective cohort study. Neurobiol Dis 2020;139:104813.

5. Gilman S, Wenning GK, Low PA, et al. Second consensus statement on the diagnosis of multiple system atrophy. Neurology 2008;71:670–676.

6. Saulnier T, Philipps V, Meissner WG, et al. Joint models for the longitudinal analysis of measurement scales in the presence of informative dropout. Methods 2022;203:142–151.

## Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

# Reply to Letter to the Editor: "Disease Progression in Multiple System Atrophy: The Value of Clinical Cohorts with Long Follow-Up"

We are pleased to read the letter by Saulnier and colleagues related to our article "Disease Progression in Multiple System Atrophy—Novel Modeling Framework and Predictive Factors,"[1] and we thank the authors for the impressive work they have done to replicate and expand on our research in a larger and more contemporary cohort.

As Saulnier and colleagues rightly point out, our study relied on a cohort of 121 patients with a relatively advanced disease stage and a limited follow-up period of 2 years. We acknowledge these limitations and fully agree on the importance of both larger sample size and longer individual follow-up duration for achieving high-quality estimates of the natural history disease trajectory in multiple system atrophy (MSA).

The authors' replication of our disease progression modeling using the larger French MSA cohort of 663 patients with a follow-up period of up to 11 years estimated a longer duration of the MSA progression trajectory compared to our findings. Although differences between the cohorts were limited in terms of average baseline disease severity and symptom duration (5.4 years in the European MSA study cohort vs. 4.5 years in the French MSA cohort), some differences are to be expected due to other cohort differences (years in which the study was ongoing, study locations, etc.). Interestingly, the authors explored how restricting longitudinal follow-up data to 2.5 years affected the estimates. The authors found that restricting samples resulted in a compressed trajectory with smaller interpatient differences compared to using long-term follow-up data. Based on these findings, Saulnier and colleagues suggest that studies of restricted follow-up time could overestimate progression rate and underestimate interpatient differences, which we agree may be the case. Our disease progression model performs temporal recalibration on a latent timescale, which requires a trade-off between the (vertical) deviation from the estimated mean trajectory and the (horizontal) deviation on the timescale. The trade-off is determined in a fully data-driven approach based on the maximum likelihood principle. When long-term patterns are not sufficiently clear in individual patient-level trajectories, the model may prioritize minimization of vertical differences over estimating temporal patterns. One aspect of the estimation that was not addressed by Saulnier and colleagues is the role of multiple outcome measures. In our study, we aligned patient samples using six different outcome measures, whereas only two outcome measures were used for replication in the French MSA cohort. Including a greater number of disease-relevant measures increases the number of observed data points per patient used to predict their latent disease time, which could possibly alleviate some of the issues related to shorter-term follow-up.

Saulnier and colleagues highlight four assumptions of disease progression models that may impact results, which we would like to comment on:

i. Sigmoid shape may lead to suboptimal fits. Generalized logistic functions provide a range of shapes that are natural candidates for modeling progressive phenomena. In our modeling framework, the mean trajectories can easily be modeled using functions with fewer shape constraints such as splines to investigate the effect of the mean trajectory shape on the fit. We acknowledge that other approaches to modeling may provide better fits to the data but at the same time want to highlight that although more optimal data fit may be useful for certain objectives, it does not necessarily imply that the model produces greater insight into the disease process (consider, eg, black-box machine learning models). Finally, we want to note that suboptimal fits of disease progression models is not a general phenomenon. In both the European MSA natural history study presently discussed and in the previous disease progression modeling in Alzheimer's disease,[2] we have found that parametric disease progression models outperformed conventional linear mixed models in terms of goodness-of-fit measures.
ii. Outcome measures may not be conditionally independent on the recalibrated timescale. We agree that correlations between the markers not relating to the latent disease time are very likely (eg, a subject may consistently overperform or underperform in a domain captured across multiple outcome measures), and modeling may improve the model fit. As demonstrated in Kühnel et al,[3] modeling correlations between outcome measures is possible within the



***Correspondence to:** Ph.d. Ingeborg Helbech Hansen, H. Lundbeck A/S, Ottiliavej 9, 2500 Valby, Denmark; E-mail: inhe@lundbeck.com

**Received:** 21 June 2023; **Accepted:** 22 June 2023

**Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.29535**