Heterogeneity in Preclinical Alzheimer's Disease Trial Cohort Identified by Image-based Data-Driven Disease Progression Modelling, a.k.a. Subtype and Stage Inference in the A4 Study

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Disclosures: Some of us (or our spouses) benefit either financially or academically from interactions with pharmaceutical and related companies.
Heterogeneity vs Clinical Trials

• Detect heterogeneity at screening?
  • Syndrome is too simplistic, especially for prodromal/mild trials
  • Extremely low trial success rates, despite imaging/biomarker screening

• Spatiotemporal subtypes of pathology discovered from observational data using SuStaIn

• SuStaIn: Subtype and Stage Inference
  • Clustering that is not confounded by disease stage/severity
  • Individualised, fine-grained, quantitative inference

Young et al., 2018 Nature Communications
This work

• Aims:
  1) Detect heterogeneity in A4
  2) Make model-based predictions
    • $A^4 =$ Anti-Amyloid treatment in Asymptomatic Alzheimer’s
    • Solanezumab (Eli Lilly)

• Experimental Setup:
  • Model trained on A4: Screening T1w MRI (cross-sectional)
    • N=1240 amyloid-positive, cognitively normal, elderly
  • Predictions for A4: model-based stratification of ADNI (longitudinal)
    • N=731 (5 MCI) matching A4 inclusion criteria
Our study: Experiment

Screening

Train SuStaIn (sc)

Stratify ADNI (bl)

A4-matched

A4 Trial: ~4 years

Forecasts for A4

Subtype outcomes

https://doi.org/10.1101/2023.02.07.23285572
Results: trained model (3 subtypes)

- 523 (42%) subtype-able
- 33/34/33% split
- Subtle differences at screening: PACC, CFI, Florbetapir SUVR
- No differences in demographics, genetics

https://doi.org/10.1101/2023.02.07.23285572
Results: forecasting model

- 341 (47%) subtype-able
- 35/35/30% split
- Differences to A4: 1yr older; <APOE4

Take Home Points:
- Identified clinical heterogeneity using MRI + SuStaIn
- Minimal cognitive decline
  - CDRSB < 0.12/yr
  - Lecanemab $\Delta_{M18}$: −0.67..−0.23
  - mPACC > −0.4/yr
- Unanswered Qs:
  - Subtypes => treatment response?
  - Heterogeneity => treatment effect?
Thanks

• A4: releasing screening data
• ADNI: eternally grateful
• Co-authors

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