

# Imaging-based Prediction of Transcriptional Subtypes in Alzheimer's Disease

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## Problem Statement

**Alzheimer's disease** (AD) is a complex neurodegenerative disease that affects millions of people worldwide. Its heterogeneity in phenotype, pathology, and cognition makes it challenging to diagnose and treat. Recent advancements in single-cell genomics and large-scale genetic studies provide an opportunity to understand the molecular basis underlying phenotypic heterogeneity in AD.

In this project, we explored the application of various methodologies to analyze **brain MRI images** and **patient omics** to predict phenotypes related to Alzheimer's disease. Specifically, we explored:

1. **Cell type-specific polygenic scores** to predict brain-related traits
2. **Deep neuro-imaging** to classify Alzheimer's disease
3. Contrastive learning for explainable **multi-modal representations**

## Gene-set Analysis of Brain Volume Measurement GWAS Data

VARIABLE	NGENES	BETA	BETA-STD	SE	P
Tx1	17	-0.035667	-0.0057486	0.3703	0.53835
Tx2	29	-0.028662	-0.005975	0.29924	0.53814
Tx3	2	-0.098749	-0.0055246	1.0821	0.53634
Tx4	23	-0.0018653	-0.00034799	0.32503	0.50229
Tx5	10	0.56288	0.06997	0.41318	0.086805
Tx6	15	-0.8003	-0.12136	0.37344	0.98375
Tx7	5	-1.9705	-0.17389	0.58833	0.99957
Tx8	12	-0.54851	-0.074573	0.38765	0.9212
Tx9	9	-0.24254	-0.028625	0.49264	0.68866
Tx10	29	0.23256	0.04848	0.29451	0.21502
Tx11	19	0.50023	0.085097	0.34979	0.0766
Tx12	16	0.29976	0.046908	0.37516	0.2123
Tx13	3	-1.0202	-0.069845	0.57944	0.96059
Tx14	10	0.95016	0.11811	0.47851	0.023759
Tx15	22	0.3704	0.067638	0.33187	0.13241
Tx16	8	0.65193	0.0726	0.48789	0.090988
Tx17	7	-1.369	-0.14273	0.57826	0.99089
Tx18	17	0.035158	0.0056665	0.37605	0.46277
Tx19	2	-0.37609	-0.021041	1.082	0.63586
Tx20	3	0.71301	0.048816	0.88384	0.21007

Multi-marker Analysis of GenoMic Annotation (MAGMA)

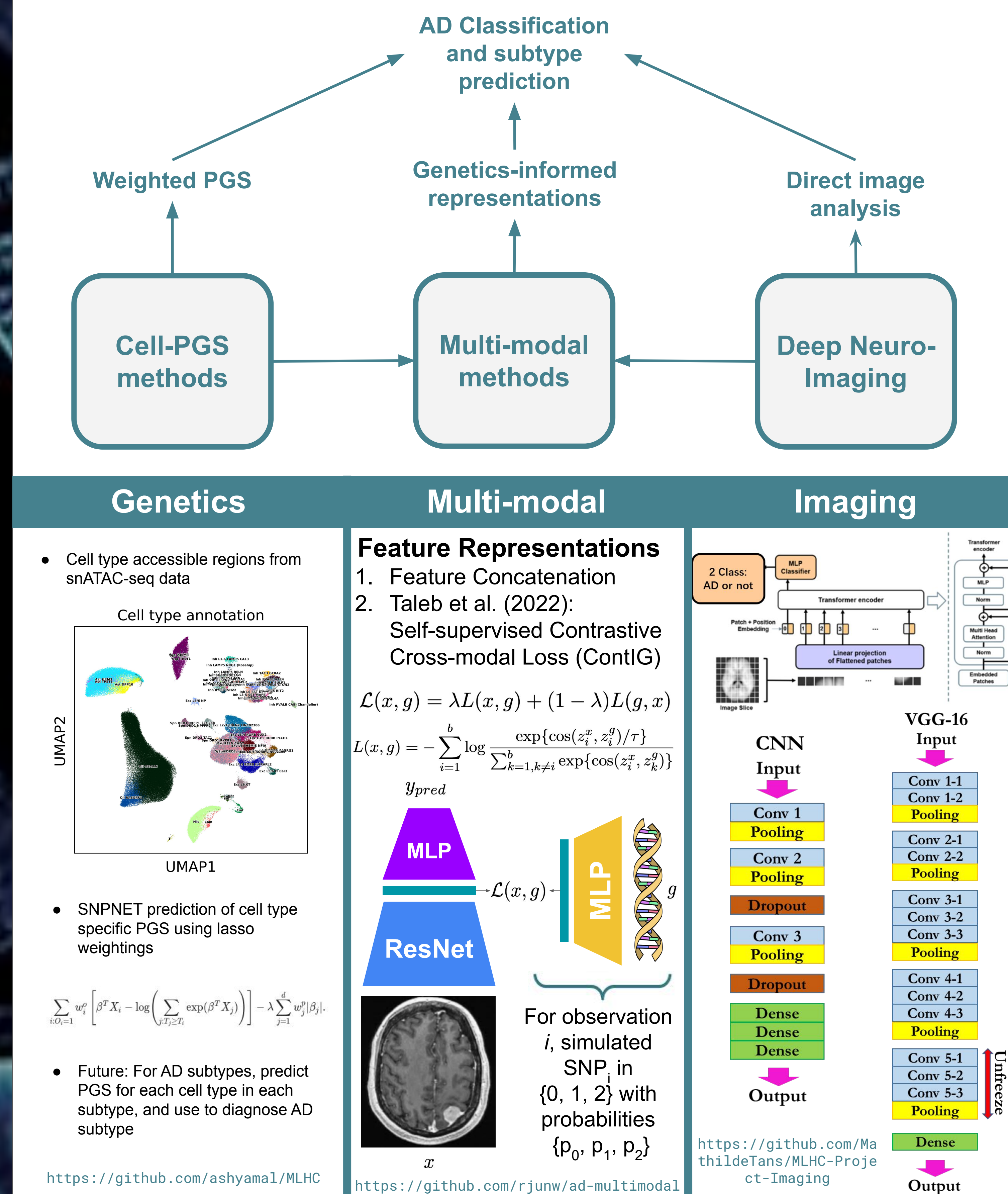
Multiple linear regression model

$$Y = \alpha_0 \vec{1} + X_g^* \alpha_g + W \beta_g + \varepsilon_g$$

Phenotype Intercept Principal Components Covariates Covariate Effect Residuals

- Gene-sets based on an AD transcriptional hallmark model were used during MAGMA gene analysis.
- Transcriptional subtype 14 had the lowest p-value

## Proposed Methodology



## Brain MRI Image Analysis

**Architectures:**

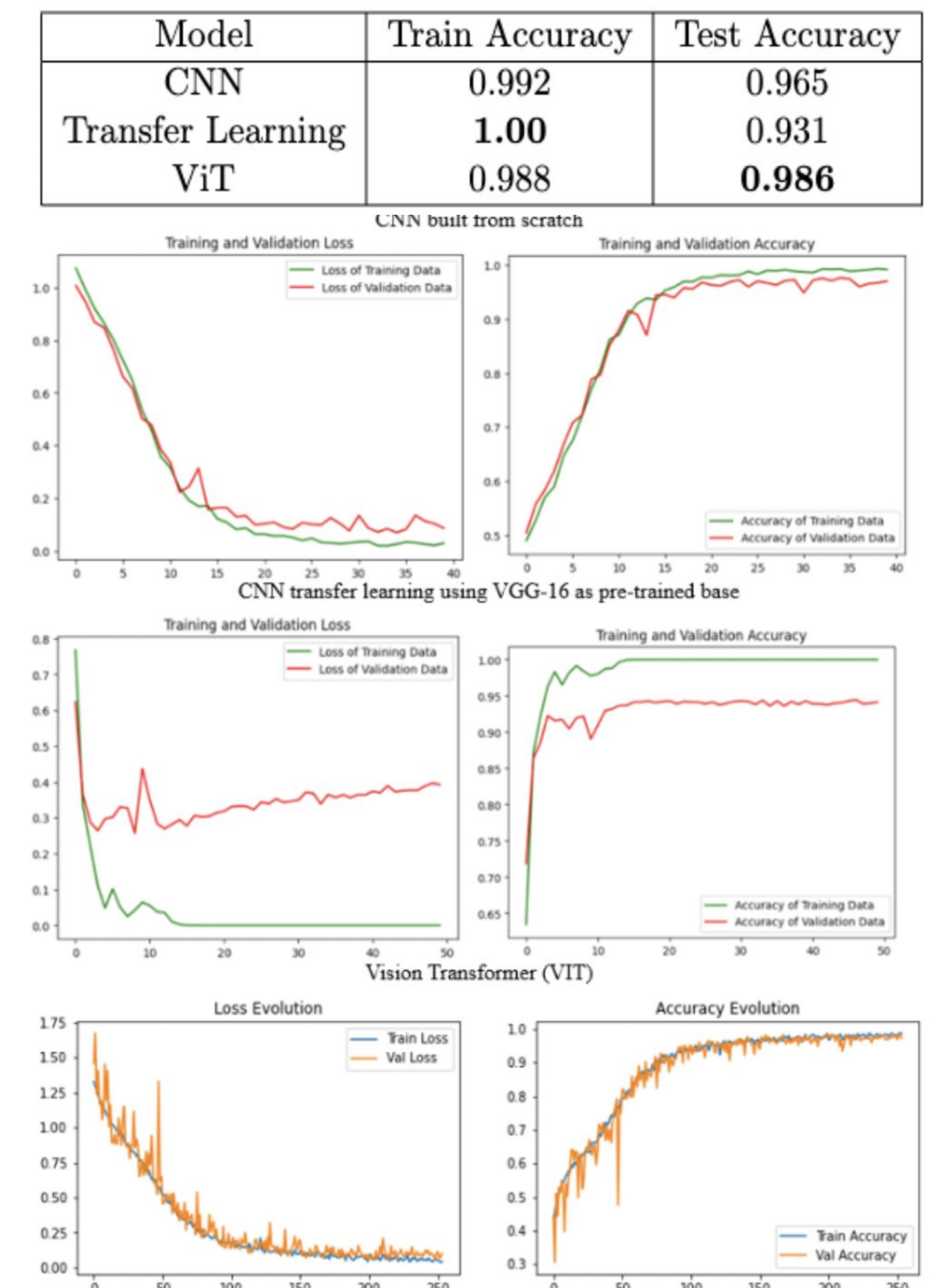
1. **CNN from scratch**
2. **Transfer Learning**
  - Fine-tuned VGG16 AD classifier

1. **Vision Transformer**
  - Applied the ViT model vit\_b32
  - Dense layers, batch normalization layers, and dropout layers were included for image classification

**Performances:**

Vision transformers are the **best performing** models for AD classification

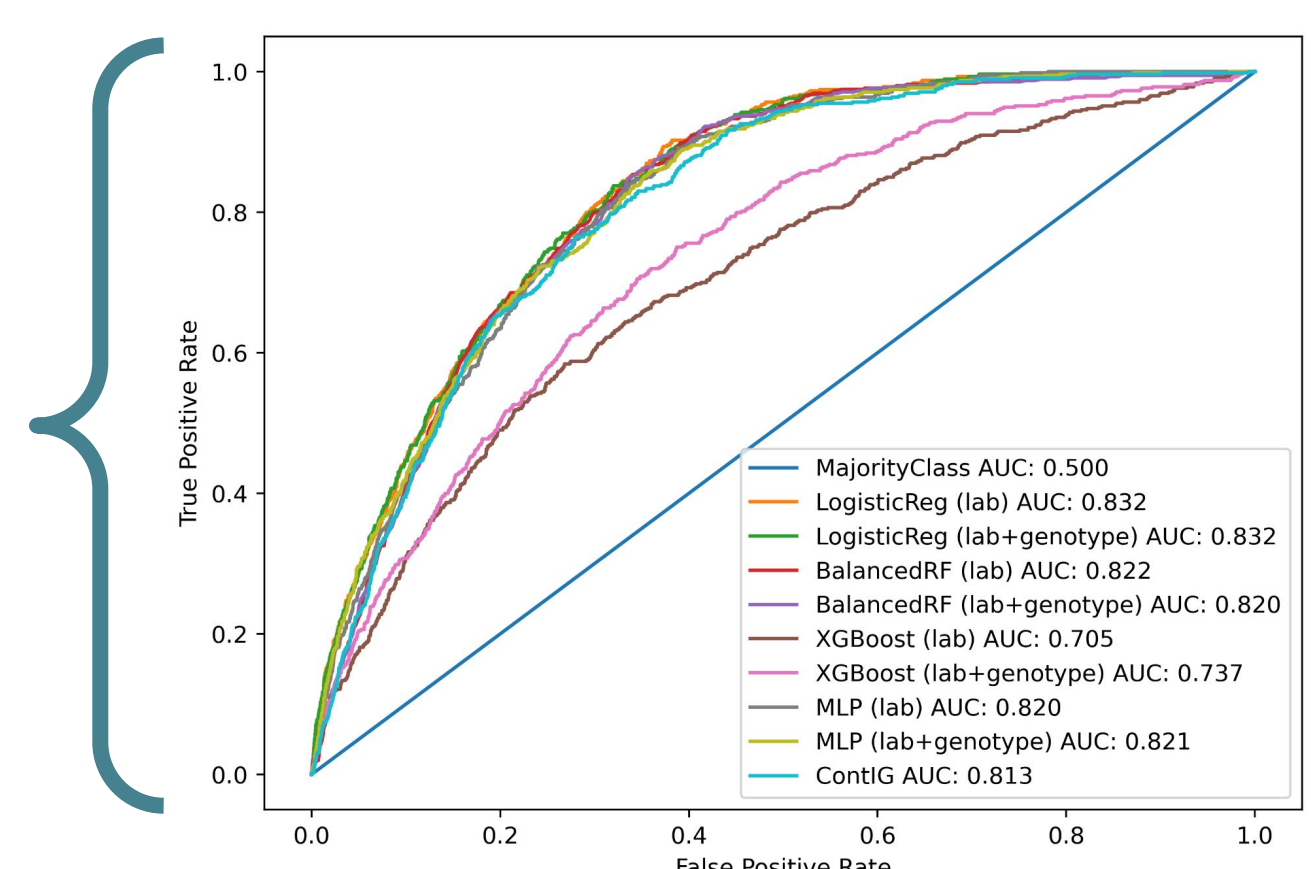
- Basic CNNs are a **close second**
- Transfer learning **quickly overfits**



## Multi-modal Experimental Results

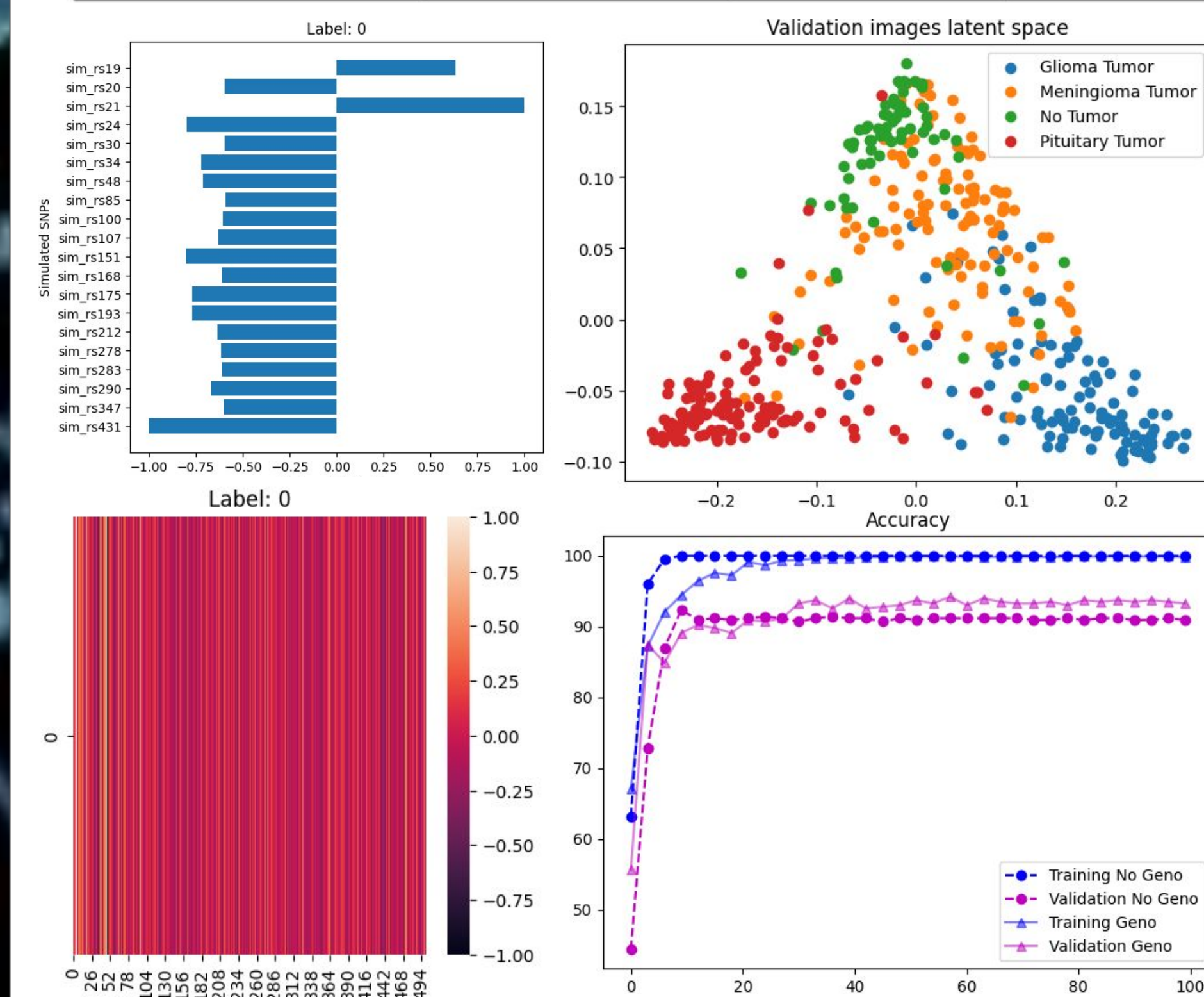
**Clinical, demographic, & genetic modalities**

- Genotype PCs **do not** significantly improve performance
- Deep learning and ContIG pre-training **do not** show significant improvement with these modalities



**Simulated image-genetic modalities**

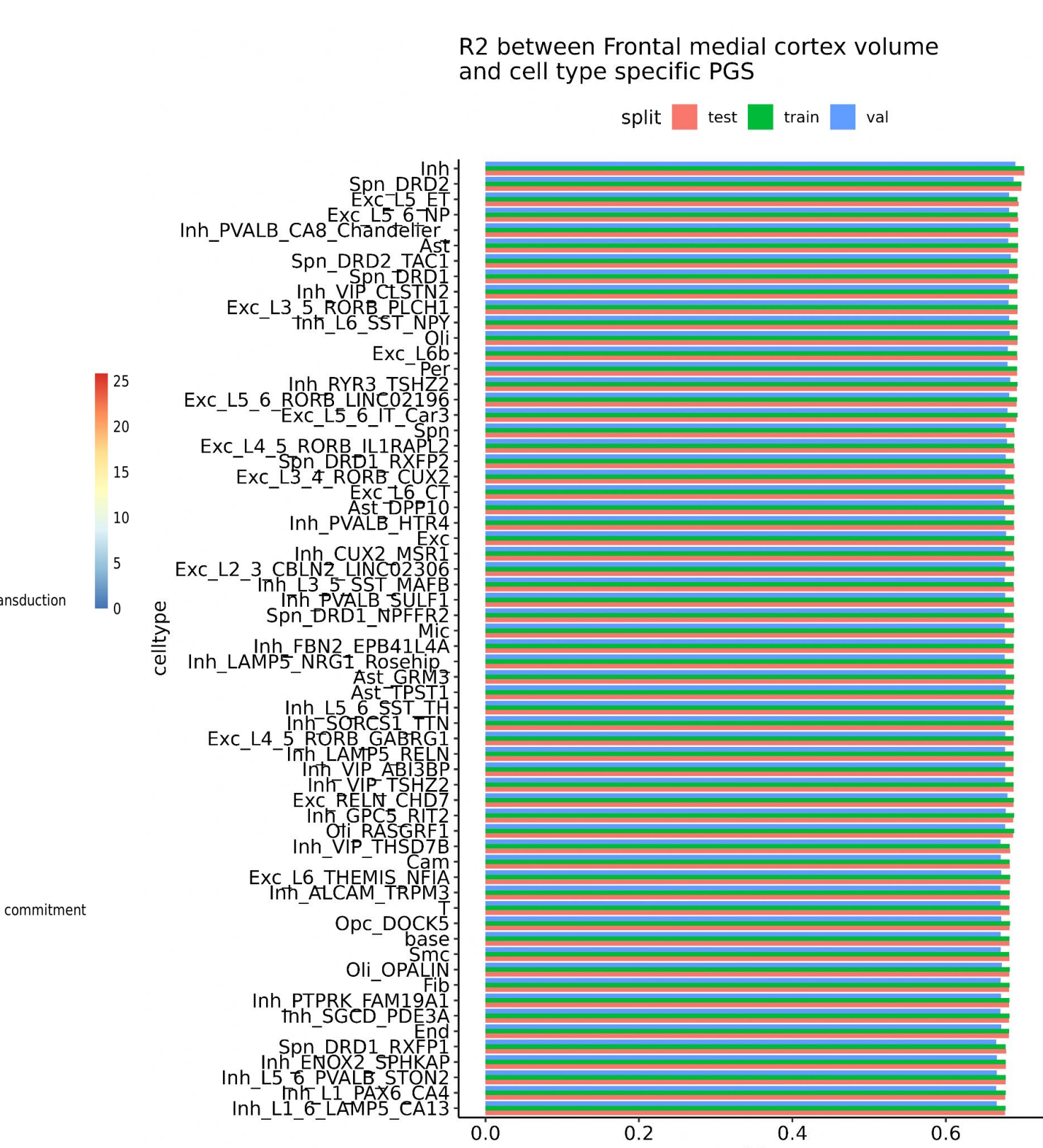
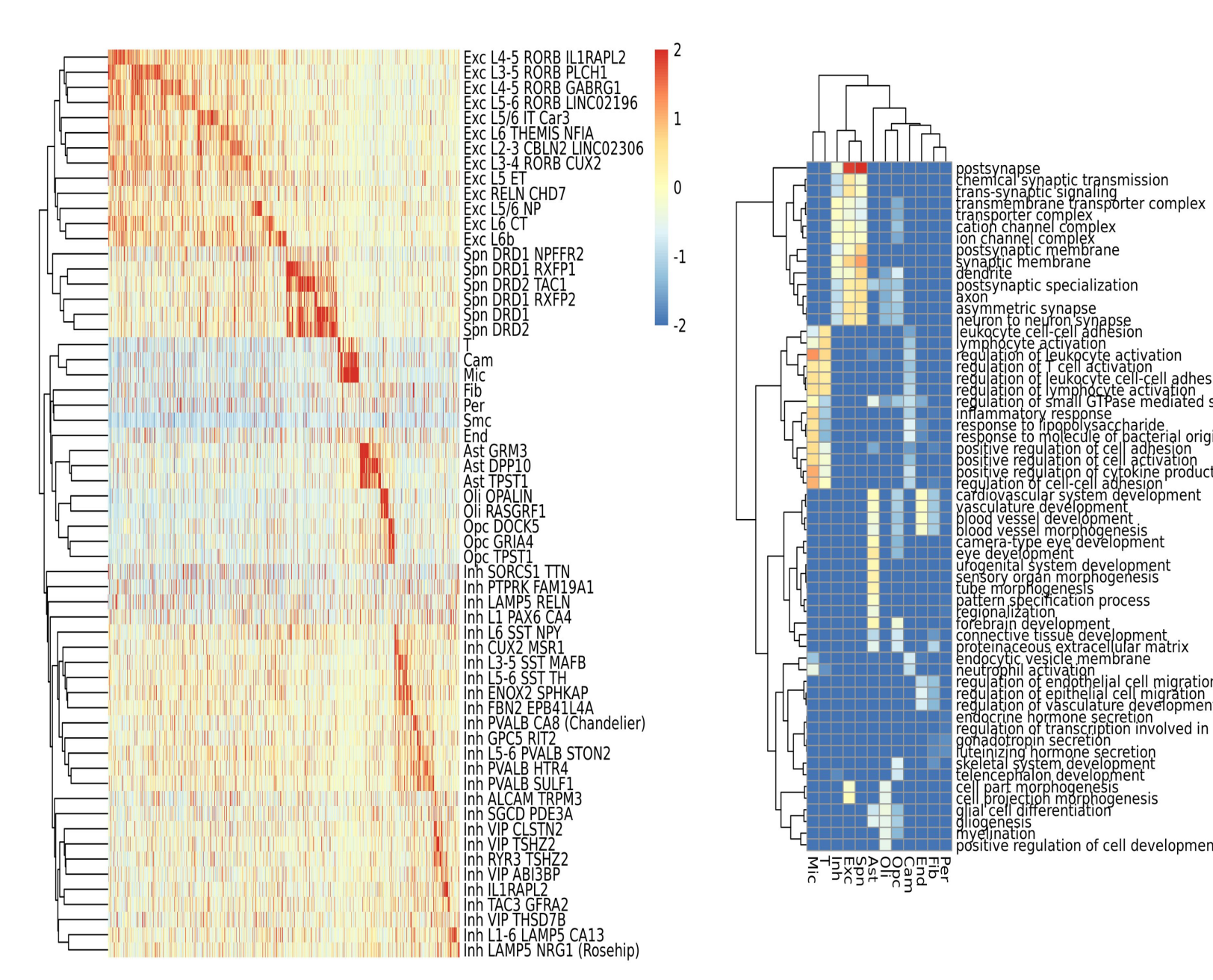
Model	Overall ACC	$y_i = 0$ TPR	$y_i = 1$ TPR	$y_i = 2$ TPR	$y_i = 3$ TPR
ResNet Base	0.887	0.870	0.833	0.878	0.967
ContIG ResNet	0.931	0.916	0.940	0.857	0.967



- ContIG pre-training learns **genetic-informed** image embeddings
- Fine-tuning image encoder results in **better** performance
- Pipeline adaptable to large multi-modal datasets (e.g. **UK Biobank**) and fine-tunable for **AD subtype classification**

## Cell type specific PGS

ATAC-seq peak set classifies genome into compartments with different molecular functions, with sharing more along similar cell types



- Enhancers were much more implicated using LDSC for blood-blood traits, We trained using PBMC (mononuclear cell) enhancers (below)
- In initial testing, we found that even in the first 50 training runs, the cell type specific PGS out-performed the un-weighted PGS.(right)
- Cell type specific PGS have high R2 in inhibitory neurons and deep layer excitatory neurons. (left)

Cell type specific PGS are feasible, even on blood traits in the first 50 training runs

Correlation of different cell type SNP weightings for PGS (WBC count, PBMC)

