

Integrative Epigenetic and Neurostructural Aging in Alzheimer’s Disease Risk

Wei Zhang¹, Tatjana Rundek², David Loewenstein³, Lily Wang¹

¹Division of Biostatistics & Bioinformatics, Department of Public Health Sciences · ²Department of Neurology & Evelyn F. McKnight Brain Institute · ³Department of Psychiatry & Behavioral Sciences, University of Miami Miller School of Medicine, Miami, FL

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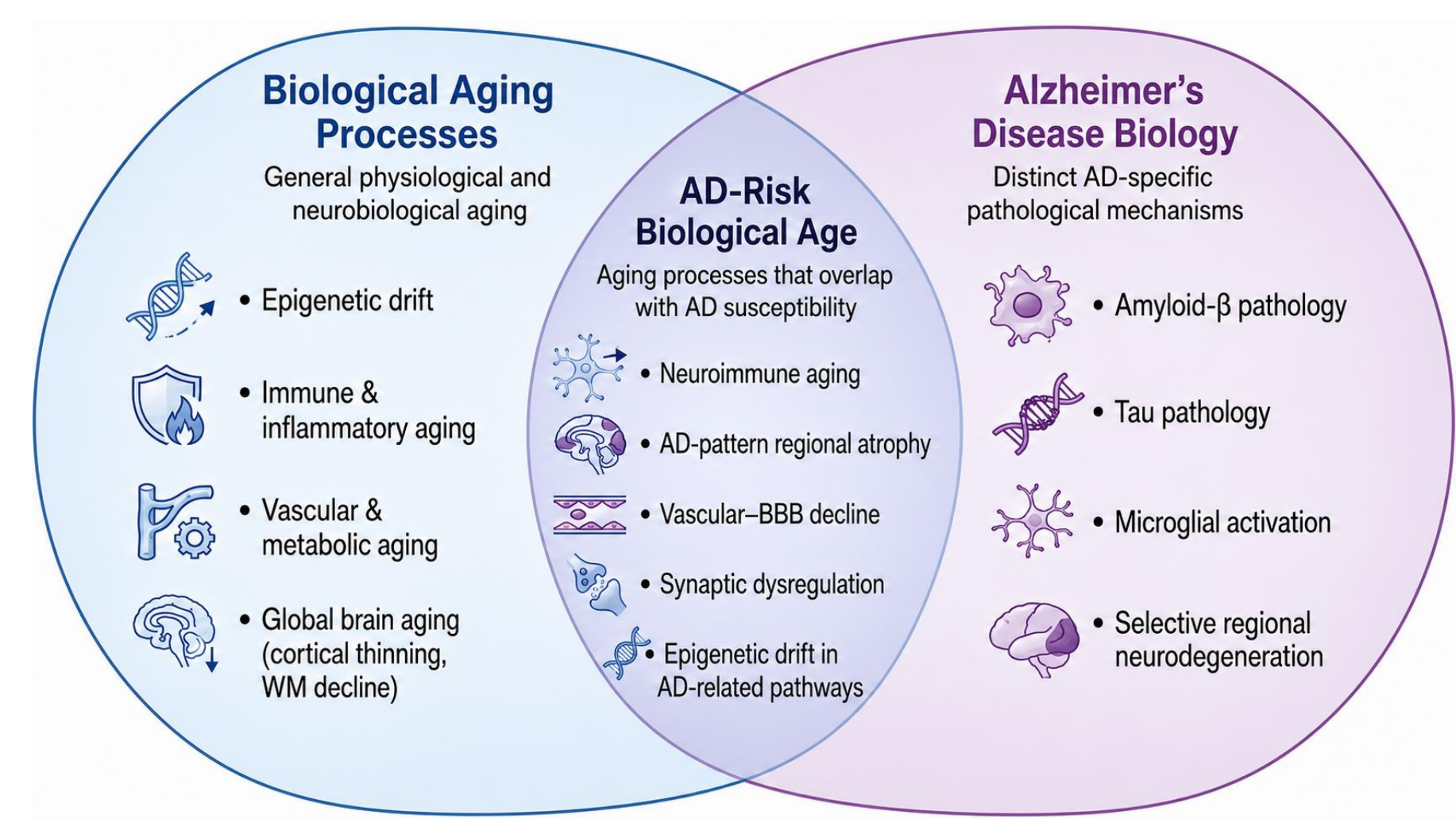
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KEYWORDS Alzheimer's disease · biological aging · DNA methylation · brain MRI · age acceleration · multimodal integration · cross-modal deep learning

INTRODUCTION

- Chronological age is the strongest but incomplete AD risk factor.
- DNAm clocks and MRI brain-age index complementary systemic vs neurostructural aging.
- Existing clocks are disease-agnostic, limiting AD-specific insight.
- Objective: benchmark integration strategies for an AD-focused biological-age index.

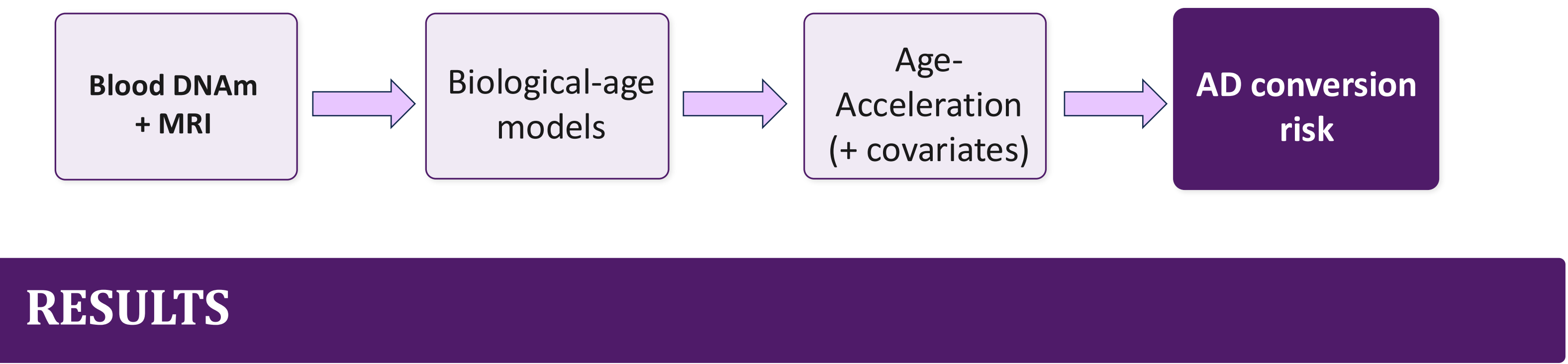


PRIOR EVIDENCE

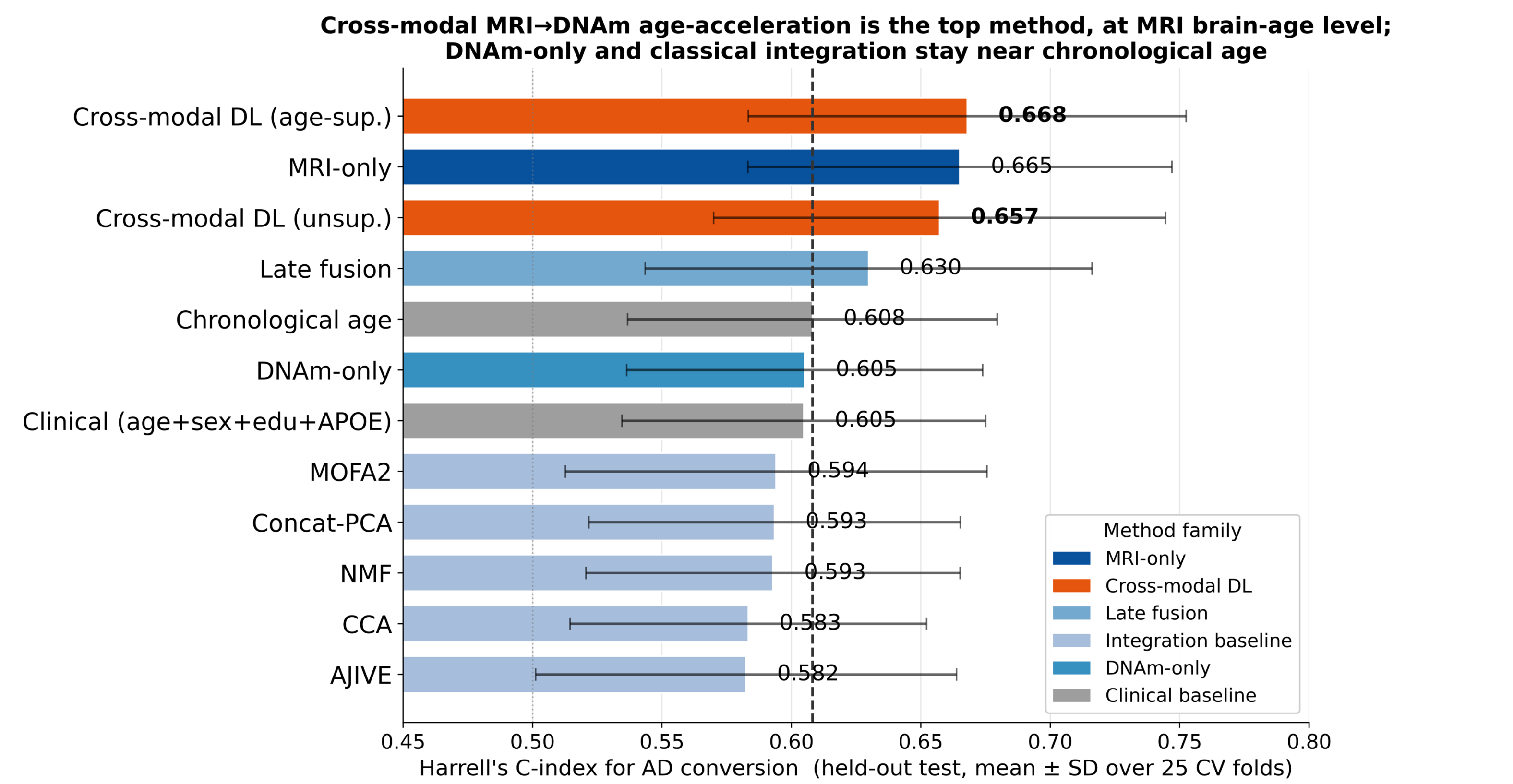
- Blood DNAm and MRI brain-age index distinct aging biology, systemic/molecular vs neurostructural, and are typically only weakly correlated within individuals (Teeuw et al., 2021).
- Organ-level studies show people often age faster in one organ system; such aging discordance predicts disease and mortality (Oh 2023; Tian 2023).
- Direct DNAm + MRI studies in AD remain sparse and mixed, motivating a discordance-focused, AD-specific view rather than naive fusion.

METHODS

- Cohort: ADNI, n = 179 with matched blood DNAm, structural MRI, and APOE/clinical covariates; conversion follow-up (55 conversions).
- Features: AD-prioritized CpGs (implicated in AD by epigenome-wide meta-analysis; Zhang L et al. 2021) and brain–blood-concordant CpGs (4,332 total), plus 85 FreeSurfer structural MRI regions.
- Brain age (and DNAm age) = a model trained to predict chronological age from that modality’s features (e.g., the 85 MRI regions).
- Age-acceleration = predicted – actual age (positive = older-appearing), tested vs. time to AD conversion by Cox (age, sex, education, APOE).
- Integration: late fusion, latent-factor models (PCA/CCA/MOFA2/AJIVE/NMF), and cross-modal deep autoencoders; compared by repeated 5×5 cross-validation (held-out Harrell’s C-index).



RESULTS



Held-out C-index for AD conversion (mean ± SD across 25 cross-validation folds). All biomarker methods enter the Cox model as age-acceleration.

- Cross-modal deep integration (MRI→DNAm) attains the highest AD-conversion discrimination ($C \approx 0.67$), matching MRI brain-age, while blood DNAm contributes a complementary, near-orthogonal aging axis ($r \approx 0.24$).

CONCLUSIONS

- An AD-focused cross-modal deep model (MRI→DNAm) is the top-performing integration method and matches MRI brain-age for predicting AD conversion.
- Blood DNAm and MRI capture complementary, near-orthogonal aging axes, two distinct windows on AD-relevant aging.
- Regularized, cross-validated benchmarking provides a principled foundation for multimodal AD-risk aging biomarkers.

FUTURE DIRECTIONS

- Additional analyses and external validation are ongoing; full manuscript in preparation.
- Treat cross-modal discordance ($\text{Brain} \pm / \text{Blood} \pm$) as an AD phenotype; resolve each subtype with CSF A β /tau, amyloid- & tau-PET, and vascular/WMH markers.
- Anchor biological-age training on AD-relevant endpoints, not chronological age.
- Test the pace question: does baseline blood DNAm predict future MRI atrophy pace?
- Use brain-specific / 2nd-generation methylation signatures to raise blood signal-to-noise.
- Larger, diverse, externally-validated cohorts with paired DNAm + MRI and longitudinal follow-up.

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