Causal *in silico* patient models can inform Alzheimer's disease patient identification and endpoint selection for early-stage clinical trials

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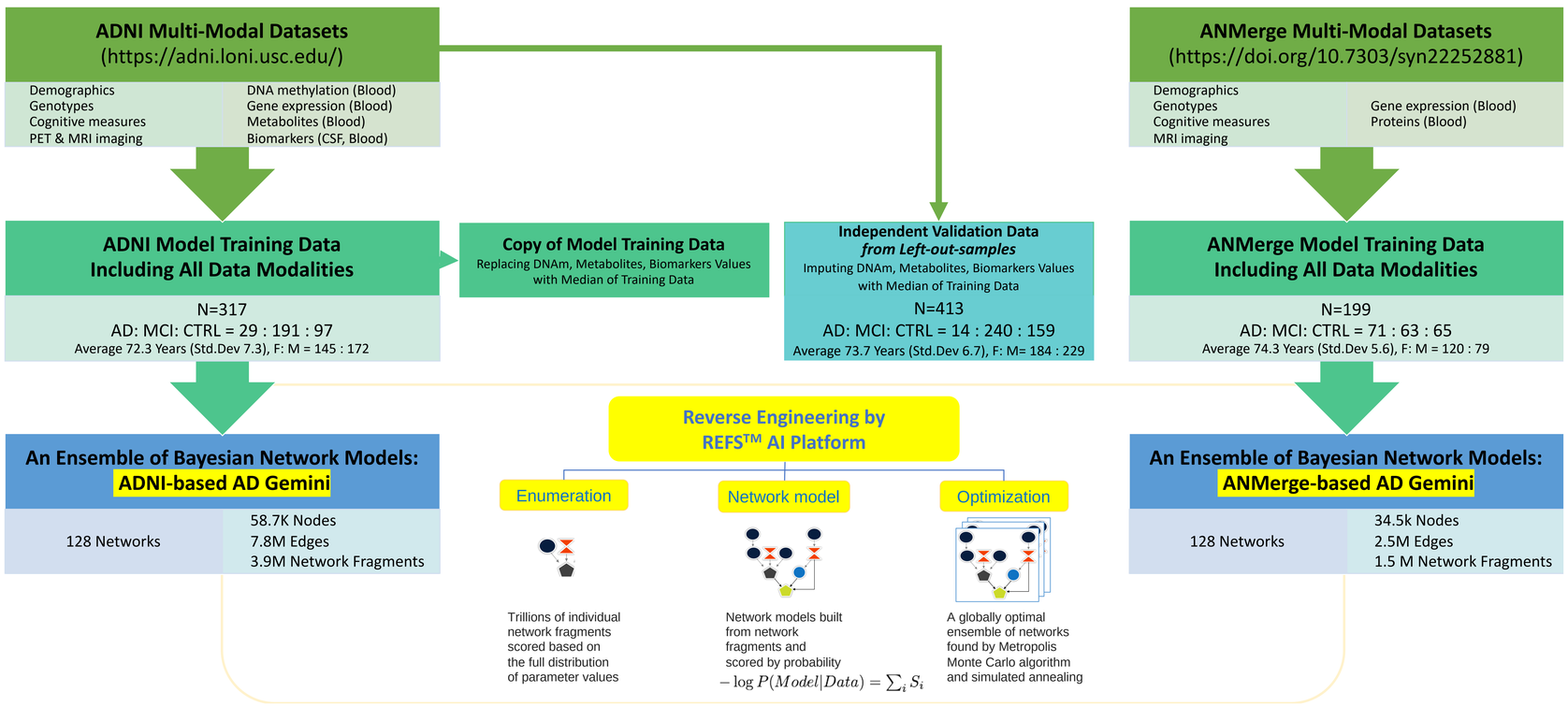
Objective

- Clinical trial simulation allows drug developers to test different trial designs *in silico* prior to enrollment.
- GNS Healthcare's *in silico* Alzheimer's Disease (AD) patient combines multi-omic, imaging, and clinical profiles from patients diagnosed with AD and mild cognitive impairment (MCI).
- Models provide patient-level predictions of disease progression-rate making them a powerful tool for optimizing trials, especially in the critical earliest stages of disease progression
- Specifically, by using the *in silico* patient models, researchers can:
  - Understand expected progression of individual patients at different disease stages.
  - Identify fastest progressing patient subsets for outcomes of interest

Data and Methods

- Two ensemble sets of Bayesian network models were generated based on the respective datasets: Alzheimer's Disease Neuroimaging Initiative (ADNI) and AddNeuroMed's ANMerge.
- After data processing, the ADNI training data included 317 subjects (with 29 AD, 191 MCI, and 97 Controls) with complete 58.7K features from clinical and multi-omics data, some of which were measured over time.
  - An independent validation dataset was generated from the left out 413 subjects in ADNI having most data features available except for DNA methylation, Metabolites and Biomarkers. These missing features were then imputed with the median of training data for the model validation.
  - A copy of the ADNI training data was created by replacing the DNA methylation, Metabolites and Biomarkers with the median of training data, so that the in-sample and out-of-sample predictive performance can be directly comparable.
- The ANMerge models included 199 subjects' data (including 71 AD, 63 MCI, and 65 controls) with 34.5K multi-modal and partially longitudinal features including gene expressions and proteins.

Figure 1. Workflow of the Study Design



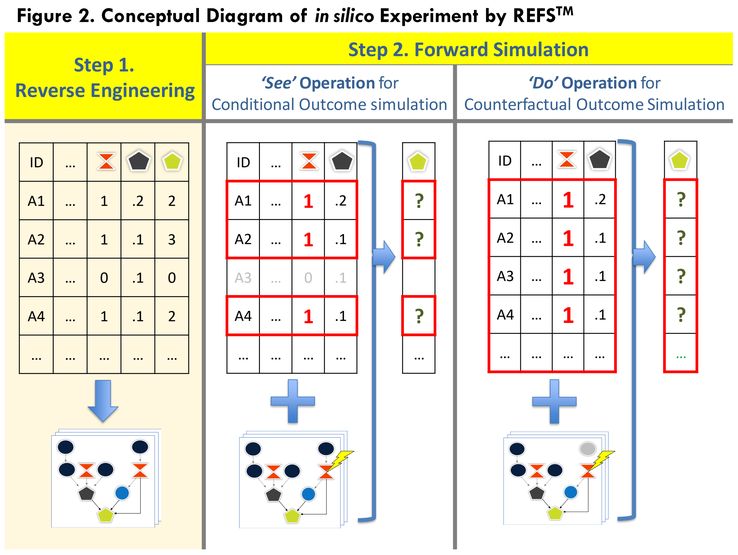
Reverse Engineering

- Each *in silico* patient is comprised of an ensemble of Bayesian network models built from the training data.
- A Bayesian network model is a directed graphical representation of relationships between variables where each node is a variable, and each arrow is a conditional dependency.
- In REFS™ AI platform, the Bayesian network models are learned and optimized using the Metropolis-Hastings Markov Chain Monte Carlo algorithm and simulated annealing technique.
- REFS™ builds an ensemble of network models, rather than a single model which tends to have little predictive power in an undetermined system, as the ensemble amplifies relationships supported by the data and dilutes spurious ones.

Forward Simulation

- Patient-level outcome values can be computationally simulated in the reverse-engineered ensemble of Bayesian network models.
- In comparison with observation-based predictive models, the REFS™ causal models can estimate *in silico* both conditional and counterfactual outcome values effectively and appropriately, by 'See' and 'Do' operations.
- These estimations are done fully adjusting for any confounding effects identified in the models, which is necessary in causal inference as emphasized in randomized experiments.

Figure 2. Conceptual Diagram of *in silico* Experiment by REFS™



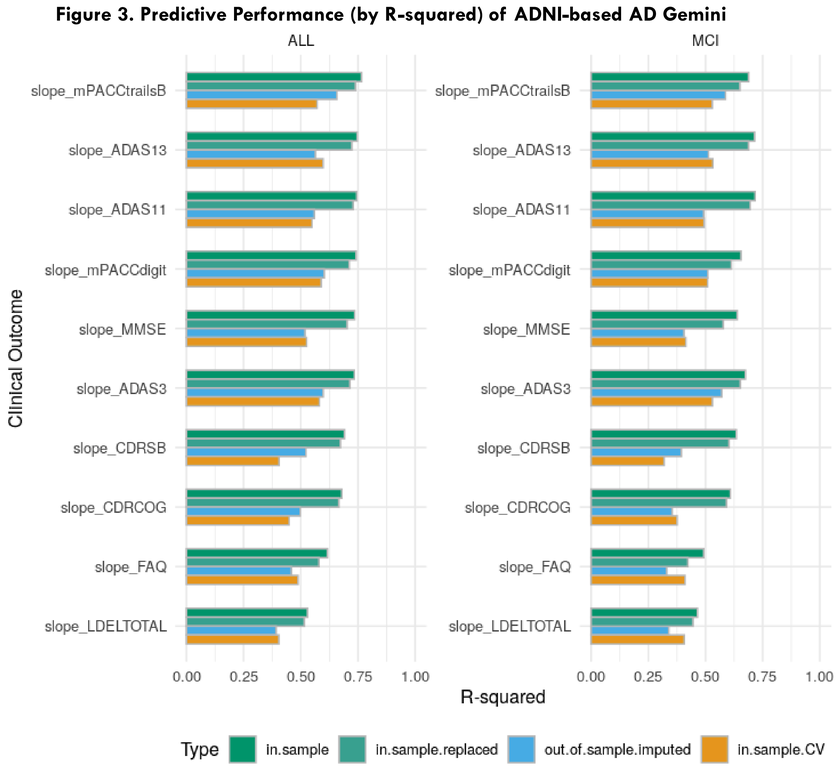
Results

- The **ADNI-based AD Gemini *in silico* patient models** had strong predictive performance across a variety of cognitive outcomes, both at baseline and for progression rate.
  - Progression rate defined as the slope estimate of outcomes regressed on time in a mixed model
- Specifically, for the progression-rate endpoints, the proportion of variability explained by the model in the training data (denoted as **in.sample R-squared** in Fig. 3) ranged from 0.53 for LDELTOTAL to 0.77 for mPACCtrailsB.
- The 5-fold Cross-Validation R-squared values (denoted as **in.sample.CV R-squared** in Fig. 3) were similarly high, greater than 0.4 across all outcomes, with an average 0.18 decrease compared to in.sample R-squared.
  - Comparison of top predictors across original and CV models suggest drop is due to sample size decrease, not overfitting
- Potential overfitting bias was further evaluated using the independent validation data (denoted as **out.of.sample.imputed** in Fig. 3) which showed only an average 0.14 reduction in R-squared from the comparable training data set (denoted as **in.sample.replaced** in Fig 3.), where the contribution of DNA methylation, Metabolites and Biomarkers to the outcome prediction was excluded due to unavailability of these data modalities in the validation data.
  - **out.of.sample.imputed:** Validation data in ADNI with missing DNA methylation, Metabolites, Biomarkers values imputed by the median of the training data
  - **in.sample.replaced:** Copy of training data in ADNI with DNA methylation, Metabolites, Biomarkers values replaced by the median of training data
- The comparable R-squared values observed in the independent data suggests that the ADNI-based *in silico* patient models are robust and generalizable.
- The predictive performance was also evaluated in the subset of patients with MCI to specifically assess how well fast progressing patients could be identified at early disease stages.
- While the predictive performance for MCI was strong in general, the best predicted progression-rate endpoints included ADAS11 (R^2=0.72), ADAS13 (R^2=0.71) and mPACCtrailsB (R^2=0.68), while the least well predicted endpoints were LDELTOTAL (R^2=0.46) and FAQ (R^2=0.49).

Table 1. Predictive Performance (by R-squared) of ANMerge-based AD Gemini

Slope	ALL		MCI		AD	
	In sample	CV	In sample	CV	In sample	CV
MMSE	0.81	0.74	0.46	0.01	0.66	0.59
CDRSB	0.86	0.84	0.54	0.32	0.68	0.63

Figure 3. Predictive Performance (by R-squared) of ADNI-based AD Gemini



- In addition, the predictive performance in both MCI and AD patients was investigated in the separately built **ANMerge-based AD Gemini models** which, despite being a smaller cohort than ADNI (N=317 vs 199), included a larger number of AD patients (n=71 vs 29).
- In ANMerge, the R-squared of MMSE and CDR-SB progression-rates was 0.81 and 0.86 in the full model, and 0.74 and 0.84 in Cross Validation.
- A more significant decrease in CV R-squared was observed in this model compared to ADNI-based when looking within the MCI strata particularly for MMSE, likely partially due to reduced sample size.
- For AD patients, both measures demonstrate robust performance with CDR-SB showing strongest performance for both AD and MCI.

Conclusions

- **GNS Healthcare's *in silico* AD Gemini patient models showed strong predictive performance across a variety of cognitive outcomes, both across and within different stages of the disease.**
- **The ability of the models to provide robust simulations demonstrates the utility to optimize trials through identification of fast progressing patients in the early stages of disease.**
- Both PACC (Preclinical Alzheimer's Cognitive Composite) and ADAS (Alzheimer's Disease Assessment Scale) tests demonstrate effectiveness for monitoring cognitive impairment in early disease stages.
- PACC measures have previously reported limitations due to lack of age correction, but the AD Gemini *in silico* models are designed for key risk factors to be accounted for by the AI algorithm and are able to leverage their sensitivity in the MCI group.
- Once dementia has developed, CDR tests are robust to monitor progression rates as shown in the ANMerge-based AD Gemini models.
- This study is limited by the small samples sizes once looking at the stratified analyses and the inability to directly validate the models with the independent data sets including all the features of the training data sets.
  - The validation data set for ADNI-based models had many missing features which added noise to the predictions. This does, however, demonstrate the robustness of the causal *in silico* patient approach even when there are underlying data differences.
- Further work will also allow understanding the relative contributions to the predictive ability of each model of different data modalities (including comparison of utility of metabolomics in ADNI-based and proteomics in ANMerge-based AD Gemini models).

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