



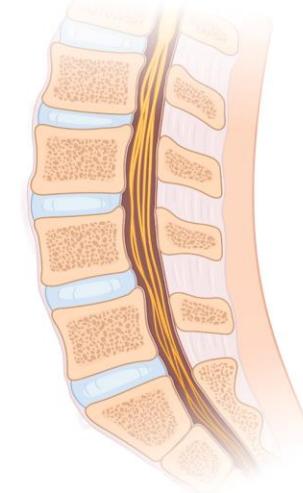
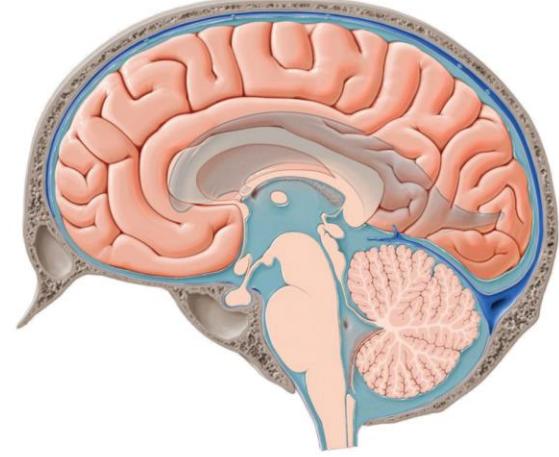
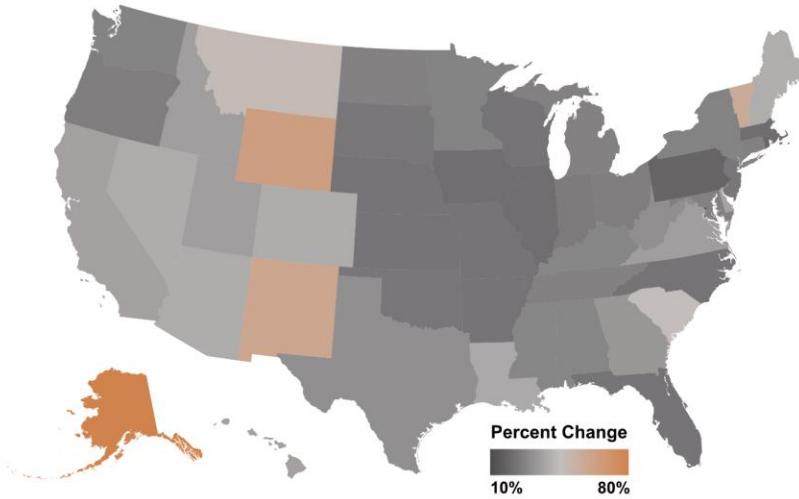
# Sample Agnostic Spectral Libraries: An Open Framework for Enhanced Data Independent Analysis Profiling Depth

Graham Delafield\*, Xiaofang Zhong\*, Qinying Yu, Chris Sauer, Henrik Zetterberg, Lingjun Li

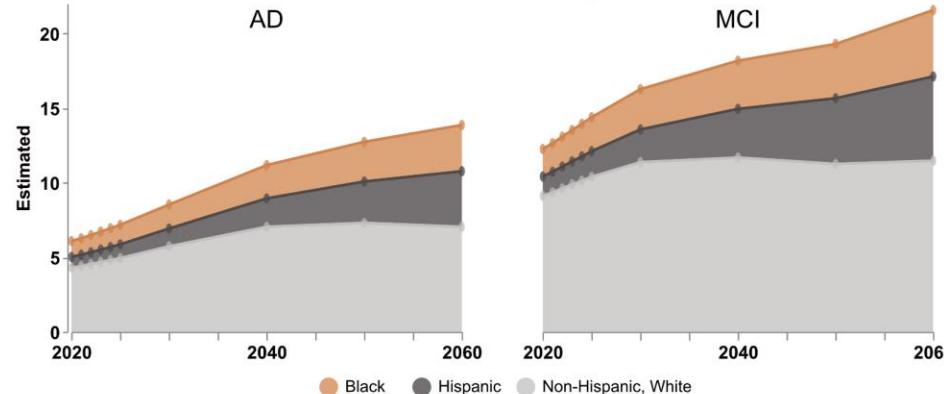
University of Wisconsin-Madison

# Current Approach Alzheimer's Disease Research

Rise in AD Diagnoses, 2010-2022

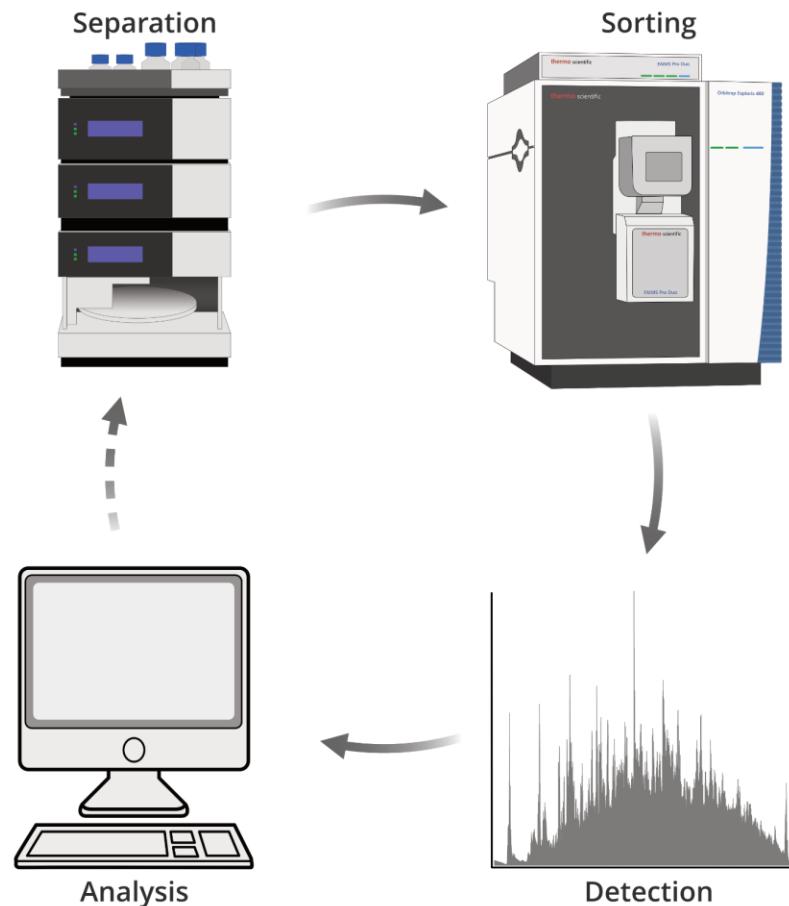


Estimated Rate of Incidence, 2020-2060

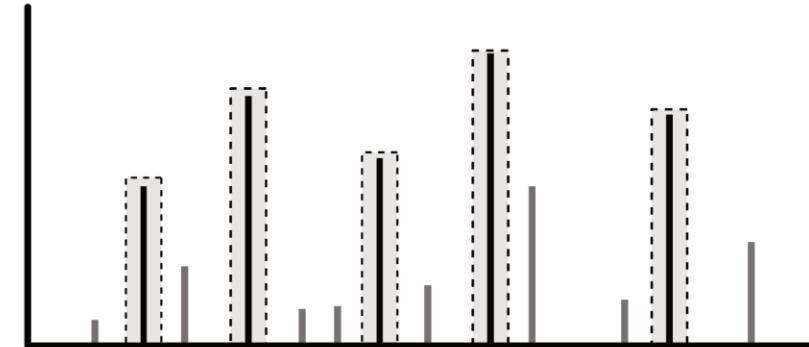


- Persistent increase in neurological disorders promotes need for early detection
- Biofluids are preferred matrix for analysis
- Invasive sampling and low availability requires dutiful handling and use

# MS-Based Biomarker Screening

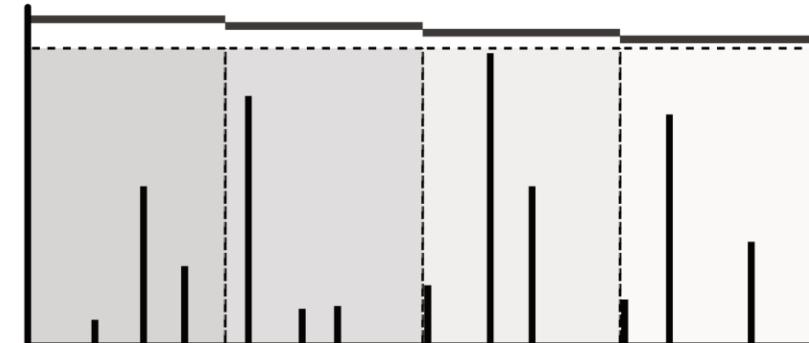


Data-Dependent Acquisition (DDA)



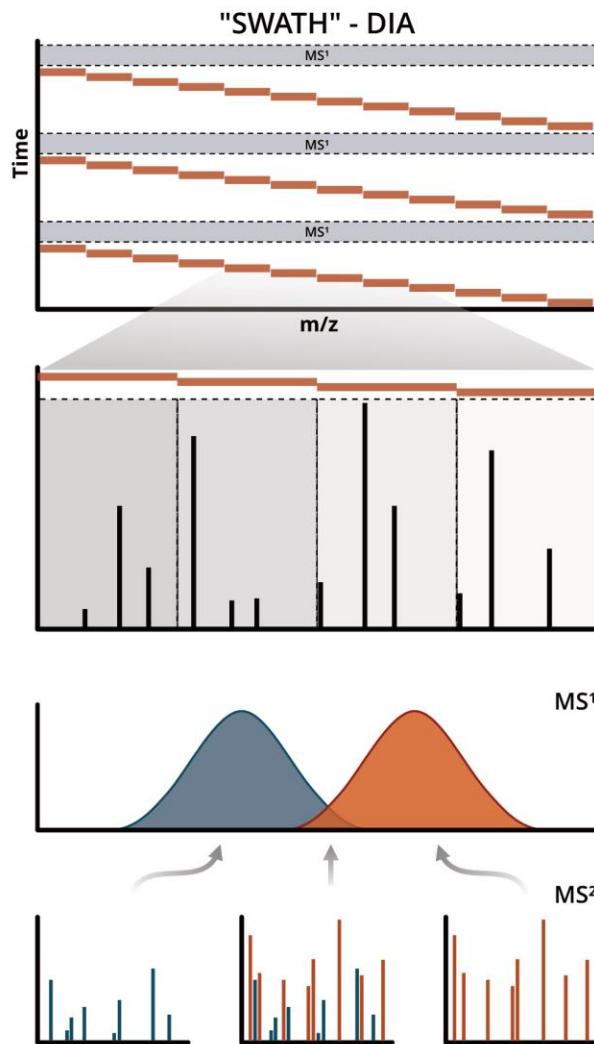
Biased ✗  
Confidence ✓  
"Cleanliness" ✓

Data-Independent Acquisition (DIA)

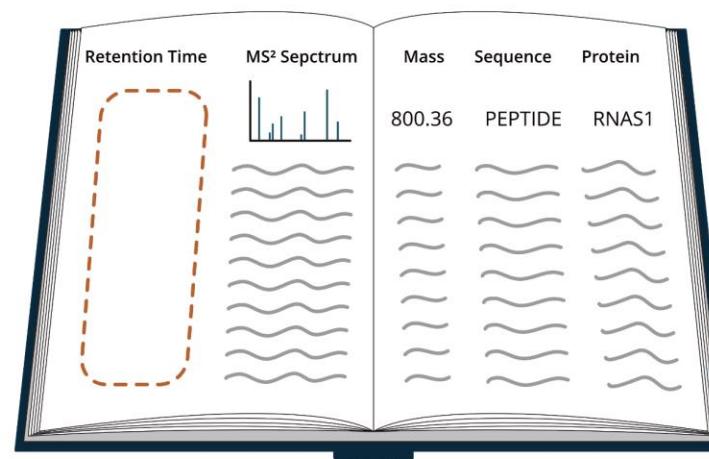


Unbiased ✓  
Throughput ✓  
Complex ✗

# DIA and Spectral Libraries

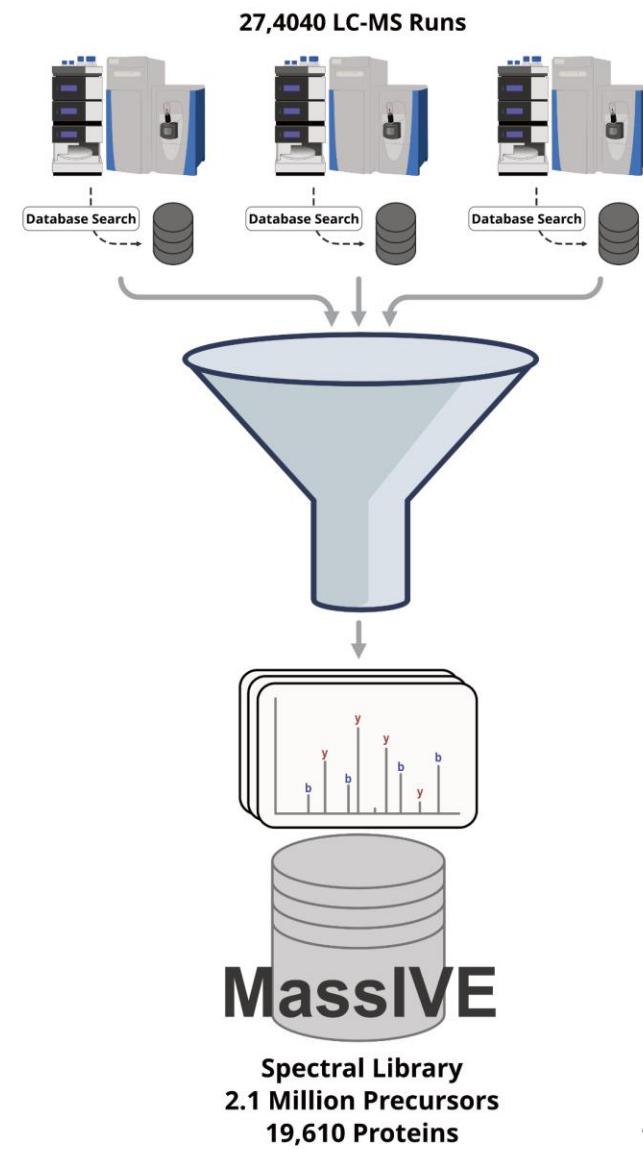


# Spectral Libraries



Is there a way to 'calibrate' a spectral library to an individual experiment?

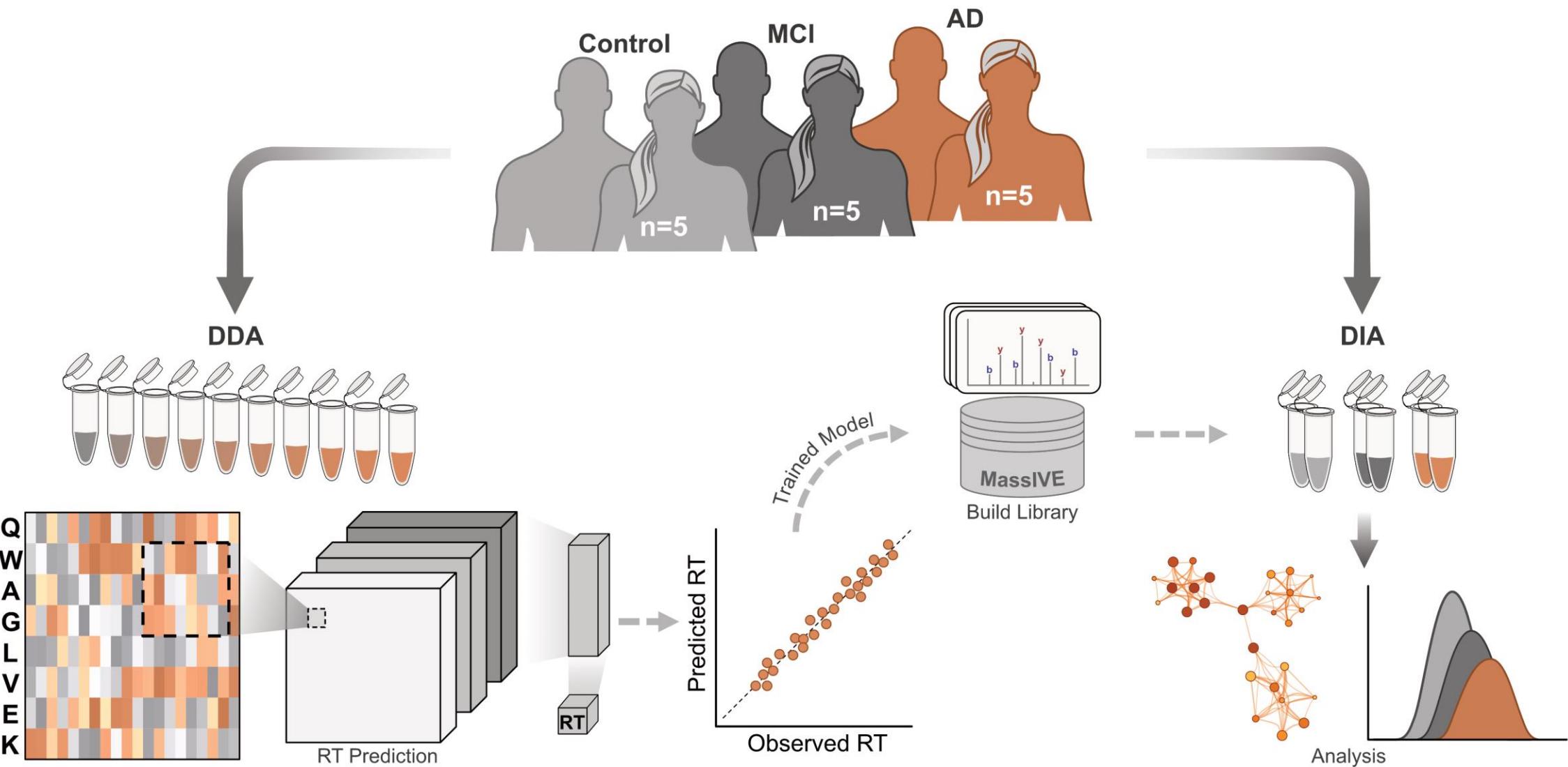
Can these sample agnostic  
libraries enhance our profiling  
depth?



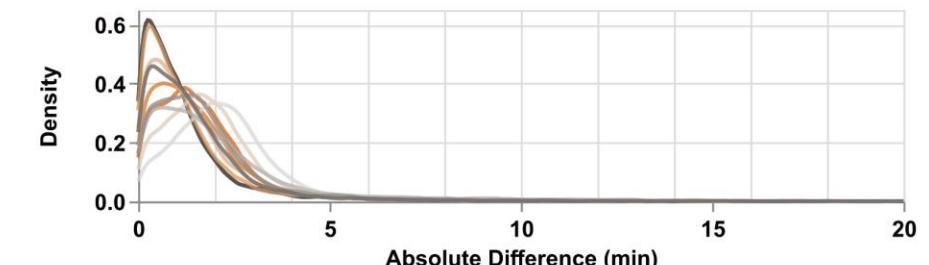
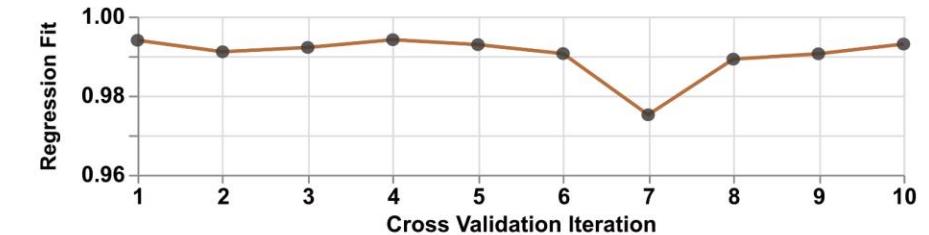
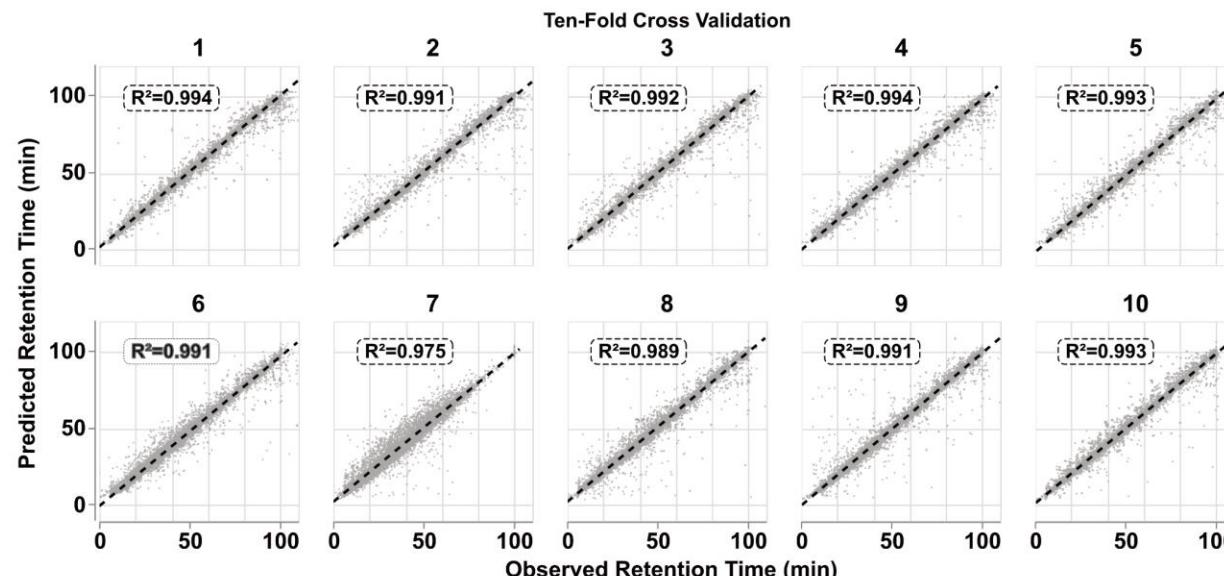
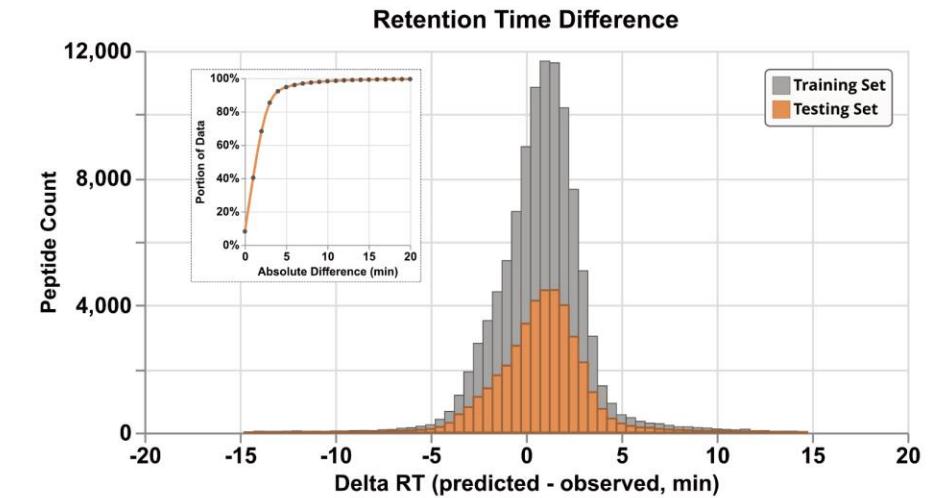
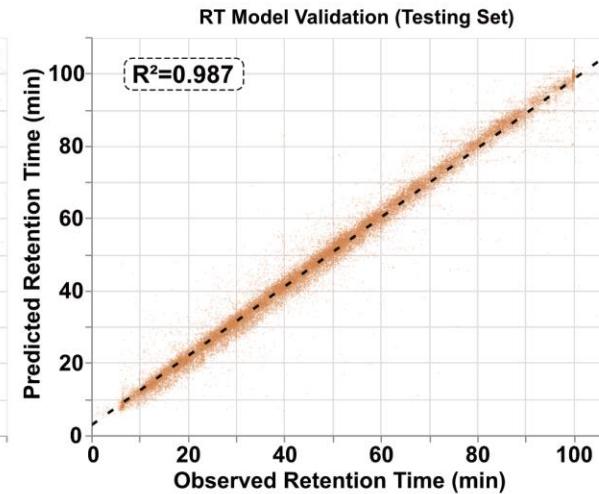
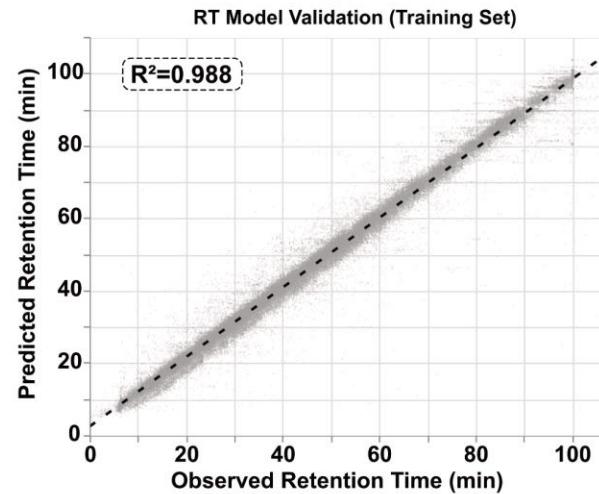
# Experimental Objectives

- 1) Validate an extensible, machine learning approach for library generation
- 2) Benchmark agnostic libraries against a typical DIA workflow
- 3) Evaluate the proteomic and quantitative depth

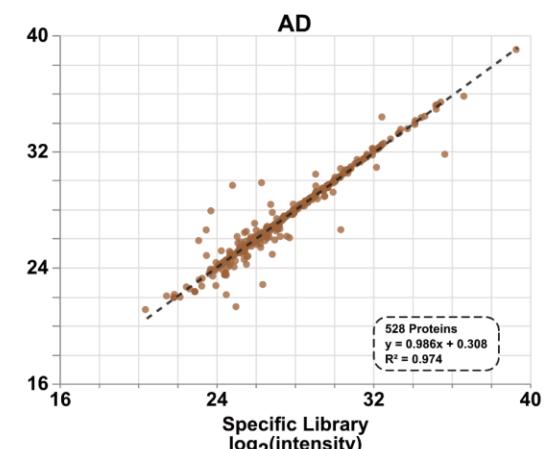
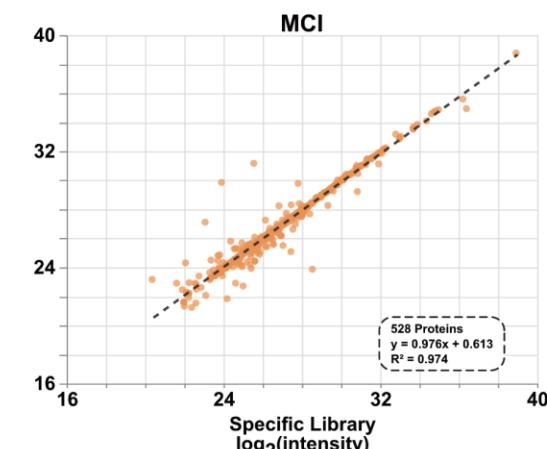
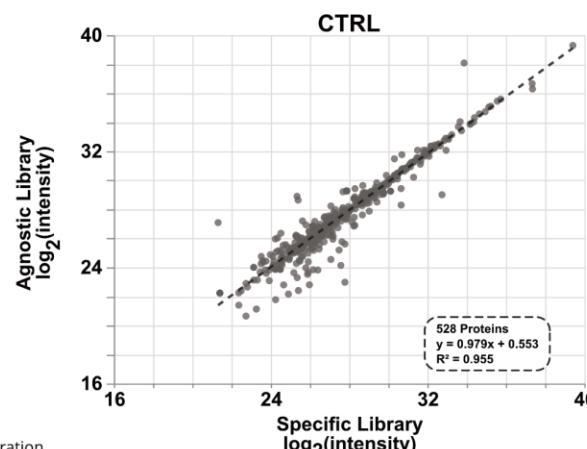
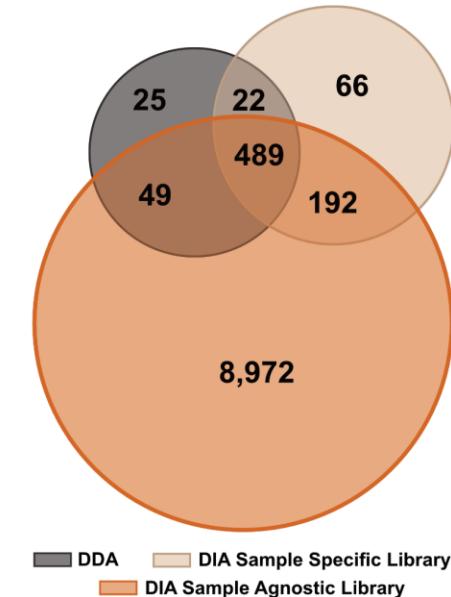
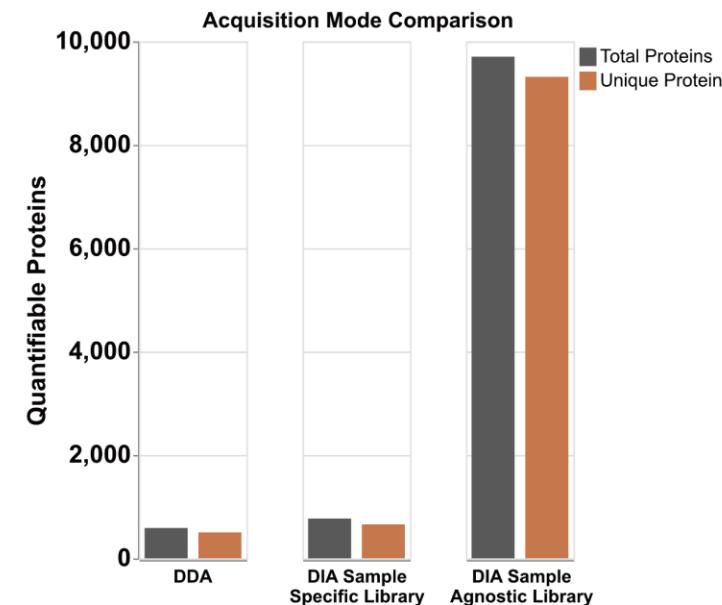
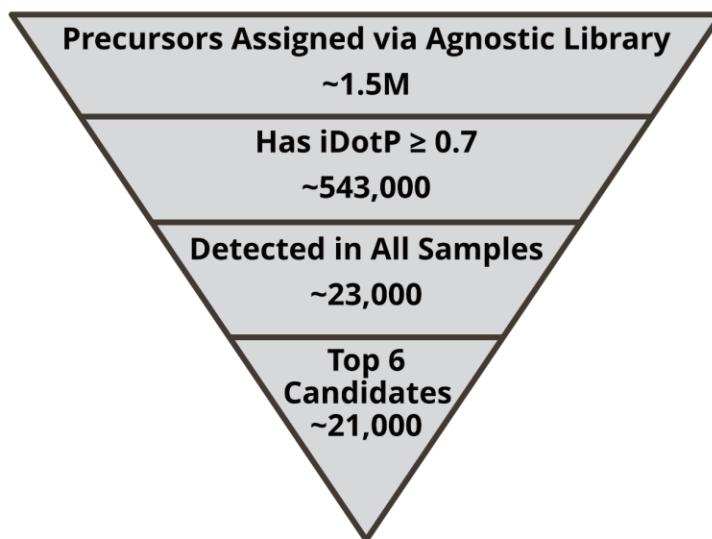
# Parallel Workflow



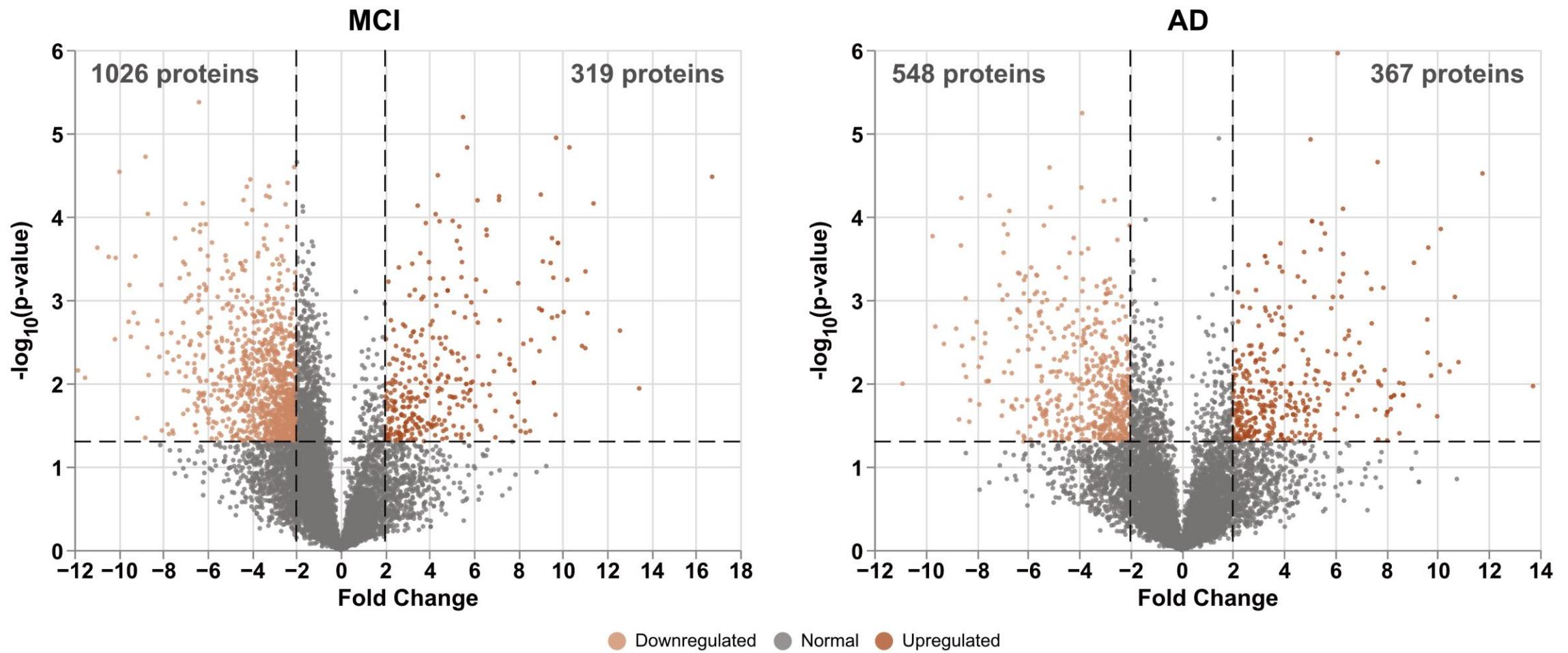
# Model Validation



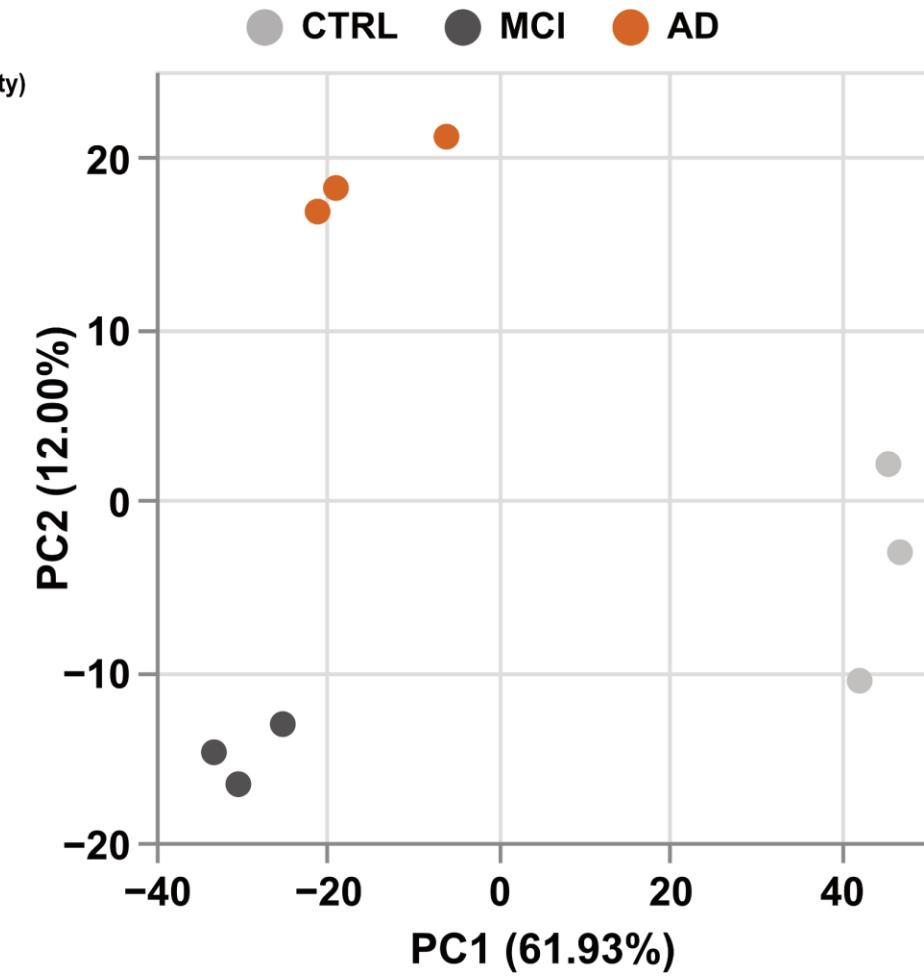
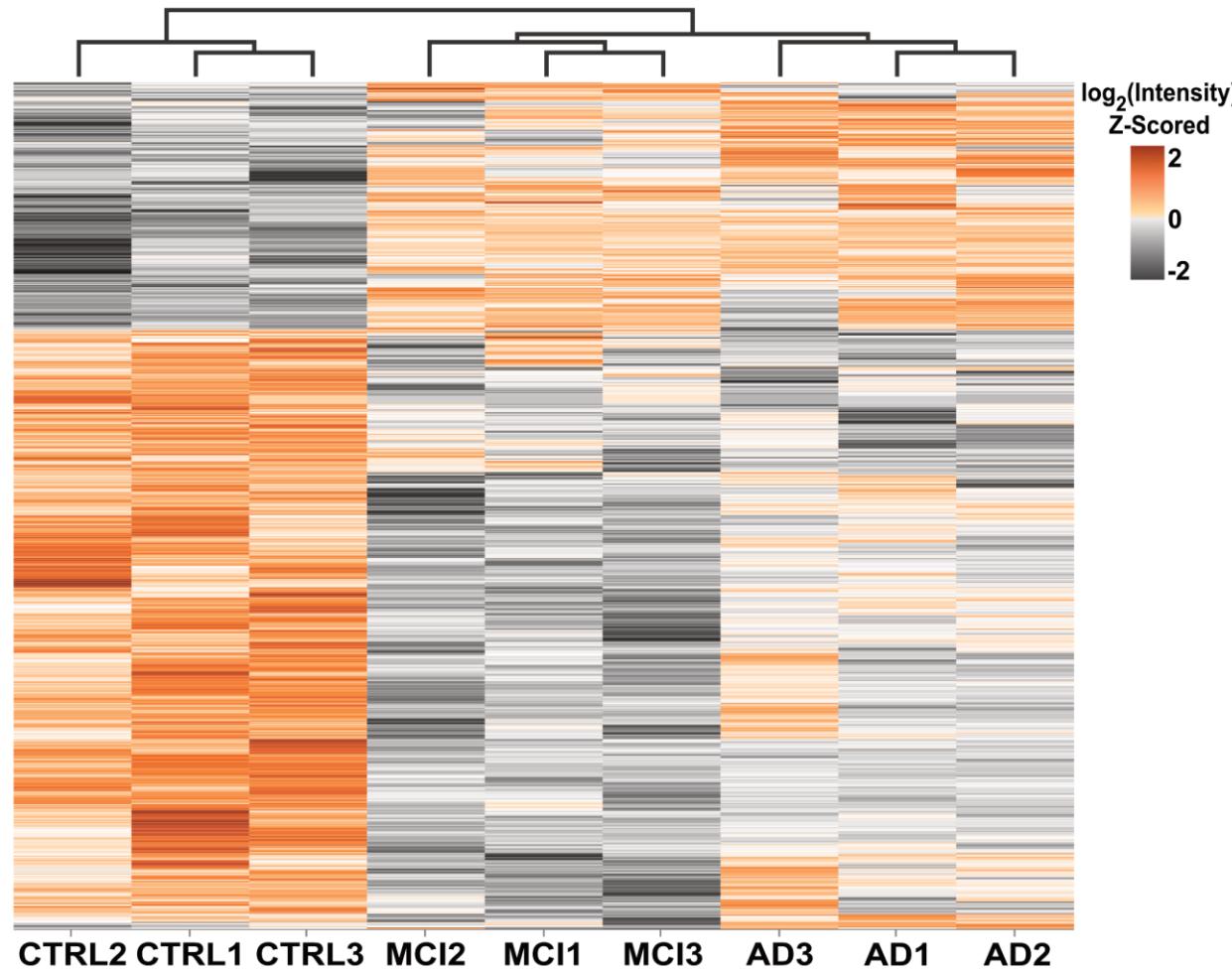
# Quantitative Comparison



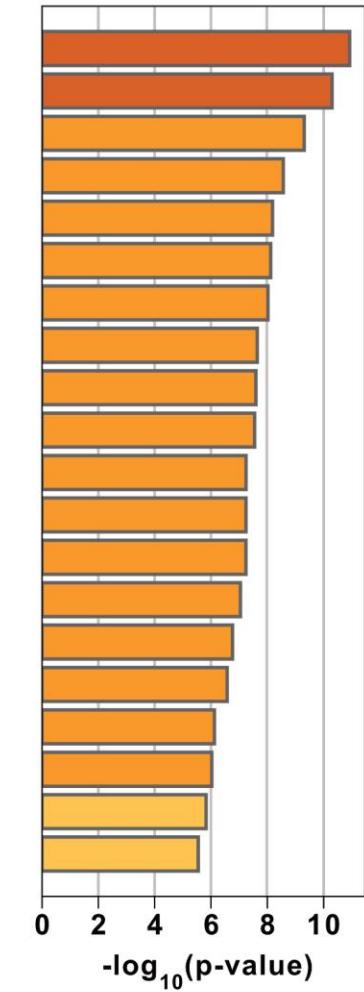
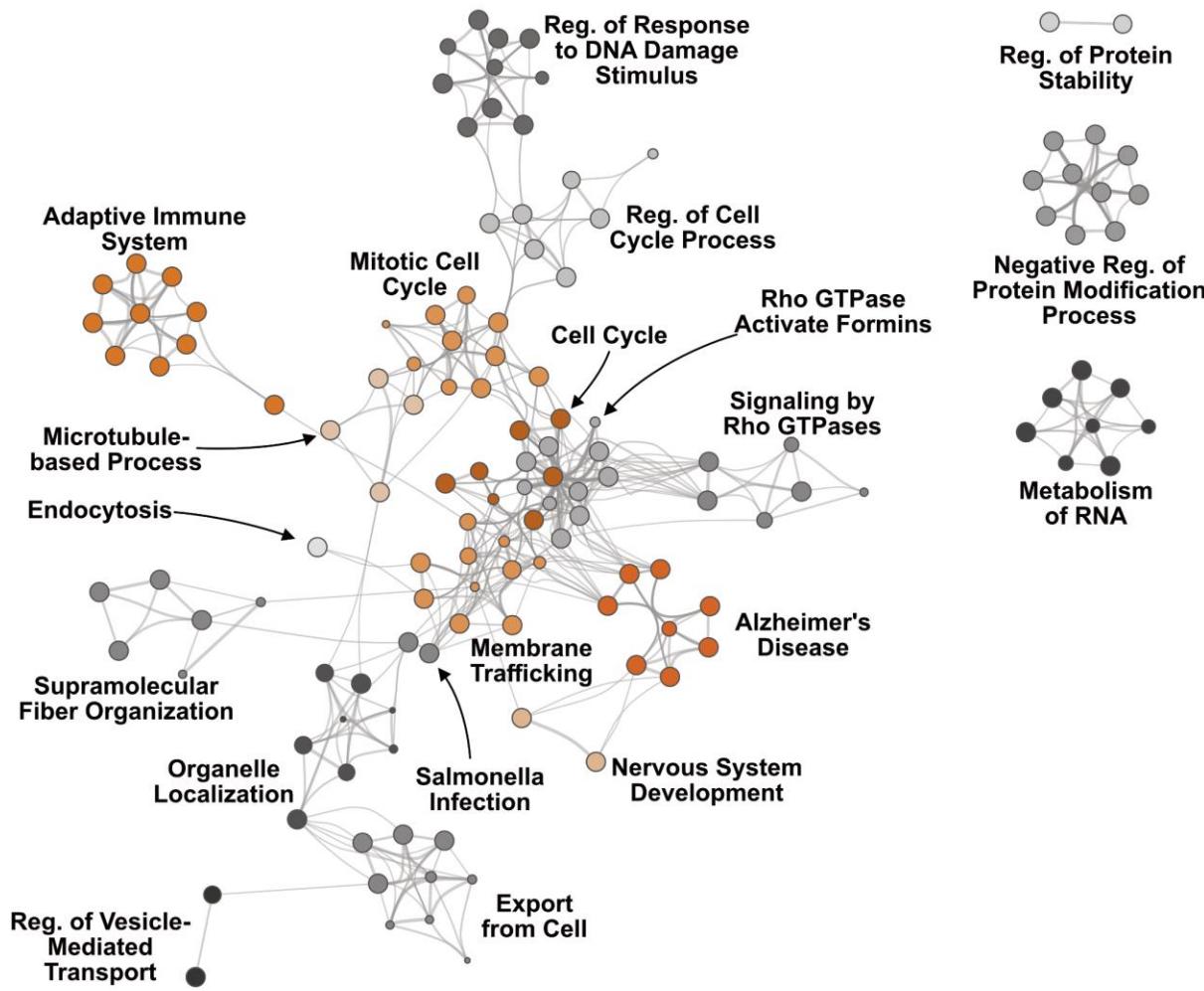
# Proteomic Perturbations in CSF



# Cohort Discrimination

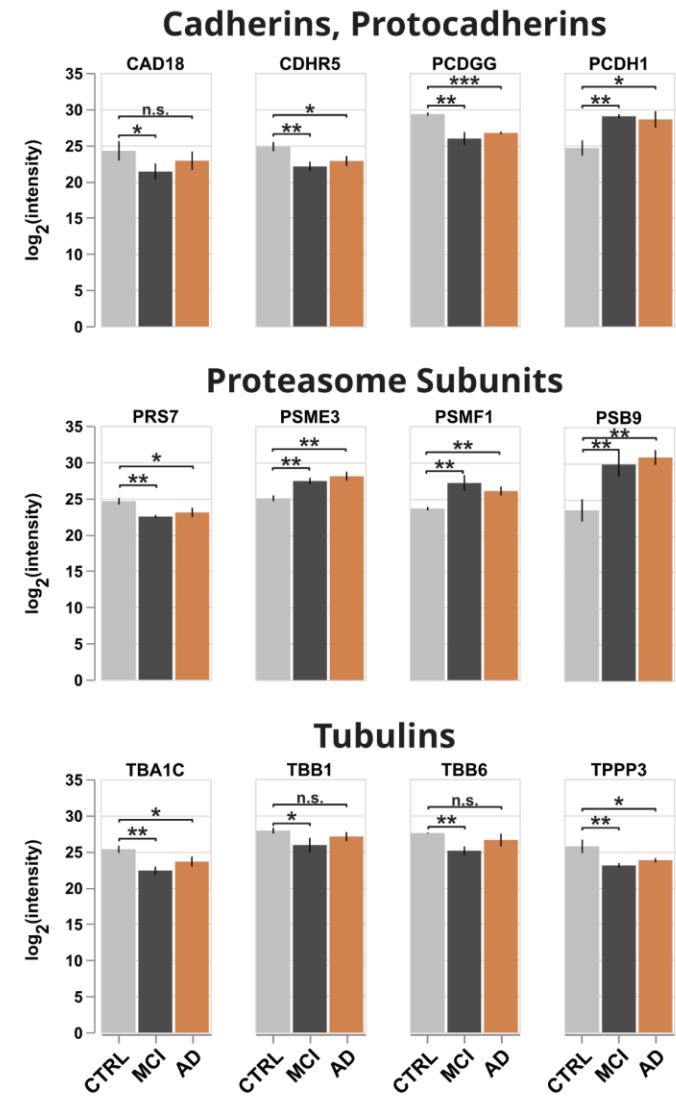
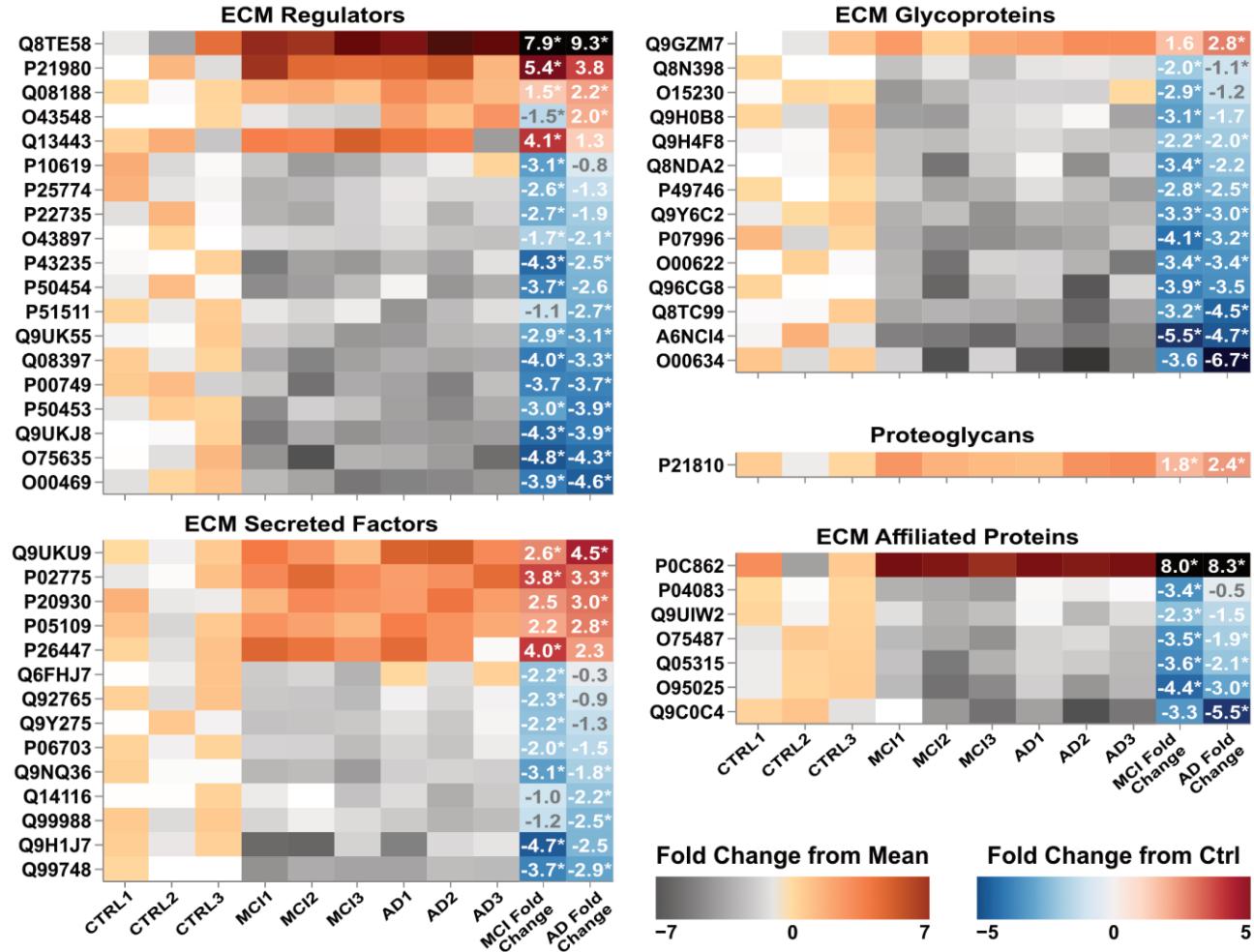


# Dysregulated Pathways



- Supramolecular fiber organization
- Adaptive Immune System
- Mitotic cell cycle
- Membrane Trafficking
- Export from cell
- Signaling by Rho GTPases
- Cell Cycle
- Regulation of vesicle-mediated transport
- Negative regulation of protein modification process
- Microtubule-based process
- Metabolism of RNA
- Organelle localization
- Regulation of response to DNA damage stimulus
- Nervous system development
- Regulation of cell cycle process
- RHO GTPases Activate Formins
- Salmonella infection
- Alzheimer's disease
- Regulation of protein stability
- Endocytosis

# ECM and Proteome Reorganization



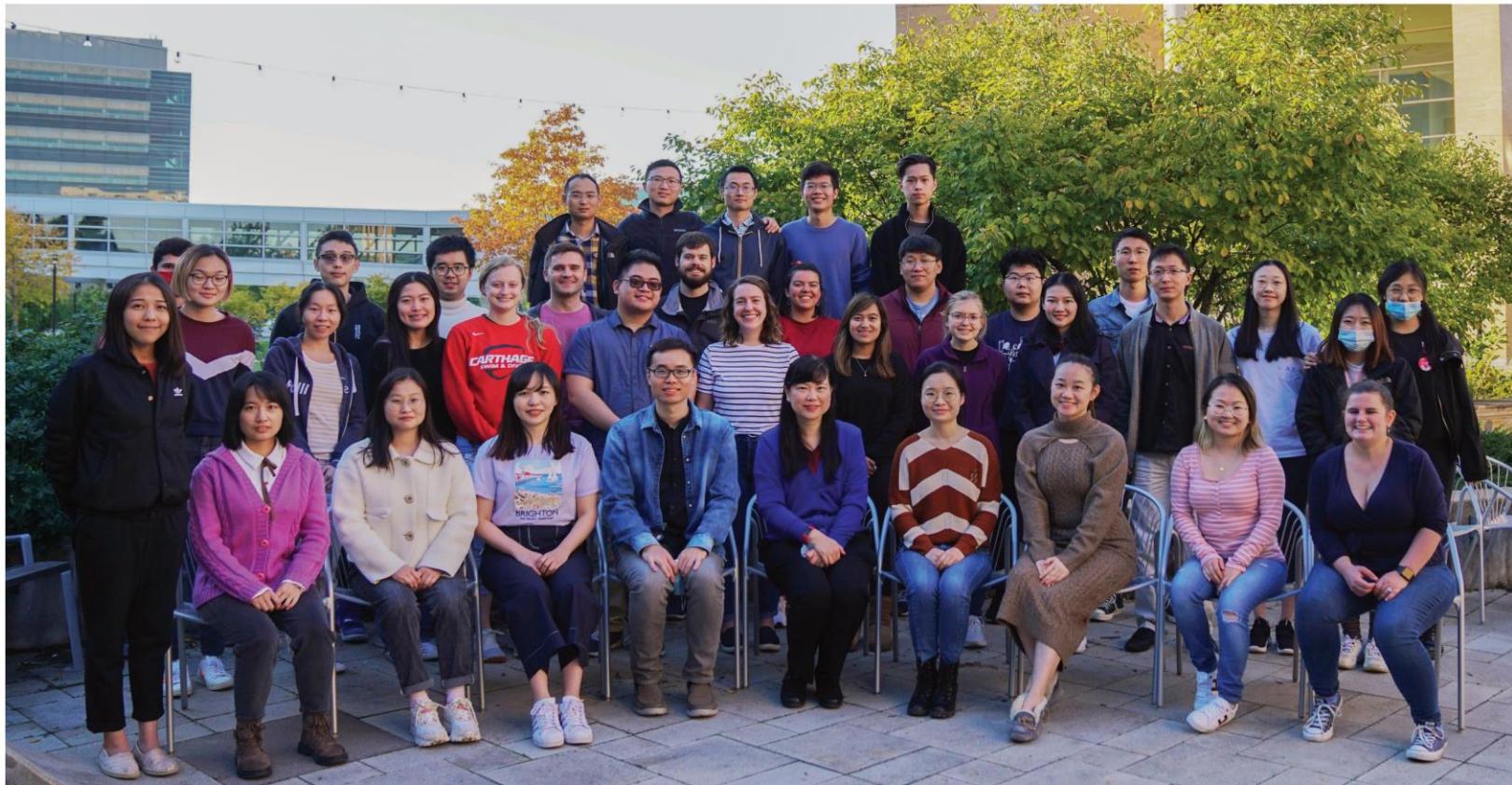
# Conclusion

Using machine learning, spectral libraries can be effectively calibrated to a new experiment.

Agnostic libraries provide significantly improved profiling depth.

We advocate for a stronger community-driven approach to translate proteomic analyses to clinical application.

# Acknowledgments



Dr. Lingjun Li  
Dr. Xiaofang Zhong  
Li Lab Members

Dr. Ying Ge  
Dr. Martha Vestling  
BTCl and WPS Organizers

