Development of a model to estimate underlying Parkinson's disease progression after initiation of symptomatic therapy
OBJECTIVE

To identify the best linear mixed model associating levodopa-equivalent daily dosage (LEDD) and Parkinson’s disease (PD) symptom severity.

BACKGROUND

Potential benefits of disease-modifying therapies for PD are obscured when trial participants initiate symptomatic therapies. Assessment in the OFF state, extrapolation by random effects after censoring at initiation of symptomatic therapy, and linear adjustment for LEDD are existing methods for managing this complication. Improved methods are needed to estimate the underlying rate of PD progression after the initiation of symptomatic therapy in disease modification trials.

METHODS

We used data from three studies (PPMI, STEADY-PD III, SURE-PD3) to develop a model for
estimating participants’ latent MDS-UPDRS trajectories. We converted symptomatic medications to LEDDs at each MDS-UPDRS assessment based on existing calibrations. To identify the pattern of dependence on LEDD and important effect modifiers, we identified the model with a minimum 10-fold cross-validated root mean squared error (CV-RMSE) by an exhaustive search over all subsets of baseline predictors in a linear mixed-effects model with random intercepts and slopes. We used random forest (RF) mixed-effects models to estimate the lowest achievable CV-RMSE and evaluate the completeness of the identified linear model.

RESULTS

The RF model minimum CV-RMSE was 6.1 points for prediction of MDS-UPDRS Part 3. The linear mixed model with the following predictors yielded a minimum CV-RMSE of 6.4 points: LEDD, time, study cohorts, age, weight, years from diagnosis, years from symptom to diagnosis, LEDD x study cohorts, LEDD x years from diagnosis, LEDD x weight, time x study cohorts, time x years from diagnosis.

CONCLUSION

The currently identified mixed model yields estimates with similar accuracy to the RF model. We are continuing to develop the parametric model by including additional candidate predictors and by addressing potential non-linear relationships and will compare model accuracy among competing approaches according to their ability to predict future clinical events.