

Alzheimer's diagnostics using PET-Scans and Blood Biomarkers

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Abstract—Alzheimer's disease (AD) is a progressive neurodegenerative disease for which accurate diagnosis is crucial for effective intervention and patient care. In this study, we used positron emission tomography (PET) imaging and blood trajectory biomarker analysis to assess the AD status of patients at different stages of cognitive decline using machine learning models.

PET-scans were pre-processed to facilitate classification and then classified using a VGG19 machine learning model. Blood biomarker features were transformed using Principal Component Analysis (PCA) using a range of machine learning classification algorithms (Support Vector Machine (SVM), Naive Bayes, Logistic Regression, Random Forest Classifier and Gradient Boosting) and then classified using a One vs One classifier. The odds from both models were then combined to produce a final classification result.

Using blood biomarkers, no model could be created that gave reliable predictions, at best achieving an overall accuracy of 57%. PET imaging performed better with an overall accuracy of 72.3%, but still did not provide a reliable result. Using a combined approach, the results improved again to 93.2% accuracy.

The results are discussed regarding limitations and implications for AD diagnostics.

Index Terms—Alzheimer's disease, dementia, PET brain scans, blood biomarkers, ADNI data, VGG19, machine learning, neurological imaging, pre-processing

I. INTRODUCTION

Alzheimer's Disease (AD) is a neurodegenerative disorder that is the leading cause of dementia worldwide, affecting millions of individuals annually [1]. It is characterized by the accumulation of amyloid-beta plaques and tau tangles in the brain, leading to progressive cognitive decline [2]. Despite advancements in medical research, accurate diagnosis of AD—particularly in its early stages—remains a significant challenge, as clinical symptoms often overlap with other forms of cognitive impairment or normal aging [3].

Conventional diagnostic methods often rely on clinical observations, which are subjective and may result in delayed or inaccurate diagnoses. Biomarker-based approaches, including cerebrospinal fluid (CSF) analysis, which many of the biomarkers are detectable in blood as well and positron emission tomography (PET) imaging, offer objective measures of pathological changes associated with AD [4], [5].

Machine learning techniques have emerged as powerful tools for analysing high-dimensional medical data and there is various literature to support such [6], [7]. Using these approaches, it is possible to extract meaningful patterns from imaging and biochemical datasets, enabling more accurate and automated classification of Alzheimer's disease [8]. Both PET imaging and blood biomarker data are significant predictors of cognitive decline [9] and as such have the potential to improve diagnostic accuracy.

II. DATA

A. Data source

All data was taken from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database [10], ADNI is a longitudinal study with the goal to detect AD early and support research in the prevention and treatment of AD. The study has been ongoing since 2004 and has since gone through various phases (ADNI1, ADNIGO, ADNI2, ADNI3, ADNI4).

B. Data Description - Tabular Data

Blood trajectory data were obtained from the FNI-HBC_BLOOD_BIOMARKER_TRAJECTORIES table from all available ADNI phases. 406 participants provided their blood biomarkers in a total of 5774 samples. The various samples were assigned to relevant AD groups (Alzheimer's disease (AD), mild cognitive impairment (MCI), control normal (CN)) using the DXSUM table in ADNI, searching for the most recent entry for each scan.

The result of the Biomarkers stem from various calibration standards, antibody reagents, dynamic measurement ranges, and pre-analytical handling protocols [11]. To mitigate these discrepancies, we standardized biomarker results within each device family, enabling comparability and facilitating downstream analysis.

Aggregating results across device families leaves us with 1231 patient profiles, 72 of which are from participants previously identified as AD, 611 MCI and 548 CN.

The dataset includes various biomarkers such as $A\beta_{42}$, $A\beta_{40}$, Glial Fibrillary Acidic Protein (GFAP), Neurofilament Light Chain (NfL), pTau181, pTau217, and $A\beta_{42}$ to $A\beta_{40}$ Ratio. Substantial evidence supports the relevance of these markers in research and clinical contexts [12]–[14].

C. Data description - imaging data

Positron Emission Tomograph-Scans (PET-Scans) were obtained from all available ADNI phases. 1308 participants have provided 4999 scans using 3 Tracers (fluorodeoxyglucose (FDG), Amyloid and Tau). Scans of each tracer were assigned to relevant AD groups using available Metadata from the PET Image Acquisition category, the distribution of these groups per tracer are as shown in Table 1 below.

TABLE I
NUMBER OF PET-SCANS ACCORDING TO TRACER AND AD-STATUS

AD Group	FDG	Amyloid	Tau
CN	495	1364	787
MCI	771	563	384
AD	313	200	122

The data were provided in DICOM image format (.DICOM) and converted to the Neuroimaging Informatics Technology Initiative open file format (NIfTI, .nii) for easier processing and classification, showing a scan of the subjects' brains in the transverse, coronal and sagittal planes over multiple points in time (as shown in Figure 1 below).

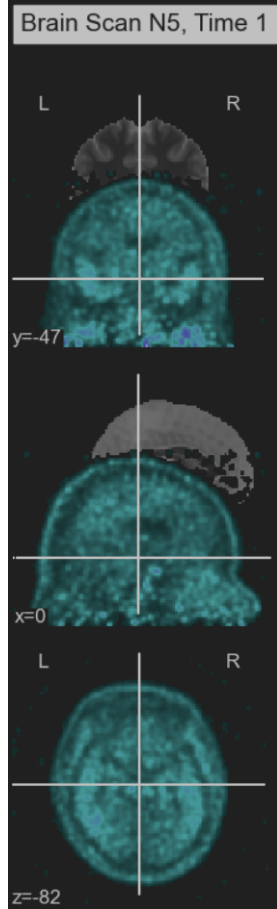


Fig. 1. PET-Imaging example (first point in time of scan)

The PET scans exhibited varying resolutions due to being acquired on different imaging systems over an extended period. Older systems generally produced lower-resolution scans, necessitating resolution adjustments during the pre-processing stage to ensure data consistency and comparability.

D. Data description - imaging data masking

Masks are template NIfTI files which are used for various pre-processing steps (refer to Preparation of imaging data for their application), the masking files used in our use-case scenario are the T1 masks of the ICBM 2009a Nonlinear Symmetric Template from the NeuroImaging & Surgical Technology Lab (NIST) Website of the Montreal Neurological Institute-Hospital (MNI) [15], Figure 2 shows 2 central slices of the MNI Mask.

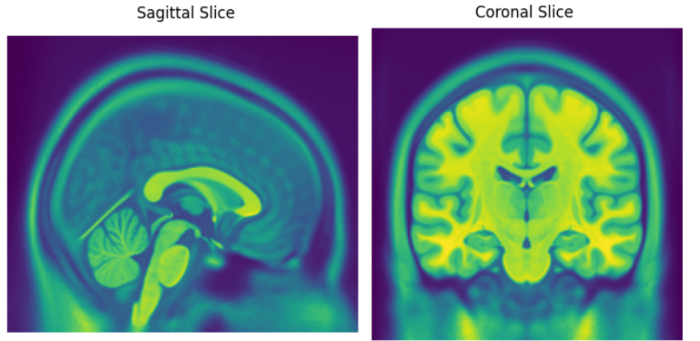


Fig. 2. Central Sagittal and Coronal slice of MNI mask

III. METHOD

A. Preparation of tabular data

Blood biomarker data were standardized using the Z-score standardization formula across device families:

$$z = \frac{x - \mu}{\sigma} \quad (1)$$

Standardized results were aggregated by calculating their mean. While the dataset was largely complete (98.76% overall completeness, with 95.61% completeness in the feature with the least available data), some patient profiles were missing measurements for features only measured by certain device families. Given the small proportion of missing data, imputation was deemed appropriate to ensure a complete dataset for classification. To address the missing values, K-Nearest Neighbors (KNN) imputation was employed, a method supported in literature for medical data imputation [16].

Given the inherent correlations among the blood biomarkers, applying Principal Component Analysis (PCA) is a logical approach to reduce noise and dimensionality, even in datasets with relatively few features, such as the one utilized in this study. This methodology is consistent with its application in similar studies in the literature [17]. As such we applied PCA to our data with 95% of data variance explained.

The dataset was partitioned into an 80/20 split, with 80% allocated for training the classification model and the remaining 20% reserved for validation.

B. Preparation of imaging data

To prepare the data for classification, the PET scans had to go through a number of pre-processing steps to make them comparable. The pre-processing pipeline is shown in Figure 3 below:

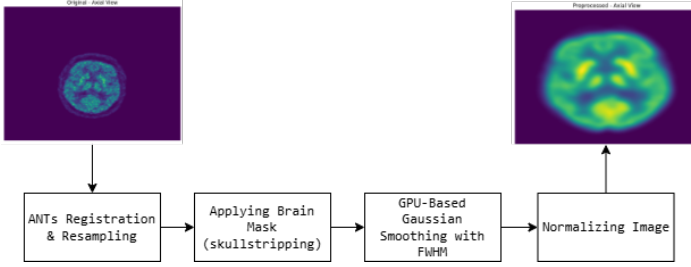


Fig. 3. Pre-Processing Pipeline of PET-Scans

In the first step, the image slices are aligned to the MNI template using ANTs registration and then resampled to ensure consistency across slices of all patients. Resampling also adjusts resolution and upscales older scans. Figure 4 shows the input image after resampling:

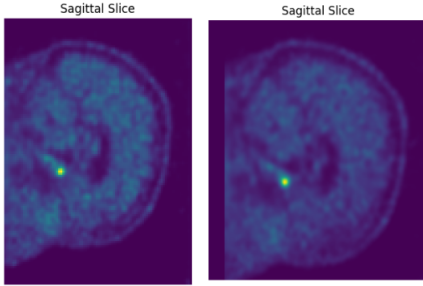


Fig. 4. Left: sagittal center slice of input PET-Scan, Right: resampled center slice

In the second step, a mask is applied to remove non-brain components such as bones, eyes, head and neck as those components are not relevant for classification, this step is referred to as "skull-stripping". Figure 5 shows the resampled image after skull-stripping has been applied:

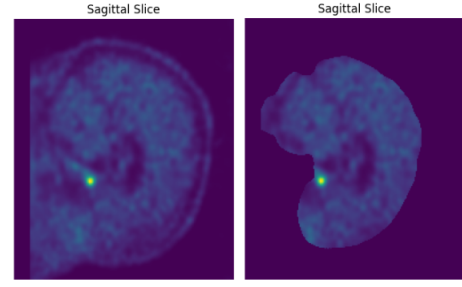


Fig. 5. Left: resampled center slice of PET-Scan, Right: center slice after skull stripping has been applied

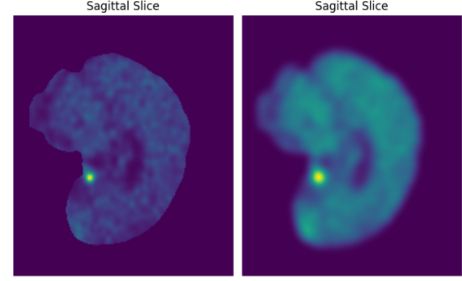


Fig. 6. Left: stripped center slice of PET-Scan, Right: center slice after Gaussian smoothing has been applied

shows the stripped image after Gaussian smoothing has been applied:

In the final step, the slices along the scan are normalized based on their intensity values to ensure consistency across scans. This normalization adjusts for variations in overall intensity levels caused by differences in scanner settings, patient physiology, or tracer uptake. By scaling intensity values to a standard range or distribution, this step facilitates accurate comparisons across scans, improves robustness in downstream analysis, and ensures that intensity differences reflect meaningful biological or functional variations rather than technical artifacts. Figure 7 shows the smoothed image after normalization has been applied:

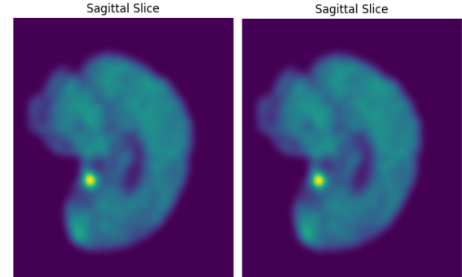


Fig. 7. Left: smoothed center slice of PET-Scan, Right: center slice after normalization has been applied

In the third step, Gaussian smoothing is applied using a full-width at half-maximum (FWHM) value. Using the Gaussian kernel's standard deviation, the image is smoothed as to filter out noise (prevalent in PET-Scans due to the stochastic nature of radioactive decay and scanner sensitivity [18]), improving image quality for easier classification. A FWHM value of 8mm was used in our case, which is a common standard for neurological imaging [19]. Smoothing is generally done in the medical analysis and expanded on in literature [20]. Figure 6

As a supplementary step, slices used for classification were resized to be 224x224 pixels to be compatible with the

classification model used.

C. Classification of blood biomarker data

For the classification of blood biomarkers, two types of models were developed: a voting ensemble model and a stacking ensemble model, which incorporated a diverse range of classification algorithms, namely:

- Support Vector Machines (SVM)
- Naive Bayes
- Logistic Regression
- Multilayer Perceptrons (MLP)
- Decision Tree Classifier
- Random Forest Classifier
- Gradient Boosting Classifier

All of these methods have been used in medical classification tasks in the past with success [21]–[23], and their nature of classifying multi-class classification problems and non-linear relationships between features is suitable for our application.

In addition, a one-vs-one (OvO) classification model was used for our classification model. By defining distinct binary decision boundaries for each class pair, OvO can enhance a model's ability to handle complex decision surfaces, which is particularly advantageous for classification problems with intricate class separations, such as Alzheimer's Disease (AD) status determination. [24]

Using the default hyperparameters for each classifier, the combination of SVM, Naive Bayes, Logistic Regression, Random Forest Classifier, and Gradient Boosting within a stacking ensemble model yielded the highest accuracy on the 20% validation test set and scored higher than any voting ensemble model.

Class weights were applied to the logistic regression and random forest classifier to address class imbalance inherent in the dataset.

After defining the best model, we tuned the hyperparameters of each model using a wide range of values for a slight improvement in performance.

D. Selecting slices for classification

Classification using VGG19 requires 2D slices from the 4D scans provided by the dataset, we used the centre slices of the sagittal scans for Tau and FDG tracer and coronal scans for Amyloid, using centre slices has been presented in a similar classification task with great success [6]. For scans at different points in time, we used the mean of the scans at all times for classification. Centre slices were used for all tracer types.

E. Classification of PET Imaging Data

To classify PET Image Data, VGG19 was used. VGG19 is a deep convolutional neural network architecture that was developed by the Visual Geometry Group (VGG) at the University of Oxford. It is a variant of the VGGNet family, consisting of 19 layers, 16 of which are convolutional layers, 3 of which being fully connected layers.

Due to its deep architecture VGG19 is well suitable for PET imaging classification as it combs through low- and high-level

details which can be crucial for differences such as subtle intensity variations or pattern identification. Generally deep convolutional networks have proven quite useful in the field [25]. Research from N. Kishore and N. Goel [6] have also used VGG19 with great success on the ADNI PET-Scan dataset.

VGG19 is traditionally a pre-trained model that is trained on a huge dataset of millions of images, but in our use case we retrained it from scratch using the pre-processed data.

Additionally each scan has the sex of the participant attached for classification, as to make sure the model would consider some functional differences as mentioned in research [26].

A model was trained for each tracer separately, parameters were set the same for each model, training for a cap of 50 Epochs (stopped once validation accuracy dropped).

For training, 80% of the pre-processed PET scans were used and 20% for testing and validation.

F. Combining classification models

To integrate multiple models, we combined the outputs of the imaging-based tracer models with the blood biomarker models. The combination was achieved by aggregating the predicted odds from both models, with equal weighting assigned to the imaging and biomarker contributions.

IV. RESULTS

A. Results blood biomarkers classification

Observing the blood biomarkers we can observe that AD shows higher mean data for various values such as GFAP, NfL, pTau181 and more, as shown in Figure 8 below:

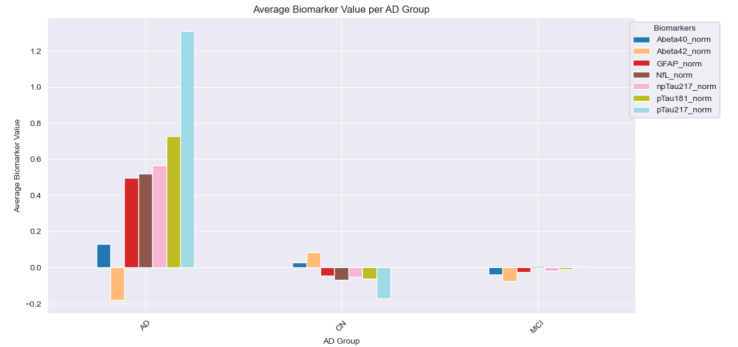


Fig. 8. Mean values of each biomarker per AD profile

Using the available data as described above, the proposed model achieved an overall classification accuracy of 57.09% when using only blood biomarker data. This relatively low accuracy can be attributed to the inherent difficulty in distinguishing between MCI and AD/CN scans. While AD scans generally have higher mean biomarker levels (and CN scans slightly lower mean levels), MCI scans are characterised by a wider range of levels, resulting in considerable overlap between the two classes. This overlap complicates the ability of the classifier to effectively discriminate between MCI and AD, as shown in Figure 9 below.

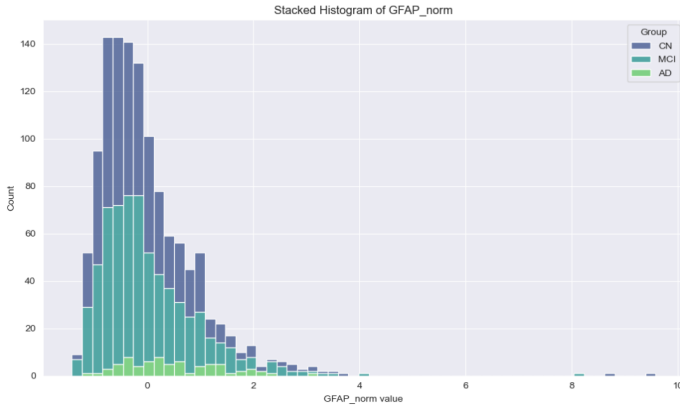


Fig. 9. Distribution of GFAP values separated by AD Group

In the one-vs-one case, CN classified well vs AD, but it gets more complicated with MCI involved as can be seen in Table 2 below:

TABLE II
RESULTS OF BLOOD BIOMARKER AD CLASSIFICATION

Matchup	Accuracy	Sensitivity	Specificity
AD vs CN	93.65%	0.00%	100.00%
AD vs MCI	91.11%	0.00%	98.80%
CN vs MCI	59.83%	60.20%	59.85%

The F1 scores for each class reveal significant variability in classification performance. The model performs poorly in classifying Alzheimer's Disease (AD), with an F1 score of 0.00, while the scores for Control Normal (CN) and Mild Cognitive Impairment (MCI) are moderate, at 0.55 and 0.62, respectively. These results suggest that blood biomarkers alone do not provide sufficient discriminatory power for reliable classification across all diagnostic categories. The overlap in biomarker profiles, particularly between MCI and AD, likely contributes to the reduced performance, indicating the need for additional modalities or features to improve classification accuracy. Outliers might also negatively impact the model.

B. Results imaging classification

Examining the pre-processed data, it is evident that amyloid and tau biomarkers exhibit higher levels of activation as cognitive decline progresses, whereas FDG demonstrates reduced activation. These findings align with established research in the field [27], [28]. The mean activation values across all scans (sagittal view) for a specific AD stage are presented in Figure 10.

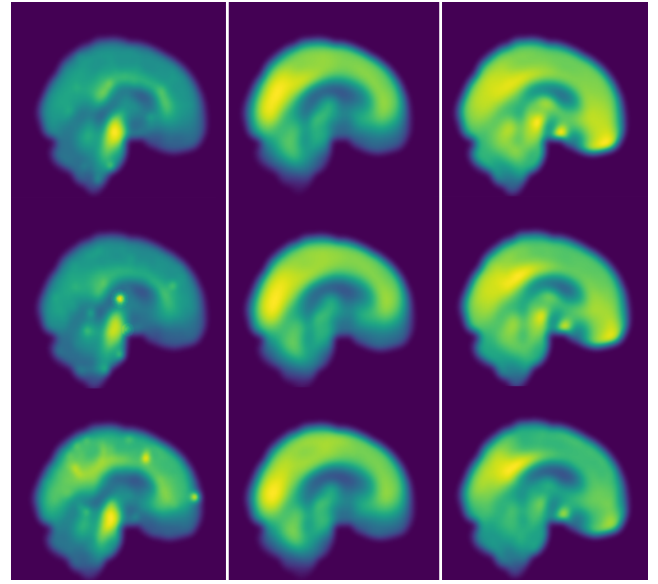


Fig. 10. Sagittal view of mean activation per stage (top: CN, middle: MCI, bottom: AD) (left: Amyloid, middle: FDG, right: Tau)

Table 3 shows the overall accuracy, sensitivity and specificity of all 3 Models which were trained on 80% of the available 4999 pre-processed scans over the 3 models and results over the 20% validation set.

TABLE III
MACRO-AVERAGED PERFORMANCE METRICS FOR AD VS. CN, AD VS. MCI AND MCI VS. CN USING DIFFERENT TRACERS.

	Precision	Sensitivity	Specificity
AD vs. CN			
Amyloid	81.9%	57.1%	57.1%
FDG	93.8%	88.9%	88.9%
Tau	84.0%	64.0%	64.0%
AD vs. MCI			
Amyloid	81.2%	57.1%	57.1%
FDG	87.1%	85.6%	85.6%
Tau	79.6%	63.3%	63.3%
MCI vs. CN			
Amyloid	69.7%	70.0%	70.0%
FDG	83.3%	84.9%	84.9%
Tau	65.5%	63.5%	63.5%

Similar to the blood biomarker classification model, the model struggles to make a clean distinction between MCI and AD/CN classifications. PET scan classification alone does not provide sufficient discriminatory power to reliably classify, especially when discerning between MCI and other states.

C. Results combined Model

Given the limited availability of blood biomarker data, PET scans and corresponding blood biomarker measurements were selected exclusively from patients who had undergone both procedures within the same year. This criterion was essential to construct a dataset of sufficient robustness for validating the combined model. The final combined model had an overall accuracy of 93.21% on a total of 780 patient profiles. Further results can be seen in Table 4 below:

TABLE IV
PERFORMANCE METRICS FOR COMBINED MODEL ACROSS ALL TRACERS.

Class	Precision	Sensitivity	Specificity	F1 Score
CN	97.14%	95.1%	90.2%	0.961
MCI	80.57%	89.2%	94.5%	0.847
AD	81.82%	60.0%	99.7%	0.692

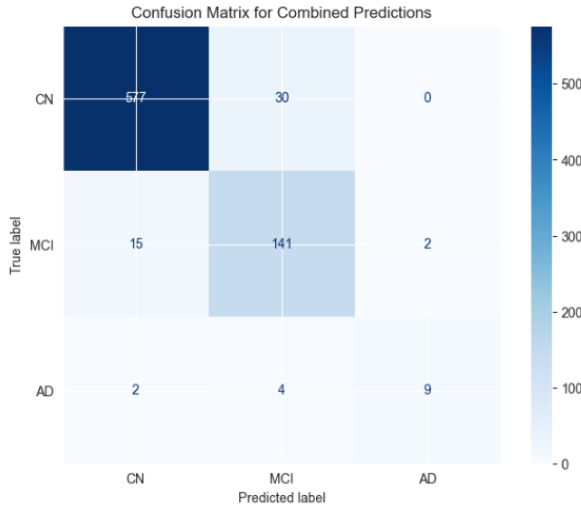


Fig. 11. confusion-matrix of final result

To note here is that the data used for this final test was from both the training and validation set.

V. DISCUSSION

Alzheimer's Disease (AD) classification presents a significant challenge for clinicians, as assessments are often complex and, in subjective cases, prone to inaccuracies [29]. In our study, which utilized machine learning models for classification, the results indicate that accurate classification is possible using machine learning. Notably, other studies employing

similar methodologies have demonstrated even higher levels of classification success, highlighting the promise of such techniques in advancing diagnostic accuracy [6].

Blood biomarkers represent a promising tool for Alzheimer's disease (AD) classification. However, in our research, the dataset size was relatively small, and improved classification performance could likely be achieved with access to a larger and more comprehensive dataset. Also the variability across device families may have introduced residual inconsistencies which influence classification accuracy.

Translating machine learning-based AD classification into clinical practice presents several challenges, including the risk of misclassification and the ethical implications of false positives or negatives. Furthermore, ensuring that these models are interpretable and explainable is critical for gaining clinician trust and facilitating adoption. Practical challenges, such as the cost and accessibility of biomarker assays, as well as training for clinicians to interpret machine learning outputs, must also be addressed.

VI. CONCLUSION

Our results show that machine learning classification of Alzheimer's disease (AD), particularly using blood biomarkers and PET scans, is a feasible approach. However, further research is required to develop a fully automated model for AD classification. In particular, further research is warranted into PET scan slice selection methods and alternative classification models, as well as research into further blood biomarker measurements. Future studies should also extend the scope by including a wider range of tracers to improve the robustness and generalisability of the approach.

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