An agnostic approach for multiple sclerosis disease states and prognosis using artificial intelligence: four clinical states allow description of the disease and its probabilities for evolution

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INTRODUCTION

Multiple sclerosis (MS) phenotypes/states have been defined to describe the disease course solely based on two dimensions: relapses and disability worsening/progression. However, prognosticating long-term outcomes or treatment response from clinical phenotypes remains challenging.

OBJECTIVE

To characterize MS by finding homogenous disease states and their transition pathways using an unsupervised approach in a large-scale study with longitudinal multidimensional (clinical and radiological) data.

METHODS

We developed a Bayesian unsupervised machine learning method to interrogate longitudinal data (up to 15 years; >120,000 visits) from the Novartis–Oxford MS clinical trial database (N=8052 MS patients [discovery: 6444; validation: 1608]) to 1) identify key-dimensions and homogeneous states of MS and their transition probabilities, 2) assess the effect of treatment and, 3) predict patients individual progression time to reach the *evolved MS* state.

RESULTS

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We discovered four key-dimensions of MS: a) physical disability; b) subclinical disease burden/associated cognitive deficits; ongoing inflammation either as c) MRI lesions and/or d) clinical relapses. We identified 4 clinical Meta-states that allow a complete description: i) *Early MS (clinically stable patients)*, ii) *acute relapse*, iii) *transition state* and iv) *evolved MS*. *Early MS* patients may develop lesions or transition to the *acute relapse* state; they can recover or move to the *transition state* (characterized by substantial subclinical disease burden, moderate physical and cognitive impairment and ongoing inflammation) from where they can recover or move to *evolved MS*. *Evolved MS* is characterized by high levels of subclinical damage, physical and cognitive impairment, very low level of new inflammation, with low/no probability of recovery (model made no distinction between patients with/without history of relapse). The model can predict the time-to-*evolved MS* from early states with high accuracy. Disease-modifying therapies significantly lowered the transition probability from *early MS* to *evolved MS*.

CONCLUSIONS

Our agnostic approach on a large dataset across traditional MS subtypes identified four states of MS. Patients with *early MS* transition to *evolved MS* through the accumulation of damage to the CNS and ongoing inflammation. *Evolved MS* is a homogenous meta-state (no distinction between primary- and secondary progressive MS). Treatment significantly improves a patient's chance of staying longer in the *early MS* state.

DISCLOSURES

The study was funded by Novartis Pharma AG, Switzerland.

Dieter Häring, Gordon Graham, Wendy Su, and Bernd Kieseier are employees of Novartis.

Douglas Arnold has received personal compensation for serving as a Consultant for Alexion, Biogen, Celgene, Eli Lilly, EMD Serono, Frequency Therapeutics, Genentech, Merck, Novartis, Roche, Sanofi, and Shionogi, and holds an equity interest in NeuroRx.

Robert Bermel has served as a consultant for Astra Zeneca, Biogen, EMD Serono, Genzyme, Genentech, Novartis and VielaBio. He receives research support from Biogen, Genentech and Novartis.

Heinz Wiendl has received honoraria for acting as a member of scientific advisory boards for Biogen, Evgen, Genzyme, MedDay Pharmaceuticals, Merck Serono, Novartis, Roche Pharma AG, and Sanofi-Aventis, as well as speaker honoraria and travel support from Alexion, Biogen, Cognomed, F. Hoffmann-La Roche Ltd., Gemeinnützige Hertie-Stiftung, Merck Serono, Novartis, Roche Pharma AG, Genzyme, Teva, and WebMD Global. Heinz Wiendl is acting as a paid consultant for AbbVie, Actelion, Biogen, IGES, Johnson & Johnson, Novartis, Roche, Sanofi-Aventis, and the Swiss Multiple Sclerosis Society. His research is funded by the German Ministry for Education and Research (BMBF), Deutsche Forschungsgemeinschaft (DFG), Else Kröner Fresenius Foundation, Fresenius Foundation, the European Union, Hertie Foundation, NRW Ministry of Education and Research,

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Habib Ganjgahi, Yang Sun, Stephen Gardiner, Thomas Nichols and Chris Holmes report no competing interests.

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