Natural disease progression model with transition probabilities to describes the continuum of Alzheimer's disease.

Noel Patson[1,2*], Marwa E.Elhefnawy [1,3], Samer Mouksassi [4], Goonaseelan (Colin) Pillai [5], Emmanuel Chigusta [5], Ivelina Gueorguieva [6]

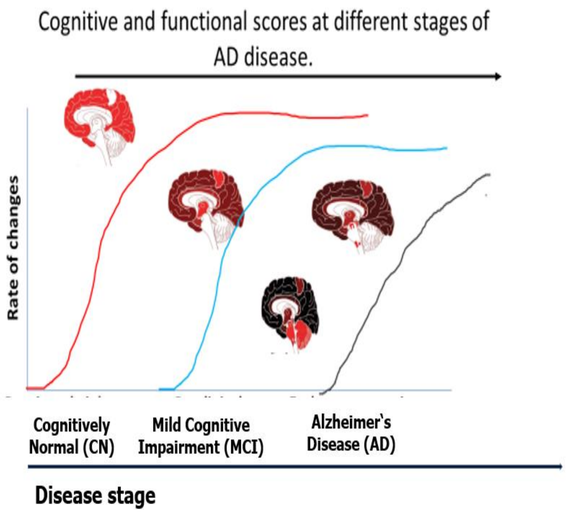
1 School of Global and Public Health, Kamuzu University Of Health Sciences, Blantyre, Malawi, 2 Applied Pharmacometrics Training – Africa Program, c/o Pharmacometrics Africa NPC, Cape Town, South Africa. 3 School of Pharmaceutical Sciences, University Sains Malaysia, 4 Integrated Drug Development, Certara, Princeton, NJ, United States, 5. Division of Clinical Pharmacology, University of Cape Town, South Africa 6. Eli Lilly and Company, Indianapolis, Indiana, United States, 7. Eli Lilly and Company, Bracknell, United Kingdom

*This project was done as part of the Applied Pharmacometrics Training Fellowship, a capacity strengthening program organised by Pharmacometrics Africa NPC and Certara

Background

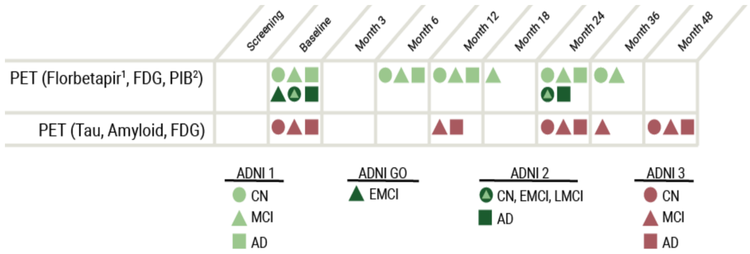
- Alzheimer's disease (AD) is a progressive neurodegenerative disorder that progresses slowly from mild memory loss to severe cognitive impairment and functional disability.
- Understanding the relationship between the Alzheimer`s natural disease progression and predictive biomarkers informs drug/interventions discovery.
- Quantifying the role of the predictive biomarkers provides rich proxy information for the disease progression trajectories even in the absence of the clinical endpoints.
- This work assessed how the brain amyloid plaque accumulation, measured using florbetapir PET scan is associated with natural disease progression using multistate markov model.

Fig 1: Natural stages of Alzheimer disease



Methods

- We used a publicly available Alzheimer's Disease Neuroimaging Initiative (ADNI) data collected from 2004 to 2022
- ADNI study longitudinally collected clinical, imaging, genetic, and biochemical biomarkers for the early detection and tracking of Alzheimer's disease (AD)



- The current work included participants who had at least a single florbetapir accumulation value over the follow-up time
- Amyloid plaque accumulation was measured as average florbetapir (AV45) standard uptake value ratio (SUVr) of frontal, anterior cingulate, precuneus, and parietal cortex relative to the cerebellum.
- Multistate markov model was used to characterize the Alzheimer's natural disease progression based on progressive transition from one stage to another among the three disease stages; cognitively normal(CN), mild cognitive impairment (MCI) and Alzheimer disease(AD).
- We estimated transition intensities and hazard ratios (HR) adjusting for gender and amyloid plaque accumulation as a time-varying covariate

Results

- We observed that 1133 patients had at least a single amyloid plaque accumulation value out of the 2426 patients in ADNI dataset

Table 1: Estimated mean time (in months) spent by a participant in a particular disease stage

State	Mean time (95 % CI)	Standard error
CN	248.2 (199.4, 309.1)	27.8
MCI	97.9 (84.0, 114.1)	7.7
AD	355.5 (169.3, 746.6)	134.6

- The highest and the lowest mean months spent by a patient in AD and MCI states was 355.5 (SE=134.6) and 97.9 (SE=7.7) respectively, reflecting a quick transition of patients from MCI to AD

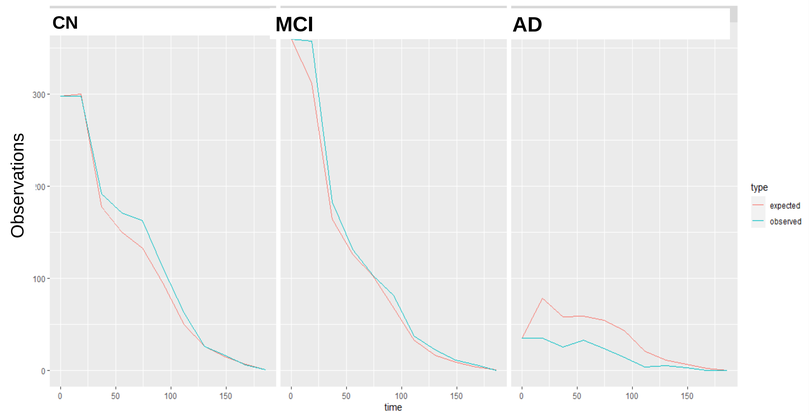
Results

Table 2: Adjusted estimates of the hazard ratios and 95% confidence intervals from the multistate Markov model

	amyloid plaque accumulation	Gender, Male (female as reference)
Transition	HR (95% CI)	HR (95% CI)
CN->MCI	7.4 (3.5, 15.5)	1.6 (0.99, 2.5)
CN->AD	0.0 (0.0, 34822390.0)	1.6 (0.04, 54.3)
MCI->AD	64.4 (26.3, 157.6)	0.85 (0.57, 1.2)

- Patients with a higher amyloid plaque accumulation were at a higher risk of transitioning from a lower to a higher stage

Fig 2: Predicted and observed prevalence over time based on the multistate markov model



Conclusion

- Increased amyloid plaque accumulation predicts the worsening of the Alzheimer's disease.
- Since the patients progresses quickly from MCI to AD interventions should focus on providing maximum medical care and evaluation for patients who are MCI
- More data from varying ethnicities and races would further inform discovery and optimization of interventions/drugs for those specific population groups.

Funding

This project was done as part of the Applied Pharmacometrics Training Fellowship, a capacity strengthening program organised by Pharmacometrics Africa NPC and Certara