Estimate the time-to-conversion for Alzheimer's Disease using neuroimaging-genomics multi-modal deep survival analysis

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Outlines

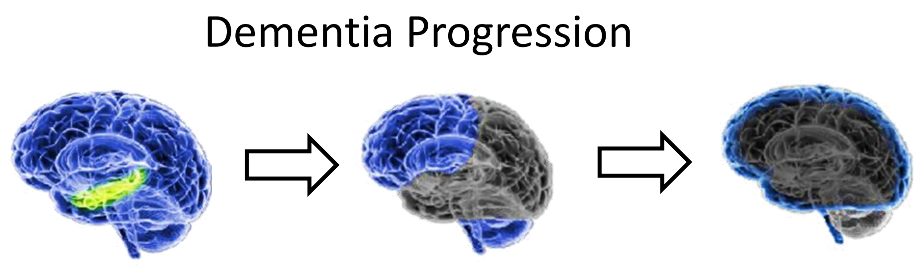
- Background / Aims
  - Predict time-to-conversion for dementia
  - Study the influence of different data modality on dementia conversion
- Study Design
  - Outcome measurement
  - Cohort Stratification
  - Independent variables
- Data processing / Feature extraction
  - Multi-type feature selection
  - Feature importance analysis – Permutation test
- Experimental setup
  - Deep Survival Model design
  - Evaluation
- Results
- Conclusion

Study Aims

- Predict time-to-conversion for Dementia of Alzheimer's Type (DAT)
  - Using multi-modal predictor, including:
    MRI, Genetics, Cerebrospinal Fluid (CSF) biomarker, Cognitive tests

- Study the influence of each data modality on disease prediction

CSF Biomarker
Cognitive Test



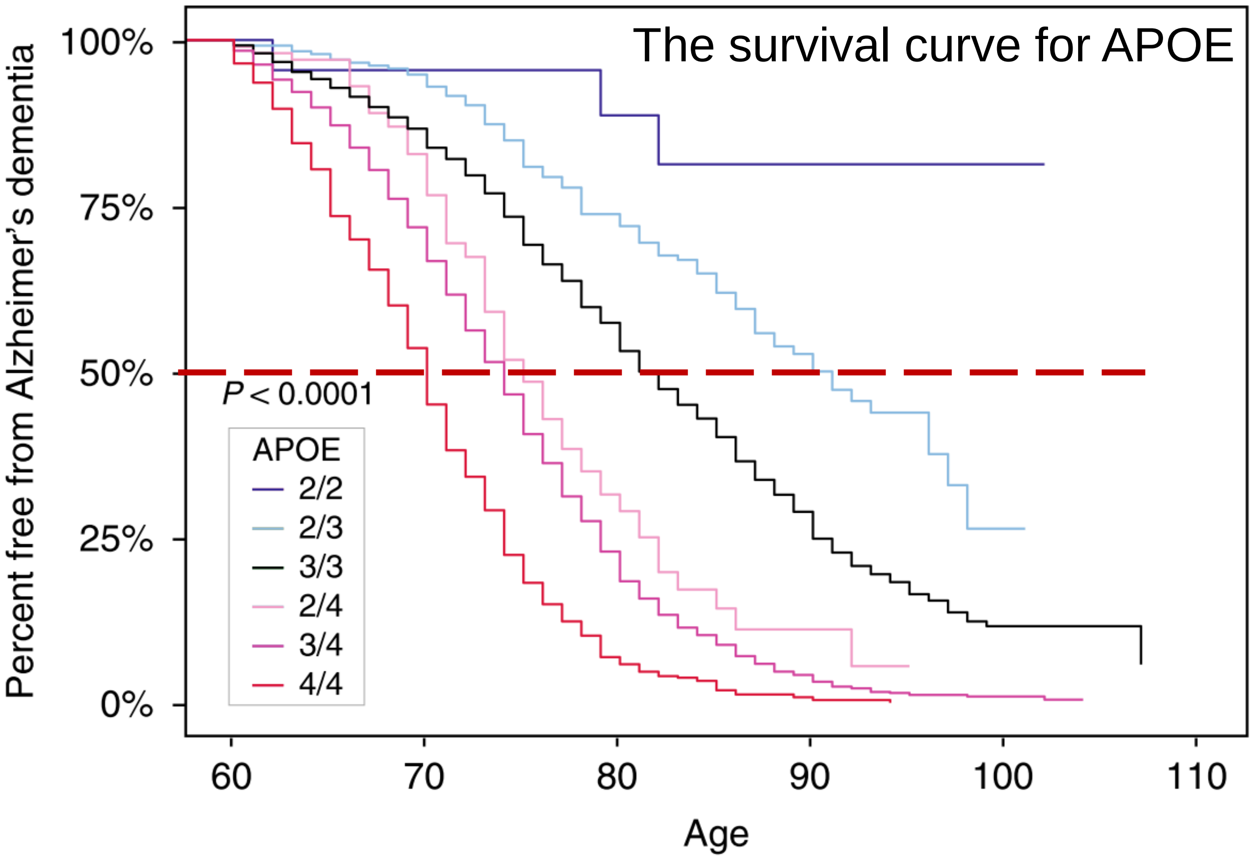
Study Design – Outcome Measurement

Predicting time-to-conversion - Survival analysis

- *Probability of dementia risk*
  - as a function of time

- Example:
  - APOE allele dementia risk

Dementia % as a function of age



Reiman et al. 2020 Nature Communication

Study Design – Outcome Measurements

Survival analysis - Sensoring

Survival Analysis:

- Analysis of the time an individual will experience an event of interest

Event of Interest

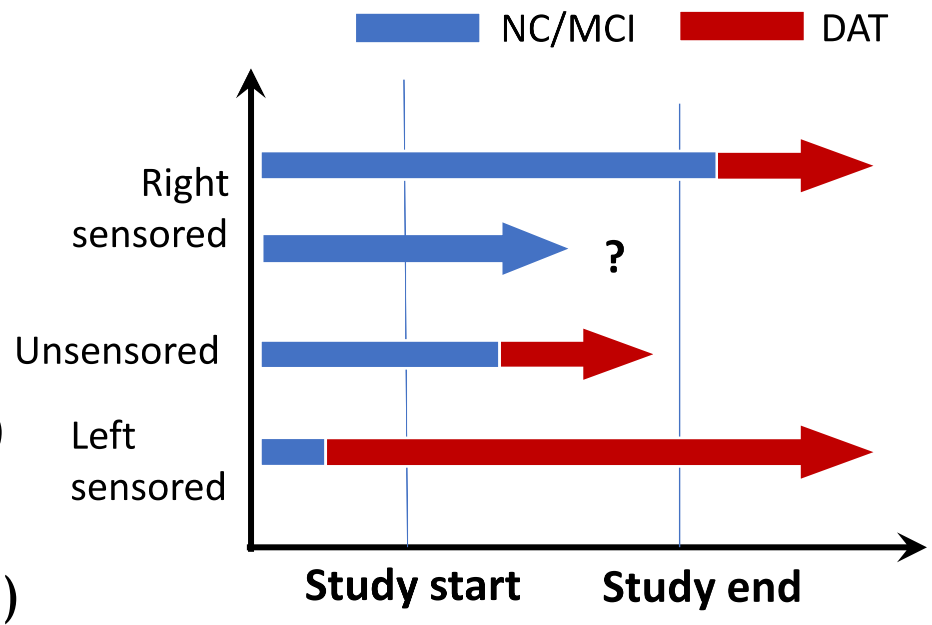
- Dementia onset (DAT diagnosis confirmation)

Left sensor

- Event happens before the first clinical visit (baseline)

Right Sensor

- Event happens after last clinical visit (final timepoint)



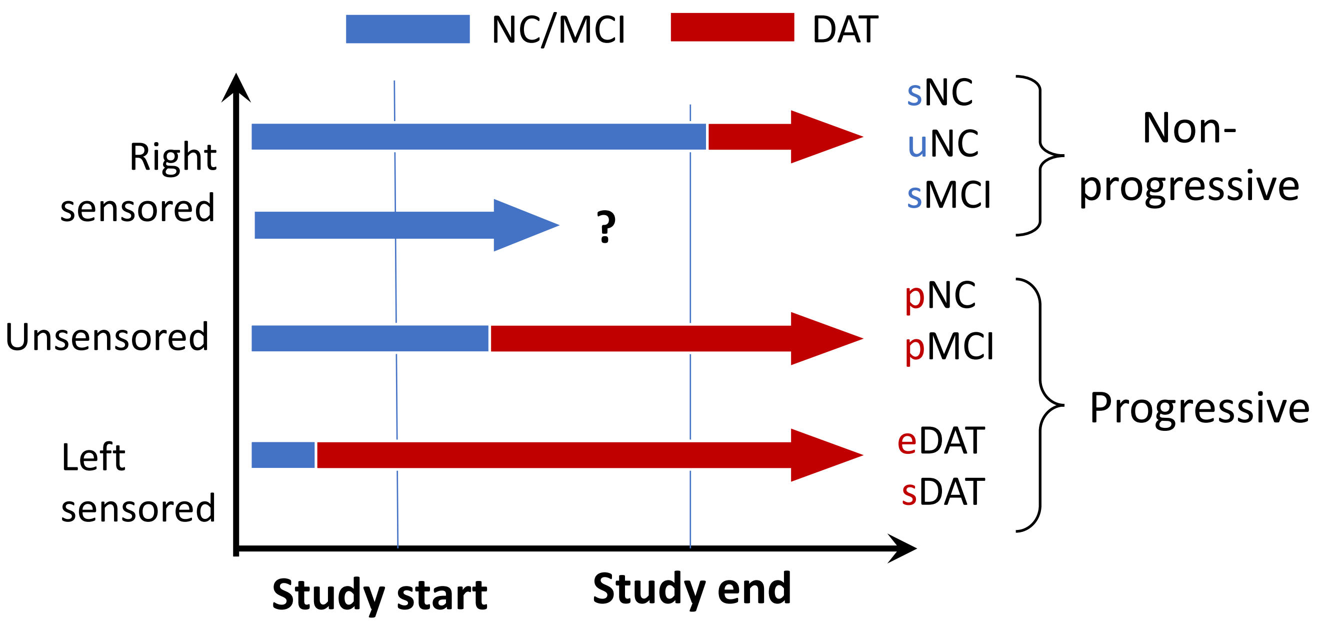
Study Design – Outcome Measurements

Predicting time-to-conversion - Survival analysis

Ground truth labels

1. Event indicator:
0 = Non-progressive (right sensored)
1 = Progressive

2. Duration:
- **Non-progressive**: Duration between the first and last visit
- **Progressive**: Duration between first visit and DAT diagnosis confirmation



Data - Study Participants

- Training/evaluation cohort: ADNI-1

Subject grouping

	Group name	Clinical progression	n
Non-progressive	sNC: stable NC	NC → NC	109
	uNC: unstable NC	NC → MCI	22
	sMCI: stable MCI	MCI → MCI	101
Progressive	pNC: progressive NC	NC → MCI → DAT	14
	pMCI: progressive MCI	MCI → DAT	155

Only baseline data were used for training

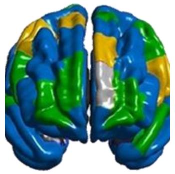
Stratified Train/Valid/Test split

Groups	Training set	Validation set	Testing set	Total
sNC	70	17	22	109
uNC	14	4	4	22
pNC	9	2	3	14
sMCI	65	16	20	101
pMCI	99	25	31	155
Total	257	64	80	401

Data – Input Features

Neuroimage & Genomic Feature Selection (Within Training Data)

Sub-bagging x 10



MRI data
(91 FreeSurfer parcellated ROI volumes)

Welch's t-test

21 MRI features

Genetic data
(521,014 "plink" quality-checked SNPs + APOE-ε2/3/4)

Fisher's exact test

21 genetic features

Feature ranking based on selection frequency

Final 21 MRI features

Final 21 genetic features

Data – Input Features

Data modalities

- **MRI:** 21 ROI volume (Z-standardized) (21 features)
- **Genetic:** 18 SNPs + 3 APOE alleles (21 features)
- **DTC:** 21 features
    - **D**emographic (4 features)
    - Cognitive **T**ests (11 features)
    - **C**SF (7 features)
- **Only baseline data was used for training**

MRI features	Genetic features	DTC features / #missing data
Amygdala - Left	APOE-ε2	Aβ40 (CSF) / 41
Amygdala - Right	APOE-ε3	Aβ42 (CSF) / 40
Entorhinal - Left	APOE-ε4	Aβ (CSF) / 176
Entorhinal - Right	rs524410	ptau (CSF) / 176
Fusiform - Left	rs746947	ptau/Aβ (CSF) / 176
Fusiform - Right	rs1010616	Tau (CSF) / 176
Hippocampus - Left	rs1864036	tau/Aβ (CSF) / 176
Hippocampus - Right	rs2085925	Age (DEM) / 0
Inferior-parietal - Left	rs2405940	Sex (DEM) / 0
Inferior-parietal - Right	rs2883782	Education (DEM) / 0
Inferior-temporal - Left	rs4953672	Marital status (DEM) / 0
Inferior-temporal - Right	rs5918417	ADAS11 (TST) / 0
Inferior-lateral-ventricle - Left	rs5918419	ADAS13 (TST) / 1
Inferior-lateral-ventricle - Right	rs6116375	CDRSB (TST) / 0
Middle-temporal - Left	rs6773506	FAQ (TST) / 2
Middle-temporal - Right	rs7627954	LDELTOTAL (TST) / 0
Parahippocampal - Left	rs10465385	MMSE (TST) / 0
Parahippocampal - Right	rs10510985	RAVLT-forgetting (TST) / 1
Precuneus - Left	rs10924809	RAVLT-immediate (TST) / 1
Precuneus - Right	rs12522102	RAVLT-learning (TST) / 1
Supramarginal - Left	rs17197559	RAVLT-%forgetting (TST) / 2

Method - Deep Survival Model

Cox regression model

- Hazard function: $h(t|x) = h_0(t)exp[g(x)]$

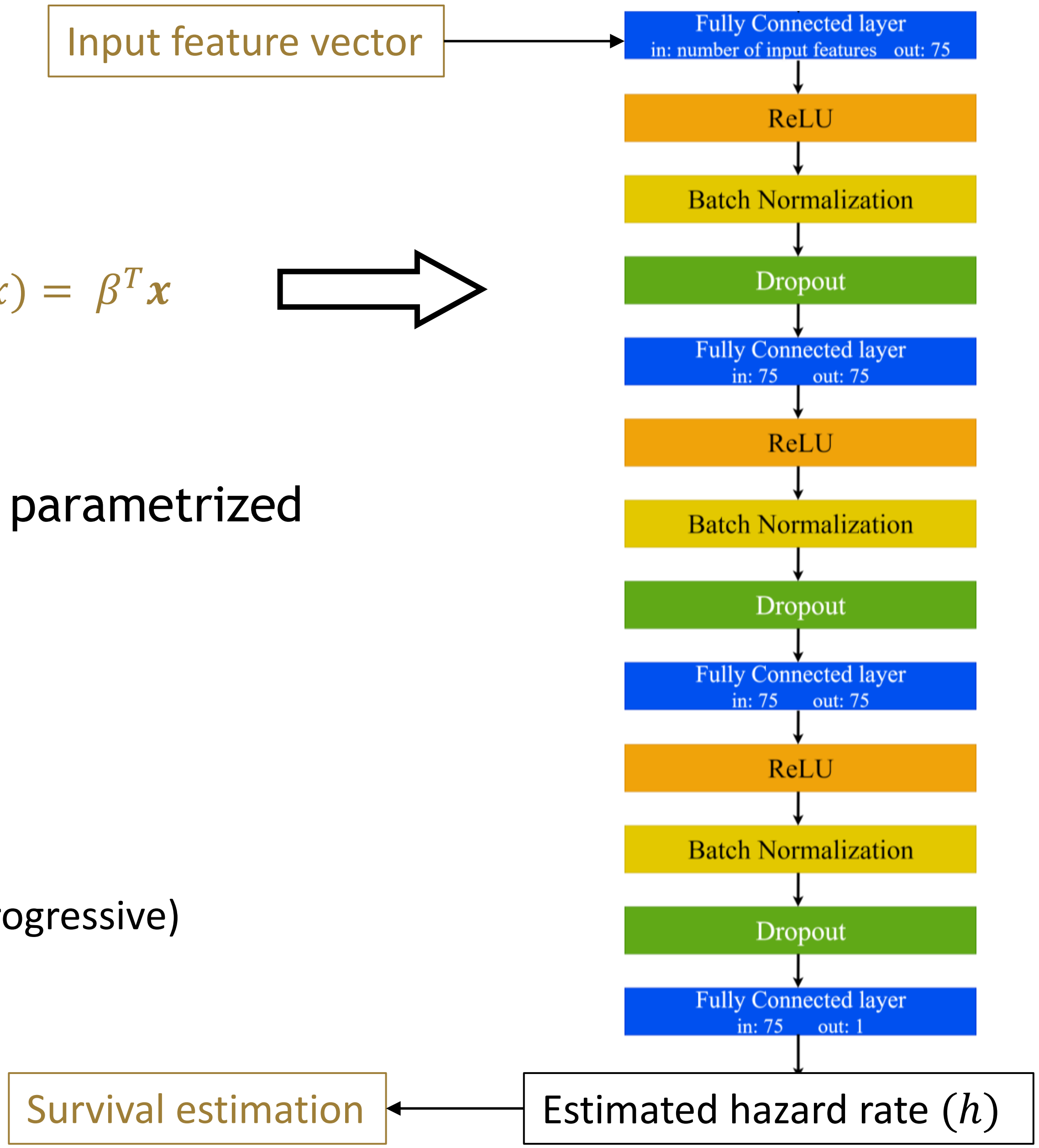
$$g(x) = \beta^T \boldsymbol{x}$$

Deep Survival Model

- a non-linear version of the Cox model where $g(x)$ parametrized by a neural network (Multi-Layer-Perceptron)

Loss function

- $loss = \sum_i D_i \log(\sum_{j \epsilon R_i} \exp[g(x_j) - g(x_i)])$
  - D_i: event indicator for subject i (1=progressive, 0=non-progressive)
  - R_i: set of all individuals at risk



Experiments

6 Feature sets combination

1. Genetic data (GEN; 21 features)
2. MRI data (MRI; 21 features)
3. Demographic + Cognitive Test + CSF (DTC; 21 features)

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4. MRI and genetic data (GEN+MRI; 42 features)
5. Genetic and DTC data (GEN+DTC; 42 features)
6. MRI and DTC data (MRI+DTC;42 features)
7. All features (GEN+MRI+ DTC; 63 features)

Evaluation Metrics 1

Integrated Brier Score (IBS)

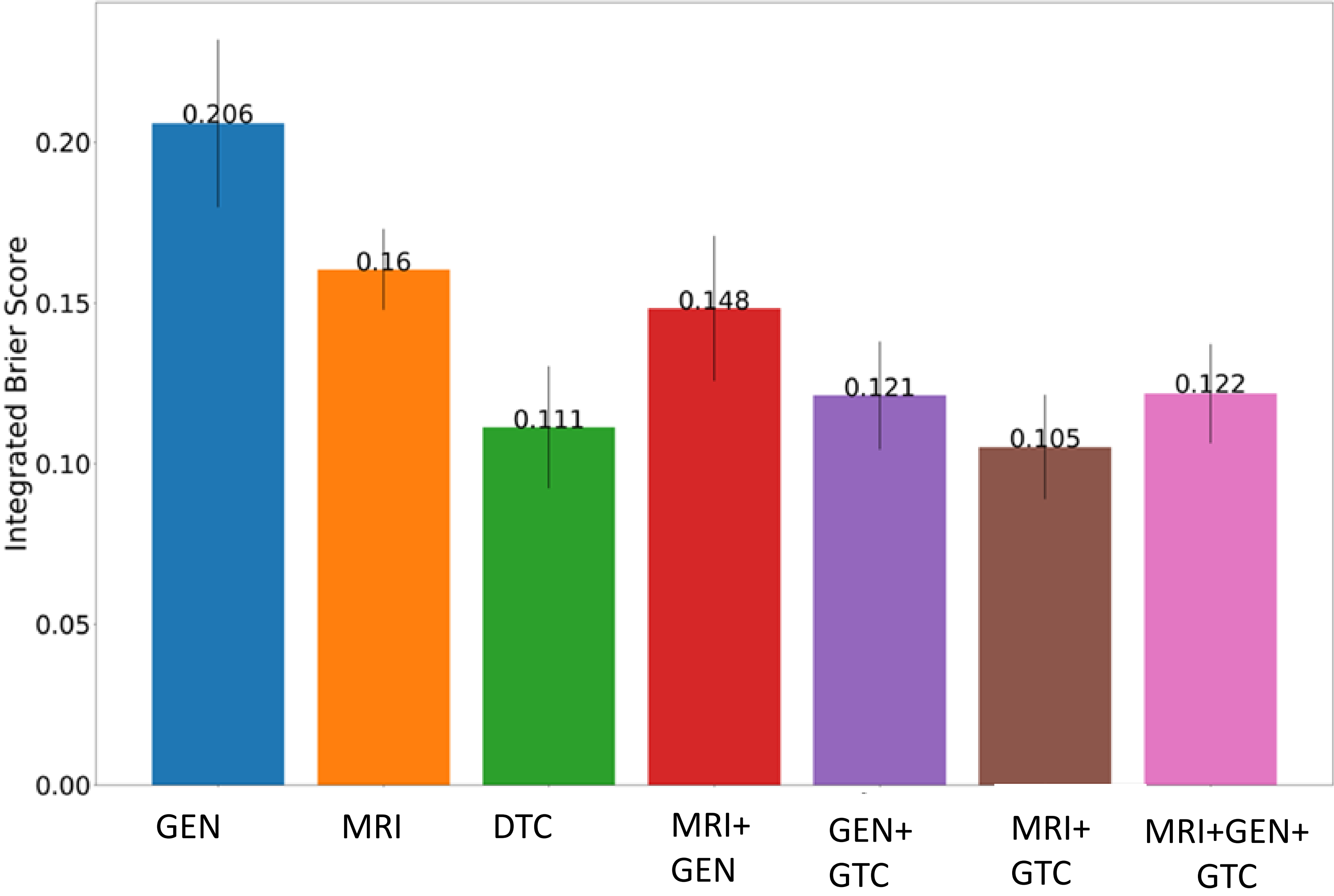
- The average squared **distances** between the observed (y_i) and predicted survival probability ($\widehat{p}_i$)
  - $BS = \frac{1}{N} \sum_i (y_i - \widehat{p}_i)^2$
- **0 < IBS < 1** (the smaller the better)

Evaluation Metrics 1 Results

IBS (the smaller the better)

Same conclusion:

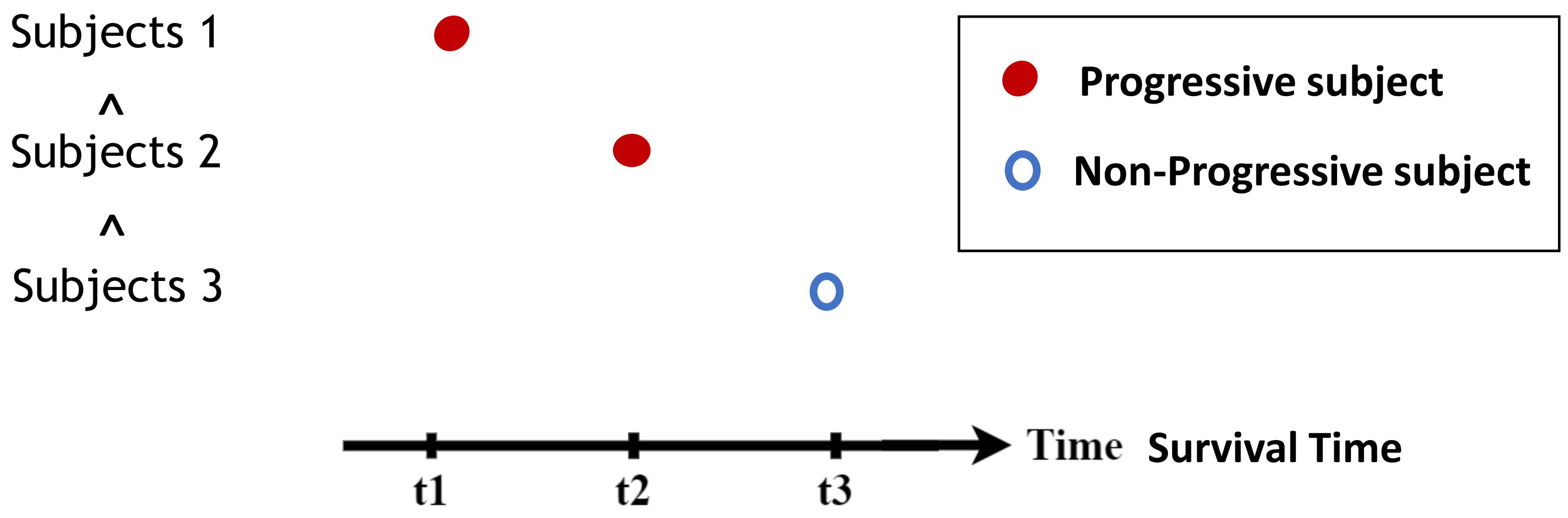
- Combining **MRI** and **GEN** (**MRI+GEN**) improves the performance
- **DTC** works best amongst single modalities
- MRI + GTC improved GTC (not statistical significant)



Evaluation Metrics 2

Time-dependent Concordance Index (C^{td}-index)

- Compares the order of predicted survival times with true survival times for a random pair of subjects



- 0 < Ctd-index < 1 (the bigger the better)

Evaluation Metrics 1 Results

C^{td}-index (the bigger the better)

- Combining MRI and **GEN** (**MRI+GEN**) improves the performance
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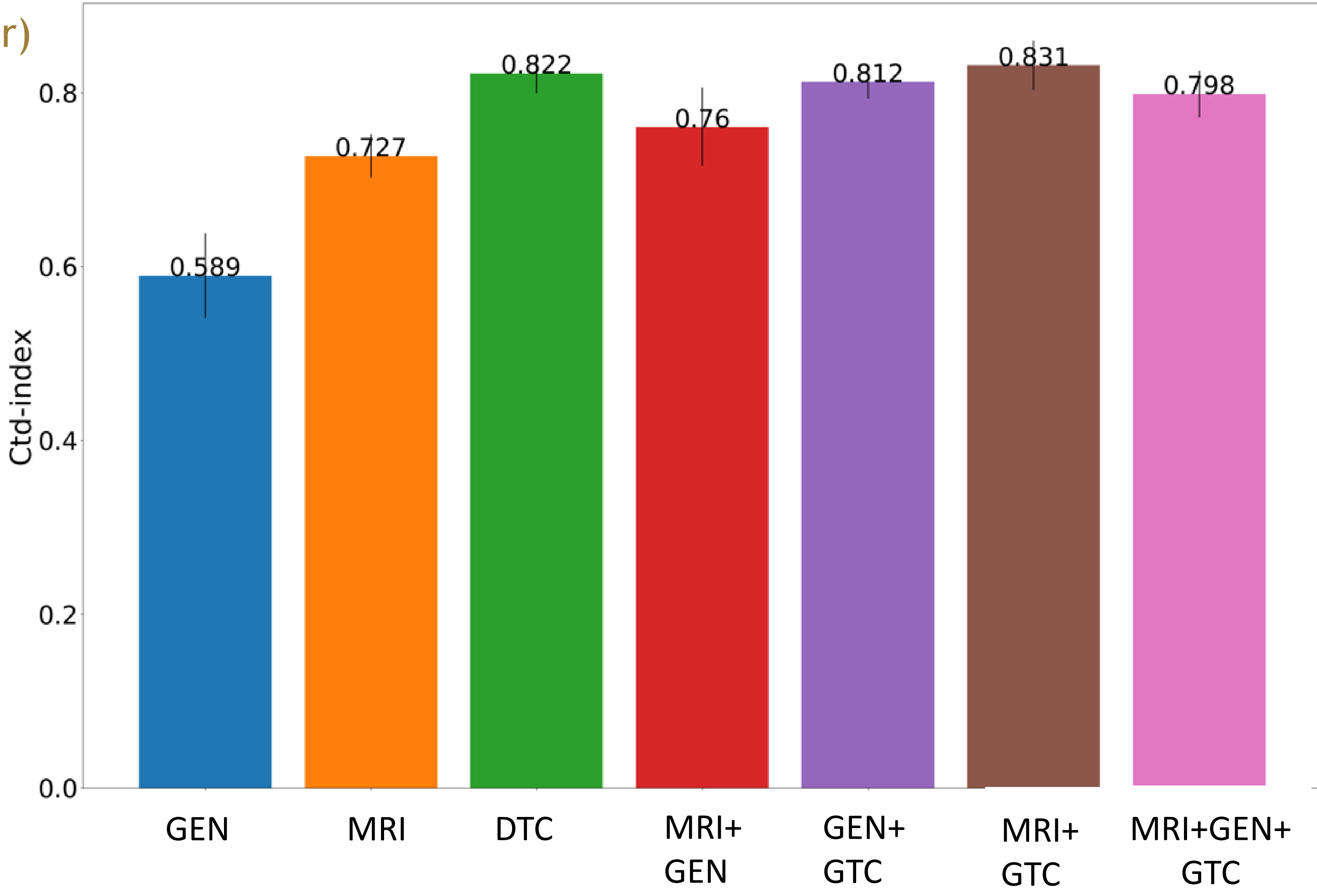
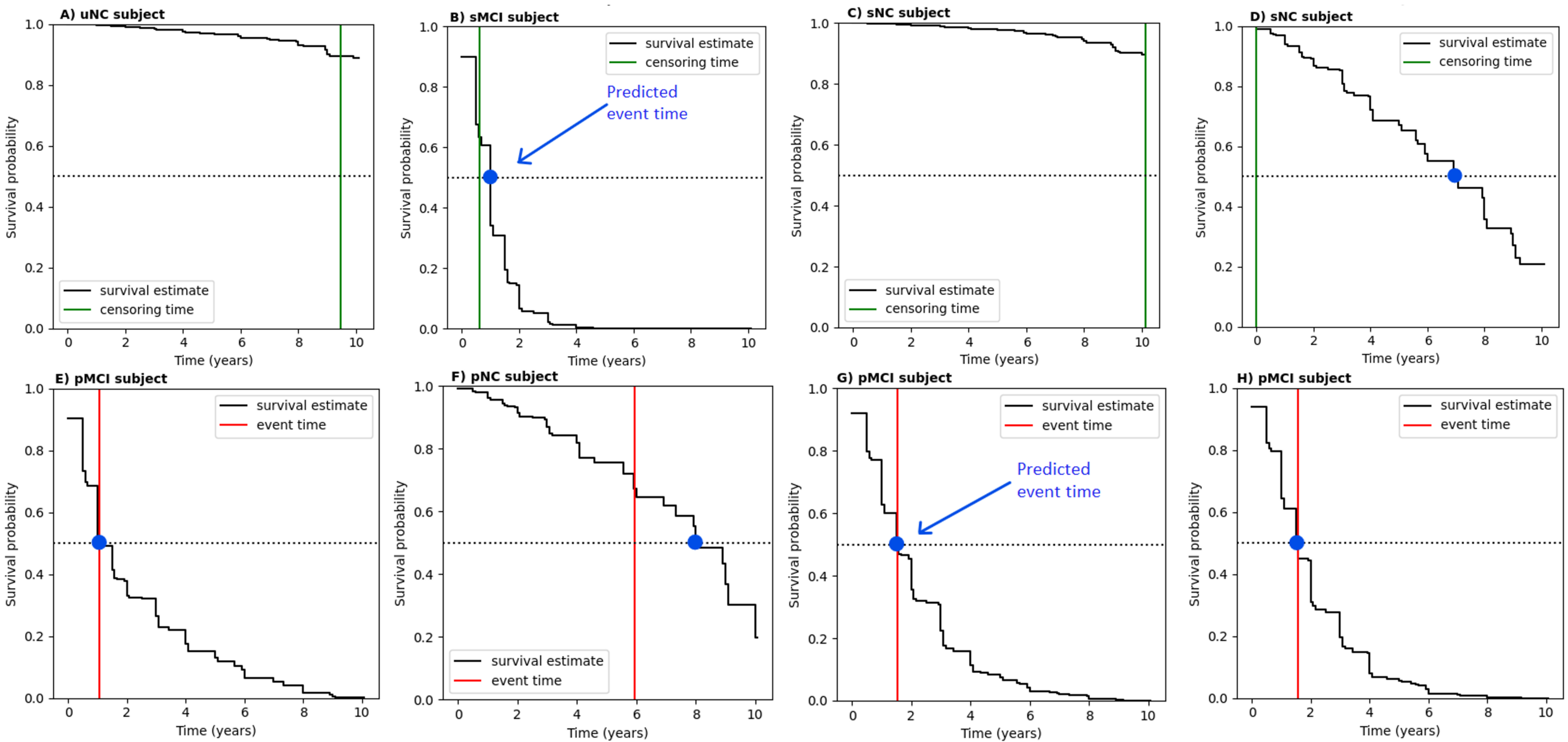


Results

Predicted vs. true time-to-conversion difference



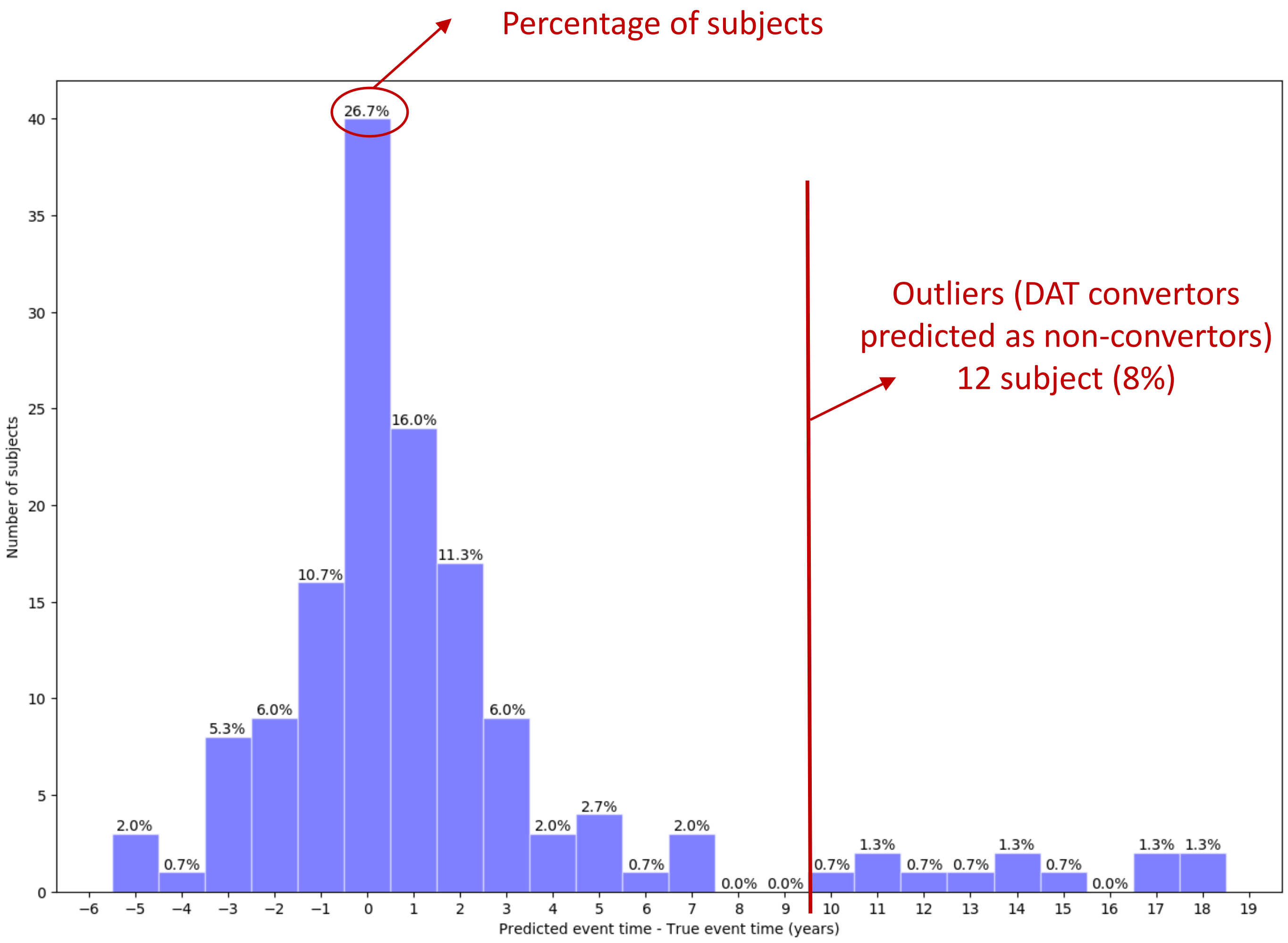
Results

Predicted vs. true time-to-conversion difference

- **Predicted time**: the time a subject's survival probability reaches 50%
    - If this doesn't happen: Predicted time = 20 years after initial visit

- More than half of the subjects (80/150 or **53.4%)** had a time difference of less than 1.5 years

- The predicted event time was earlier than the actual event time for 37 subjects (**24.7%)**

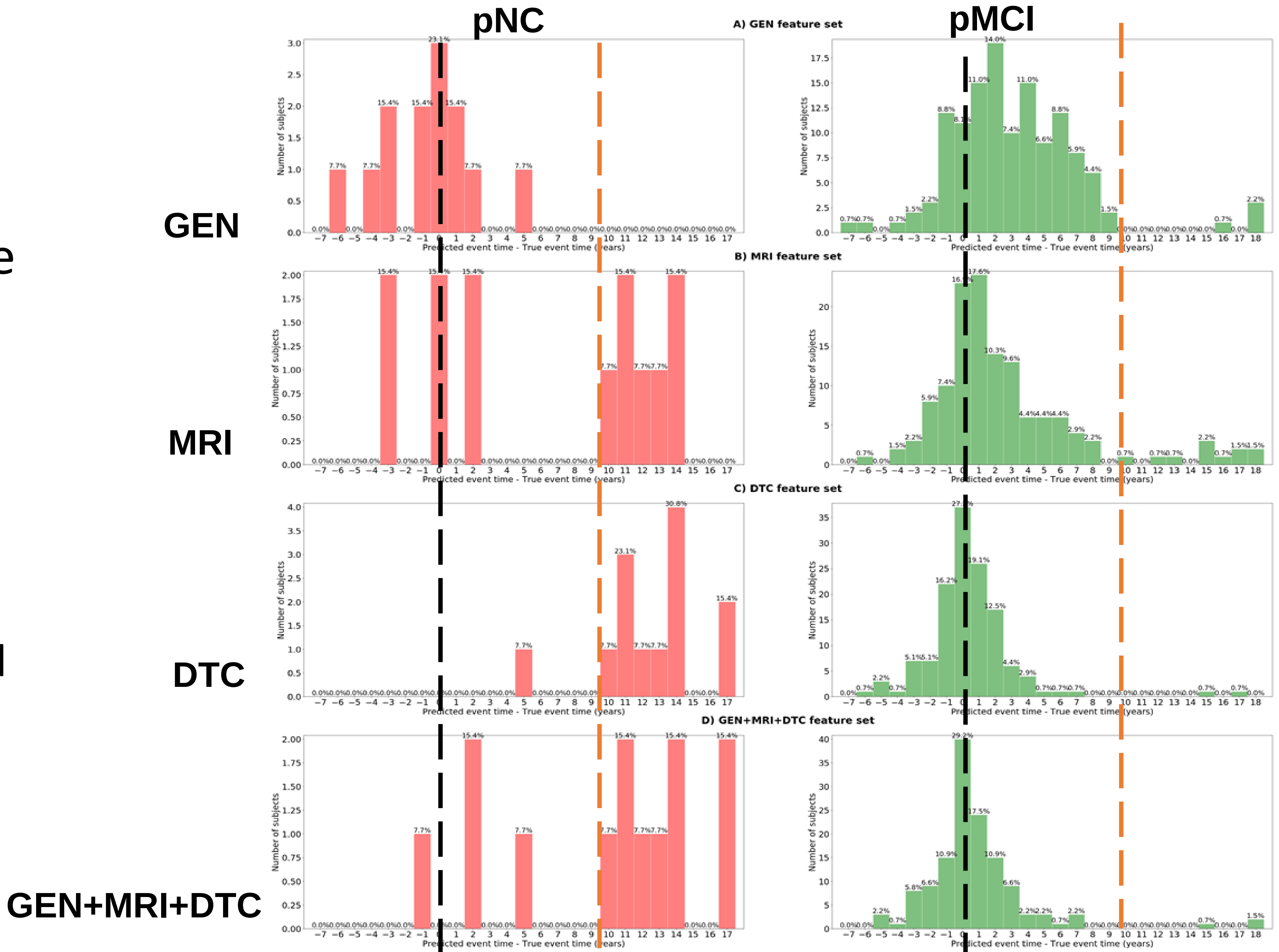


Histogram of the differences between the predicted and true event times for **progressive** subjects (150 subjects) using the **GEN+MRI+DTC** feature set

Results

Feature type comparison

- Dementia onset time prediction
- DTC
  - Demographic
  - Cognitive test
  - Cerebral Spinal Fluid Biomarker



Results

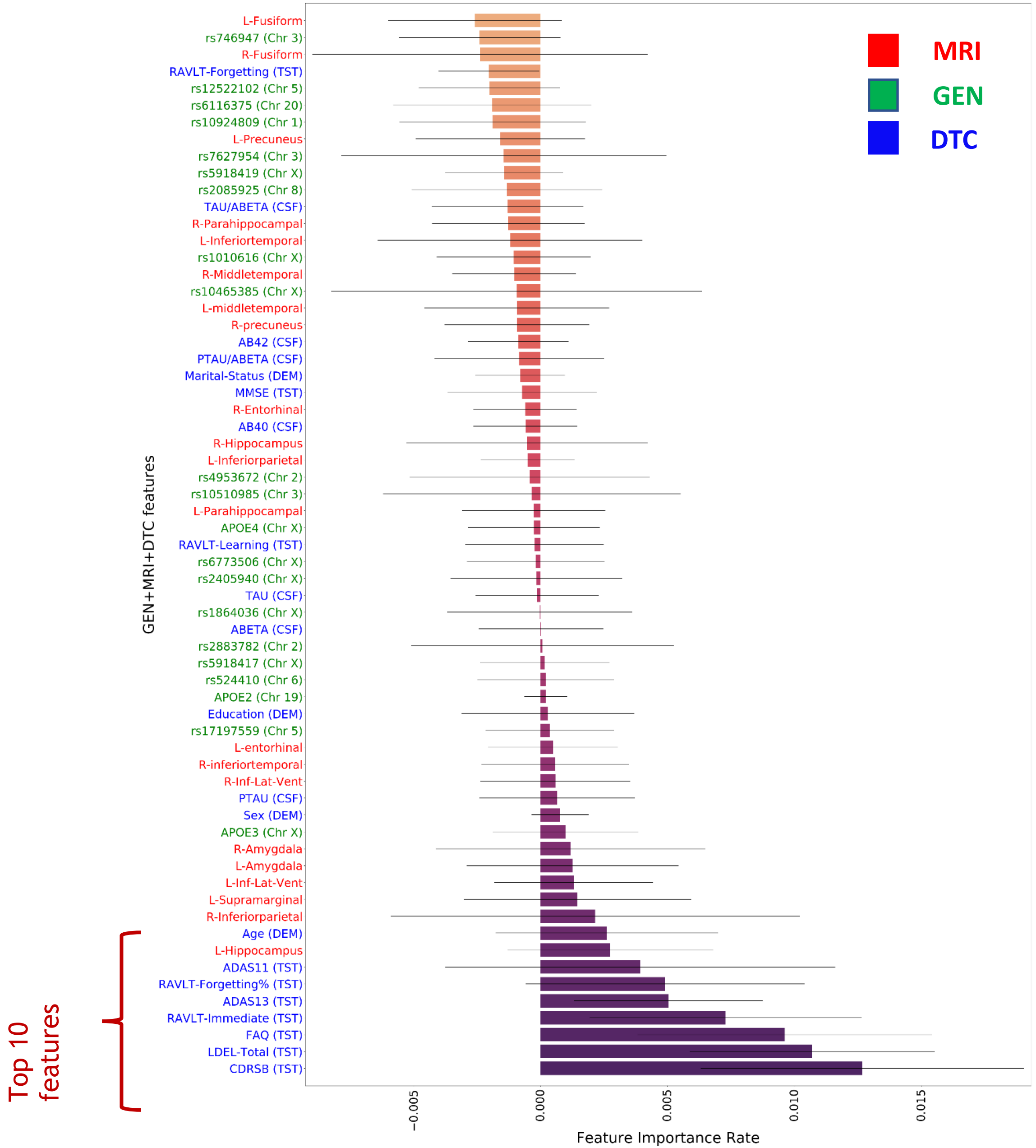
Feature Importance Analysis

- Explain and compare the contributions of each feature toward the time-to-conversion prediction
- Determine feature contributions through the permutation importance analysis
- Random shuffling of each feature

Results

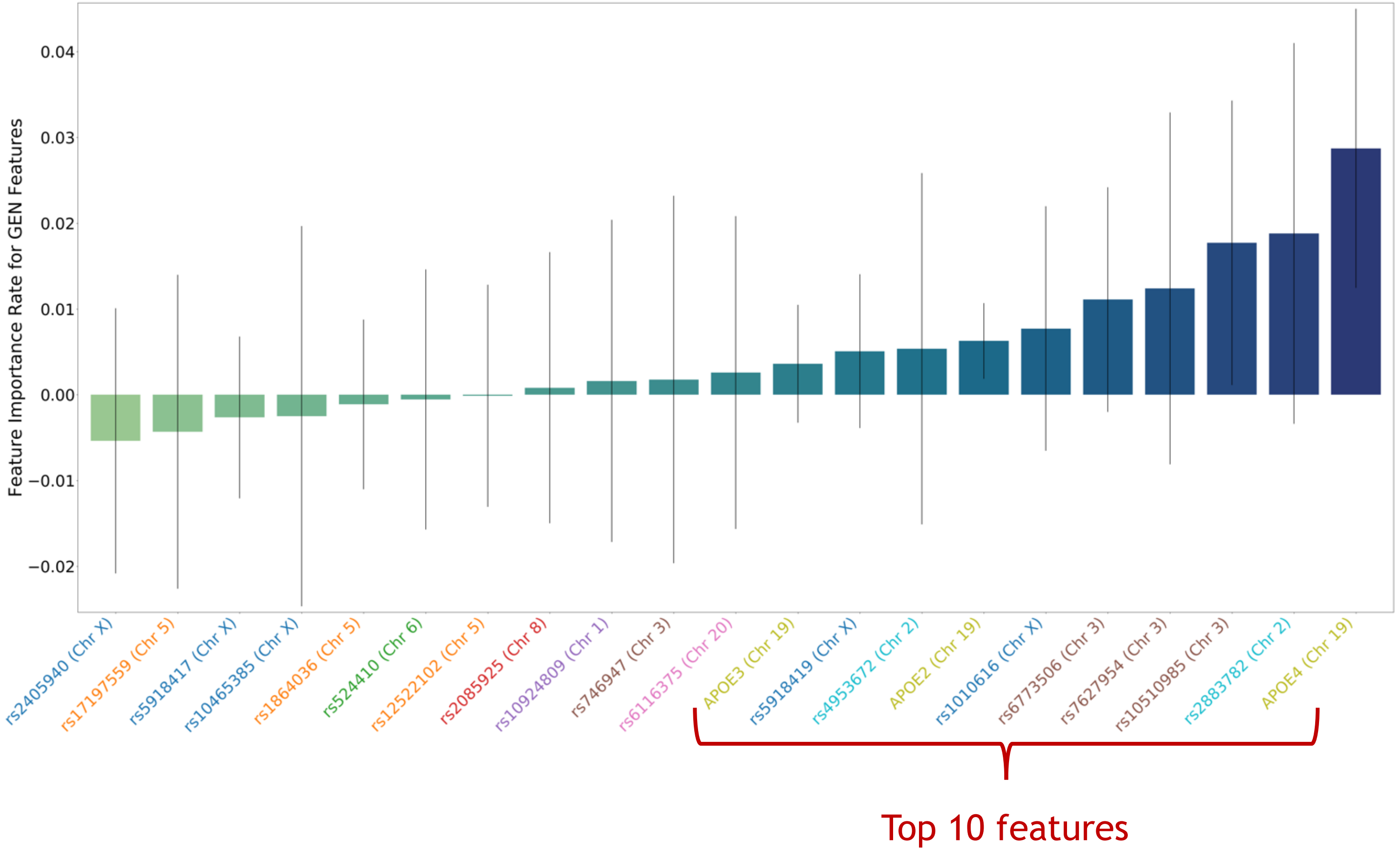
Feature importance: ALL

- **27/36 features** had a positive effect on performance
  - 6 GEN
  - 9 MRI
  - 12 DTC
- 8 of the top 10 features were from DTC including **7 TST** features and **1 DEM**
- The most important feature was **CDRSB** (Clinical Dementia Rating Scale)



Results

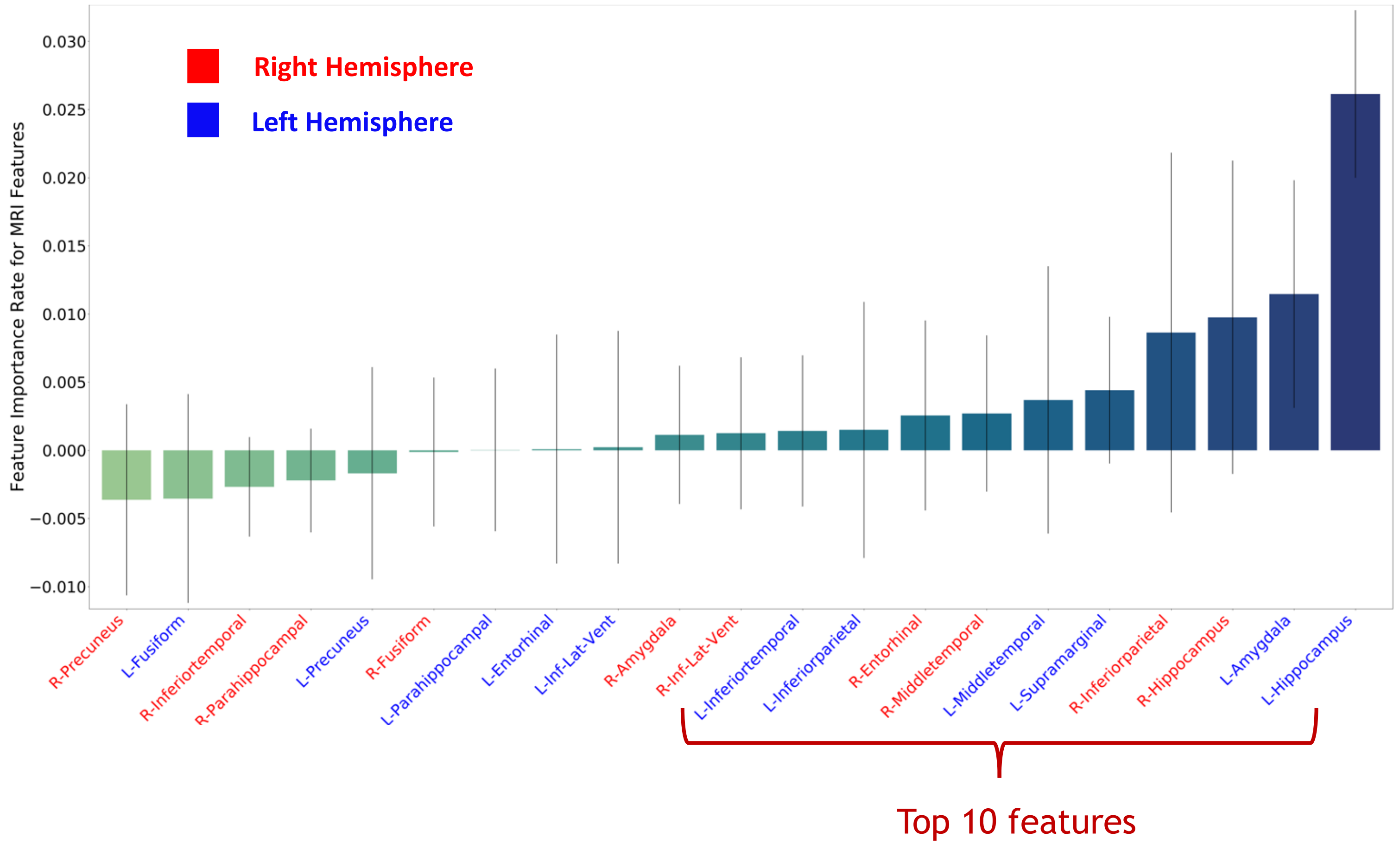
Feature importance: GEN



- **14/21 features** had a positive effect on performance
- The most important feature was **APOE-ε4**
- Top 10 most important features were from **chromosomes 2, 3, 19, and X**

Results

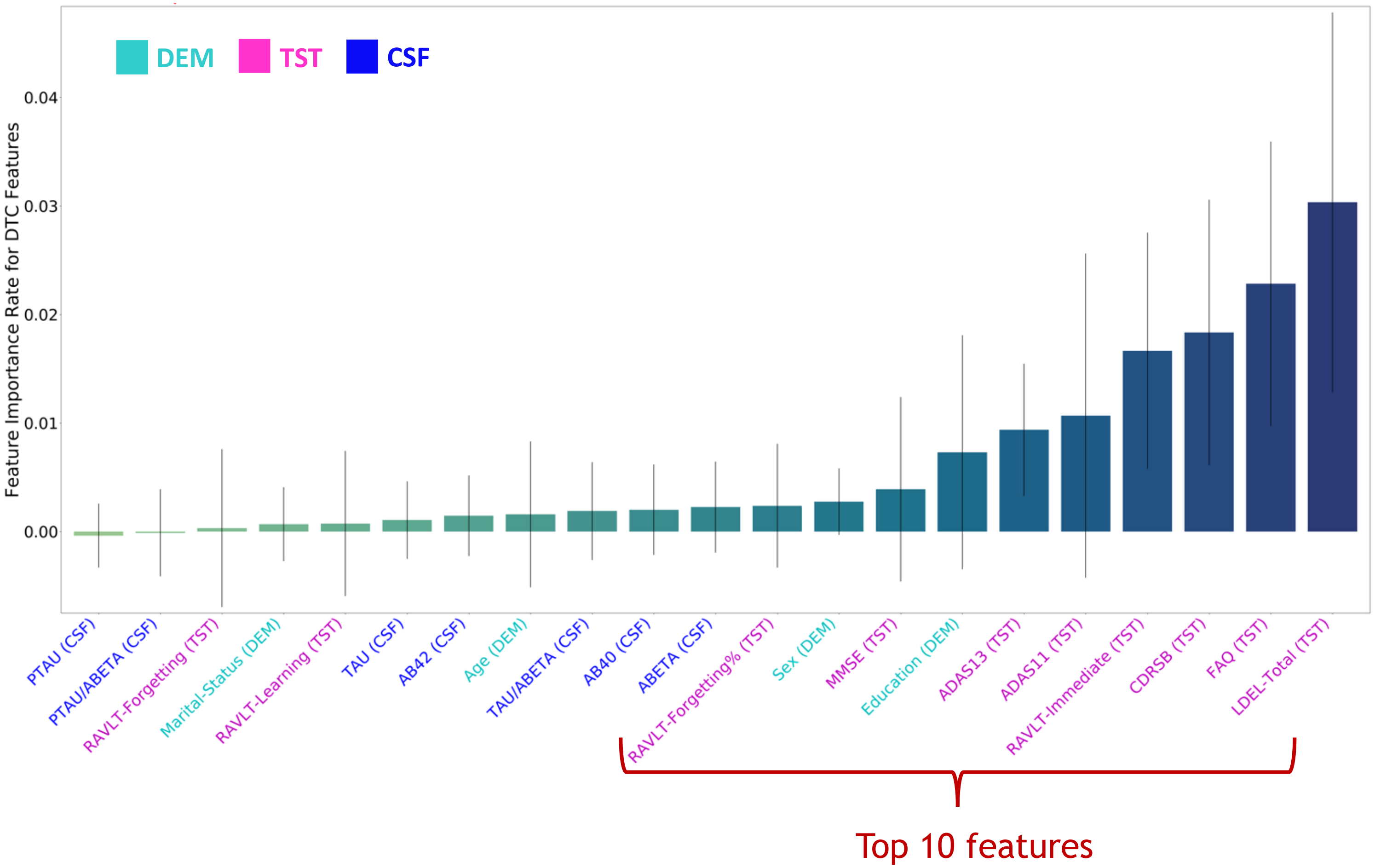
Feature importance: MRI



- **15/21 features** had a positive effect on performance
- The most important feature was **L-Hippocampus**
- Other important features include: **L-Amygdala**, **R-Hippocampus**, and **R-inferiorparietal**

Results

Feature importance: DTC



- **19/21 features** had a positive effect on performance
- 8 of the top 10 features were from **cognitive tests (TST)** and the other 2 were **demographic (DEM)** features
- The most important feature was Delayed recall variable from the Logical memory test (**LDEL-Total**)

Conclusions

- Modality comparison for Alzheimer's disease time-to-conversion prediction estimation for subjects at different stages of the disease
  - Genomic factor is better at the prodromal stage (pNC)
  - Neuroimage + CSF is better at early disease stage (pMCI)
- Novel AD-related genomic factors are discovered Explainable AI to explore feature importance

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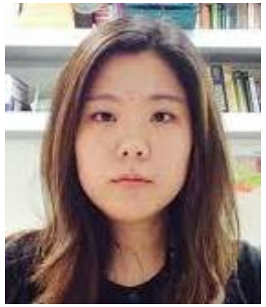
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Thank you!

Q&A