Prediction of HD-related Clinical Outcome Progression and Imaging arkers using AI-based Digital Twins

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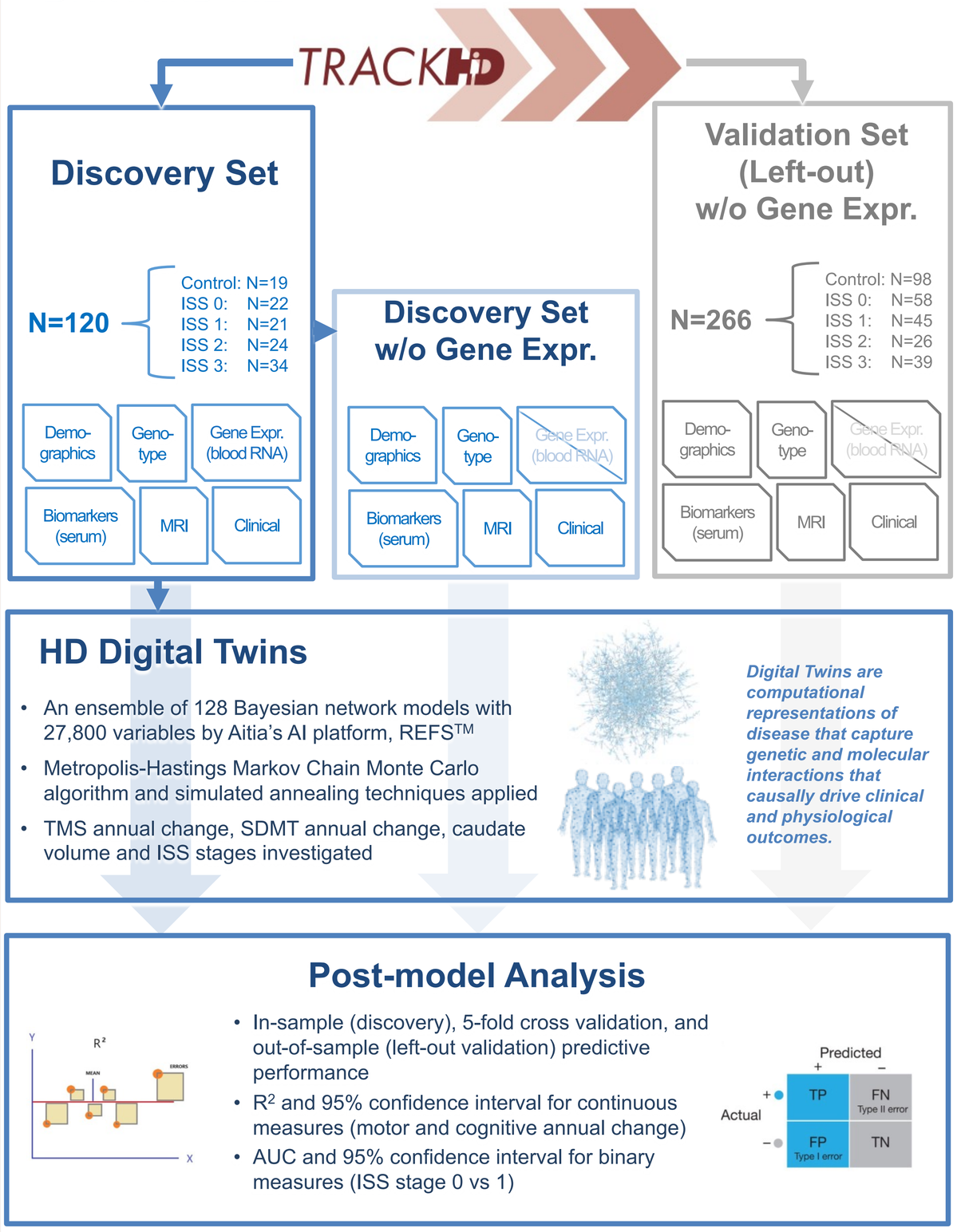
Objective

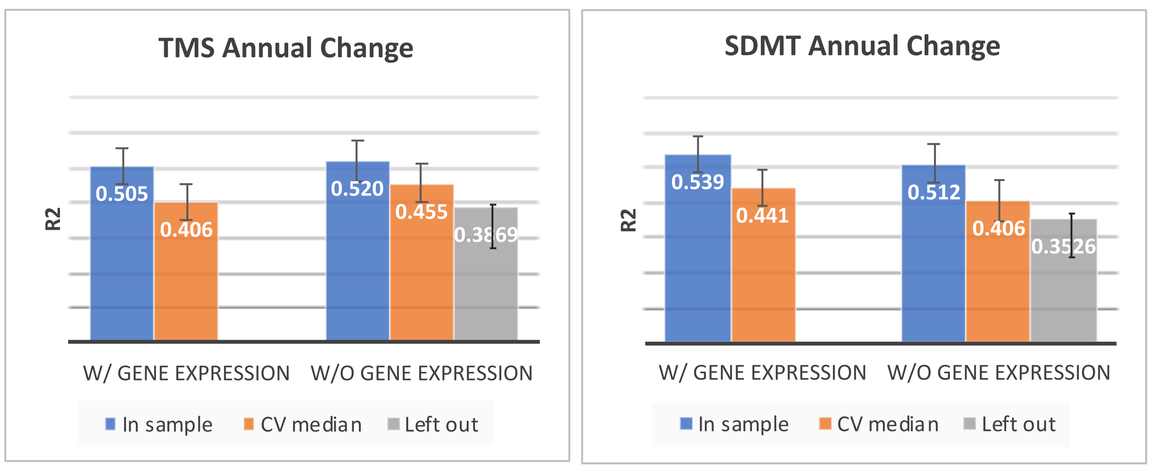
- To forecast individual-level cognitive and motor progression rates and identify faster progressing patients
- To prospectively identify individuals likely to have neuroimaging atrophy sufficient to be classified as ISS stage 1 ***before*** MRIs

Data and Methods



Results

Figure 1. Performance of Digital Twins to predict TMS and SDMT progression both with and without use of gene expression data were compared.



- The Digital Twins demonstrated strong predictive performance for annual changes in TMS and SDMT, with in-sample R^2 values ranging from 0.505 to 0.539. Cross-validation indicated a marginal decrease in R^2 (~0.1 on average).
- Exclusion of gene expression did not yield significant differences in predictive performance (α=0.05).
- Models without gene expression were validated in independent left-out samples and exhibited comparable performance trends.

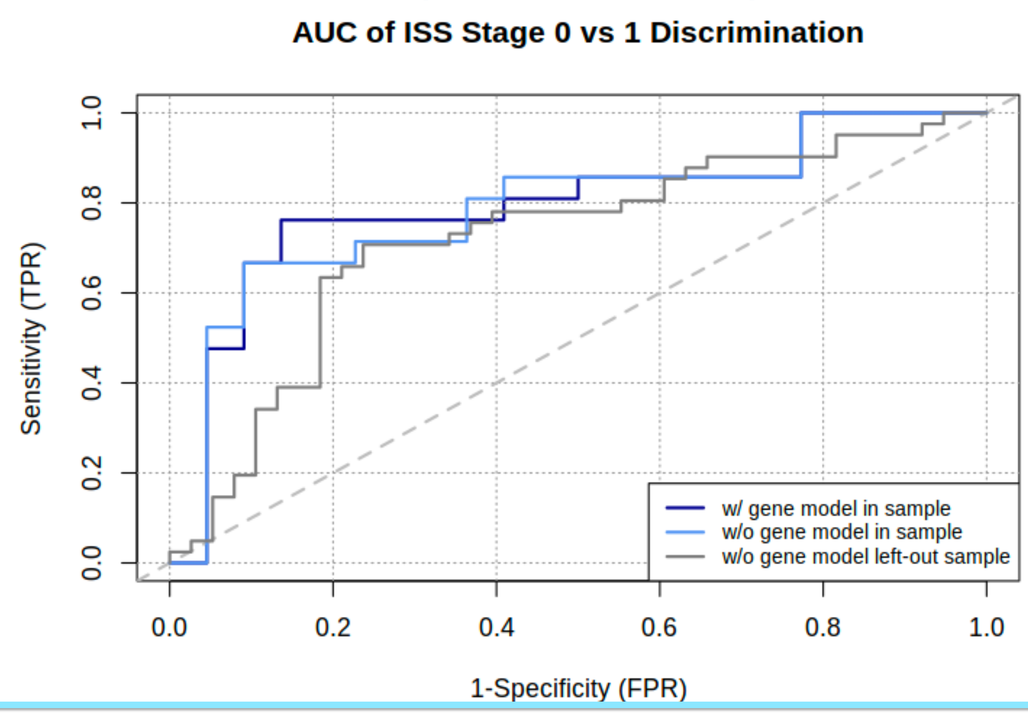
Results

Table 1. Performance of Digital Twins, both with and without including gene expression data, to discriminate between ISS stage 0 vs 1, in comparison with a simple model based on TMS and SDMT scores

	AUC discriminating ISS stage 0 vs 1 (95% confidence interval)		
	Digital Twins		TMS and SDMT scores measured at baseline
	w/ including gene expr.	w/o including gene expr.	
In-sample ISS 0: N=22 ISS 1: N=21	0.794 (0.649-0.940)	0.788 (0.643-0.933)	0.687 (0.526-0.848)
CV median	0.750 (0.3499-1.000)	0.800 (0.408-1.000))	-
Left-out sample ISS 0: N=58 ISS 1: N=45	-	0.720 (0.603-0.837)	0.643 (0.519-0.768)

- The Digital Twins are able to predict patients who have reached stage 1 in the absence of MRI data, more effectively than current TMS and SDMT scores.
- Notably, the neurofilament light chain protein (NfL) biomarker emerged as the most robust individual predictor of atrophy, highlighting its pivotal role.
- The 0 to 1 ISS stage transition can be better predicted by the Digital Twin (higher AUC) than by TMS and SDMT at baseline, as expected. However, the difference in AUCs was not statistically significant (at α=0.05) which might be due to the limited sample size.
- Discriminative performance did not significantly differ (at α=0.05) between predictions using all available data modalities (AUC=0.794) and those excluding gene expression information (AUC=0.788).

Figure 2. ISS stage 0 vs 1 discriminative performance across Digital Twins, both with and without including gene expression data, showed a similar trend in both in-sample and left-out samples.



Conclusions

- This study underscores the robustness of the Digital Twin approach and demonstrates that strong predictive performance can be sustained in the absence of RNA expression data and in the early stages of the disease.
- The use of Digital Twins for efficient identification of stage 1 patients without incurring the cost of imaging or RNA profiling represents a notable advancement.
- *in silico* patient models capable of identifying fast-progressing patients and those likely to be at ISS stage 1 hold significant promise.