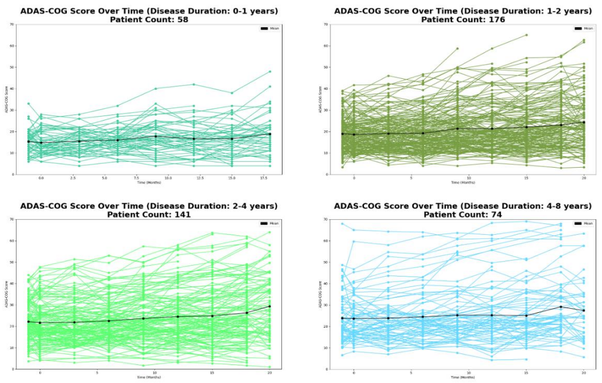
Towards predicting individual cognitive trajectories in AD using Quantitative Systems Pharmacology

Ivo Schuttel, Shaina Short, **Hugo Geerts,** Certara Predictive Technologies, USA

Background

- Functional readouts in AD is highly variable, due to different comedications, genotypes, amyloid- and tau loads. We explore whether a mechanism-driven QSP model, calibrated with group average data could be used to predict individual cognitive ADAS-Cog trajectories
- We test this model using data from the ADNI database

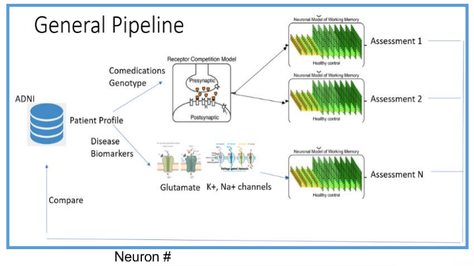


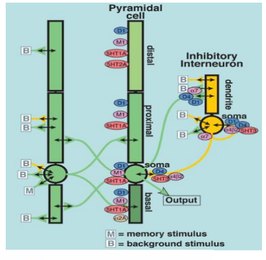
Individual ADAS-Cog trajectories from ADNI subjects illustrating the large variability

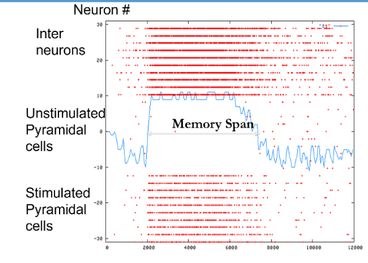
Methods

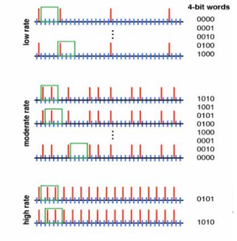
Individual patient profiles were created from their baseline features usin the effect of comedications, genotypes, amyloid- and tau load on voltage- and ligand gated ion channels.

A previously calibrated NEURON model is used to predict the individual cognitive trajectory. This is compared to the actual clinical readouts.









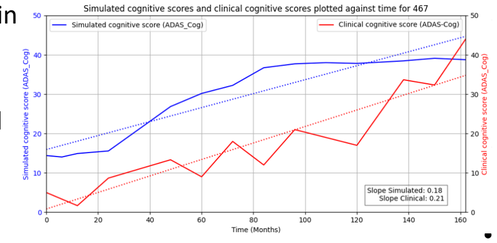
Comedications and Genotypes

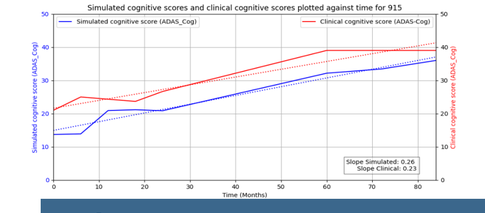
Genotype	Effect
APOE4	Synapse density
COMT Val156Met	Dopamine, Adrenerge half-life
5-HTTL Rrs23352	Serotonin half-life

Genotype effect from PET imaging studies
Drug exposure from PET imaging studies
Calculate Receptor Activation from competition with neurotransmitter

Group	Medication	Receptors
Cholinergic inhibitors	Donepezil, Galantamine, Rivastigmine	M1, M2, a4b2, a7
Anti-depressants	Paroxetine, Zoloft, Cymbalta, Sertraline, Venlafaxine, Lexapro, Escitalopram,Citalopram , Celexa, Trazadone, Fluoxetine	5HT1A, 5HT2A, 5HT4, 5HT3, 5HT6
Benzodiazepine	Lorazepam, Clonazepam, Temazepam, Oxazepam, Midazolam, Zoldipem	GABA
Protein Pump Inhibitors	Lansoprazole, Omeprazole, Pantoprazole, Rabeprazole, Esomeprazole, Eciphex	M1, M2, a4b2, a7
NMDA-inhibitor	Memantine	NMDA
Anti-convulsant	Gabapentin	GABA
Antipsychotics	Aripiprazole , Haloperidol, Quetiapine, Risperidone	D1, D2, D4, 5HT1A, 5HT2A, 5HT4, 5HT3, 5HT6, M1, a4b2, a7

Individual Patient Readouts vs Clinical ADAS-Cog



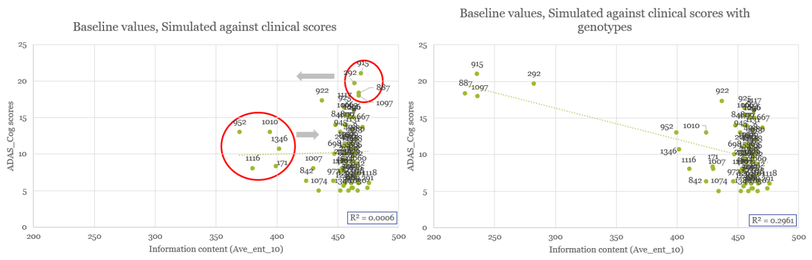


- Proper trendline seen in simulated versus clinical cognitive readouts
- Slopes used to mitigate variability
- Simulated scores follow directions of clinical scores, only in different effect size

References

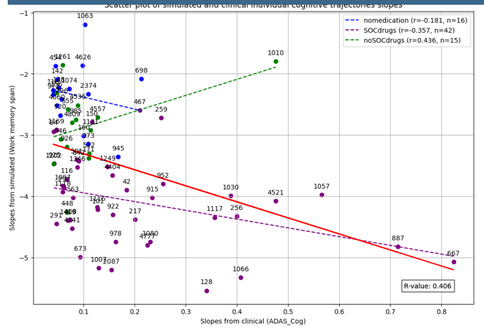
- Geerts et al 2018 Alzheimers Res Ther.;10(1):14
- Geerts et al 2020 Alzheimers Dement.16(6):862-872
- Roberts 2012, Alzheimer Research & Therapy, 2012, 4:50
- Walsh JR, *Alzheimer's & Dementia*. 2022;18(S10):e065386. doi:10.1002/ALZ.065386
- Wang C,. *Transl Psychiatry*. 2024;14(1). doi:10.1038/S41398-024-02819-W.

Identifying Genotype from Baseline Prediction



- Subjects with high ADAS-Cog scores and high information content are identified as the fast progressor genotype. They have higher serotonin receptor, lower dopaminergic and adrenergic receptors activations than wildtype genotype. Slow progressors have the opposite outcome.

Comparisons of Simulated versus Clinical Slopes



- Correlation score of 0.41
- Proper trendline seen in simulated versus clinical cognitive readouts
- SOC cohort is best preforming cohort with largest dynamic range

Conclusions

- Pearson correlation coefficient of 0.406 is close to range of data-driven analyses (r= 0.46[1] – 0.6[2])
- Large fraction of patients have very slow clinical progression
- Standard of care (SOC) medication best performing cohort
- Increase of 0.6 points/year in this population, expected to be 1.8 points/year for APOE e4-negative [1]
- Advantages of mechanism-vs data driven predictions
  - Account for change of medication
  - Account for acute change in amyloid-tau biomarkers
- Next steps
  - Select patients with faster progression
  - Identify fast progressors