

INTRODUCTION

- High throughput proteomics may enable more fine-grained clinically relevant staging beyond basic cerebrospinal fluid (CSF) biomarkers like A β 42 and p-Tau181.
- Data-driven disease progression models (DPM) can help understand how proteins evolve over the disease course.
- We estimated the pathophysiological cascade of CSF proteins using an Event Based Model (EBM) [1,2] of disease progression.

METHODS: Protein selection

- N=730 Alzheimer's disease Neuroimaging Initiative (ADNI) participants with SomaScan7k proteomics data
- Sparse LASSO models to predict imaging, cognitive and CSF biomarkers from CSF proteomics levels (Figure 1).
- Proteins selected by LASSO in at least four of the 16 models were considered for DPM
- Logistic Regression is fit for 15 proteins to separate CN (N=174) from AD (N=153) to convert protein levels into event probabilities

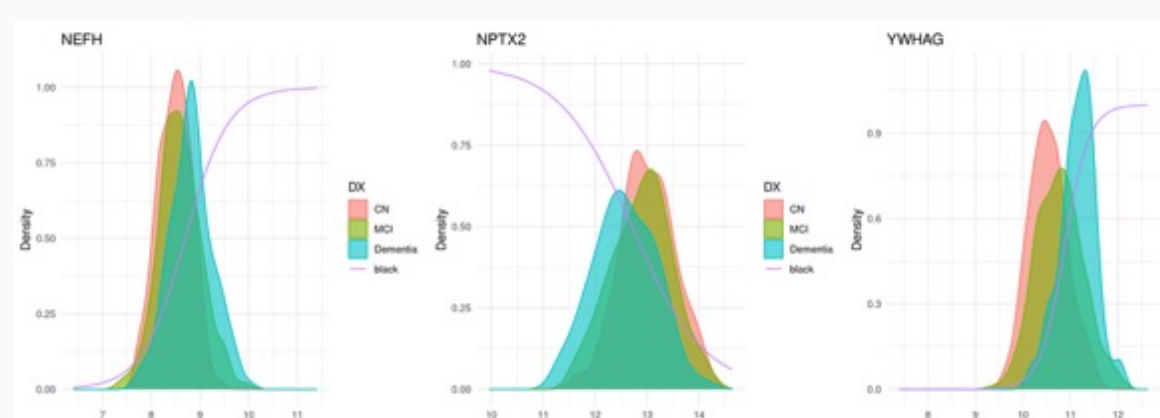


Figure 2: Distribution of protein levels in ADNI (CN, MCI, AD) for three selected proteins including the logistic fit.

References:

- Fonteijn (2012) *Neuroimage*. doi: 10.1016/j.neuroimage.2012.01.062
- Young (2014) *Brain*. doi: 10.1093/brain/awu176

TL;DR: Proteomic disease staging adds clinical value to CSF A β and pTau

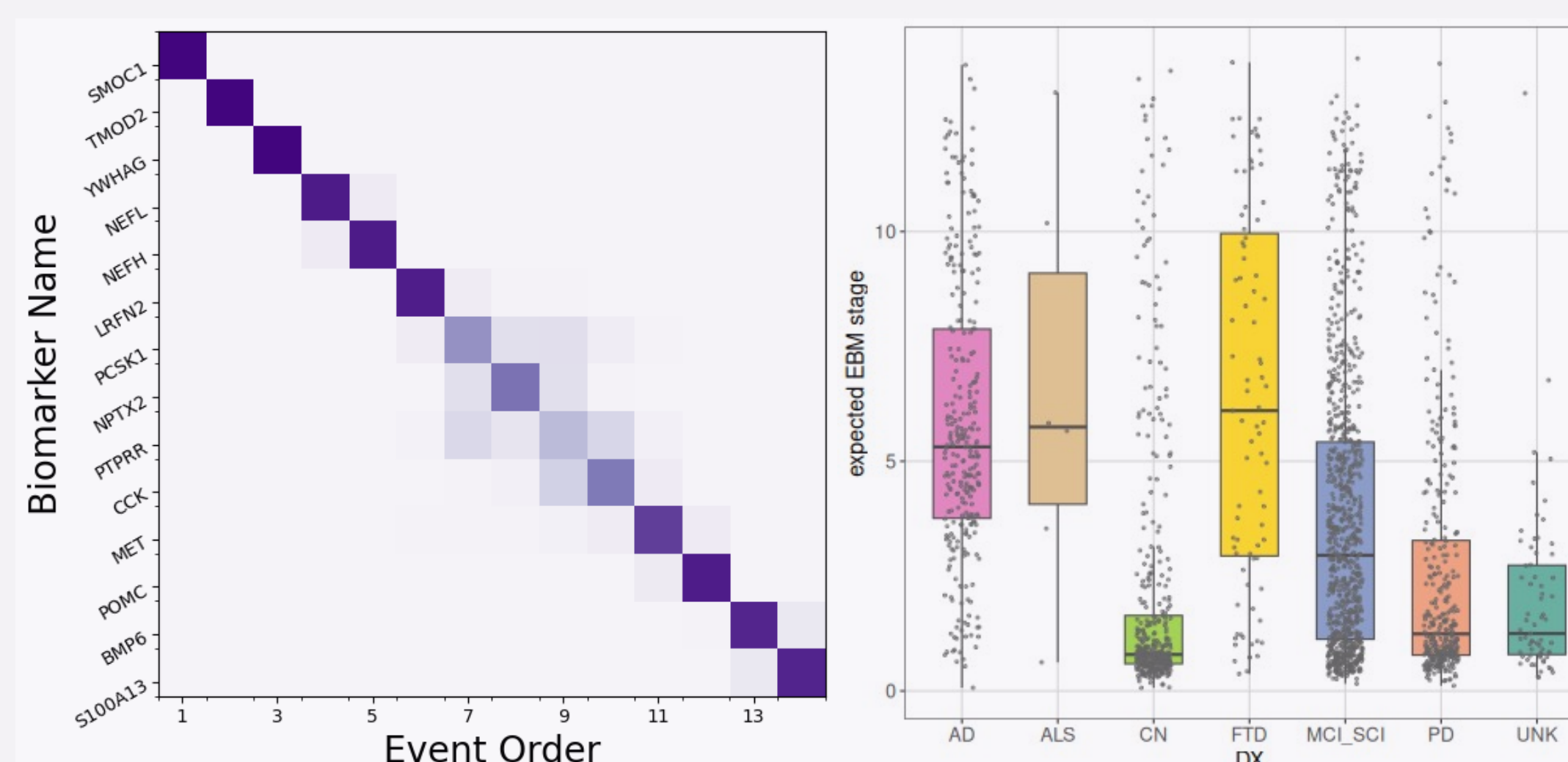


Figure 3: Estimated protein ordering by the EBM. Positional variance diagram based on the selected 15 proteins (left). AV45 and CSF PTAU become abnormal after SMOC1 and before TMOD2. Distribution of expected EBM stage by diagnosis (x-axis) in GNPC (right).

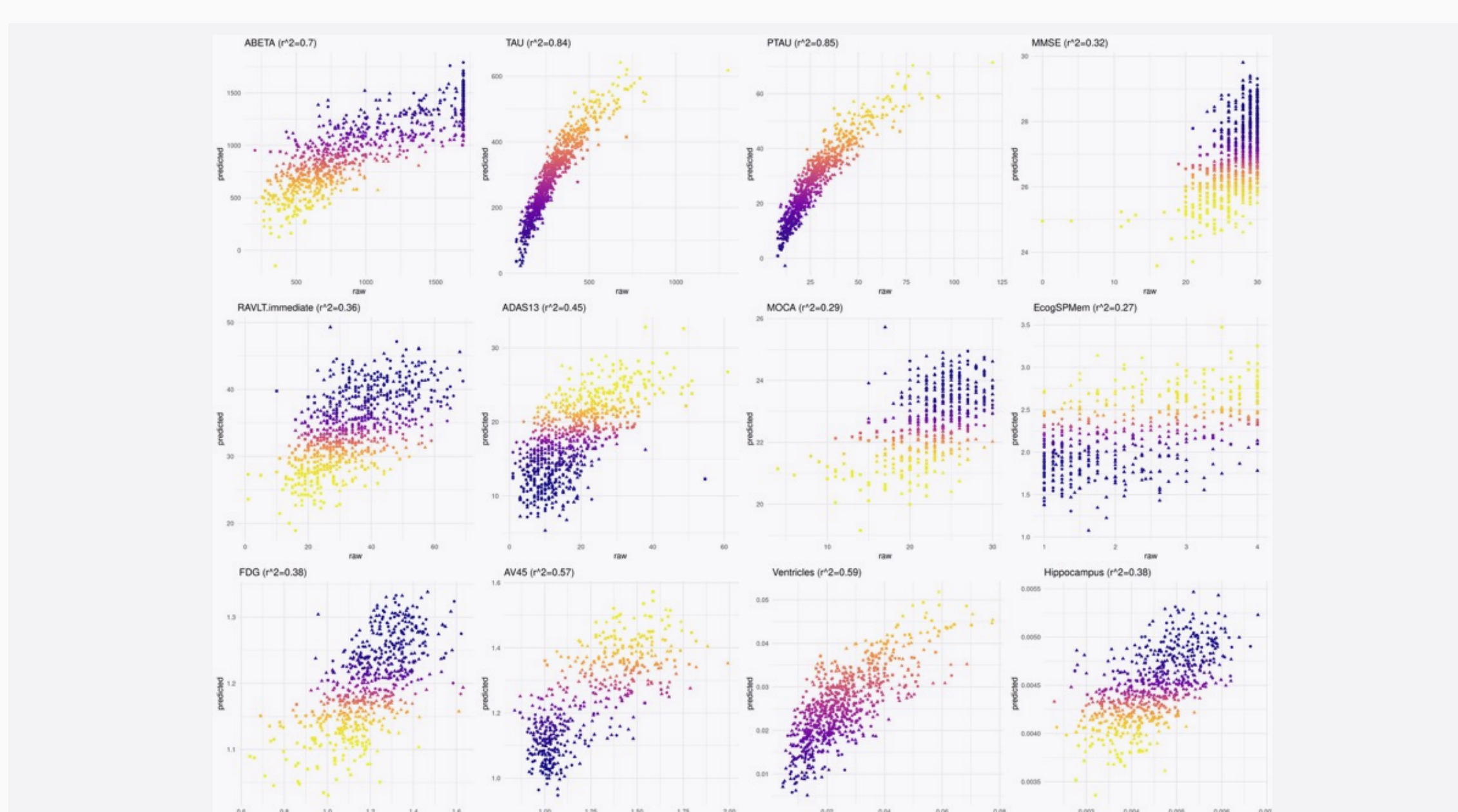


Figure 1: Observed vs predicted biomarker levels. Examples of twelve CSF, cognitive and imaging biomarkers that were predicted using CSF protein levels with a LASSO model. Colors are based on CN-like (purple) vs AD-like (yellow). Proteins selected by the LASSO model were considered for DPM.

METHODS: EBM

- EBM was trained on data from N=1,128 Global Neurodegeneration Proteomics Consortium (GNPC) participants (N=284 AD, N=844 MCI/SCI). **Figure 3 (left)**
- EBM was applied to N=2,072 GNCP participants to derive a fine-grained proteomics-based disease stage (EBM stage). **Figure 3 (right)**
- EBM applied to N=403 ADNI participants with MCI. Cox proportional tested for the association of EBM stage and conversion to AD. Adjusted for age, sex, CSF A β and p-Tau.

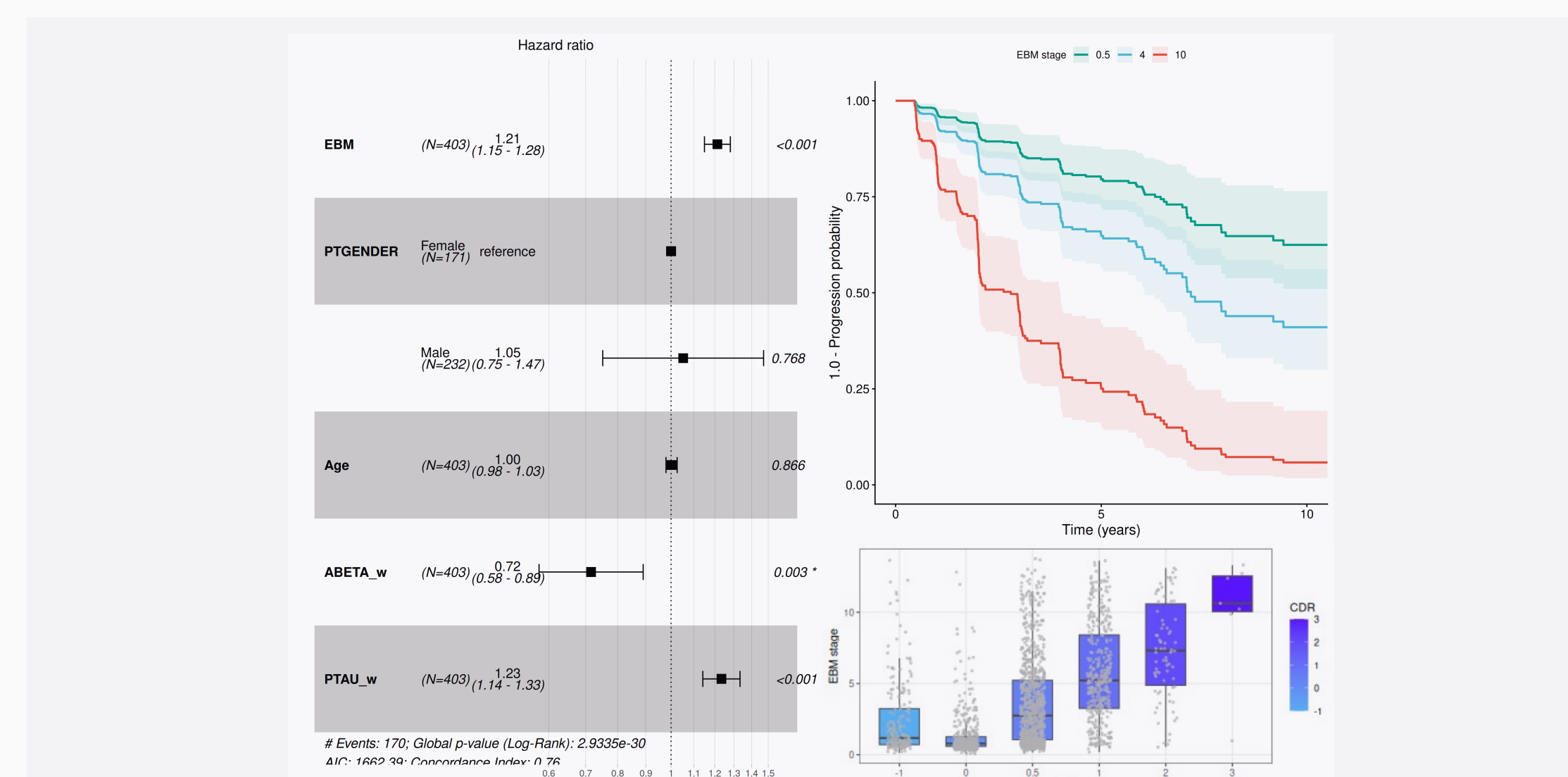
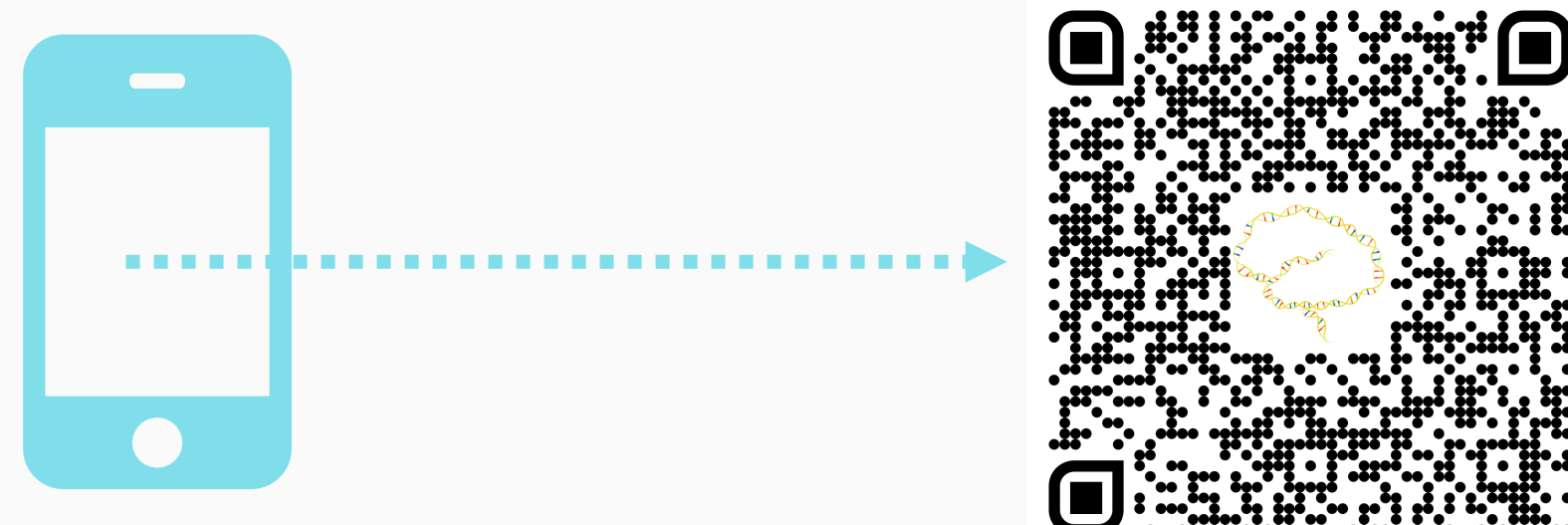


Figure 4: EBM stage associated with conversion to AD and CDR. Left: Forest plot of CPH coefficients; CSF Abeta and pTau are w-scored. Top right: Exemplary survival curves for participants with different EBM stages (10th, 50th, 90th percentile). Bottom right: EBM stage distribution grouped by CDR in the GNPC cohort.

CONCLUSION

- Proteomics EBM provides a fine-grained chronology of molecular alterations in AD
- EBM yields a staging metric that robustly tracks cognitive impairment
- Clinical potential of high dimensional CSF proteomics



Contact

Andre Altmann
email: a.altmann@ucl.ac.uk
web: <http://combine-lab.science/>

MO-0401

