



Predicting disease progression in multiple sclerosis with clinically accessible information and technology

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Received: 16 September 2025 / Revised: 13 March 2026 / Accepted: 27 March 2026
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Abstract

Background Predicting disease progression at the individual level is essential for personalized medicine. We previously developed machine-learning tools to estimate 5-year progression risk in people with multiple sclerosis (PwMS). Such models should account for disease-modifying therapy (DMT) and objective outcome definitions.

Methods In a retrospective multicenter case–control study, we evaluated adults with relapsing–remitting multiple sclerosis (RRMS) at baseline. Using machine-learning, we developed two complementary tools for individualized 5-year risk estimation: DAAE-M, optimized for transparency, software-neutral use, and mitigation of indication bias, and ELIE, optimized for dynamic landmark-based modeling, complex treatment histories, and mitigation of immortal-time bias. Disease progression was defined using both a clinical outcome (RRMS-to-progressive MS) and an objective outcome (late-stage confirmed progression independent of relapse activity).

Results Among 34,510 people with RRMS (72.6% female, mean age = 37.1, mean disease duration = 5.8), 9.8% and 21% met clinical and objective progression criteria, respectively, over five years. Both models demonstrated good calibration across risk-groups (Brier scores 0.06–0.16). DAAE-M provided patient-level risk estimates with monotonic risk escalation across risk-groups for clinical (3.1%/11.2%/22.6%/33.0%) and objective (8.4%/14.5%/23.3%/38.8%) progression. For DAAE-M, high-efficacy DMT was associated with approximately half the progression risk compared with low-efficacy DMT (risk-ratios: 0.42–0.59; $p < 0.01$). ELIE also showed good calibration across risk deciles with increasing incidence for both clinical (0.3%/1.2%/1.7%/2.5%/3.7%/5.5%/7.2%/10.2%/14.3%/21.5%) and objective (0.9%/1.6%/2.5%/4.0%/5.8%/7.8%/10.2%/15.3%/20.9%/32.5%) outcomes.

Conclusion We developed two well-calibrated machine-learning-based tools for individualized 5-year prediction of clinically- and objectively-defined MS progression, each with distinct strengths in usability, bias handling, and treatment modeling. These findings support future tool use in personalized risk stratification and secondary prevention.

Keywords Multiple sclerosis · Decision support tools · Prediction · Clinical · Disease progression · Secondary progressive multiple sclerosis

Introduction

Predicting disease progression is critical for decision support and personalized patient care—such as through identification of high-risk patients for secondary prevention and restorative treatment [1]. Consequently, numerous investigations have identified predictors of disease progression in people with multiple sclerosis (PwMS) [2].

With this background, we previously aimed to translate this science toward clinical practice by developing the DAAE score, a decision support tool for estimating individual patient risk of disease progression over 5 years using clinically accessible information and technology [3].

While DAAE score development employed machine learning techniques, its user-end functionality was purposefully designed to be transparent, software neutral, and easy to use with clinically available information and technology. Accordingly, the DAAE score incorporates four factors: Disease duration, Age, Age at disease onset, and the Expanded Disability Status Scale (EDSS), each weighted differently, offering a 0 to 12-point scale for patient risk stratification.

In line with WHO guidance emphasizing transparency, explainability, and intelligibility for AI-enabled clinical decision-making [4], we prioritized an explicit, user-facing scoring system that clinicians can compute rapidly and audit

conceptually, rather than an opaque ‘black-box’ predictor. To facilitate implementation within heterogeneous health ecosystems, we designed the prognostic tool as a software-neutral scoring algorithm with lookup tables, aligning with WHO’s SMART Guidelines approach to standards-based, interoperable digital decision support components [5].

To ensure generalizability of risk estimates, it is important that performance is evaluated across clinical centers and heterogeneous populations using clinical [6, 7], and objective [8] definitions of disease progression. Additionally, such a tool has the greatest clinical benefit if it can help physicians make treatment decisions. It is therefore important to incorporate disease-modifying therapy (DMT) treatment effects and to establish whether risk estimates meaningfully vary according to therapy [9].

To improve the potential to support personalized patient care, this study had the following aims: using machine-learning, we aimed to develop two complementary tools for individualized 5-year risk predictions: The first, DAAE-M (Disease duration, Age, Age of onset, EDSS, disease Modifying therapy), was optimized according to guidelines for clinical interoperability and for mitigation of indication bias. The second for comparison, ELIE (Empirical Landmark-based Individualized Estimation of MS progression risk), was optimized for dynamic landmark modeling, complex treatment histories, and mitigation of immortal-time bias. Disease progression was defined using both a clinical outcome (RRMS-to-progressive MS) and an objective outcome (Lorscheider criteria, late-stage confirmed progression independent of relapse activity).

For both models, we aimed to:

1. Integrate DMT information: incorporate risk predictions depending on DMT use.
2. Multi-center validation: validate risk-stratification performance in a large multi-center clinical dataset
3. Validate against clinically defined disease progression
4. Validate against objectively defined disease progression

We hypothesized that (1) high-efficacy therapy would be associated with lower risk, (2) risk predictions would be well-calibrated to actual event proportions, (3) risk of transition would escalate across stratified risk groups for clinically defined and objectively defined disease progression.

Methods

Study design and participant selection

A multi-center longitudinal study was conducted using participant data from the MSBase registry, collected from 1964 to 2023. All participants provided written informed consent.

Ethics approval for the MSBase registry was granted by the Alfred Health Human Research and Ethics Committee and the local ethics committees of all the participating centers. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines [10]. The criteria for patient inclusion were: (A) relapsing–remitting multiple sclerosis (RRMS) at baseline, (B) no other neurological disorder, (C) age 18 or older, (D) two or more clinical evaluations, (E) > 3 years longitudinal clinical follow-up [target of 5 years (± 2)], (F) baseline neurologic testing of disability using the EDSS, (G) data not previously used in DAAE score development. ‘Baseline’ was defined as the point of contact at year zero of the target 5-year observation window.

Measures and outcome

A previous predictive algorithm was applied as described [3]. Briefly, four clinical factors (Disease duration, age, age at disease onset, EDSS) are considered, each with different weighting, to generate a score from 0 to 12 points. Then, PwMS are stratified into risk groups according to their score (very-low = 0–2, low = 3–7, medium = 8–9, high ≥ 10) and associated risk of disease progression. Original development of this employed machine-learning techniques, training and testing, and four key development stages: (1) feature identification with systematic literature review, (2) feature ordinalization using generalized additive modeling (GAM), (3) feature selection with least-absolute-shrinkage and selection operator regression (LASSO), (4) and feature weighting using training and testing paradigms with GAM and LASSO coefficients. See Fuchs et al. 2024 [3] for further details. Missing values were handled using multiple imputation with chained equations [11].

Disease progression was defined both clinically and objectively:

Clinical disease progression. First, to ensure tool validation was harmonized with real-world use, disease progression was defined according to neurologists’ judgment of transition to secondary progressive multiple sclerosis (SPMS). This outcome was chosen because people with SPMS accumulate disability more rapidly, do not respond to most disease modifying therapies, and benefit less from restorative rehabilitation [12–14]

Objective disease progression. We also defined disease progression objectively with regard to late-stage confirmed progression independent of relapse using the MSBase-Lorscheider criteria [8] (all criteria met):

- EDSS ≥ 4.0 overall, pyramidal functional subsystem score ≥ 2

- EDSS increase ≥ 1.0 in patients with EDSS ≤ 5.5 or EDSS increase ≥ 0.5 in patients with EDSS ≥ 6
- Disability worsening was confirmed stable after three months in EDSS and in leading functional subsystem
- No relapses were detected between the event date and the preceding clinical evaluation.

DMT efficacy scheme

High: rituximab, ocrelizumab, mitoxantrone, alemtuzumab, natalizumab, ofatumumab.

Low: interferon-beta, glatiramer acetate, teriflunomide, dimethyl fumarate.

Intermediate: fingolimod, siponimod, daclizumab, laquinimod, cladribine.

Predictive model optimized for transparency, interoperability, and mitigation of indication bias

Integrate DMT information

For this model, DAAE-M, user-functionality and clinical translational potential were optimized in the design of the final models in accordance with WHO guidelines [4, 5], with a focus on transparency, interoperability, and software-neutral design practices.

We hypothesized that risk of clinical disease progression would be lower for PwMS receiving high-efficacy DMT relative to those receiving low-efficacy DMT, and therefore aimed to integrate these risk differences. For these analyses, we categorized PwMS as either receiving low-efficacy or high-efficacy DMT. This was done in two ways, accounting for majority use of DMT over the observation time-horizon and for baseline DMT.

Majority DMT use: defined depending on which therapies were received over the majority ($> 50\%$) of the 5-year observation period. After this, PwMS were considered to have switched therapy classes if they also received another class of DMT for $> 25\%$ of the observation period. Therapy efficacy was defined according to previously established categories [9, 15], and is described the DMT efficacy scheme section, above.

Baseline DMT: defined according to the therapy being used at baseline.

For direct comparison between these groups, we corrected for indication bias [16]. In this context, indication bias is the tendency for high-risk patients to receive high-efficacy therapy and for stable patients to receive no or low-efficacy therapy. To mitigate the effects of this bias, we

used propensity-score matching between PwMS receiving high- versus low-efficacy DMT. Propensity scores were estimated using a logistic regression model, with the following baseline covariates: age, sex, disease duration, and EDSS. Matching was completed using nearest-neighbor 1:1 matching without replacement. Then, the DAAE score was applied to establish proportions of PwMS with disease progression in PwMS receiving high-efficacy versus low-efficacy DMT for each of the risk groups. This analysis approach was then repeated for PwMS receiving no treatment.

Statistical analyses

Proportions of events within each treatment group were compared to the low-efficacy DMT group using z-tests for proportions. Due to limitations in sample-size, these analyses excluded PwMS receiving intermediate-efficacy DMT.

Multi-center validation

Clinically defined disease progression

For primary validation, we completed calibration analyses, comparing risk predictions to actual event proportions per stratified risk group. Additionally, although the tool was developed to stratify PwMS according to risk (percent) of disease progression over 5 years, we also evaluated discriminative prediction performance for comparison with other models and tools. For this secondary validation, we evaluated the area-under-receiver-operating-curve (AUROC) and percent prediction accuracy with bootstrapped 95% confidence intervals. To address class imbalance in discriminative predictions, we employed the synthetic minority oversampling technique combined with Tomek links (SMOTE + TK, $k = 10$) [17].

Objectively defined disease progression

Here, we aimed to establish the risk of disease progression according to objective disease progression criteria using the MSBase-Lorscheider [8]. In short, the MSBase-Lorscheider criteria provides a standardized approach for defining SPMS and late-stage confirmed disease progression independent of relapse by applying a disability cutoff and evidence of relapse-free disability worsening sustained over three months. For details, see Measures and Outcome.

For this analysis, the sample was reduced to PwMS that met initial inclusion requirements and these additional criteria needed for calculating the Lorscheider-MSBase criteria: (H) clinical relapse reporting (yes/no, date), (I) availability of all EDSS functional subsystem data, (J) > 3 months between evaluations, and (K) RRMS at baseline according to objective criteria. Finally, because MSBase-Lorscheider

criteria are less conservative than clinical judgment [8], DAAE score risk-group stratification cut-offs were adapted for this outcome.

Statistical analysis

To compare predicted vs actual risk estimates, 95% confidence intervals and z-tests for proportions were applied. These were also applied to evaluate the distinctness of event proportions across each of the DAAE-M score-stratified risk groups.

Predictive model optimizing for dynamic estimation of risk and mitigation of immortal time bias

To optimize for dynamic predictions, incorporate more complex treatment histories, and mitigate immortal time bias [18] in predictive modeling with retrospective data, we developed a dynamic landmark-based prediction model, ELIE, to estimate individual patient risk of disease progression. Disease progression was defined clinically [SPMS] and objectively [Lorschieder criteria], as above, within a 5-year fixed prediction horizon after the landmark visit. Each eligible clinical visit served as a landmark time point, generating a visit-level prediction dataset in which patients could contribute multiple observations over follow-up. Only visits occurring prior to the outcomes were included. Landmarks were censored if follow-up was insufficient to determine outcome status.

Predictors included demographic and clinical variables measured at the landmark visit (age, disease duration, EDSS, age at onset, time since baseline), as well as a categorical summary of disease-modifying therapy (DMT) exposure up to the landmark. DMT history was derived from longitudinal treatment records and summarized as a time-varying categorical variable reflecting predominant exposure and treatment switching patterns prior to each landmark.

For each landmark, treatment intervals were intersected with the observation window (baseline → landmark date). The proportion of time exposed to each efficacy class was calculated relative to the total observed time. DMTs were categorized into three efficacy classes (low-, intermediate-, and high-efficacy), consistent with prior classification schemes.

A majority exposure class was defined as $\geq 50\%$ of observed time spent on a given efficacy class. A “switcher” flag was defined when $\geq 50\%$ of observed time was spent on treatment and $\geq 25\%$ of treated time was spent on a non-dominant efficacy class. In addition, transitions between efficacy classes were enumerated in chronological order to

detect escalation, de-escalation, initiation, discontinuation, and bidirectional switching. Each landmark was assigned to one mutually exclusive treatment history category as follows:

Never treated, no DMT exposure prior to the landmark (majority class = None; no switching); Stable low-efficacy, $\geq 50\%$ of time on low-efficacy DMT with no detected switching; Stable intermediate-efficacy, $\geq 50\%$ of time on intermediate-efficacy DMT with no detected switching; Stable high-efficacy, $\geq 50\%$ of time on high-efficacy DMT with no detected switching; Switcher escalation, at least one transition from lower- to higher-efficacy therapy (e.g., low → high), without reverse transition; Switcher de-escalation, at least one transition from higher- to lower-efficacy therapy (e.g., high → low), without reverse transition; Switcher bidirectional, both escalation and de-escalation occurred prior to the landmark; Switcher initiation, transition from no therapy to treated state (None → any efficacy), without discontinuation; Switcher discontinuation, transition from treated to untreated (any efficacy → None), without re-initiation; Switcher complex, switching patterns not captured by the above rules (e.g., multiple transitions not fitting a single directional pattern).

To prevent information leakage, data were split into training and test sets (80:20) at the patient level, and cross-validation was likewise grouped by patient. Models were fitted using weighted LASSO regression (glmnet), with class weights to address outcome imbalance. Preprocessing, including imputation, dummy encoding of categorical predictors, and standardization of continuous variables, was performed using a fixed recipe learned on the training data. Within the training set, the LASSO penalty parameter was optimized using patient-grouped cross-validation under class-weighted loss. Finally, resulting model performance was evaluated in the independent test set using calibration (primary validation) and discrimination (secondary validation) metrics, as described in previous sections.

Statistical analyses

To compare predicted vs actual risk estimates, 95% confidence intervals and z-tests for proportions were applied. Due to the high degree of comparisons (10 deciles per outcome), p-values were Bonferroni-corrected.

Study funding

This work was supported by the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), financially supporting the salary of the principal author Dr. Tom A.N. Fuchs.

Result

Descriptive statistics

Of the 114,476 patient records available within the MSBase registry, 34,510 PwMS (100% RRMS at baseline) met inclusion criteria for the present study, with 72.6% being female ($n=25,071$). For further details, see the CONSORT diagram in Supplemental. At baseline, the mean (SD) age was 37.1 (10.8) years, and the disease duration was 5.8 (7.3) years. The baseline median [IQR] EDSS score was 2.0 (1.0–3.0). The PwMS were observed for a mean (SD) of 4.8 (1.2) years. For further details, see Table 1.

Table 1 Sample characteristics

RRMS (n , %)	34,510, 100%
Female (n , %)	25,071, 72.6%
Age in years (mean, SD)	37.1, 10.8
Disease duration in years (mean, SD)	5.8, 7.3
Majority DMT use (> 50%) by efficacy*	
Low efficacy (n , %)	14,691, 42.6%
High efficacy (n , %)	2482, 7.2%
Switch (n , %)	4133, 12.2%
No therapy (n , %)	11,179, 32.4%
Baseline DMT use by efficacy	
Low efficacy (n , %)	19,041, 55.2%
High efficacy (n , %)	2596, 7.5%
No therapy (n , %)	12,873, 37.3%
Majority DMT use (> 50%) by name*	
Cladribine	110, 0.32%
Fingolimod	2417, 7.0%
Interferon	9621, 27.88%
Teriflunomide	787, 2.28%
Alemtuzumab	57, 0.17%
Daclizumab	30, 0.09%
Laquinimod	3, 0.01%
Mitoxantrone	43, 0.12%
Natalizumab	1823, 5.28%
Ocrelizumab	681, 1.97%
Ofatumumab	5, 0.01%
Rituximab	208, 0.6%
Siponimod	4, 0.01%
EDSS (median, IQR)	2.0, 1.0–3.0
Transition to SPMS	3391, 9.8%
Years observed	4.8, 1.2

RRMS relapsing–remitting multiple sclerosis, SPMS secondary progressive multiple sclerosis, SD standard deviation, DMT disease modifying therapy, EDSS Expanded Disability Status Scale, IQR interquartile range

*Majority DMT use was considered if receiving therapy for > 50% of the observation period. See methods for additional details

Predictive model optimized for transparency, interoperability, and mitigation of indication bias (DAAE-M)

Majority DMT use

Here, we aimed to account for time-varying DMT use in a risk-stratification system for predicting risk of disease progression in individual patients over 5 years—optimized for clinical usability, software interoperability, transparency, and mitigation of indication bias. This new scoring system is referred to as the DAAE-M score, named for the predictors included in the final model: Disease duration, Age, Age at disease onset, EDSS, and disease Modifying therapy. Over the 5-year time-horizon, 42.6% (14,691) of the PwMS were receiving low-efficacy DMT and 7.2% (2,482) were receiving high-efficacy DMT for the majority (> 50%) of the observation period.

In propensity-score-matched majority low-efficacy ($n=2482$) and high-efficacy ($n=2482$) DMT groups, the proportion of PwMS exhibiting clinically-defined disease progression escalated concordantly with stratified risk groups (very-low, low, medium, high). However, the risk was nearly half for PwMS receiving high-efficacy DMT in each stratified risk group (very-low = 1.8%, low = 6.6%, medium = 13.5%, high = 15.2%) relative to PwMS receiving low-efficacy DMT (very-low = 3.2%, low = 10.3%, medium = 18.4%, high = 40.6%). This reduced risk was significant in particular for those in the very low- (risk-ratio(RR) = 0.54 [95% CI 0.30–0.96], $p=0.038$), low (RR = 0.64 [95% CI 0.48–0.85], $p=0.002$), and high-risk groups (RR = 0.37 [95% CI 0.25–0.55], $p<0.001$), and non-significant for the medium-risk group (RR = 0.73 [95% CI 0.49–1.08], $p=0.114$).

Proportions of PwMS exhibiting clinical disease progression in the propensity-score-matched no-treatment group ($n=2482$) also escalated concordantly with stratified risk groups (very-low = 5.4%, low = 15.7%, medium = 25.6%, high = 34.5%). Additionally, relative to the low-efficacy treatment group, risk was significantly higher, in particular for the very-low- (RR = 1.58 [95% CI 1.03–2.44], $p=0.003$), low- group (RR = 1.62 [95% CI 1.31–2.03], $p<0.001$), and medium-risk group (RR = 1.46 [95% CI 1.03–2.06], $p=0.032$). This difference was non-significantly different for the high-risk group (RR = 0.86 [95% CI 0.64–1.16], $p=0.323$). For details, see Table 2 and Fig. 1A.

Risk-stratification analyses were not completed for the group that switched DMT classes for the following reasons: Small representation of study sample (< 1% per paradigm); Sample distribution largely without representation in the medium- ($n=1$) and high-risk ($n=0$) groups; Heterogeneity of treatment histories in this sample in which 0.6% ($n=245$)

Table 2 Clinical disease progression risk stratification, accounting for DMT use* over the 5-year observation window (DAAE-M)

		DAAE-M score	0–2	3–7	8–9	≥ 10
		Risk group	Very low	Low	Medium	High
Clinical disease progression % (95% CI)						
Unspecified therapy	–		3.1% (2.9–3.4)	11.2% (10.7–11.8)	22.6% (21.1–24.1)	33.4% (31.0–35.1)
Majority DMT*	Low-efficacy DMT		3.3% (2.3–4.6)	10.3% (8.5–12.3)	18.4% (13.8–23.8)	40.6% (33.9–47.5)
	High-efficacy DMT		1.8% (1.0–2.8)	6.6% (5.2–8.2)	13.5% (9.8–17.9)	15.2% (10.1–21.5)
	No DMT		5.2% (3.9–6.8)	16.7% (14.6–19.0)	26.9% (21.0–33.5)	35% (26.5–44.2)
Baseline DMT	Low-efficacy DMT		3.8% (2.6–5.3)	12.3% (10.4–14.5)	24.4% (20.2–29.1)	35.5% (30.0–41.2)
	High-efficacy DMT		2.1% (1.2–3.3)	8.7% (7.2–10.5)	18.8% (14.9–23.0)	25.4% (19.7–31.7)
	No DMT		3.6% (2.5–5.1)	12.1% (10.3–14.2)	23.0% (18.5–28.0)	29.3% (23.9–35.1)

CI confidence interval, DMT disease-modifying therapy

*DMT history is defined according to the majority (>50%) use of the five-year observation period. Unspecified therapy relates to data from the full study sample, regardless of DMT history

**Insufficient data was available for risk stratification in people who switched DMT class over the observation period

represent treatment escalation (low-efficacy to high-efficacy) and 0.5% ($n = 213$) represent de-escalation (high-efficacy to low-efficacy). For details on sample sizes across risk groups, see Supplementary Table A.

Baseline DMT use

Here, we aimed to account for baseline DMT use. At baseline, 55.2% ($n = 19,041$) of the PwMS were receiving low-efficacy DMT and 7.5% ($n = 2596$) were receiving high-efficacy DMT.

In propensity-score-matched low-efficacy ($n = 2596$) and high-efficacy ($n = 2596$) DMT groups, the proportion of PwMS exhibiting clinically-defined disease progression escalated concordantly with stratified risk groups (very-low, low, medium, high). Proportions of PwMS exhibiting clinical disease progression in the propensity-score-matched no-treatment group ($n = 2596$) also escalated concordantly with stratified risk groups (very-low, low, medium, high). Risk was similar regardless of baseline treatment. For details, see Table 2.

Multi-center validation (DAAE-M)

Clinical disease progression (transition to SPMS)

Here, we aimed to validate the DAAE-M risk-stratification tool in a heterogeneous multi-center dataset according to

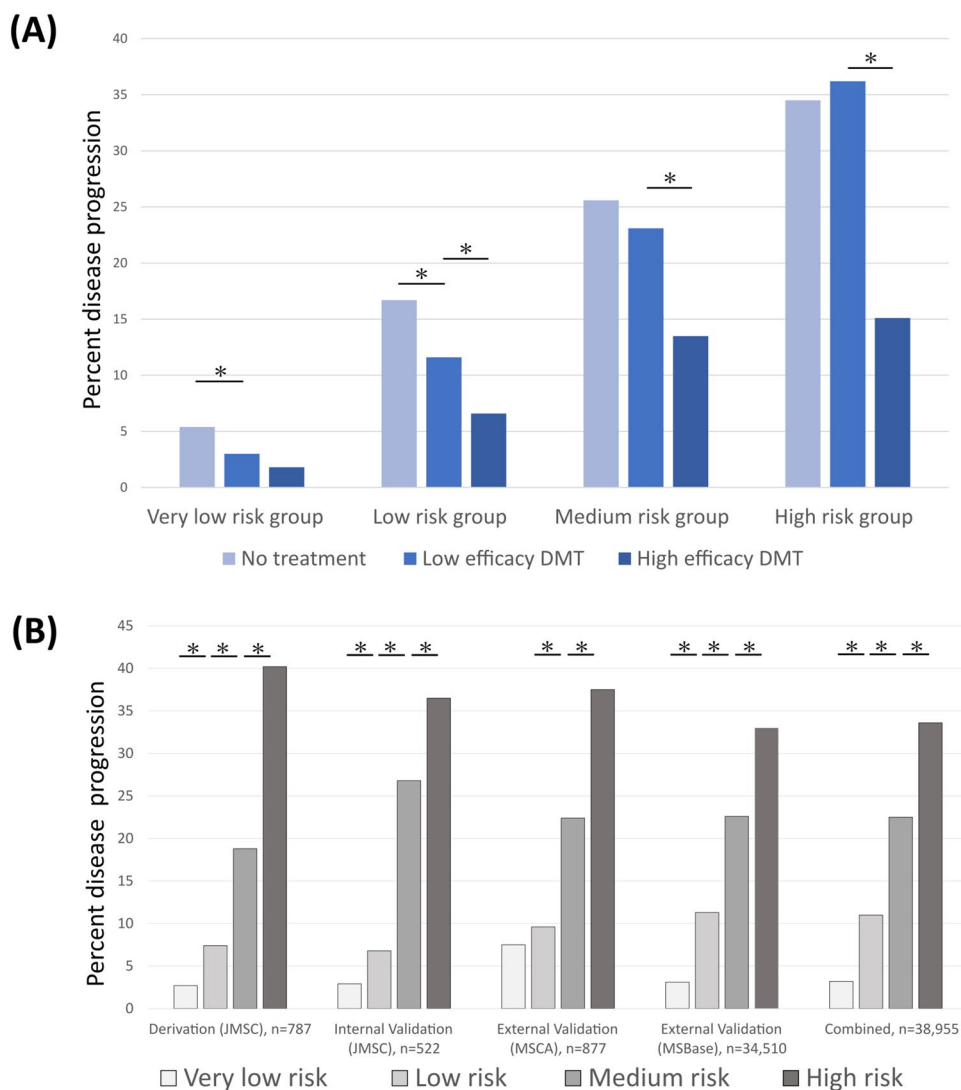
clinically-defined disease progression (Transition to SPMS; Fig. 1B; Supplementary Table B). For details, see Methods and for score calculation, see supplemental materials. Using the DAAE-M score, PwMS were stratified into risk groups of very-low ($n = 15,614$), low ($n = 13,904$), medium ($n = 2975$), and high ($n = 2017$). The proportion of PwMS exhibiting clinical disease progression increased proportionally across these groups: very-low = 3.1%, low = 11.2%, medium = 22.6%, and high = 33.4%. These proportions per risk group were statistically significantly different from each other ($p < 0.001$), indicating the DAAE-M score successfully generated distinct escalating stratified risk groups. As well, in calibration testing, actual event proportions were consistent with predicted risk for the very-low, medium, and high-risk groups ($p > 0.05$), though different for the low-risk group ($p = 0.002$), Brier score = 0.08 (Fig. 2A).

Secondary validation discriminative testing using SMOTE + TK balanced case–control data (case $n = 10,173$; control $n = 10,173$) resulted in an AUROC = 0.809 (95% CI 0.803–0.815) (Fig. 2B), and an accuracy of 75.7% (95% CI 75.0–76.3).

Objective disease progression (Lorscheider criteria)

Here, we aimed to evaluate DAAE-M score performance in relation to objective disease progression criteria, namely late-stage confirmed disability progression independent of relapse using the MSBase-Lorscheider criteria [8]. Within PwMS meeting criteria for this analysis ($n = 23,102$), all

Fig. 1 Validation and DMT integration (DAAE-M score). DMT integration (A) Risk of clinically-defined disease progression (transition to SPMS) in propensity-score-matched patient groups receiving low-efficacy DMT, high-efficacy DMT, or no treatment over the 5-year observation window. Event proportions (B). The proportion of patients with clinical disease progression across DAAE score-stratified risk groups (very-low, low, medium, and high) for the development (JMISC), internal validation (JMISC), external validation (MSCA), and the present multi-center external validation (MSBase). * $p < 0.05$ using a z-test for proportions. Abbreviations: DMT disease-modifying therapy, JMISC Jacobs Multiple Sclerosis Center, MSCA Multiple Sclerosis Center Amsterdam, CUMC Charles University Medical Center



PwMS (100%) were RRMS at baseline (per criteria). From these, 4856 (21.0%) exhibited objective disease progression over 5 years. This was significantly higher ($p < 0.001$) than the proportion exhibiting clinically-defined disease progression (9.8%).

DAAE-M score risk group stratification cutoffs were adapted for objective disease progression criteria as follows: very-low (0–1 points, $n = 5586$ [24.2%]), low (2–3 points, $n = 6000$ [25.9%]), medium (4–6 points, $n = 6116$ [26.5%]), and high (7–12 points, $n = 5401$ [23.4%]). With this schema, the proportion of PwMS exhibiting objective disease progression increased stepwise across DAAE-M score stratified risk-groups: very-low = 8.6% (95% CI 7.7–9.2), low = 14.5% (95% CI 13.6–15.4), medium = 23.3% (95% CI 22.2–24.3), high = 38.8% (95% CI 37.5–40.1). In an 80–20 randomized split, risks were well-calibrated across development [very-low = 8.6% (95% CI 7.7–9.2), low = 14.4

(95% CI 13.4–15.4), medium = 22.9% (95% CI 21.8–24.1), high = 38.5% (95% CI 37.1–40.0)] and validation [very-low = 7.7% (95% CI 6.2–9.4), low = 15.1% (95% CI 13.1–17.2), medium = 24.4% (95% CI 21.9–26.9), high = 39.7% (95% CI 36.8–42.6)] data; Brier score = 0.16 (Fig. 2C).

Results pertaining to DAAE-M risk group stratification according to DMT use are presented in Table 3. In the majority-use high-efficacy treatment group, relative to the low-efficacy treatment group, risk was significantly reduced in particular for the low- (RR = 0.34 [95% CI 0.12–0.97], $p = 0.043$), and high risk groups (RR = 0.49 [95% CI 0.35–0.69], $p < 0.001$). In the no-treatment group relative to the majority low-efficacy treatment group, risk was significantly higher, in particular for the very-low- (RR = 3.4 [95% CI 1.5–7.5], $p = 0.004$) and medium risk groups (RR = 1.4 [95% CI 1.1–1.9], $p = 0.049$). Differences were non-significant for the remaining comparisons.

DAAE-M predictive performance validation

Clinical disease progression (transition to SPMS)

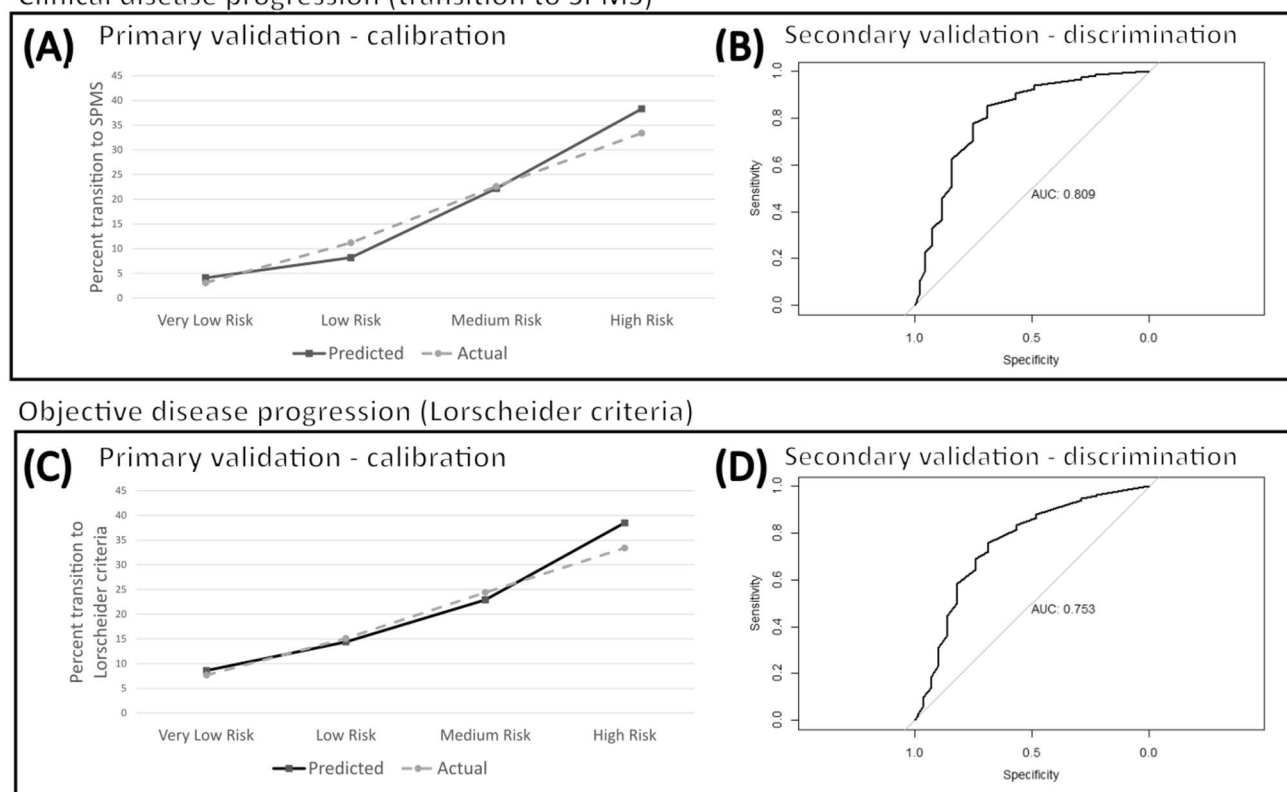


Fig. 2 Predictive performance (DAAE-M score). Primary calibration analyses for clinically defined disease progression (**A**); the clinician-determined transition to SPMS) and secondary validation with discriminative testing (**B**). Primary calibration analyses for objectively-

defined disease progression (**C**; the Lorscheider MSBase criteria for late-stage confirmed progression independent of relapse) and secondary discriminative testing (**D**) over the 5-year observation window. Abbreviations: AUC area under the receiver operating curve

According to baseline DMT use, the high-efficacy therapy group had reduced risk in comparison with the low-efficacy therapy, in particular for the low-risk group (RR=0.49 [95% CI 0.25–0.98], $p=0.043$). Differences were non-significant for the remaining comparisons.

Secondary discriminative validation in SMOTE+TK balanced case-control data (case $n=9712$; control $n=9712$) resulted in an AUROC=0.753 (95% CI 0.744–0.757) (Fig. 2D), and accuracy of 71.1% (95% CI 70.3–72.5).

Predictive model optimizing dynamic estimation of risk and mitigation of immortal time bias (ELIE)

The model for optimization of complex treatment histories, immortal time-bias mitigation, and dynamic landmark-based estimation of risk is referred to as ELIE

(Empiric Landmark-based Individualized Estimation of MS progression risk).

Clinical disease progression (transition to SPMS)

Risk of clinical disease progression (Fig. 3A) increased stepwise across ELIE stratified risk deciles in the training (0.3%, 1.2%, 1.7%, 2.5%, 3.7%, 5.5%, 7.2%, 10.2%, 14.3%, 21.5%) and test set (0.3%, 1.2%, 2.2%, 2.5%, 3.3%, 6.1%, 6.6%, 10.3%, 12.9%, 18.8%); Brier score=0.057. The incidence values between train and test data for each risk decile were not statistically different from each other ($p>0.05$) except for decile-10 (Fig. 3A; $p<0.001$). For more details, see Supplementary Table C.

Secondary discriminative validation (Fig. 3B, C) resulted in an AUROC=0.768 and an accuracy of 73.1% in the training data and an AUROC=0.767 and an accuracy of 72.6% in the test data.

Table 3 Objective disease progression (Lorscheider criteria for late-stage confirmed progression independent of relapse) risk stratification, accounting for DMT use over the five-year observation window (DAAE-M score)

DAAE-M score	0–2	3–7	8–9	≥ 10
Risk group	Very low	Low	Medium	High
Risk of transition % (95% CI)				
Unspecified therapy	8.4% (7.7–9.2)	14.5% (13.6–15.4)	23.5% (22.2–24.3)	38.8% (37.5–40.1)
Majority DMT*				
Low-efficacy DMT	1.9% (0.8–3.8)	6.1% (4.1–8.5)	10.6% (8.1–13.6)	27.8% (23.5–32.4)
High-efficacy DMT	2.0% (0.4–5.8)	2.1% (0.6–5.3)	7.8% (5.0–11.6)	13.8% (9.9–18.5)
No DMT	6.3% (4.1–9.4)	6.1% (4.1–8.9)	14.8% (11.8–18.3)	32.4% (27.9–37.1)
Baseline DMT				
Low-efficacy DMT	4.9% (2.8–8.0)	9.5% (6.8–12.7)	12.3% (9.5–15.5)	26.1% (22.3–30.1)
High-efficacy DMT	7.0% (3.4–12.5)	4.7% (2.3–8.5)	11.2% (7.9–15.3)	21.9% (17.8–26.6)
No DMT	3.2% (1.6–5.6)	4.9% (3.0–7.6)	12.7% (9.9–15.9)	24.9% (21.1–29.0)

CI confidence interval, DMT disease-modifying therapy

*Majority DMT use is defined according to majority (>50%) use of the five-year observation period. Unspecified therapy relates to data from the full study sample, regardless of DMT history

**Insufficient data was available for risk stratification in people who switched DMT class over the observation period

Objective disease progression (Lorscheider criteria)

Risk of objective disease progression (Fig. 3D) increased stepwise across ELIE stratified risk deciles in the training (0.9%, 1.6%, 2.5%, 4.0%, 5.8%, 7.8%, 10.2%, 15.3%, 20.9%, 32.5%) and the test set (0.7%, 2.0%, 3.0%, 4.7%, 6.2%, 8.5%, 11.0%, 13.6%, 19.5%, 29.9%); Brier score = 0.084. These incidence values between the train and test data for each risk decile were not statistically different from each other (Fig. 4D; $p > 0.05$) except for decile-10 ($p < 0.001$). For more details, see Supplementary Table D.

Secondary discriminative validation (Fig. 3E–3F) resulted in an AUROC = 0.779, and accuracy of 76.5% in the training data and AUROC = 0.759 and accuracy of 74.9% in the test data.

Open science and public tools

With the results from this study, we have generated the DAAE-M score and ELIE. A sample of the free online apps is presented in Fig. 4 and is available online (https://bit.ly/ms_public_tools). Printer-friendly versions of the tools are available in the supplemental materials.

Discussion

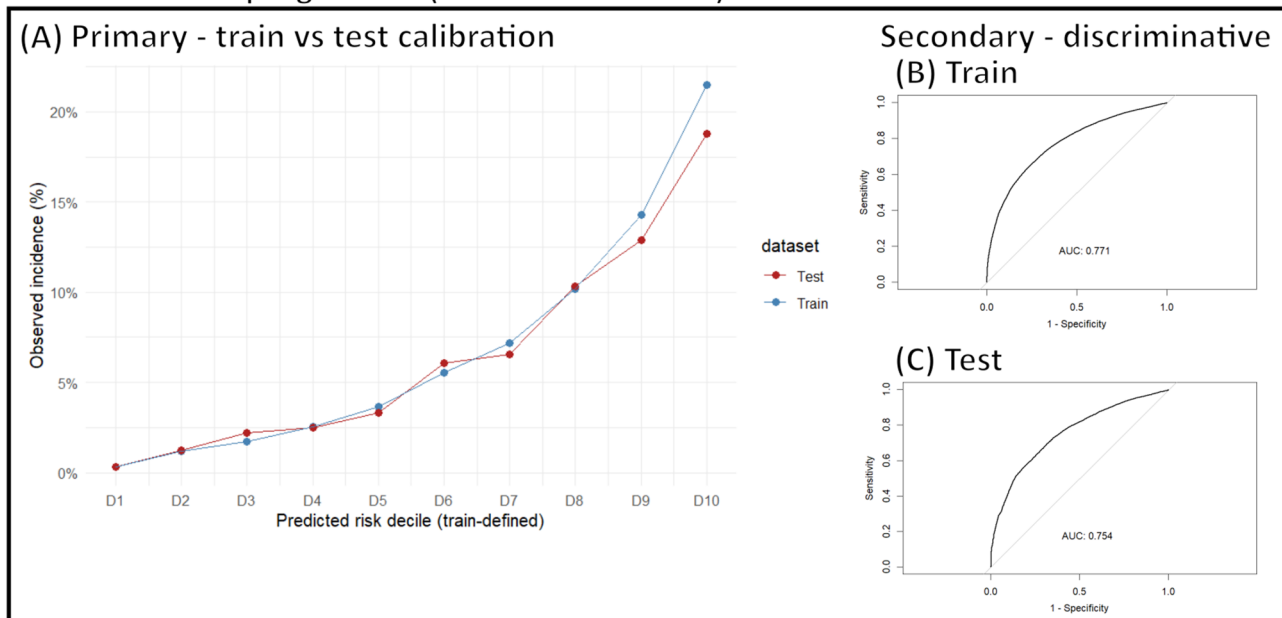
To promote personalized patient care, we developed two models for individualized predictions of disease progression in PwMS; each has distinct trade-offs depending on what was optimized in the models. Herein, we present the DAAE-M score (Disease duration, Age, Age at disease onset, EDSS, Disease modifying therapy) and ELIE (Empiric Landmark-based Individualized Estimation of MS progression risk), which both integrate DMT information and multiple definitions of disease progression into probabilistic risk prediction.

Principal findings

The DAAE-M score was developed in accordance with WHO guidelines for clinically-directed decision-support model development [4, 5]. Thus, this system was optimized for user operability (30 seconds to use), model transparency, and software-neutral interoperability to promote integration in clinics and electronic medical systems. This system was also optimized for mitigation of indication bias. As expected, in these analyses PwMS were stratified into groups of escalating risk concordantly with higher scores. As well, PwMS receiving high-efficacy DMT over

ELIE predictive performance validation

Clinical disease progression (transition to SPMS)



Objective disease progression (Lorscheider criteria)

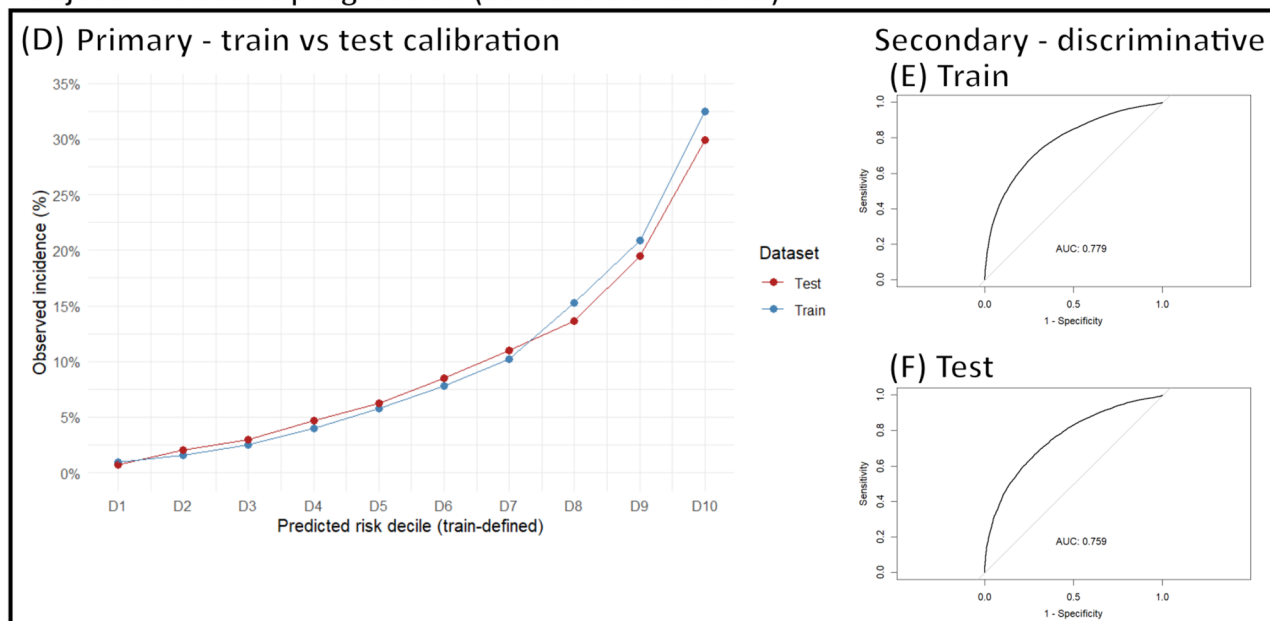


Fig. 3 ELIE (empirical landmark-based individualized estimation of MS progression risk) predictive performance validation over a 5-year time-horizon. Primary calibration validation according to clinical disease progression (transition to SPMS) over a 5-year time-horizon

(A) and secondary discriminative testing (B, C). Primary calibration validation according to objective disease progression (Lorscheider criteria) over a 5-year time-horizon (D) and secondary discriminative testing (E, F)

the majority of the observation period exhibited half the risk relative to those receiving low-efficacy DMT across the risk groups (Fig. 1A, Table 2). Risks were similar when comparing patients in relation to baseline therapy.

Next, we aimed to enhance the generalizability of the scoring system by validating it in a large heterogeneous multi-center dataset. The DAAE-M score demonstrated strong performance in primary validation. Specifically, higher scores were associated with a higher actual likelihood

(A) DAAE-M score

(B) ELIE

Fig. 4 Sample use of the DAAE-M score (A) and ELIE (B) online web apps. Abbreviations: *CI* confidence interval; *DAAE-M* disease duration, age, age at onset, Expanded Disability Status Scale, disease-

modifying therapy; *ELIE* empirical landmark-based individualized estimation of MS progression risk

of clinically defined disease progression (Fig. 1B), where event proportions were commensurate with risk predictions (Fig. 2A).

Then, we aimed to validate the performance of this tool against objective disease progression criteria. In this analysis, the DAAE-M score performed well stratifying PwMS according to risk of transition to the MSBase–Lorscheider criteria for late-stage confirmed progression independent of relapse activity, with escalating risk in association with higher risk groups and good performance in primary calibration analyses (Fig. 2C) and secondary discriminative

analyses (Fig. 2D). The DAAE-M score public web app and development reference code are freely available https://bit.ly/ms_public_tools

Finally, we also developed an alternate predictive system, ELIE. This system, optimized for dynamic estimation of risk and mitigation of immortal time bias, performed well according to primary calibration analyses (actual event proportions commensurate with predictions) and according to secondary discriminative analyses. The dynamic landmark-based predictions allowed for more complex modeling—which also promoted greater potential

for fine-tuned risk stratification schema and improved Brier scores (Fig. 3). However, this model is more opaque in its predictions, takes longer to use, and the model could not be stored in a software-neutral algorithm. Nonetheless, we have also made this model freely available on a public web app: https://bit.ly/ms_public_tools

Relevance and comparison with external literature

These findings affirm the clinical risk stratification performance of new tools across clinically heterogeneous multi-center data, thus increasing generalizability for making prognostic estimates. Both the DAAE-M score and ELIE use similar predictors to those described in clinical trials [19]. They are inspired by previously developed tools [20, 21], they and function in a similar manner to known risk-stratification tools used in neurologic [22], and non-neurologic [23] populations. The DAAE-M score specifically matches the format of individual patient risk reporting using ordinalized scoring and software-neutral reference tables.

This tool has performed well in calibration analyses of risk predictions across several clinical environments [3, 24, 25]. The present work reflects a significant milestone, as it represents a large international validation, reinforcing generalizability across diverse clinical settings and countries. Importantly, this work also incorporates DMT history into new tools for providing patient risk estimates and also extends beyond subjective clinical judgment-based end-points by incorporating objective outcomes, thereby underscoring performance not only across new populations but also against standardized measures.

Additionally, the integration of DMT efficacy into DAAE-M score risk reports now allows for patients and physicians to simulate risk estimates specific to DMT types, according to baseline or majority use. This improves utility for personalized patient care associated with preliminary therapeutic choices or decisions to change therapies in high-risk patients. Importantly, our use of propensity-score matching for the model development mitigated the effects of indication bias [26] which can at times result in retrospective effects that paradoxically oppose [27] observed effects of treatment on clinical progression in randomized clinical trials [28]. With this methodology, our findings showing lower risk of clinical disease progression in PwMS receiving high-efficacy DMT are consistent with existing literature. For instance, in one study by Brown et al. [29], high-efficacy DMT was associated with a hazard-ratio of 0.66 in relation to risk of transition to SPMS for PwMS receiving low-efficacy DMT. This is similar to the hazard ratios reported in the present work, indicating that PwMS receiving high-efficacy DMT had hazard ratios ranging from 0.42 to 0.59 relative to low-efficacy DMT treated PwMS across the DAAE-M score stratified risk groups.

The modeling systems presented also performed well in predicting risk of transition to objectively defined disease progression using the MSBase-Lorscheider criteria. This is important because clinical definitions of disease progression can be heterogeneous between physicians and research centers [30]. Additionally, low sensitivity of testing and non-standardized definitions may result in diagnostic delay of SPMS [6], making use of objective criteria particularly important for identifying PwMS in transitional phases [31].

Finally, the findings presented, in addition to the previously described high ratings of the previous risk score on the System Usability Scale (90.3 out of 100) from physicians in over 20 countries [3], support its utility and feasibility for use in clinical environments. This tool can be used in personalized clinical care such as for supporting decisions whether to start or stop certain medicines [9], or deciding whether rehabilitation or other behavioral changes are appropriate [13, 32]. Similarly, the DAAE-M score can open conversations between PwMS and physicians about goals of care [33] and the desired path for care in balance with known risks.

In comparison with the DAAE-M score, ELIE's strong performance in primary calibration and secondary discriminative testing is also worth consideration. This system has a number of strengths. Foremost, this tool provides dynamic risk estimates along the course of patient observation histories—accounting for observation time within its predictions. Along its dynamic handling of immortal time bias, ELIE also supports more complex retrospective treatment histories and treatment timing in its predictions and avoids selection biases in which certain treatment histories are excluded [9, 15]. Likewise, early success of the Barcelona risk score [34] and the SP-RiSc [21] illustrates the potential for alternate more complex predictive systems. However, these strengths of the ELIE model come with trade-offs, namely that it is less transparent, requires more time to be used, and requires specific software (e.g. R with appropriate machine-learning libraries) for integration into distinct international medical systems. Illustrated sample use of both DAAE-M and ELIE is presented in Fig. 4.

Limitations and future directions

One key limitation of this work is that all results are derived from adult PwMS, thus neglecting applications in pediatric populations. Future work is needed to fill this gap. Additionally, neither of the presented tools incorporates MRI data. This, and the low proportion of patients in the present sample receiving high-efficacy therapy (7.2%) should be addressed in future work. Similarly, given the critical role of therapy timing [35], it is important to weigh trade-offs of inclusion of such information against priorities such as

transparency and interoperability of models. As brain and spine MRI are shown to predict MS disease progression [36, 37], with the inclusion of MRI data in future models it will be vital to consider the feasibility of translation of MRI metrics depending on their complexity [38]. For instance, lesion counts and linear brain atrophy measures have low granularity, but are accessible in clinical environments, making translation more feasible [37]. Likewise, time required for tool use and availability of data (e.g. MRI scan type) must be heavily considered. For instance, FLAIR images are widely available clinically and improve predictions of future disease worsening [39], making them more ideal targets for clinical translation. The Barcelona risk score [34] and the SP-RiSc [21] illustrate the potential for MRI incorporation into similar models—demonstrating a step towards such approaches in future clinical practice.

Importantly, neither DAAE-M nor ELIE considers subtle forms of disability not well-captured by the EDSS, such as fatigue and cognition [40], nor subtle disability accrual independent of relapse in early MS stages [41]. It is important for future work to consider these limitations to improve predictive systems and to enable a wider range of prognostic clinical tools for PwMS.

Conclusion

To promote personalized patient care, we developed two well-calibrated machine-learning-based tools for individualized 5-year predictions of clinically and objectively defined MS progression. The DAAE-M score was optimized according to WHO guidelines for transparency, software-neutral interoperability, and for mitigation of indication bias. In comparison, ELIE was optimized for dynamic modeling, complex treatment histories, and mitigation of immortal-time bias. Both systems performed well in primary calibration analyses, with predicted risk closely matching actual incidence, albeit with distinct trade-offs per system depending on what was optimized for in development. These results support the use of such risk stratification systems for identifying target PwMS for relevant secondary prevention and restorative treatment strategies. Future work should incorporate MRI and neuropsychological data to further enhance use for prognostication and personalized patient care.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00415-026-13802-4>.

Acknowledgements This work was supported by the European Committee for Treatment and Research in Multiple Sclerosis. We would also like to acknowledge the following contributors: Dr Matteo Diamanti, Dr Clara Chisari, Dr Emanuele D'Amico, Dr. Michael G. Dwyer, Dr Lo Fermo Salvatore, Dr Mark Marriott, Dr Trevor Kilpatrick, Dr John King, Dr Ai-Lan Nguyen, Dr Chris Dwyer, Dr Mastura Monif, Dr Izanne Roos, Ms Lisa Taylor, Ms Josephine Baker, Dr Raymond

Hupperts, Dr Javier Olascoaga, Dr Marzena Fabis-Pedrini, Dr Freek Verheul, Juan Camilo Carrillo.

Author contributions The following authors contributed to conception and design of the study, acquisition and analysis of the data, and drafting a significant portion of the manuscript or figures: Tom A.N. Fuchs, Menno M Schoonheim, Julia R Jelgerhuis, Eva M Strijbis, Bianca Weinstock-Guttman. The remaining authors contributed to data acquisition, critical feedback, and manuscript revision.

Funding This work is supported by the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), financially supporting the fellowship of the principal author Dr. Tom A.N. Fuchs.

Data availability Anonymized data use for the present analyses are available upon reasonable request from the MSBase patientregistry

Declarations

Conflict of interest The co-authors have the following disclosures: P. Grammond has served on advisory boards for Novartis, EMD Serono, Roche, Biogen Idec, Sanofi Genzyme, Pendopharm and has received grant support from Genzyme and Roche, and has received research grants for his institution from Biogen Idec, Sanofi Genzyme, EMD Serono. S. Khoury received compensation for scientific advisory board activity from Merck and Roche, and received compensation for serving on the IDMC for Biogen. M. Sa received consulting fees, speaker honoraria, and/or travel expenses for scientific meetings from Alexion, Bayer Healthcare, Biogen, Bristol Myers Squibb, Celgene, Janssen, Merck-Serono, Novartis, Roche, Sanofi and Teva. J. Lorscheider received research support from Innosuisse–Swiss Innovation Agency, The University of Basel, Biogen and Novartis; received speaker fees, travel support, and/or compensation for advisory boards from Bristol Myers Squibb, Novartis, Roche, and Teva. D. Maimone received speaker honoraria for Advisory Board and travel grants from Alexion, Almirall, Bayer, Biogen, Bristol Myers Squibb, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva. C. Orja-Guevera received honoraria as consultant on scientific advisory boards or as speaker from Biogen, Celgene-BMS, Janssen, Merck, Novartis, Roche, Sanofi-Genzyme, Sandoz, Teva and Viatrix. M. D'hooghe received consultancy and advisory board fees from Roche, Sanofi-Genzyme, Biogen, Merck-Serono, Bayer-Schering, Novartis and Allergan; received congress support from Biogen, Merck-Serono, Teva and Roche. She has also received research support from Novartis, Biogen, Roche, FWO (Research Foundation Flanders) and Fonds D.V. (Ligue Nationale Belge de la Sclérose en Plaques, Fondation Roi Baudouin). M. Fabis-Pedrini received travel compensation from Merck. J. Oh has received research funding from the MS Society of Canada, National MS Society, Brain Canada, Biogen, Roche, EMD Serono (an affiliate of Merck KGaA); and personal compensation for consulting or speaking from Alexion, Biogen, Celgene (BMS), EMD Serono (an affiliate of Merck KGaA), Novartis, Roche, and Sanofi-Genzyme. P. Lalive received honoraria for speaking and/or travel expenses from Biogen, Merck, Novartis, Roche; consulting fees from Biogen, GeNeuro, Merck, Novartis, Roche; research support from Biogen, Merck, Novartis. None were related to this work. Barbara Willekens received honoraria for acting as a member of Scientific Advisory Boards/Consultancy for Alexion, Almirall, Biogen, Celgene/BMS, Merck, Janssen, Novartis, Roche, Sandoz, Sanofi-Genzyme and speaker honoraria and travel support from Biogen, Celgene/BMS, Merck, Novartis, Roche, Sanofi-Genzyme; research and/or patient support grants from Biogen, Janssen, Merck, Sanofi-Genzyme, Roche. Honoraria and grants were paid to UZA/UZA Foundation. Further, B.W. Dana Horakova received research funding from FWO-TBM, Belgian Charcot Foundation, Start-2Cure Foundation, Queen Elisabeth Medical Foundation for Neuro-

sciences and the National MS Society USA. She was supported by the Charles University: Cooperatio Program in Neuroscience, by the project National Institute for Neurological Research (Programme EXCELES, ID Project No. LX22NPO5107)—Funded by the European Union—Next Generation EU, and by General University Hospital in Prague project MH CZ-DRO-VFN64165. She also received compensation for travel, speaker honoraria and consultant fees from Biogen Idec, Novartis, Merck, Bayer, Sanofi Genzyme, Roche, and Teva, as well as support for research activities from Biogen Idec. Eva Kubala Havrdova received honoraria/research support from Biogen, Merck Serono, Novartis, Roche, and Teva; has been a member of advisory boards for Actelion, Biogen, Celgene, Merck Serono, Novartis, and Sanofi Genzyme; and has been supported by the Czech Ministry of Education—project Cooperatio LF1, research area Neuroscience, and the project National Institute for Neurological Research (Programme EXCELES, ID project No LX22NPO5107)—funded by the European Union—Next Generation EU. Sara Eichau has received speaker honoraria and consultant fees from Biogen Idec, Novartis, Merck, Janssen, Bristol Myers, Bayer, Sanofi Genzyme, Roche and Teva. Pierre Duquette served on editorial boards and has been supported to attend meetings by EMD, Biogen, Novartis, Genzyme, and TEVA Neuroscience. He holds grants from the CIHR and the MS Society of Canada and has received funding for investigator-initiated trials from Biogen, Novartis, and Genzyme. Francesco Patti received personal compensation for serving on advisory boards for Almirall, Alexion, Biogen, Bristol, Janssen, Merck, Novartis and Roche. He further received research grants from Alexion, Almirall, Biogen, Bristol, Merck, Novartis and Roche and by FISM, Reload Association (Onlus), Italian Health Minister, and University of Catania. Raed Alroughani received honoraria as a speaker and for serving on scientific advisory boards from Bayer, Biogen, GSK, Merck, Novartis, Roche and Sanofi-Genzyme. Alessandra Lugaresi has received personal compensation for consulting, serving on a scientific advisory board, speaking or other activities from Alexion, Biogen, Bristol Myers Squibb, Horizon, Janssen, Merck Serono, Novartis, and Sanofi/Genzyme, and her institutions have received research grants from Novartis and Sanofi/Genzyme. Prof. Tomassini has received consultation and speaker fees, travel grants and research support from Biogen, Sanofi Genzyme, Merck, Novartis, Roche, Alexion, Viatrix, Janssen, Bristol Myers Squibb, Almirall. Murat Terzi received travel grants from Novartis, Bayer-Schering, Merck and Teva; has participated in clinical trials by Sanofi Aventis, Roche and Novartis. Maria Pia Amato received honoraria as a consultant on scientific advisory boards from Biogen, Bayer-Schering, Merck, Teva and Sanofi-Aventis; has received research grants from Biogen, Bayer-Schering, Merck, Teva and Novartis. Tomas Kalincik served on scientific advisory boards for MS International Federation and World Health Organization, BMS, Roche, Janssen, Sanofi Genzyme, Novartis, Merck and Biogen, steering committee for Brain Atrophy Initiative by Sanofi Genzyme, received conference travel support and/or speaker honoraria from WebMD Global, Eisai, Novartis, Biogen, Roche, Sanofi-Genzyme, Teva, BioCSL and Merck and received research or educational event support from Biogen, Novartis, Genzyme, Roche, Celgene and Merck. Izanne Roos has served on scientific advisory boards, received conference travel support and/or speaker honoraria from Roche, Novartis, Merck and Biogen. Izanne Roos is supported by MS Australia and the Trish Multiple Sclerosis Research Foundation. Michael Barnett served on scientific advisory boards for Biogen, Novartis and Genzyme and has received conference travel support from Biogen and Novartis. He serves on steering committees for trials conducted by Novartis. His institution has received research support from Biogen, Merck and Novartis. Anneke van der Walt served on advisory boards and receives unrestricted research grants from Novartis, Biogen, Merck and Roche. She has received speaker's honoraria and travel support from Novartis, Roche, and Merck. She receives grant support from the National Health and Medical Research Council of Australia and MS Research Australia. Jeannette Lechner-Scott received travel compensa-

tion from Novartis, Biogen, Roche and Merck. Her institution receives the honoraria for talks and advisory board commitment as well as research grants from Biogen, Merck, Roche and Novartis. Vincent van Pesch received travel grants from Merck Healthcare KGaA (Darmstadt, Germany), Biogen, Sanofi, Bristol Meyer Squibb, Almirall and Roche. His institution has received research grants and consultancy fees from Roche, Biogen, Sanofi, Merck Healthcare KGaA (Darmstadt, Germany), Bristol Meyer Squibb, Janssen, Almirall, Novartis Pharma, and Alexion. Andrea Surcinelli received travel and meeting attendance support from Novartis, Biogen, Roche, Merck, Bristol, Sanofi-Genzyme, Almirall. Piam Matteo Foschi received travel and meeting attendance support from Novartis, Biogen, Roche, Sanofi-Genzyme and Merck. Emanuele D'Amico received speaker honoraria for Advisory Board and travel grants from Alexion, Biogen, Bristol Myers Squibb, Merck, Novartis, Roche and Sanofi-Genzyme. Suzanne Hodgkinson has received consulting fees and speaker honoraria from Biogen, Novartis, Roche, Merck, and has received grants for her institution from Biogen, Merck, Novartis, and Roche. Jens Kuhle received speaker fees, research support, travel support, and/or served on advisory boards for Swiss MS Society, Swiss National Research Foundation (320030_189140/1), University of Basel, Progressive MS Alliance, Alnylam, Bayer, Biogen, Bristol Myers Squibb, Celgene, Immunic, Merck, Neurogenesis, Novartis, Octave Bioscience, Quantarix, Roche, Sanofi, Stata DX. Rana Karabudak received consulting fees, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events, support for attending meetings and travel, and participation on a data safety monitoring board or advisory board from Gen Turkey. Daniele Spitaleri received honoraria as a consultant on scientific advisory boards from Bayer-Schering, Novartis and Sanofi-Aventis and compensation for travel from Novartis, Biogen, Sanofi Aventis, Teva and Merck. Guy Laureys received travel and/or consultancy compensation from Sanofi-Genzyme, Roche, Teva, Merck, Novartis, Celgene, Biogen. Bruce Taylor received funding for travel and speaker honoraria from Bayer Schering Pharma, CSL Australia, Biogen and Novartis, and has served on advisory boards for Biogen, Novartis, Roche and CSL Australia. Tamara Castillo-Triviño received speaking/consulting fees and/or travel funding from Almirall, Biogen, Bristol Myers Squibb, Janssen, Merck, Novartis, Roche, Sanofi-Genzyme and Teva. Ayse Altintas received speaker honoraria from Novartis and Alexion. Orla Gray received honoraria as consultant on scientific advisory boards for Genzyme, Biogen, Merck, Roche, and Novartis; has received travel grants from Biogen, Merck, Roche, and Novartis; has participated in clinical trials by Biogen and Merck. Her institution has received research grant support from Biogen. Riadh Gouider has received research grant and/or advisory board honoraria from Biogen, Hikma, Merck, Roche and Sanofi. Jose E Meca-Lallana has received honoraria as a consultant, as a chairman or lecturer in meetings and has participated in clinical trials and other research projects promoted by Alexion, Almirall, Biogen, Bristol-Meyers-Squibb, Horizon, Johnson & Johnson, Merck, Neuraxpharm, Novartis, Roche, Sandoz, Sanofi and UCB. Allan Kermode served on Scientific Advisory Boards for Bayer, BioCSL, Biogen-Idec, Clene Nanomedicine, Eisai, Innate Immunotherapeutics, Lgpharma, Merck, Mitsubishi Tanabe Pharma, NeuroScientific Biopharmaceuticals, Novartis, Roche, Sanofi-Aventis, Sanofi-Genzyme, Teva, and View Health. Koen de Gans served on scientific advisory boards for Roche, Janssen, Sanofi-Genzyme, Novartis and Merck, received conference fee and travel support from Novartis, Biogen, Sanofi-Genzyme, Teva, AbbVie and Merck and received educational event support from Novartis. Jose Luis Sanchez-Menoyo accepted travel compensation from Novartis, Merck and Biogen, speaking honoraria from Biogen, Novartis, Sanofi, Merck, Almirall, Bayer and Teva and has participated in clinical trials by Biogen, Merck and Roche. Abdullah Al-Asmi received personal compensation for serving as a Scientific Advisory or speaker/moderator for Novartis, Biogen, Roche, Sanofi-Genzyme, and Merck. Pamela McCombe received speakers fees and travel grants

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- ²⁷ Nemocnice Jihlava, Jihlava, Czech Republic
- ²⁸ Hospital Universitario Donostia and IIS Biodonostia, San Sebastián, Spain
- ²⁹ Koc University, Istanbul, Turkey
- ³⁰ South Eastern HSC Trust, Belfast, UK
- ³¹ Razi University Hospital, Tunis, Tunisia
- ³² Virgen de la Arrixaca Clinical University Hospital. IMIB-Arrixaca, Murcia, Spain
- ³³ Perron Institute for Neurological and Translational Science, The University of Western Australia, Perth, Australia
- ³⁴ Groene Hart Ziekenhuis, Gouda, The Netherlands
- ³⁵ Galdakao-Usansolo University Hospital, Osakidetza-Basque Health Service, Galdakao, Spain
- ³⁶ MS Institute, Osfahan, Iran
- ³⁷ College of Medicine and Health Sciences and Sultan, Qaboos University Hospital, Sultan Qaboos University, Al-Khodh, Oman
- ³⁸ Royal Brisbane and Women's Hospital, Brisbane, Australia
- ³⁹ Department of Neuroscience Clinic of Neurology, University of Medicine and Pharmacy Victor Babes Timisoara, Timisoara, Romania
- ⁴⁰ Department of Neurology, Erciyes University, Kayseri, Turkey

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- ⁴² Department of Neurology, University of Debrecen, Debrecen, Hungary
- ⁴³ Faculty of Medicine, Geneva University Hospitals, Geneva, Switzerland
- ⁴⁴ Concord Repatriation General Hospital, University of Sydney, Sydney, Australia
- ⁴⁵ Department of Neurology, Antwerp University Hospital, Edegem, Belgium
- ⁴⁶ Hospital General Universitario de Alicante, Alicante, Spain
- ⁴⁷ Hospital Universitario Nacional de Colombia, Bogota, Colombia
- ⁴⁸ University Hospital Center Zagreb, Zagreb, Croatia
- ⁴⁹ Bombay Hospital Institute of Medical Sciences, Mumbai, India
- ⁵⁰ AHEPA University Hospital, Thessaloniki, Greece
- ⁵¹ Semmelweis University Budapest, Budapest, Hungary
- ⁵² Isfahan University of Medical Sciences, Isfahan, Iran
- ⁵³ Hospital Clinic de Barcelona, Barcelona, Spain
- ⁵⁴ University of Cordoba, Cordoba, Spain
- ⁵⁵ Department of Neurology, Westmead Hospital, Sydney, Australia
- ⁵⁶ Department of Neurology, Galliera Hospital, Genoa, Italy
- ⁵⁷ Vincent's Hospital, Fitzroy, Melbourne, Australia
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- ⁵⁹ Alma Ziekenhuis, Sijsele, Damme, Belgium
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- ⁶³ Aarhus University Hospital, Aarhus C, Denmark