

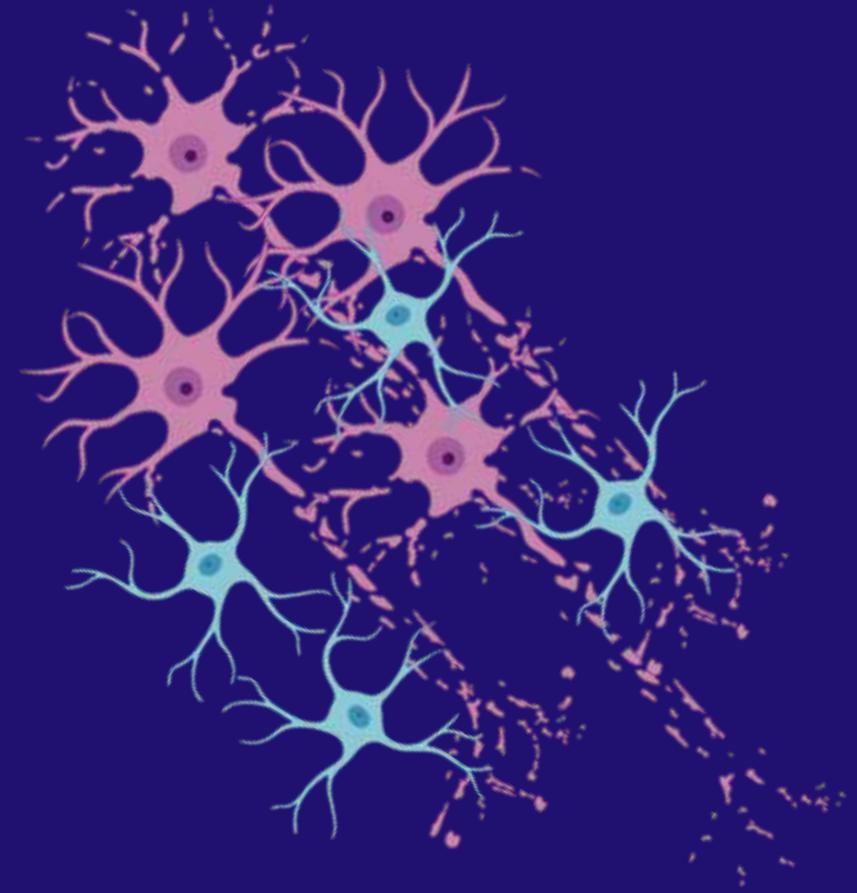


University of Pisa  
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Artificial Intelligence and Data Engineering

# CogniPredictAD

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Project for Data Mining and Machine Learning



# Table of Contents

I Motivations and Clinical Background

II Dataset ADNI

III Preprocessing

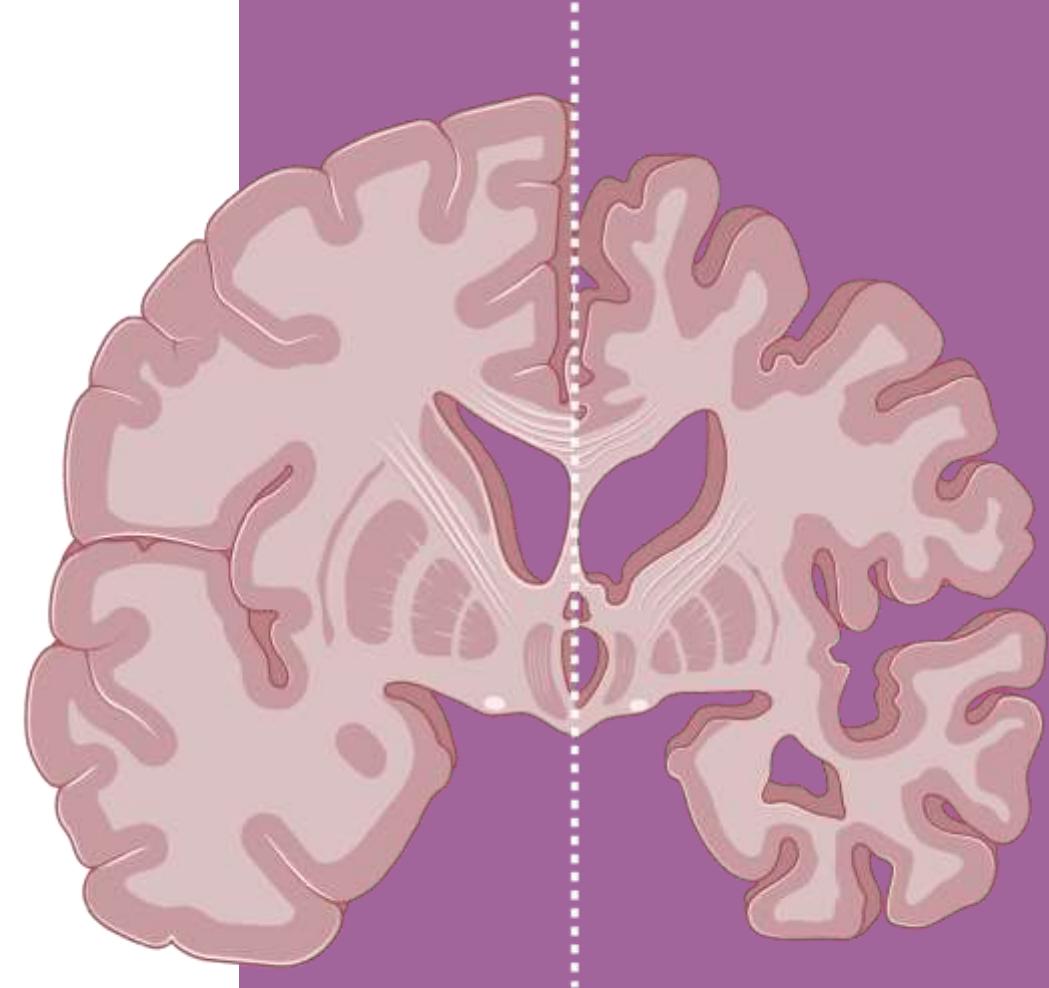
IV Classification & Results

V Application & Conclusions

# Motivations and Clinical Background

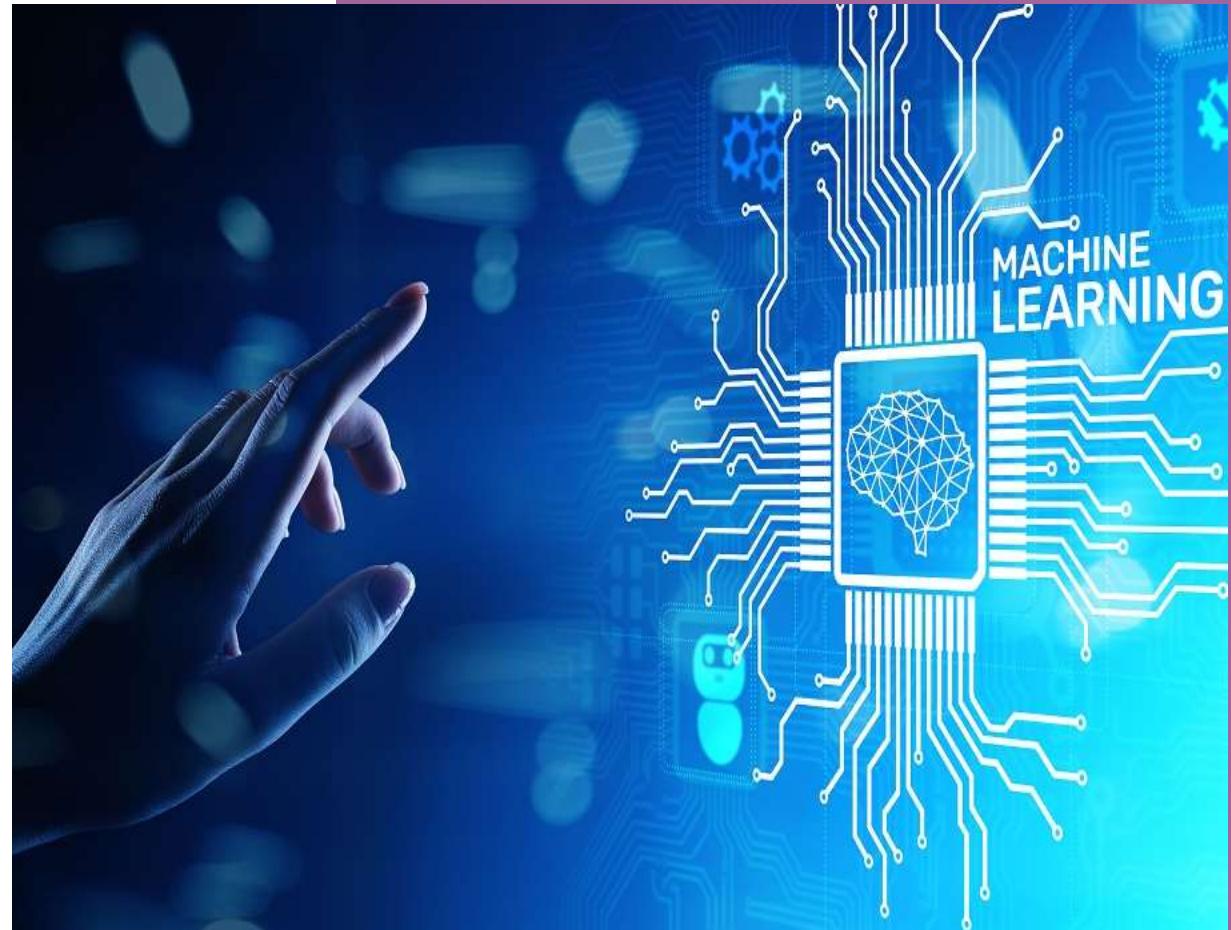
# Alzheimer's Disease

- **Alzheimer's Disease** is a progressive neurodegenerative disease that affects memory, cognitive function, and daily living skills. It is the most common form of dementia and has no definitive cure.
- It primarily affects the **elderly** and its incidence is increasing as the population ages. It has a **significant social, family, and economic impact**, requiring **long-term care**.
- **Early diagnosis is difficult but crucial** for slowing the progression of the disease and improving quality of life.



# So why Machine Learning?

- Machine Learning models could support doctors in diagnosis by analyzing large amounts of data, identifying hidden patterns, and improving accuracy and speed.
- Alzheimer's disease is multifactorial. Machine Learning helps integrate complex and nonlinear information.
- They help personalize clinical pathways and identify at-risk patients before the most serious symptoms appear.



# Dataset ADNI

## ADNIMERGE.csv

- The **Alzheimer's Disease Neuroimaging Initiative (ADNI)** is a longitudinal, multicenter, observational study involving over 60 clinical sites in the United States and Canada.
- Launched in **2004** and divided into the following phases: **ADNI1** (2004–2009), **ADNIGO** (2009–2010), **ADNI2** (2011–2016), and **ADNI3** (2016–2022).
- **ADNI4**, the most recent phase of the study, was initiated in **2022**.
- **16,420 rows x 116 columns**. The columns are divided into current visit columns and baseline visit columns (with the "\_bl" suffix) to aid quick comparison.
- Obtained from the **fusion of clinical data** collected during phases ADNI1, ADNIGO, ADNI2 and ADNI3. Unfortunately, the ADNI4 data has not yet been merged.
- The dataset contains **numerous visits** from different patients, with **associated diagnoses**.

## Features of ADNIMERGE.csv

- **Diagnosis (target)**: DX, DX\_bl
- **Administrative**: RID, COLPROT, ORIGPROT, PTID, SITE, VISCODE, update\_stamp
- **Timestamps**: EXAMDATE
- **Demographics**: AGE, PTGENDER, PTEDUCAT, PTETHCAT, PTRACCAT, PTMARRY, APOE4
- **PET Imaging**: FDG, PIB, AV45, FBB
- **CSF Biomarkers**: ABETA, TAU, PTAU
- **Clinical Scores**: CDRSB, ADAS11, ADAS13, ADASQ4, MMSE, RAVLT\_immediate, RAVLT\_learning, RAVLT\_forgetting, RAVLT\_perc\_forgetting, LDELTOTAL, DIGITSCOR, TRABSCOR, FAQ, MOCA
- **ECog (self-report)**: EcogPtMem, EcogPtLang, EcogPtVisspat, EcogPtPlan, EcogPtOrgan, EcogPtDivatt, EcogPtTotal
- **ECog (informant-report)**: EcogSPMem, EcogSPLang, EcogSPVisspat, EcogSPPlan, EcogSPOrgan, EcogSPDivatt, EcogSPTotal
- **MRI Imaging**: FLDSTRENG, FSVERSION, IMAGEUID, Ventricles, Hippocampus, WholeBrain, Entorhinal, Fusiform, MidTemp, ICV
- **Composite Scores**: mPACCdigit, mPACCtrailsB
- **Baseline Values**: all variables with the suffix \_bl
- **Time Measures**: Years\_bl, Month\_bl, Month, M

## Strengths and Weaknesses of ADNIMERGE.csv

### Strengths

- It groups demographic, cognitive, imaging (MRI, PET) and CSF biomarker data into a **single large dataset, useful for integrated analyses**.
- **Rigorous post-data acquisition** correction procedures, which reduce technical variability and increase the statistical reliability of the features;
- One of the most **widely used datasets** in Alzheimer's disease research, with well-documented protocols and support for harmonization and comparative studies.

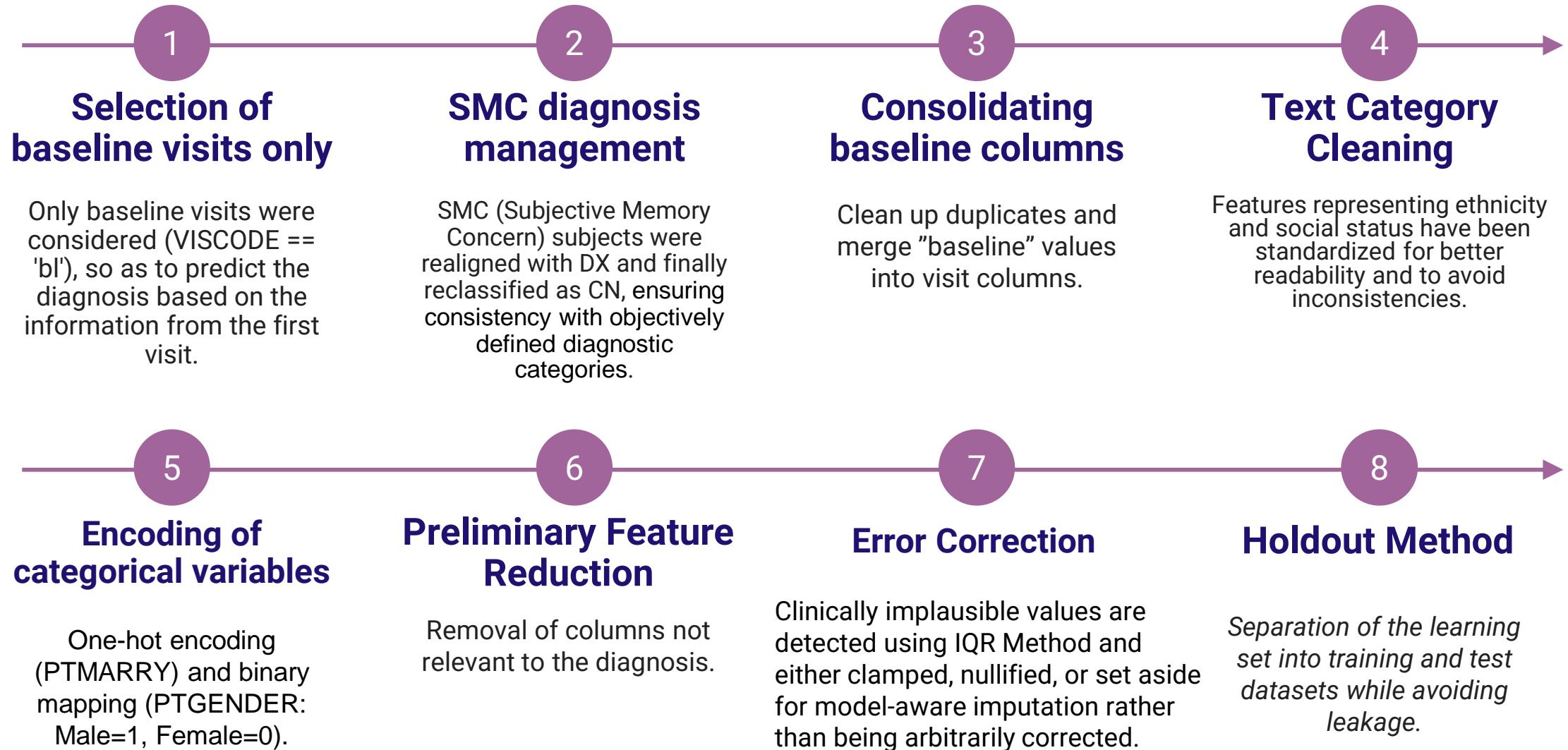
### Weaknesses

- Many variables have **numerous missing values**, and the missingness varies depending on the diagnosis or phase of the visit, so it is **not Missing Completely at Random**.
- Participants are predominantly **white, highly educated, motivated, and married**, reducing their **representativeness** of the general population.
- Many features are **highly correlated or duplicated**, increasing computational complexity and the risk of **overfitting** in ML models.

## Data Preparation

The **Data Preparation** involves building the **learning set** from the original ADNIMERGE table file. This phase concentrates on converting the visit-centric csv file into a single-row-per-subject, analysis-ready baseline cohort and on producing compact, multimodal feature tables for modelling.

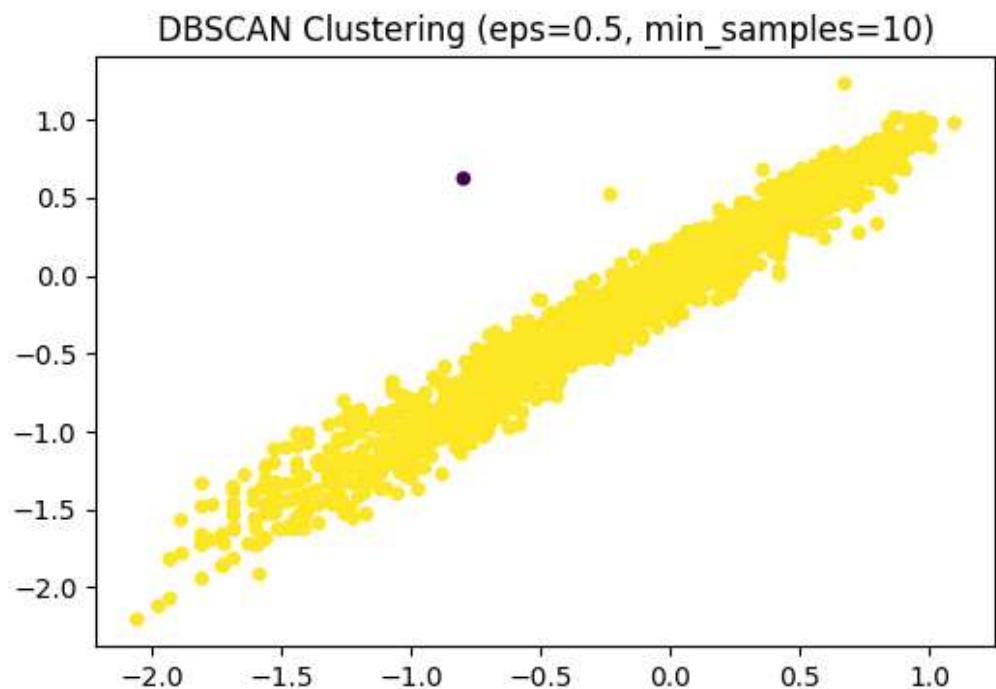
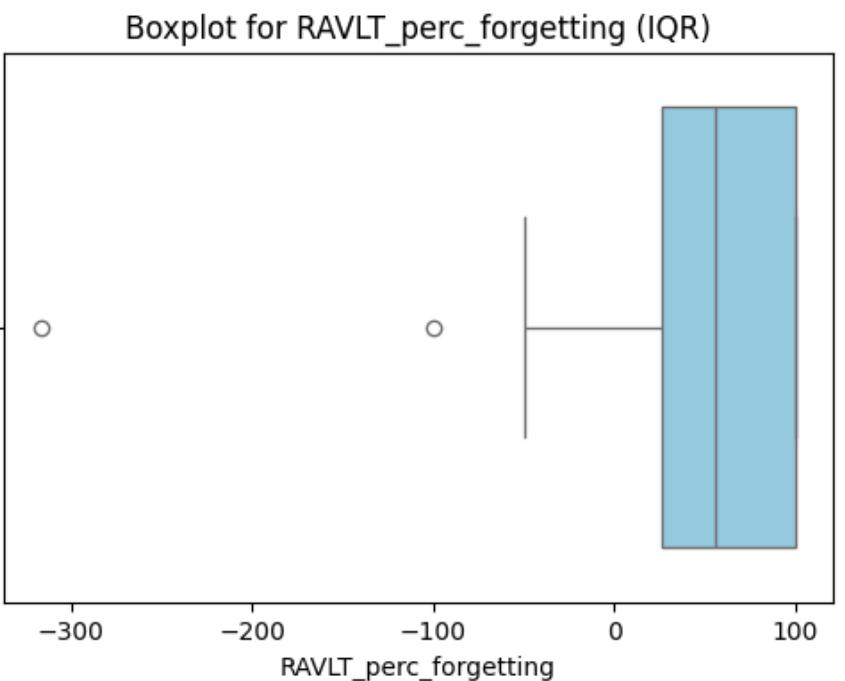
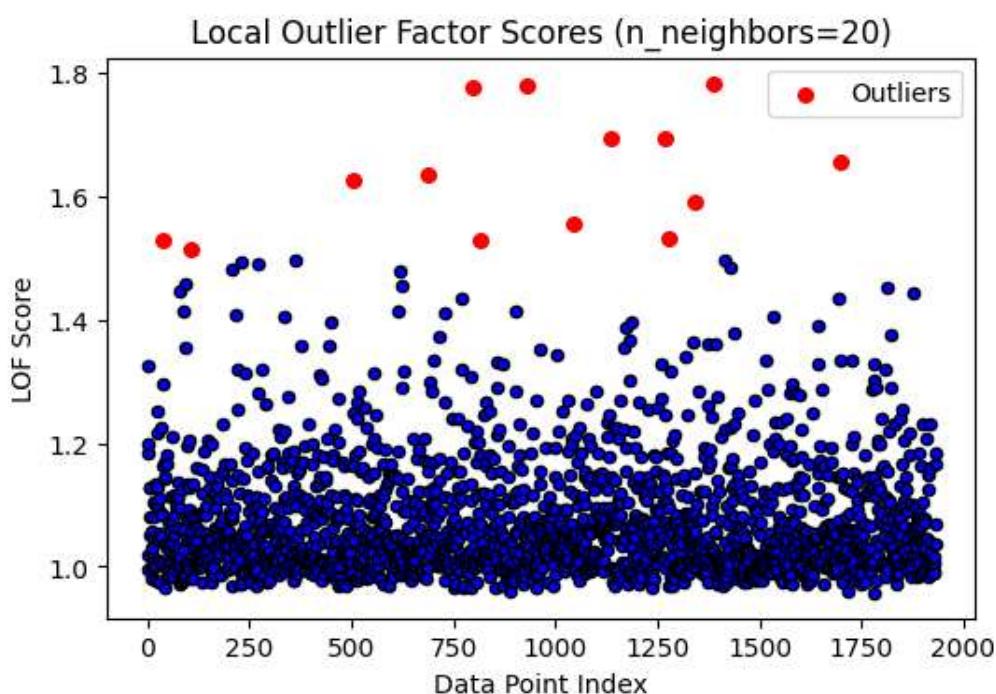
# Data Preparation



## II Dataset ADNI

# Outlier Detection

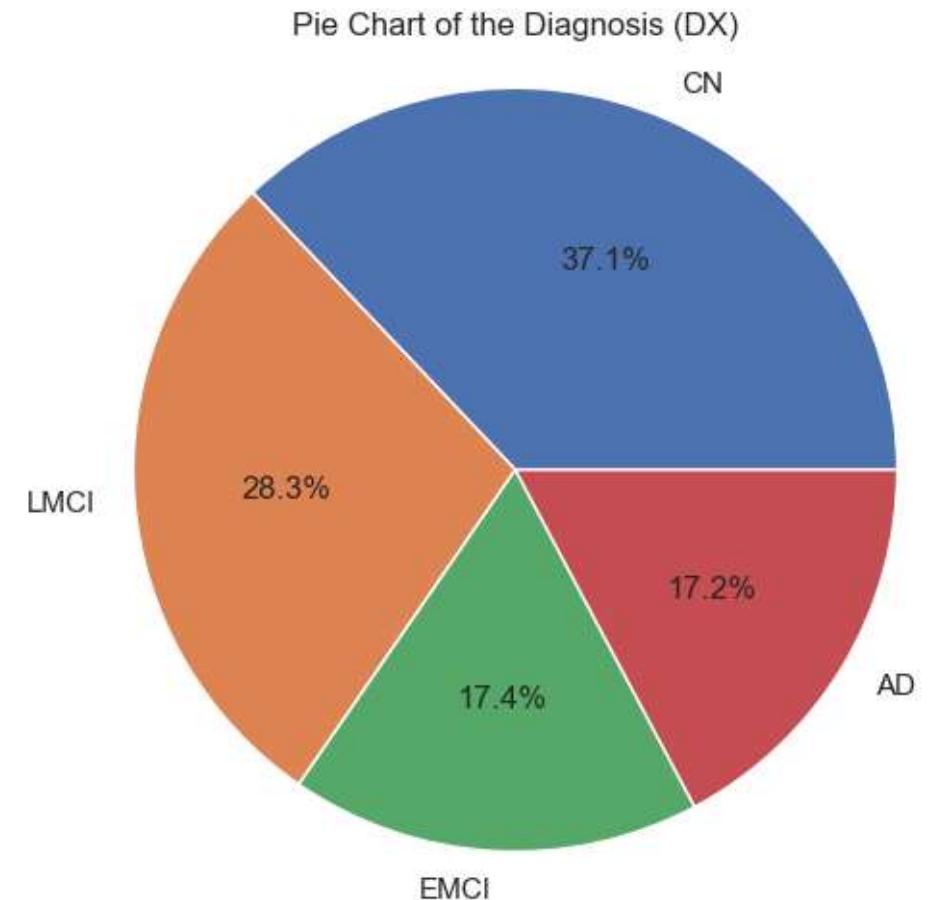
- **Univariate Analysis:** use *IQR* for each column to find outliers and *to remove problematic outliers*.
- **Multivariate Analysis:** create groups of columns (Cognitive Score, MRI/ICV, CSF/ABETA), apply *LOF* on the normalized data (RobustScaler) to find outliers and *to analyze them*.



### III Preprocessing

## Multiclass Problem: DX and DX\_bl

- DX\_bl has 5 possible values:
  - CN: Cognitively Normal
  - SMC: Subjective Memory Concern
  - EMCI: Early Mild Cognitive Impairment
  - LMCI: Late Mild Cognitive Impairment
  - AD: Alzheimer's Disease
- DX has 3 possible values:
  - CN: Cognitively Normal
  - MCI: Mild Cognitive Impairment
  - Dementia: Alzheimer's Disease
- **We create a new DX as our target with this 4 classes:**
  - CN: Cognitively Normal
  - EMCI: Early Mild Cognitive Impairment
  - LMCI: Late Mild Cognitive Impairment
  - AD: Alzheimer's Disease



# Preprocessing

## Data Preprocessing

This *phase* involves *transforming* the *dataset* to make it *suitable* for *Machine Learning*. These operations would risk *data leakage* if evaluated on the entire dataset. Therefore, they are performed on the *train set*, and the *test set* is modified accordingly to make it consistent, before evaluating the models built on the train. It is divided into *Data Cleaning*, *Data Transformation*, *Data Reduction* and eventually *Hybrid Sampling*.

## Data Cleaning

- **Handling missing values:**  
Identifying percentages of missing values and using KNN Imputer for continuous variables.
- **Numeric Value Conversion:**  
Converted nearly all cognitive scales and age from float to int, correcting approximations to imputation or format errors.

## Data Transformation

- **Creation of new CSF metrics:**  
TAU/ABETA and PTAU/ABETA ratios more predictive than single measures according to the literature.
- **MRI normalization to ICV:**  
Necessary to correct for differences due to gender and cranial size.

### III Preprocessing

## Data Reduction

- **Biomarker raw values replaced by ratios:**  $TAU$ ,  $PTAU$ ,  $ABETA$  are replaced by  $TAU/ABETA$  and  $PTAU/ABETA$ ;
- **MRI are normalized by ICV:** *Ventricles*, *Hippocampus*, *Entorhinal*, *Fusiform*, *MidTemp*, *WholeBrain*, *ICV* are replaced by  $Ventricles/ICV$ ,  $Hippocampus/ICV$ ,  $Entorhinal/ICV$ ,  $Fusiform/ICV$ ,  $MidTemp/ICV$ , and  $WholeBrain/ICV$ ;
- **Removal of redundant features:** *ADAS11*, *ADASQ4*, *EcogPtTotal*, *EcogSPTotal*, and *mPACCtrailsB* were removed because they had a high correlation with other features and their informative value was low compared to correlated features.
- **Outcome of reduction:** The dataset is streamlined to key demographic, cognitive, CSF, and MRI features, minimizing noise and redundancy while preserving diagnostic information. This focused baseline table enhances model interpretability, prevents data leakage, and provides a robust foundation for multiclass classification.



## Hybrid Sampling

To overcome class imbalance, we used a combination of:

- **Random Under-Sampling (RUS)** to reduce the number of instances in the majority classes (CN and LMCI), preventing the dataset from becoming excessively biased toward synthetic examples;
- **Synthetic Minority Over-Sampling Technique for Nominal and Continuous features (SMOTENC)** to generate new synthetic examples of the minority classes (EMCI and AD).

We use another pipeline to evaluate performance on the dataset with and without sampling.

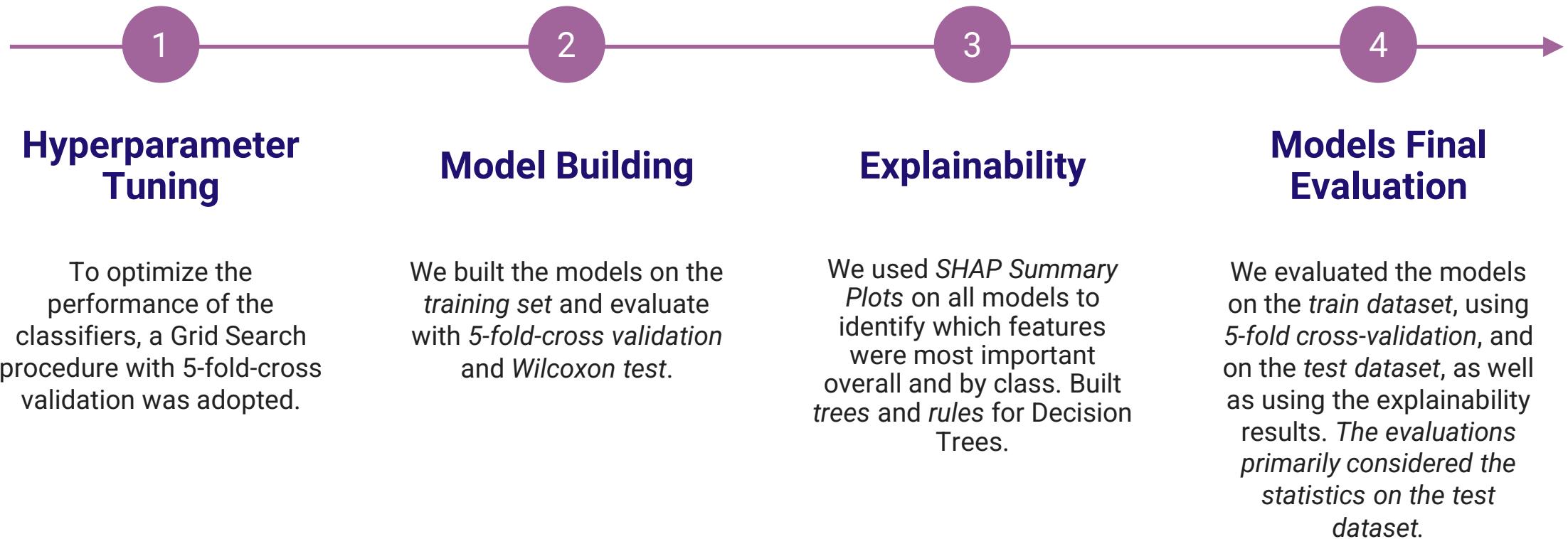
# Classification & Results

## Model Selection

We selected the following classification models:

- **Decision Tree**
- **Random Forest**
- **Extra Trees**
- **Adaptive Boosting**
- **Multinomial Logistic Regression**

# Model Construction



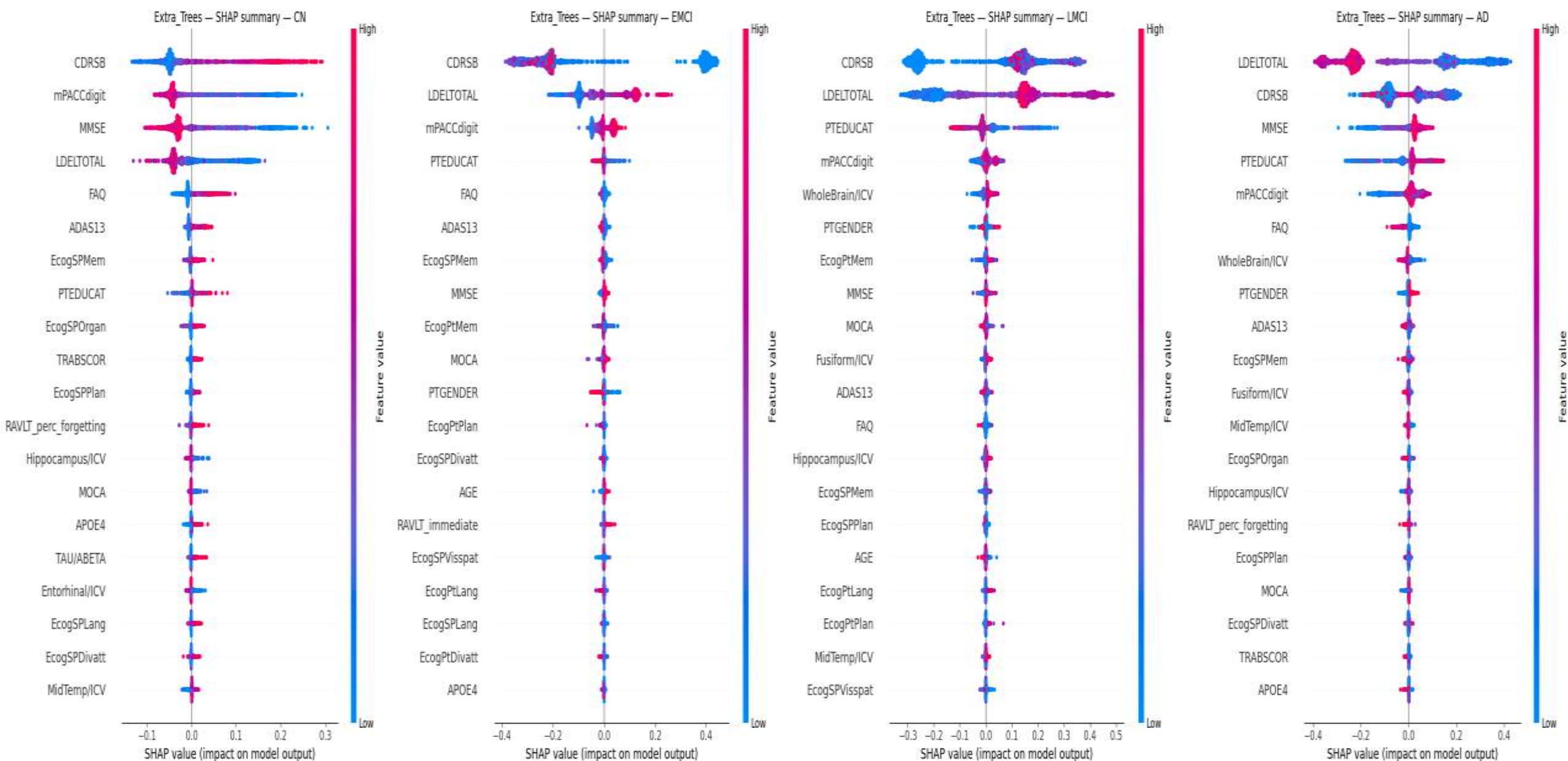
# Results (on Test set)

Model	F1 Score (macro)	Accuracy	Balanced Accuracy	Precision (weighted)	Recall (weighted)	F1 Score (weighted)	ROC AUC (macro)
Extra_Trees	0.9376	0.9442	0.9408	0.9448	0.9442	0.9443	0.9867
Extra_Trees_Sampled	0.9359	0.9421	0.9411	0.9435	0.9421	0.9425	0.9890
Random_Forest	0.9301	0.9380	0.9341	0.9387	0.9380	0.9381	0.9886
Adaptive_Boosting	0.9285	0.9360	0.9347	0.9378	0.9360	0.9363	0.9878
Random_Forest_Sampled	0.9271	0.9339	0.9358	0.9367	0.9339	0.9344	0.9863
Adaptive_Boosting_Sampled	0.9262	0.9339	0.9329	0.9361	0.9339	0.9343	0.9890
Decision_Tree_Sampled	0.9131	0.9236	0.9178	0.9244	0.9236	0.9235	0.9804
Decision_Tree	0.8934	0.9050	0.9026	0.9096	0.9050	0.9057	0.9824
Multinomial_Logistic_Regression	0.8700	0.8843	0.8816	0.8893	0.8843	0.8843	0.9825
Multinomial_Logistic_Regression_Sampled	0.8677	0.8822	0.8754	0.8851	0.8822	0.8826	0.9827

## The problem with CDRSB, LDELTOTAL, and mPACCdigit

- The **CDRSB, LDELTOTAL, and mPACCdigit** cognitive scores show significantly higher predictive power than other variables.
- This **can improve model accuracy**, but creates the **risk of feature dominance**, where a few variables excessively influence predictions.
- This imbalance can cause **local overfitting**: excellent performance on ADNI but possible loss of accuracy on external or more heterogeneous populations.
- It is not possible to definitively determine whether these variables **are simply very strong predictors of Alzheimer's disease diagnosis**.
- We divided the pipeline into datasets **with** CDRSB, LDELTOTAL and mPACCdigit and **without** CDRSB, LDELTOTAL and mPACCdigit.

## IV Classification & Results



# Without CDRSB, LDELTOTAL and mPACCdigit

Model	F1 Score (macro)	Accuracy	Balanced Accuracy	Precision (weighted)	Recall (weighted)	F1 Score (weighted)	ROC AUC (macro)
Adaptive_Boosting	0.7303	0.7459	0.7327	0.7456	0.7459	0.7437	0.9037
Adaptive_Boosting_Sampled	0.7112	0.7293	0.7157	0.7316	0.7293	0.7277	0.9001
Random_Forest	0.7061	0.7252	0.7052	0.7256	0.7252	0.7245	0.9022
Random_Forest_Sampled	0.7035	0.7190	0.7050	0.7251	0.7190	0.7208	0.9041
Extra_Trees_Sampled	0.7011	0.7211	0.7075	0.7258	0.7211	0.7202	0.9003
Extra_Trees	0.6998	0.7293	0.6952	0.7215	0.7293	0.7238	0.9105
Multinomial_Logistic_Regression _Sampled	0.6829	0.7066	0.6933	0.7135	0.7066	0.7063	0.8921
Multinomial_Logistic_Regression	0.6768	0.7004	0.6882	0.7055	0.7004	0.6996	0.8952
Decision_Tree	0.6603	0.6632	0.6622	0.6960	0.6632	0.6736	0.8467
Decision_Tree_Sampled	0.6482	0.6508	0.6543	0.6990	0.6508	0.6626	0.8445

# Model Choosing

- **With CDRSB, LDELTOTAL, and mPACCdigit:**  
Extra\_Trees was chosen as the main model and Decision\_Tree\_Sampled as the XAI model, due to the best metrics (Balanced Accuracy, F1, ROC-AUC).
- **Without CDRSB, LDELTOTAL, and mPACCdigit:**  
Adaptive\_Boosting was chosen as the main model and Decision\_Tree as the XAI, based on testing performance.
- The saved models are **Model.pkl** (Extra\_Trees), **XAIModel.pkl** (Decision\_Tree\_Sampled), **AltModel.pkl** (alternative/Adaptive\_Boosting), and **AltXAIModel.pkl** (alternative/Decision\_Tree).

# Applications & Conclusions

## V Applications & Conclusions

# APP

**CogniPredictAD: Medical Classifier for Alzheimer**

**CogniPredictAD**

Appearance mode: Light

Please start to continue

Start

**Model selection**

- Model.pkl
- Model2.pkl
- XAIModel
- XAIModel2

**Model descriptions:**

**Model1.pkl:**  
This model is based on an Extra Tree classifier, which builds many decision trees using randomized feature splits to improve robustness and reduce overfitting. It draws on multiple clinical and cognitive measures, including CRIB2, CDR.TOTAL, and mPACCdigit, to evaluate the patient's cognitive status. Its primary strength is the ability to capture complex, non-linear relationships in the data, though the internal decision process can be difficult to interpret.

**XAIModel.pkl:**  
This model uses a Decision Tree, a simpler method where predictions are made by following a clear series of if-then rules based on the patient's test scores. It includes CRIB2, LDEL.TOTAL, and mPACCdigit in its analysis. Because of its structure, the model is easier to explain, doctors can easily verify which variables and thresholds lead to the final diagnosis. Model1.pkl is less accurate than more complex models, it provides valuable transparency for clinical decision-making.

**Model2.pkl:**  
This model uses Adaptive Boosting (AdaBoost), an ensemble technique that combines many weak learners (typically shallow decision trees), by iteratively reweighting the training samples to focus on harder cases. It analyzes several clinical and cognitive features but excludes CRIB2, LDEL.TOTAL, and mPACCdigit from the predictor, so it may be less accurate.

**XAIModel2.pkl:**  
This model is also based on a Decision Tree, but it makes predictions without using CRIB2, LDEL.TOTAL, and mPACCdigit. Like XAIModel1, it follows a transparent rule-based structure, making its decisions easy to trace and understand. The absence of those three variables makes it useful in clinical contexts where those specific tests are not available, while still allowing doctors to follow the diagnostic reasoning step-by-step.

Select a model and then click "Load Model" to continue.

**Load Model**   **Reset**   **Exit**

Model not loaded yet.

**Inputs for Model1.pkl**

CRIB2	0	DogpMem	1.2
MMS	29	DogpPlaq	0.2
CDR2B	0.5	DogpTauquel	1.2
ADAS13	8	DogpTaupe	1.2
LDEL.TOTAL	12	DogpTauOrg	0.2
FAG	0	DogpTauVert	1.2
MoCA	28	FDG	1.25
TRACODR	76	PTAU/ABeta	0.04
RAVLT_immediate	35	Hippocampus/IV	0.004
RAVLT_learning	8	Entorhinal/IV	0.001
RAVLT_last_repeating	5.0	Frontal/IV	0.001
mPACCdigit	7.2	MultiTemp/IV	0.000
DogpMem	1.1	Verbalfluency/IV	0.018
DogpLang	1.2	Visualobject/IV	0.64
DogpPrincip	1.3		

Predict   Back to Selection

0 [Cognitively Normal (CN)]

Correct Diagnosis   Current Diagnosis   LMCI   Home Care

Model Model1.pkl predicted: 0 (Cognitively Normal (CN))

**Inputs for Model2.pkl**

AGE	76	DogpMem	3.1
PTGENDER	Female	DogpPlaq	3.0
PTEDUCAT	12	DogpTauVert	2.9
APSIQ	2	DogpTaupe	3.4
MMS	19	DogpTauOrg	3.2
CDR2B	6.0	DogpTauSel	3.3
ADAS13	36	DogpTauRes	3.1
LDEL.TOTAL	2	DogpTauOrg	3.0
FAG	12	DogpTauSel	3.2
MoCA	15	FDG	0.98
TRACODR	210	PTAU/ABeta	0.72
RAVLT_immediate	12	Hippocampus/IV	0.022
RAVLT_learning	3	Entorhinal/IV	0.009
RAVLT_last_repeating	7.0	Frontal/IV	0.001

Data used to RAVLT\_immediate (positive diagnosis)

Predict   Back to Selection

1 [Alzheimer's Disease (AD)]

Correct Diagnosis   Current Diagnosis   LMCI   Home Care

Model Model2.pkl predicted: 1 (Alzheimer's Disease (AD))

V Applications & Conclusions

## Conclusions

- **Dataset limitations:** only 2,419 patients, many missing values (CSF, PET), strong dependence on three cognitive scores. Risk of local overfitting, dataset bias, and imputations increasing noise. External validation required.
- **Model Performance:** The models perform well overall, especially *Model.pkl*. Furthermore, *XAIModel.pkl* and *AltXAIModel.pkl* are easily interpretable. If the three features prove unpredictable in external validation, *AltModel.pkl* and *AltXAIModel.pkl* can be used instead.
- **State of the Art:** Although it was not possible to make a precise state of the art due to the lack of similar studies, the statistics make it a solid project.
- **Application value:** Useful as a support (screening, risk stratification), but obviously does not replace clinical evaluation.
- **Future developments:** Expand cohorts (ADNI4, external), integrate with similar datasets, and include geographic area as a feature.

# Thanks for your attention!



Brain  
(sagittal cut)



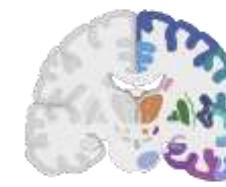
Brain  
(coronal cut)



Brain  
(lateral)



Brain with  
Alzheimer's



Brain with regions  
(coronal cut)



Amyloid-beta plaque



Myelinated  
motor neuron



Degenerating  
motor neuron



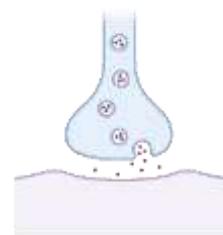
Microglia



Astrocyte



Dynamic line  
neurons



Synaptic cleft