

Individualized treatment response in multiple sclerosis predicted with machine learning

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Introduction

- Treatment response varies between patients, creating a need for individualized prediction of future disease activity across DMT options.

- Machine-learning models can integrate multiple clinical characteristics to generate patient-specific prognostic predictions and examine how predicted outcomes vary across DMT-conditioned scenarios.

- Robust evaluation is required to determine whether these individualized predictions are reliable across outcomes, prediction horizons and independent populations.

Methods

Data source and cohort

- Training / testing: MSBase Registry
- External validation: Naples MS cohort
- Eligible treatment episodes required a valid baseline EDSS assessment and sufficient longitudinal follow-up.

Prediction tasks

- Four outcomes: relapse, confirmed disability worsening (CDW), confirmed disability improvement (CDI), and progression independent of relapse activity (PIRA).
- Predictions were generated at 12, 24 and 48 months.

Predictors and treatments

- 27 demographic, disease-history, relapse, disability and functional-system predictors.
- Nine DMT groups: interferon beta, glatiramer acetate, fingolimod, teriflunomide, fumarates, cladribine, natalizumab, alemtuzumab and anti-CD20 therapies.

Model development

- XGBoost models used patient-level 70% training, 15% validation and 15% locked-test partitions.
- Predicted probabilities were calibrated using validation-only Platt scaling.

DMT-conditioned prediction

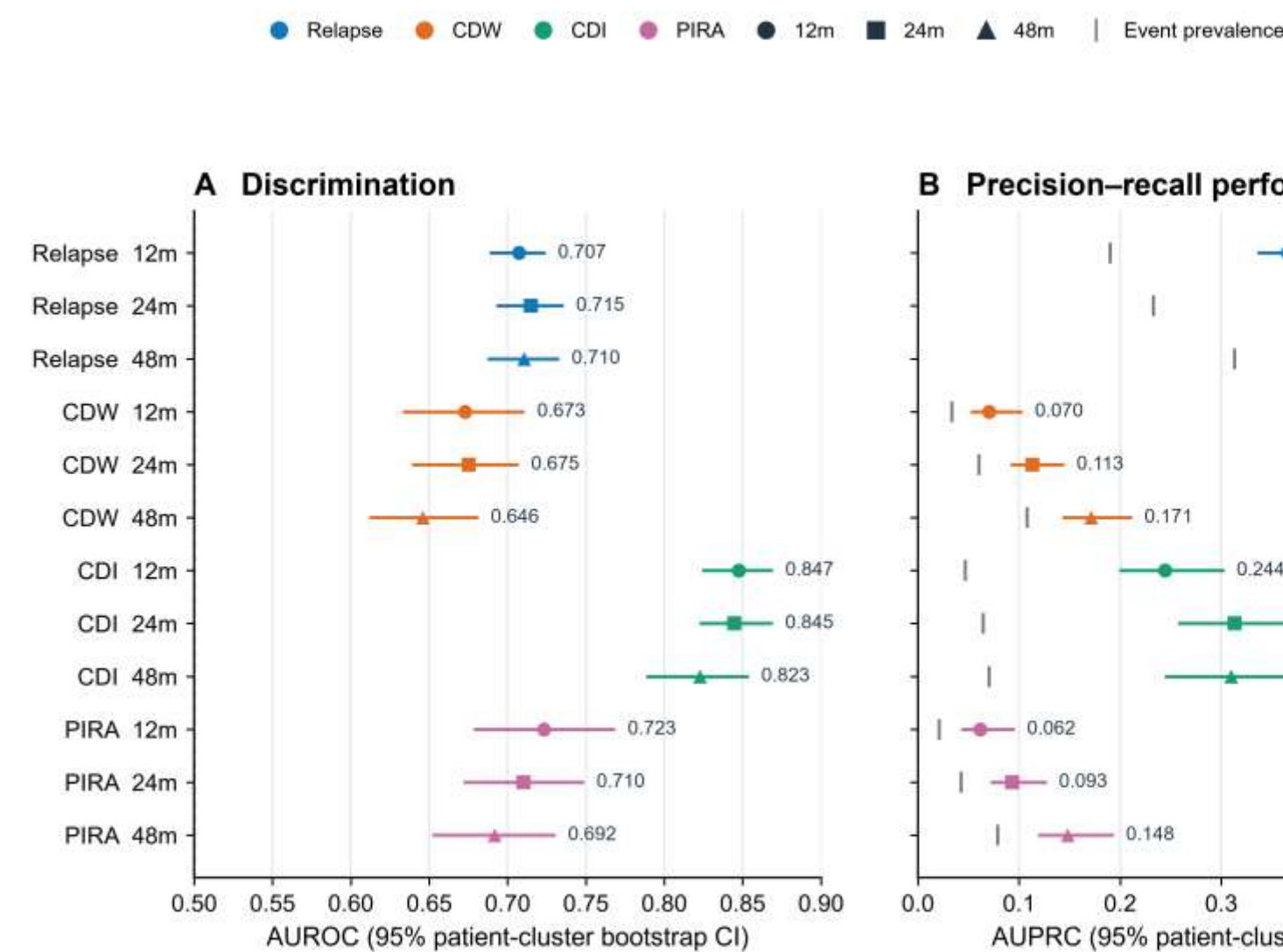
- A pooled S-Learner included treatment as a predictor. For each patient, the DMT input was substituted across the nine treatment groups while all clinical characteristics were held constant.

Model evaluation

- Performance was assessed using AUROC, AUPRC, calibration and Brier score.
- DMT-conditioned heterogeneity and model interpretation were examined using within-patient scenario predictions and SHAP.
- Relapse predictions were additionally evaluated in an independent external cohort.

Results: Prognostic performance

Prognostic performance across 12 prediction tasks



Treatment-aware XGBoost model, observed-treatment predictions only. AUPRC should be interpreted relative to outcome prevalence.

Figure 1. Prognostic model performance. Discrimination was strongest for CDI and remained stable for relapse across 12-, 24- and 48-month horizons.

Relapse across prognostic strata

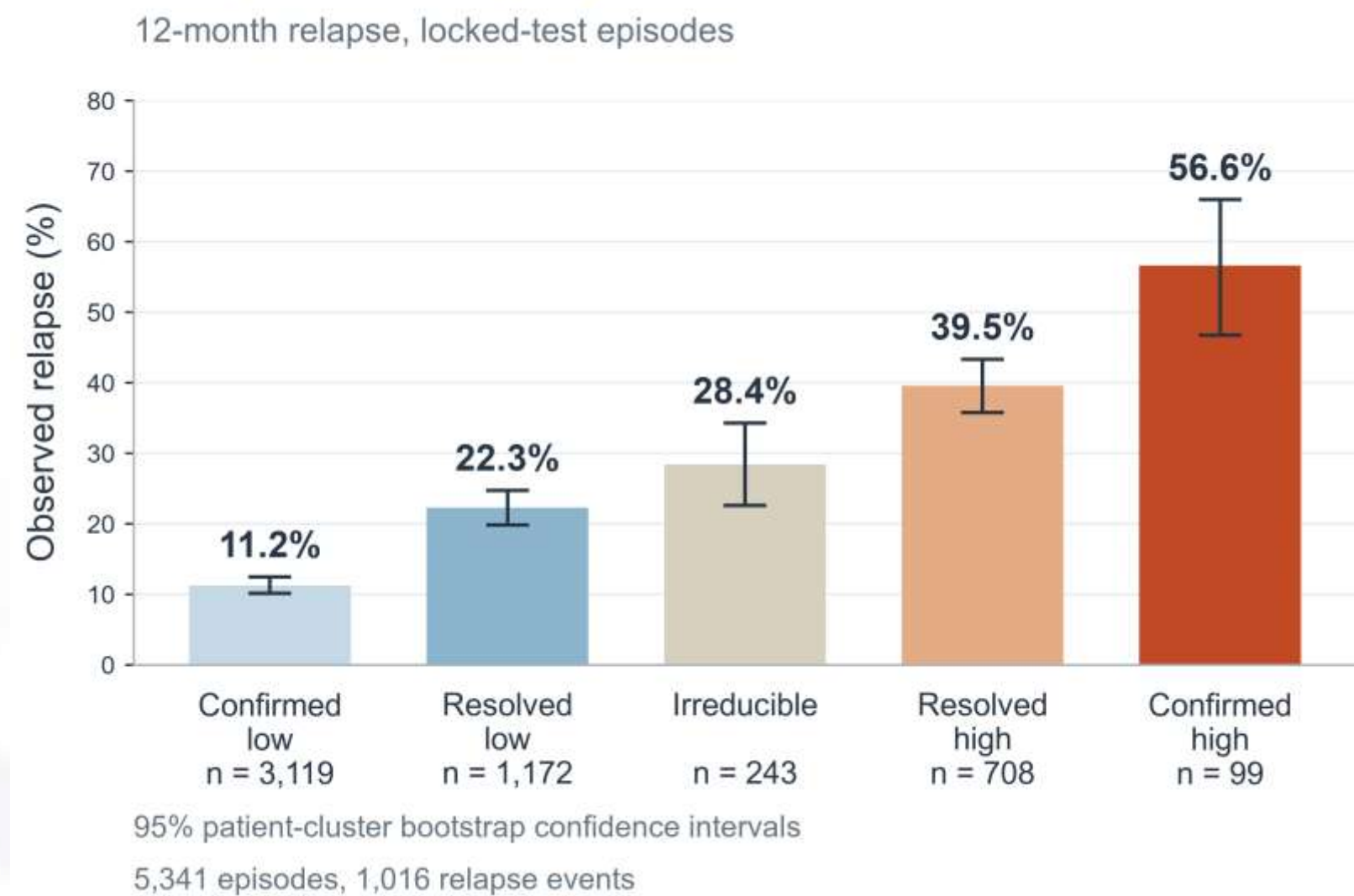
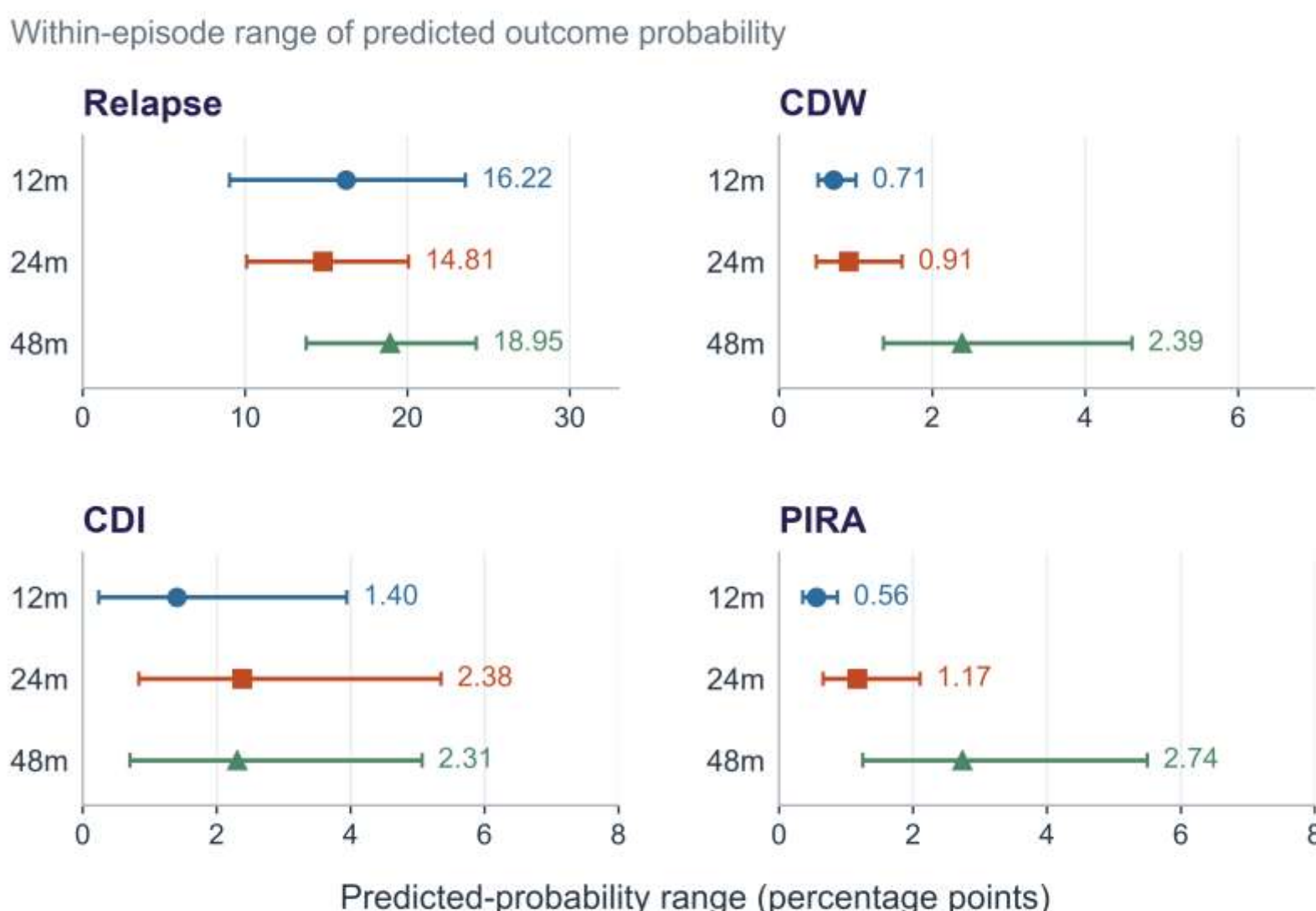


Figure 2. Prognostic risk stratification. Observed 12-month relapse frequency increased across validation-defined prognostic strata.

Results: DMT-conditioned predictions

Variation across nine DMT scenarios



Dots show medians. Whiskers show interquartile ranges.

Panels use different scales. Prognostic model scenarios.

Figure 3. DMT-conditioned prediction variability. Within-patient predictions varied across nine DMT scenarios, with the greatest separation for relapse.

Personalised DMT scenario profiles

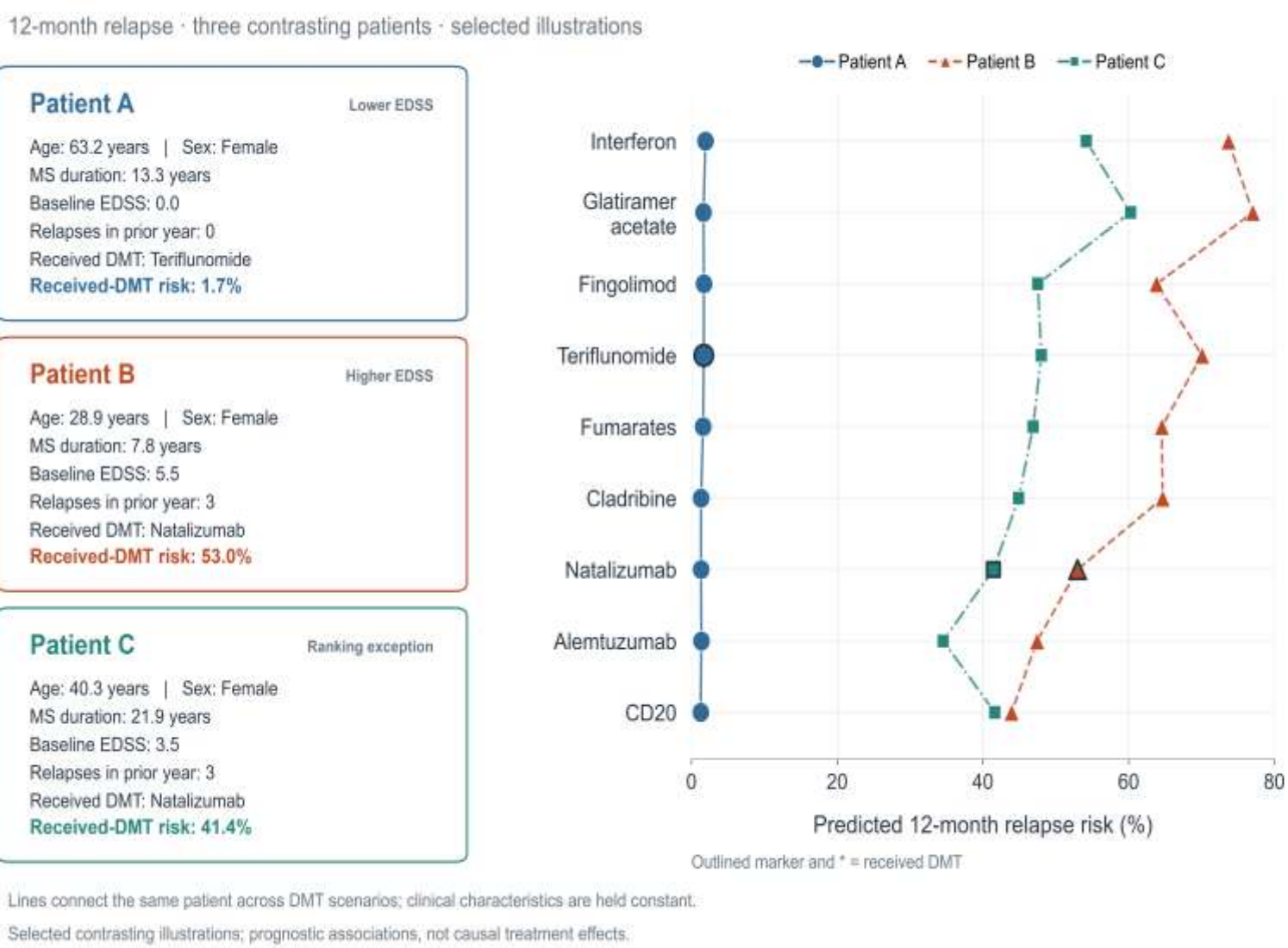
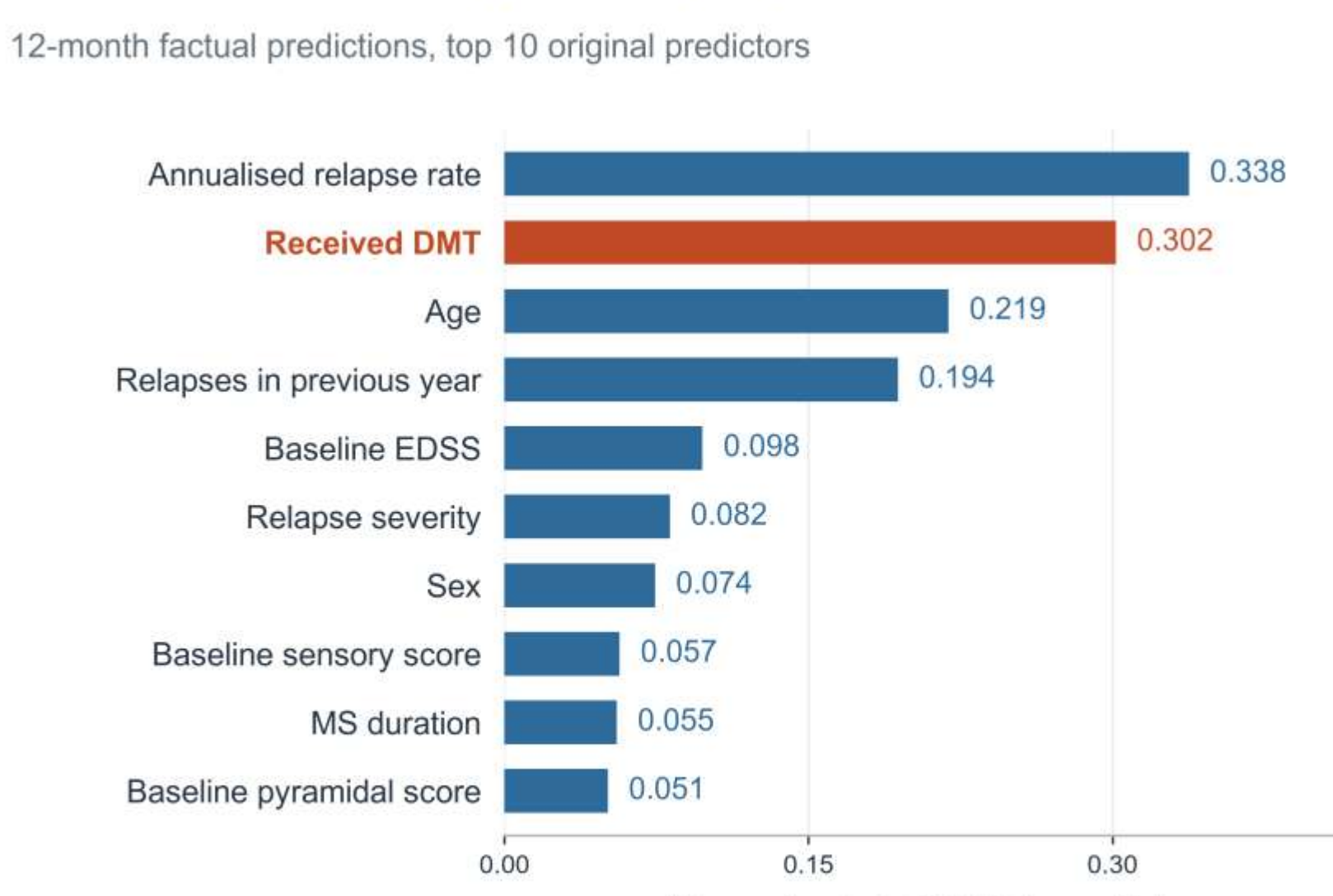


Figure 4. Individual DMT-conditioned profiles for three patients with different clinical characteristics. For each patient, changing only the DMT input produced different 12-month relapse probabilities.

Results: Interpretation & validation

Features contributing to relapse prediction



Grouped Tree-SHAP on the raw XGBoost margin

Feature contributions describe the fitted model

Figure 5. Clinical drivers of relapse prediction. Relapse history, received DMT, age, baseline disability and relapse severity were leading contributors.

External relapse discrimination

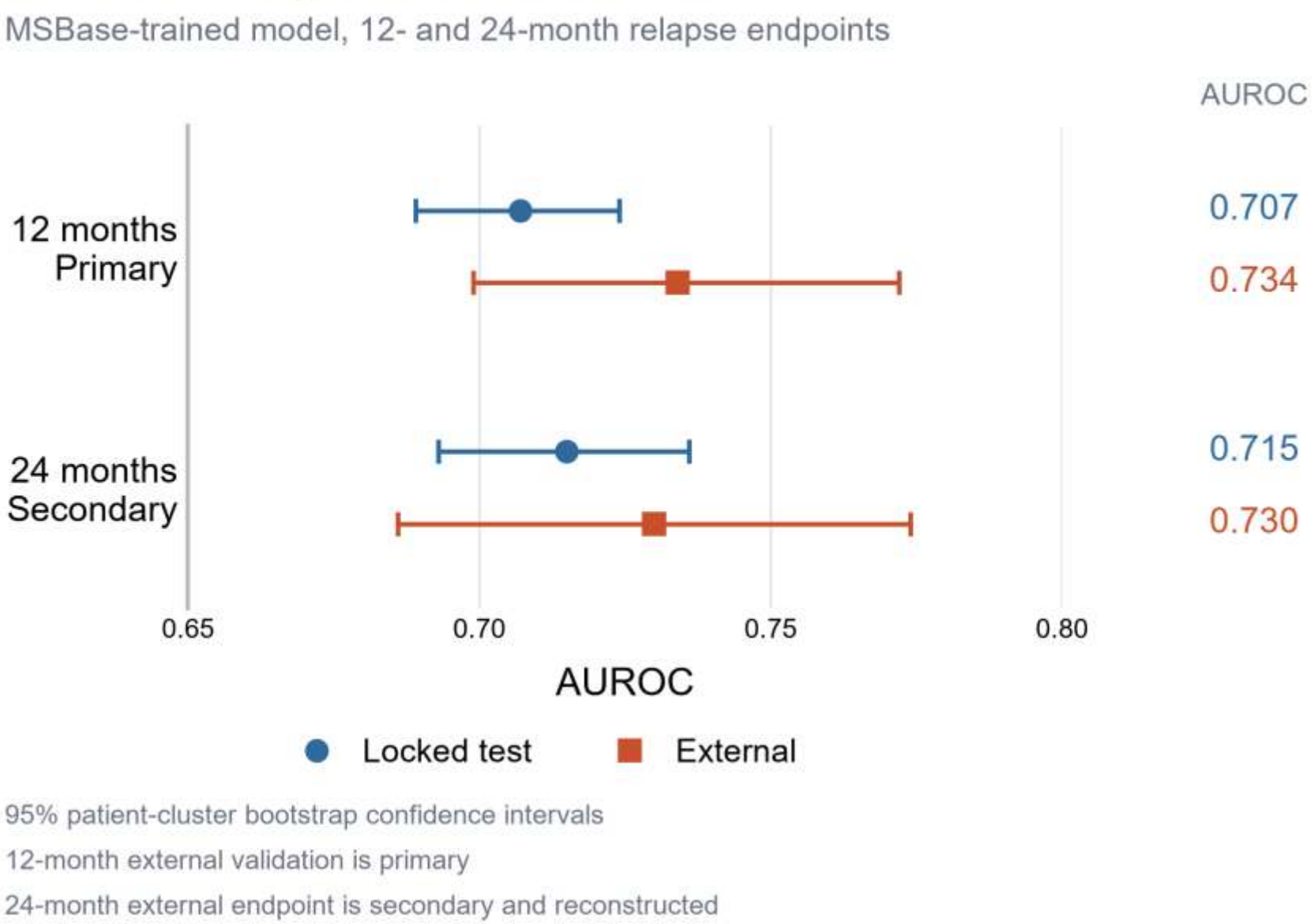


Figure 6. External prognostic validation. The MSBase-trained relapse model was applied to the independent Naples cohort without retraining and maintained discrimination.

Conclusion

- Machine-learning models are suitable for individualized prognostication of relapse risk, CDW, CDI and PIRA across 12-, 24- and 48-month horizons.
- The predicted outcomes varied across patient characteristics and nine DMTs, demonstrating interaction between patient/disease characteristics and treatment response.
- The relapse model maintained prognostic discrimination in an independent external validation cohort, supporting the transportability of the approach.
- These findings demonstrate the potential of machine learning to support individualized prediction of treatment response in multiple sclerosis.

Machine learning can identify the interaction between patient/disease characteristics and disease modifying therapy related to future MS activity and disability.

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