Predicting Dementia Subtypes at Early Stages using Machine Learning and Structured Data

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Abstract

Dementia is a heterogeneous and non-curable condition with multiple distinct subtypes including Alzheimer's disease (AD) and Lewy body dementia (LBD) among others. As of today, all clinical trials aiming to reverse dementia have failed, and this failure is partly attributed to late intervention and heterogeneity of the disease. Accurate diagnosis of dementia subtypes in clinical setting, particularly at early stages, is difficult due to the subtypes manifesting similarly at initial disease onset. Patients' true disease subtype can currently only be confirmed via brain autopsy, post-mortem. In this work, we focus on detection of autopsy confirmed dementia subtypes at early stages. Specifically, looking at patients' clinical data with mild cognitive impairment stage (Cognitive Dementia Rating global score of 0.5 or 1), we build machine learning models that can differentiate autopsy-confirmed pure AD, pure LBD, the Lewy body variant of AD, and other subtypes. We compare our results against the clinical diagnosis of the subtype done at the early stage at a clinical visit. Our analysis based on data of 40,858 patients in National Alzheimer's Coordinating Center (NACC) longitudinal cohort indicates that First: Mixed dementia is significantly under-diagnosed by clinicians, and Second: Machine learning can improve accuracy of diagnosis of mixed dementia by a large margin, while matching the accuracy of clinicians for pure AD. Our analysis and code is open-source and available at: `https://github.com/NYUMedML/NACC_Dementia_Subtypes`

Keywords: Dementia Subtypes, Alzheimer's disesase, Lewy body dementia, Mixed Dementia, NACC dataset, Multiclass Logistic Regression, Multilayer Perception

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia, accounting for 60% to 80% of demented cases (Scheltens et al., 2016). Patients with AD suffer from brain atrophy, which leads to memory loss, language problems and declining problem-solving abilities. Until now, the cause of AD has not been fully understood, which makes AD hard to diagnose and treat. Pathologically, AD is closely related to the distribution of abnormal amyloid and tau proteins in the brain, along with neurodegeneration. Genetically, patients with APOEϵ gene can progress to more severe stages faster than those ones without it (Scheltens et al.,

2016; Williams et al., 2013). Moreover, lifestyle factors like diabetes, obesity, smoking and low educational level can also contribute to AD.

Lewy body dementia (LBD) is the second most prevalent dementia subtype (Walker et al., 2015; Mueller et al., 2017). Patients with LBD often experience visual hallucinations, anxiety, depression, and extrapyramidal effects when exposed to antipsychotics (Walker et al., 2015; Sfiimomura et al., 1998). Unlike AD, LBD does not draw sufficient clinical attentions (Walker et al., 2015). However, compared to patients with AD, LBD patients suffer from a more severe prognosis, which includes accelerated cognitive declines and shorter lifespans (Mueller et al., 2017). Due to overlapping biomarkers, genetics and symptoms with other dementias, LBD is more difficult to identify, especially from AD (Walker et al., 2015; Mueller et al., 2017; Nelson et al., 2010).

Besides AD and LBD, a more severe subtype of the disease involving both has also been identified, referred as the Lewy body variant of Alzheimer's disease (Mix AD + LBD) (Förstl, 1999). In this concomitant case, symptoms of AD and LBD can manifest at the same time, such as plaques and tangles, hallucinations, delusions and slow wave transients in electroencephalogram (EEG) (Weiner et al., 1996; Förstl, 1999; van der Zande et al., 2018). Available clinical diagnostic criteria for AD (McKhann, 2012) and LBD (McKeith et al., 2005) perform poorly when applied to this mixed dementia. Also, treatments should be used with special caution, since required dopaminergic treatments can lead to aggressive hallucination and delusion, and antipsychotics will result in Parkinsonian symptoms (Weiner et al., 1996). Thus, how to identify and treat this mixed subtype is still an open research area.

Dementia subtypes diagnosis at early stages is significant since clinicians can take specific treatments based on the result. In this paper, we focus on classifying four dementia subtypes: pure AD,ure LBD, Mix AD+LBD and other subtypes, at the first time patients manisfest very mild or mild cognitive impairment. Their cognitive status are measured by global CDR score (CDRGLOB), and we use CDRGLOB of 0.5 and 1.0 as our indicator for very mild or mild cognitive impairment. We utilized demographics, medication, health history, physical, neuropsychological tests, cerebrospinal fluid (CSF) biomarker and genetic variables of patients at first indication of mild impairment as the input for our classification, and rely on National Alzheimer's Coordinating Center (NACC) longitudinal data for our analysis. (Nelson et al., 2010) and (Gaugler et al., 2013) showed that misdiagnosed rate is high for both AD and LBD, therefore we used neuropathologic results obtained post-mortem via autopsy, instead of clinician judgements as ground truth diagnosis. We train and validate two machine learning models: Multiclass Logistic Regression (LR) and Multilayer Perceptron (MLP).After selecting the best model, its performance was compared with clinician's diagnosis at the very mild or mild cognitive impairment state of the patient. We also investigated clinician errors to identify where the model improves diagnosis quality the most. Compared to prior works using unstructured biomarkers such as MRI or EEG, our work use only structured data to differentiate dementia subtypes. To our knowledge, this is the first work using machine learning and structured data to distinguish autopsy-confirmed pure AD, pure LBD, Mix AD+LBD, and other subtypes, based on data of the first visit when patients show mild symptoms of dementia.

2. Related Works

Despite difficulties to distinguish AD and LBD, several tentative works have investigated the probability to combine machine leanring with biomarkers including imaging data and EEG to do the classification.

(Lebedev et al., 2013) uses multivariate sparse partial least squares classification of MRI cortical thickness measurements to differentiate between AD and LBD. Although it can achieve a fairly good accuracy of 77.78%, the performance declines significantly when the model is tested on the cohort of a distinct protocol without protocol alignment (an important image preprecessing step to harmonize MRIs between different cohorts so that models trained on an unified dataset can be applied to other cohorts without significant performance drop). (Wada et al., 2019) investigates the utility of convolutional neural networks (Lecun et al., 1998) and structural MR connectomes (generated from raw diffusion tensor imaging, T1/T2 MRI, and BOLD imaging). Their method cannot outperform previous studies which used CT or EEG. 3D local binary pattern texture features, which are extracted from T1 MRIs, combined with a random forest (RF) classifier is investigated by (Oppedal et al., 2017). It shows separating AD and LBD is much harder than distinguishing between normal control (NC) and either of them. (Katako et al., 2018) demonstrates Positron Emission Tomography with fluorodeoxyglucose pattern is able to accurately classify AD and NC, but the specificity remains low when use it between dementia subtypes, especially AD and LBD.

Besides imaging data, EEG is also explored. (Lee et al., 2015) shows grand total EEG cut-off score of 6.5 can be used for clinically distinguishing between AD and LBD, with sensitivity of 79% and specificity of 76%. Combining RF and quantitative EEG, (Dauwan et al., 2016) argued that EEG can improve diagnosis accuracy for AD and LBD, and it is the most discriminative feature selected by RF classifier compared to clinical tests, MRI, CSF, and visual EEG. Furthermore, (Colloby et al., 2016) uses both EEG and MRI to do the differential diagnosis, whose result is better than EEG-only and MRI-only methods. (van der Zande et al., 2018) is the first work to investigate EEG to diagnose pure LBD, pure AD and Mix AD + LBD, and is the most related work to our task. Although they confirmed that EEG characteristics can separate pure LBD and pure AD, it cannot be applied for pure LBD and Mix AD + LBD. Also, unlike our work, their model cannot distinguish pure AD, pure LBD and Mix AD+LBD at the same time.

It is worth noticing that all above works lack neuropathological diagnosis, so the validity of their findings is limited by accuracy of clinical diagnosis, which is low.

3. Methods

3.1 Data Description and Analysis

We work with data from participants of National Alzheimer's Coordinating Center (NACC) initiative, including 40,858 patients that have participated since 2005. The variables in our study are limited to non-imaging data including demographics, health history, neuropsychological tests, clinician judgements, CSF values (for Amloyde beta, P-tau, T-tau), APOE genotypes and autopsy-based neuropathological findings. For a list of features used in this paper, please see the supplementary material.

As a measure for cognitive impairment we focus on Cognitive Dementia Rating Global Score (CDRGLOB). CDRGLOB indicates five levels of impairment: 0.0 (no impairment), 0.5 (very mild), 1.0 (mild), 2.0 (moderate), 3.0 (severe).

Table 1 shows a summary of our population data.

Table 1: Cohort Characteristics Statistics

Characteristics	**Statistics**
Gender	
Male	17493
Female	23365
Ethnicity	
White	32482
Black or African American	5106
American Indian or Alaska Native	252
Native Hawaiian or Pacific Islander	32
Asian	1009
Multiracial	1278
Unknown or ambiguous	699
Number of visits	
Mean	3.49
Max	14
Min	1
Clinically diagnosed subtypes	
Pure AD	17296
Pure LBD	1406
Mix AD+LBD	944
Other sutypes	21212
Neuropathologically defined subtypes	
Pure AD	970
Pure LBD	53
Mix AD+LBD	751
Other subtype	775
Average age at initial visits	71.78
Average CDRGLOB at initial visits	0.55
Average educational years	15.07

3.2 Dementia Subtype Definitions and Qualified Patients

We used autopsy confirmed neuropathological results, which are the gold standard for identifying dementia subtypes, as the labels for training and validating our models. Specifically, for AD, we used NIA-AA Alzheimer's disease neuropathologic change score (ADNC) ("ABC" score) available as NPADNC, and Lewy body pathology available as NACCLEWY, in the data. The specific definition is in Table 2.

Table 2: Autopsy-confirmed definition for each dementia subtype

Dementia Subtype	Pure AD	Pure LBD	Mix AD+LBD	Other Types
Definition	NPADNC=2 or 3 and NACCLEWY=0	NPADNC=0 or 1 and NACCLEWY=3	NPADNC=2 or 3 and NACCLEWY=1,2, or 3	others

NPADNC: 0=Not AD, 1=Low ADNC, 2=Intermediate ADNC, 3=High ADNC
NACCLEWY: 0=No Lewy body pathology, 1=Brainstem-predominant, 2=Limbic (transitional) or amygdala-predominant, 3=Neocortical(diffuse).

To compare the performance between our best model and clinicians, we also need clinicians' diagnosis as reference. To capture that, we used Presumptive etiologic diagnosis of Alzhiemer's disease (available as NACCALZD) and Presumptive etiologic diagnosis of Lewy body disease (available as NACCLBDE) Table 3 includes derived definitions of clinicians' diagnosis.

Table 3: Definition of clinician labels

Dementia Subtype	Pure AD	Pure LBD	Mix AD+LBD	Other Types
Definition	NACCALZD=1 and NACCLBDE=0 or 8	NACCALZD=0 or 8 and NACCLBDE=1	NACCALZD=1 and NACCLBDE=1	others

NACCALZD: 0=Cognitive impairment (dementia, MCI, or impaired, not MCI) and no AD. 1=Any cognitive impairment and AD etiologic diagnosis. 8=Normal cognition.
NACCLBDE: 0=Cognitive impairment and no LBD. 1=Any cognitive impairment and LBD etiologic diagnosis. 8=Normal cognition.

Our inclusion criteria includes availability of at least one visit with documented mild cognitive impairment (CDRGLOB = 0.5 or 1), availability of autopsy-based neuropathology NPADNC and NACCLEWY. For each patient, the first early-stage visit (CDRGLOB = 0.5 or 1) is used as the classification point. The statistics for qualified patients is in Table 4.

Table 4: Statistics of all qualified patients

Dementia Subtype	Pure AD	Pure LBD	Mix AD+LBD	Other Types	Total
# of qualified patients	757	46	572	512	1887

3.3 Training, Validation, and Heldout Test Set

After all qualified patients are selected, they are split randomly at the patient level into training, validation and test set, which means one patient data can only exist in one set to avoid data leakage between different sets. In order to keep the same distribution for all three sets, patients of each dementia subtype were divided by the ratio of 6:2:2. Then

shuffled patients for each subtype were combined to training, validation and test set with the number of 1127, 380, 380, respectively.

3.4 Data Preprocessing

The input for each patient is the data captured at the first visit at which they get a CDR-GLOB score of 0.5 or 1.0. This data originally includes 721 features. However, to further avoid any information leakage, we adopt following criteria to remove features from the original set: We exclude: (1) all features that include clinician notes and any feature concluding text data.(2) all administrative information, such as visited ADC and Packet code of investigation forms. (3) utilization of anti-Alzheimer or anti-Parkinson medicine at the visit, whether patients have Parkinson's Disease in the health history, clinician judgement of symptoms, clinician diagnose, time information of diseases (since this will imply the patient has already had the disease), all features from NP dataset and death information. (4) features which the summary score can be derived from. We only keep CDRSUM for CDR, NACCGDS for GDS score, NACCMMSE for MMSE score, MOCATOTS for MOCA. After removing all those features, there are 191 left. These features are listed in supplementary material.

In clinical data, missing values are common. In NACC dataset, there are three kinds of missing values: (1) denoted by NaN (2) unknown data (3) not applicable or available data because of different ways to collect data. In preprocessing, all of them are treated in the same way and used the same symbol to represent. In addition, there are two data formats: continuous and categorical data. For continuous data, we assume that data of different visits have more similarity and closer relationship within the same patient than between different patients; thus, we fill the missing continuous data using the median of records from the same patient, which is more robust than mean values. After this step, there are still patients having continuous missing values, since feature values are missed entirely for all visits of that patient. In this case, those data are filled using the median of that feature among ALL patients. For the categorical features, we assume that they are not missed randomly and they can provide extra information for the model, so we just keep them as an additional category.

After filling the missing data, both categorical and continuous data are further processed by feature engineering, so that they can be directly fed into machine learning models. For continuous features in three sets, we normalize them using mean and standard deviation of the training set by $(feature\_value - training\_mean)/training\_std$. For categorical features, each category is encoded by a one-hot vector.

3.5 Model Description

We used Multiclass Logistic Regression (LR) and Multilayer perceptron (MLP) to predict dementia subtypes.

In Multiclass LR model, the probability of each class is computed as,

$$\hat{y} = \text{softmax}(Wx + b) \tag{1}$$

where $\hat{y}$ is the output vector (of dimension 4), W is model wight matrix, x is an input feature vector (of dimension 557 here), b is bias, and $\text{softmax}(z_i) = \frac{e^{z_i}}{\sum_k e^{z_k}}$.

MLP is a fully connected feedforward neural networks, which has one input layer and one hidden layer followed by an output layer. MLP models the output probabilities as follows.

$$\hat{y} = \text{softmax}(W_1\sigma(W_2x + b_2) + b_1) \tag{2}$$

In our experiments, $\sigma(z)$ is Leaky ReLu with negative slop of 0.1, the the hidden layer diemension is searched within the values of [256, 512, 1024], and dropout with probability of 0.5 is added on the hidden layer.

We use Cross Entropy Loss to train the model. Within the training set, the ratio of patients of each disease is 453:26:342:306. We weight the loss function for each disease by (# of total training samples) / (# of training samples of this disease). To avoid overfitting, L1 regularization term is added to the loss function, with the coefficient α. We tuned α within the values of [0, 0.001, 0.01, 0.1] using the validation set.

Specifically, our loss function is

$$\text{Loss Function} = -\frac{1}{N}\sum_{i\in[1,N]}\sum_{j\in[1,4]} p^{(i)}y_j^{(i)}\log\hat{y}_j^{(i)} + \alpha\sum_k |w_k| \tag{3}$$

where $p^{(i)}$ is the weight for i-th dementia subtype in the training set, y is the true label, $\hat{y}$ is the model output, w is the model parameter set.

3.6 Data Augmentation

In preprocessing, patients with no autopsy-confirmed labels at the first visit of early stages were removed. However, all visits of such patients have corresponding clinician diagnosed labels, so we tested four strategies to expand the training set using those excluded visit data. The training data in these strategies are as follows: (1) all autopsy: all visits with autopsy-confirmed labels instead of only the first visit of early stages (2) all first early stages: first early stage visits of all patients in the original dataset no matter whether they have autopsy-confirmed labels or not (3) all early stages: all visits of early stages from the original dataset instead of only the first one (4) all stages: all visits of not only early stages, but later stages (CDRGLOB=2 or 3) as well. In all strategies, for those visits who have no neuropathological result, clinician diagnosed labels defined in section 3.2 are used as target labels for the model. In addition, since our task is for cognitively impaired patients, for those visits with only clinician labels, we eliminate all visits whose clinician diagnosis are No Cognitive Impairment (NACCALZD=8 and NACCLBDE=8). For the number of training dataset of each data augmentation strategy, please see Table 5.

Table 5: The number of training dataset for each data augmentation strategy

Augmentation Strategy	None	All autopsy	All first early stages	All early stages	All stages
Training set size	1,127	8,083	22,458	53,509	73,529

4. Experiments and Results

4.1 Model Training and Evaluation

For the convenience and flexibility to train and compare our models, we use Pytorch (Van Merriënboer et al., 2018) to implement both LR and MLP. Specifically, we train our model for 300 epochs, using batch size of 16 and Adam optimizer (Kingma and Ba, 2015) with (ϵ=1e-8, β1=0.9, β2=0.98). The initial learning rate is 0.001, then decreases by 0.5 when the training loss does not drop.

For each data augmentation strategy, both LR and MLP are trained and validated. To select the best model to compare with clinicians, (1) we tune hyperparameters of each model based on the best Macro and Micro F1 score, (2) among all the tuned models, we remove overfitting ones, and select one model with the best overall Macro F1 score and one with the best overall Micro F1 score. (3) the overall best model which has lowest validation loss is selected from these two models. The result is in Table 6.

Table 6: Valiation F1 scores of pure AD, pure LBD, Mix AD+LBD and other subtypes

Augmentation Strategy	Model	Max Macro and Micro F1 scores of Max Macro F1 model	Max Macro and Micro F1 scores of Max Micro F1 model
None	LR	(0.376797, **0.471053**)	overfitting
	MLP	overfitting	overfitting
All autopsy	LR	overfitting	overfitting
	MLP	overfitting	overfitting
All first early stages	LR	(0.368162, 0.431579)	(0.350656, 0.442105)
	MLP	overfitting	(0.357514, 0.452632)
All early stages	LR	(0.364346, 0.457895)	(0.364346, 0.457895)
	MLP	(**0.382694**, 0.452632)	overfitting
All stages	LR	(0.362265, 0.463159)	(0.362265, 0.463159)
	MLP	overfitting	overfitting

Column 3 and 4 in Table 6 are maximum Macro F1 score and maximum Micro F1 score of the model we tuned based on the best Macro (column 3) and the best Micro (column 4) F1 score, which is non-overfitting. Maximum Macro and Micro F1 scores can be obtained at different epochs. Among all the tuned non-overfitting models, LR (L1 coefficient α=0.01, No Augmentation, epoch=3) has the best overall Micro F1 score, and MLP (hidden dimension=256, α=0.001, All early stages, epoch=3) has the best overall Macro F1 score. The overall best model is LR, which has a lower validation loss (1.525938 vs. 1.536219).

4.2 Interpretability

In the computational healthcare, interpretability is important, we also examine which features the overall best model focuses on when it makes decisions for each disease. From the previous section, the best model we selected is LR, so we can rank the input feature importance for each disease based on weights in the linear layer. For each disease, top 10 features are shown in Table 7. If a feature name is followed by a number, it means that feature is categorical, and the number is the category the model attends on. The float number in the parenthesis is the weight of this particular feature in best LR. Please refer to supplement

materials, and UDS[1], CSF[2] and Genetic[3] data of NACC data set to see the descriptions of features and each category.

Table 7: Top 10 features with weights of the best model for each disease

Dementia Subtype	Top Features
Pure AD	CSFTTAU(5.738-02), NACCAGE(5.726e-02), DEPDSEV-4(5.568e-02), IRRSEV1(5.355e-02), INEDUC(4.733e-02), NITESEV-4(4.494e-02), NACCNE4S1(4.396e-02), NACCFAM1(4.212e-02), INCONTF0(3.703e-02), TRAUMEXT0(3.606e-02)
Pure LBD	DEPD1(4.913e-02), INCONTF2(4.712e-02), INCONTU1(4.049e-02), INRELTO2(3.912e-02), BOSTON(3.182e-02), NACCGDS(3.121e-02), INSEX2(3.004e-02), BILLS3(2.977e-02), DIGIBLEN(2.804e-02), BIPOLAR-4(2.581e-02)
Mix AD + LBD	NACCNE4S2(7.646e-02), NACCAPOE4(7.039e-02), NACCFAM1(6.808e-02), INCONTU0(5.135e-02), NACCAPOE2(4.691e-02), UDSVERLC(4.327e-02), ANXSEV1(4.000e-02), ANX1(3.948e-02), SEX2(3.059e-02), MEMTIME(3.028e-02)
Other subtypes	DISN1(8.437e-02), NACCAPOE3(6.790e-02), NACCBMI(6.484e-02), NACCFAM0(5.500e-02), UDSBENTD(5.092e-02), WAIS(4.808e-02), TRAVEL0(4.628e-02), NACCGDS(4.526e-02), CSFABMD-4(4.422e-02), PAYATTN0(4.202e-02)

From those top features, some conclusions align with medical findings, which proves the validity and credibility of our best model. Take pure AD for example, T-tau(CSFTTAU) and ages(NACCAGE) are the most important factors examined by the best model. Also, the model tend to consider patients with mild irration(IRRSEV1), APOE e4 alleles (NACCNE4S1) and familial history of cognitive impairement (NACCFAM1) as pure AD.

4.3 Comparison with Clinicians

To see how well the best model performs for each subtype, we set clinician diagnosis on the test set as the baseline. In Table 8, bootstrap (sample size = 80% of the whole test set, 1000 iterations) is used to compute mean F1 score for each subtype, followed by 95% confidence intervals in the parenthesis.

Table 8: F1 scores of the best model and clinicians

Dementia Subtype	Best Model	Clinicians
Pure AD	0.569 (0.506, 0.633)	0.556 (0.489, 0.624)
Pure LBD	0.000 (0.000, 0.000)	**0.283 (0.100, 0.526)**
Mix AD + LBD	**0.283 (0.183, 0.381)**	0.062 (0.000, 0.133)
Other subtypes	0.523 (0.422, 0.609)	0.584 (0.492, 0.667)

1. https://www.alz.washington.edu/WEB/rdd_uds.pdf
2. https://www.alz.washington.edu/WEB/csfded.pdf
3. https://www.alz.washington.edu/WEB/rdd_gen.pdf

From Table 8, we can see that for all diseases except for pure LBD and Mix AD + LBD, mean F1 scores of the best model and clinicians fall within each other's 95% confidence interval. Thus, their ability to distinguish these subtypes is significantly the same. Additionally, clinicians outperforms the best model on pure LBD, while the best model performs better on Mix AD+LBD. From confusion matrices in Figure 1, the best model greatly increased the number of true positive patients with Mix AD + LBD, which indicates that it outperforms clinicians by a large margin for this more severe subtype.

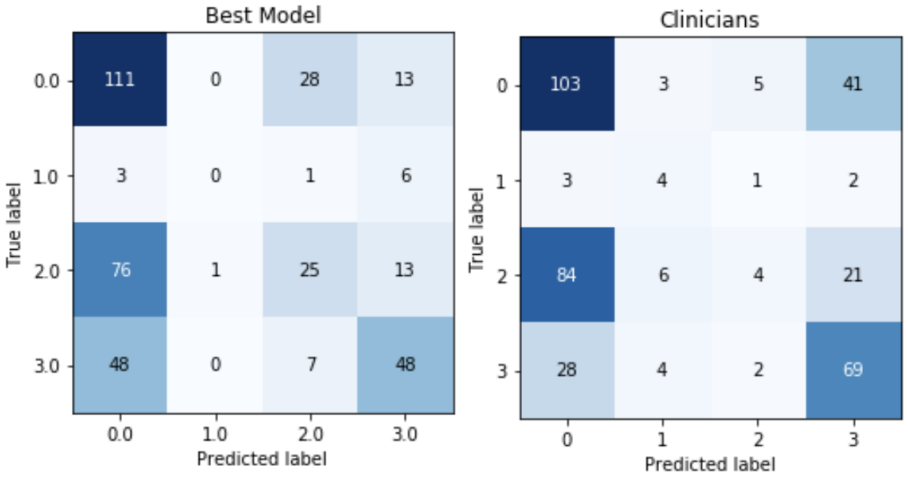

Figure 1: Confusion matrix of the best model and clinicians on the entire test set (0=Pure AD, 1=Pure LBD, 2=Mix AD+LBD, 3=None of these).

Compared with F1 scores, sensitivity and specificity are more meaningful in the medical field. Table 9 and Table 10 compare sensitivity and specificity of both the best model and clinicians for each dementia subtype. As F1 scores in Table 8, bootstrap (sample size = 80% of the whole test set, 1000 iterations) is also used to compute 95% confidence intervals shown in the parenthesis following the mean value.

Table 9: Sensitivity of the best model and clinicians

Dementia Subtype	Best Model	Clinicians
Pure AD	0.730 (0.650, 0.805)	0.680 (0.597, 0.761)
Pure LBD	0.000 (0.000, 0.000)	**0.406 (0.000, 0.800)**
Mix AD + LBD	**0.215 (0.130, 0.300)**	0.033 (0.000, 0.075)
Other subtypes	0.464 (0.360, 0.570)	**0.671 (0.567, 0.764)**

Table 10: Specificity of the best model and clinicians

Dementia Subtype	Best Model	Clinicians
Pure AD	0.442 (0.370, 0.511)	0.495 (0.426, 0.563)
Pure LBD	**0.997 (0.990, 1.000)**	0.965 (0.942, 0.983)
Mix AD + LBD	0.864 (0.820, 0.903)	**0.970 (0.946, 0.990)**
Other subtypes	**0.885 (0.837, 0.926)**	0.770 (0.714, 0.822)

For pure AD, specificity is relatively lower compared to sensitivity. The reason is that pure AD is the most common dementia, and overlaps greatly with other subtypes, so when similar symptoms appear, both the model and clinicians tend to diagnose patients as pure AD. For pure LBD, low sensitivity and high specificity demonstrates that they are always misdiagnosed unless some extremely typical features appear. This is also confirmed by a large confidence interval range, which implies that some pure LBD patients are easy to be identified, while others are not. Therefore, more research should be done on finding more explicit and differentiable features and criteria for this specific dementia. The same case is also for Mix AD + LBD, and it is more severe due to the much lower clinician sensitivity compared to pure LBD, which confirms that current criteria performs extremely poorly for this subtype.

As F1 scores, sensitivity and specificity for pure AD of the best model and clinicians fall within 95% confidence interval of each other, demonstrating that the best model and clinicians have the same clinical performance for this subtype. For pure LBD, the best model cannot identify it at all, and clinicians also has a fairly low sensitivity. For Mix AD + LBD, the best model has higher sensitivity, where our model performs better. For other subtypes, clinicians achieve higher sensitivity, probably because they can refer to more explicit symptoms and criteria of each of those subtypes. However, for our model, other dementias are grouped together, which is harder to diagnose. Additionally, moderate clinician specificity (0.770) of other subtypes implies that symptoms between AD, LBD and other dementias are also overlapping.

Table 11: Clinician wrong probabilities given each group for pure AD and Number of falsely predicted labels for each subtype. The highlighted number is the highest wrong probability within each group.

Features	Groups	Wrong probabilities	# of falsely predictive labels
CSFTTAU	$0 \sim 500$	**0.600 (3/5)**	[0, 0, 0, 3]
	$500 \sim 1000$	0.000 (0/1)	[0, 0, 0, 0]
NACCAGE	$30 \sim 40$	0.000(0/1)	[0, 0, 0, 0]
	$50 \sim 60$	0.267(4/15)	[0, 0, 0, 4]
	$60 \sim 70$	0.292(7/24)	[0, 0, 1, 6]
	$70 \sim 80$	0.345(19/55)	[0, 1, 2, 16]
	$80 \sim 90$	**0.354(17/48)**	[0, 2, 2, 13]
	$90 \sim 100$	0.222(2/9)	[0, 0, 0, 2]
DEPDSEV	1	**0.447 (17/38)**	[0, 0, 4, 13]
	2	0.286 (4/14)	[0, 0, 1, 3]
	3	0.000 (0/2)	[0, 0, 0, 0]
IRRSEV	1	**0.433 (13/30)**	[0, 0, 3, 10]
	2	0.357 (5/14)	[0, 0, 0, 5]
	3	0.400 (2/5)	[0, 0, 1, 1]
INEDUC	$0 \sim 12$	0.000 (0/1)	[0, 0, 0, 0]
	$12 \sim 16$	0.171 (6/35)	[0, 1, 1, 4]
	$16 \sim 18$	0.250 (12/48)	[0, 1, 2, 9]
	$18 \sim 20$	0.484 (15/31)	[0, 0, 1, 14]
	$20 \sim 36$	**0.500 (5/10)**	[0, 0, 0, 5]

Table 12: Clinician wrong probabilities given each group for pure LBD and Number of falsely predicted labels for each subtype. The highlight number is the highest wrong probability for each group.

Features	Groups	Wrong probabilities	# of falsely predictive labels
DEPD	0	0.500 (3/6)	[2, 0, 0, 1]
	1	**0.750 (3/4)**	[1, 0, 1, 1]
INCONTF	0	0.556 (5/9)	[2, 0, 1, 2]
	1	**1.000 (1/1)**	[1, 0, 0, 0]
INCONTU	0	0.571(4/7)	[2, 0, 0, 2]
	1	0.500 (1/2)	[1, 0, 0, 0]
	2	**1.000(1/1)**	[0, 0, 1, 0]
INRELTO	1	0.571 (4/7)	[1, 0, 1, 2]
	2	**1.000 (1/1)**	[1, 0, 0, 0]
	3	0.500 (1/2)	[1, 0, 0, 0]
BOSTON	$20 \sim 25$	**1.000 (3/3)**	[3, 0, 0, 0]
	$25 \sim 30$	0.429 (3/7)	[0, 0, 1, 2]

After comparing the performance of the best model and clinicians from macro perspective, we are further interested in (1) in what population clinicians make more errors (2) where our best model improves. Since others subtypes is an aggregated category, reasons cannot be explored explicitly for each subtype. Based on it, we only analyze pure AD, pure LBD, and Mix AD+LBD in this part. Since our model outperforms clinicians on clinicians, we analyze top 10 factors for it, while top 5 factors for pure AD and pure LBD. For each subtype, we first divide the population truly with this subtype into several groups according to a specific feature, then compute the probability of errors for each particular group $p(wrong|group)$. If the probability of a group is the highest, then clinicians will most likely make errors for this specific group. Table 11 and Table 12 show the probabilities of clinician errors for pure AD and pure LBD. Combining them with Table 13, we can see in what population clinicians are easier to misdiagnose. For exploring the second question, we listed error probabilities for both clinicians and the best model, and compare them to see why the best model performs better. The number in parenthesis is the proportion of patients belonged to this group are misdiagnosed, and each number in brackets is the number of misdiagnosed patients who are falsely assigned to each subtype.

Table 13: Clinician and Best Model wrong probabilities given each group for Mix AD+LBD and Number of falsely predicted labels for each subtype. The highlighted number is lower wrong probability for each group.

Features	Groups	Clinicians	Best Model
NACCNE4S	0	0.978 (44/45) [33, 3, 0, 8]	**0.889 (40/45)** [28, 1, 0, 11]
	1	0.957 (44/46) [36, 1, 0, 7]	**0.761 (35/46)** [34, 0, 0, 1]
	2	0.909 (10/11) [7, 0, 0,3]	**0.545 (6/11)** [6, 0, 0, 0]
NACCAPOE	1	0.974 (38/39) [30, 2, 0, 6]	**0.872 (34/39)** [24, 0, 0, 10]
	2	0.956 (43/45) [35, 1, 0, 7]	**0.756 (34/45)** [33, 0, 0, 1]
	3	1.000 (6/6) [3, 1, 0, 2]	1.000 (6/6) [4, 1, 0, 1]
	4	0.909 (10/11) [7, 0, 0, 3]	**0.545 (6/11)** [6, 0, 0, 0]

	5	1.000 (1/1) [1, 0, 0, 0]	1.000 (1/1) [1, 0, 0, 0]
NACCFAM	0	0.972 (35/36) [25, 5, 0, 5]	**0.833 (30/36)** [22, 0, 0, 8]
	1	0.957 (67/70) [51, 1, 0, 15]	**0.757 (53/70)** [48, 0, 0, 5]
INCONTU	0	0.979 (94/96) [71, 5, 0, 18]	**0.760 (73/96)** [63, 1, 0, 9]
	1	0.882 (15/17) [11, 1, 0, 3]	0.882 (15/17) [12, 0, 0, 3]
	2	1.000 (1/1) [1, 0, 0, 0]	**1.000 (1/1)** [1, 0, 0, 0]
UDSVERLC	$0 \sim 5$	1.000 (1/1) [1, 0, 0, 0]	1.000 (1/1) [0, 1, 0, 0]
	$5 \sim 10$	1.000 (3/3) [3, 0, 0, 0]	**0.000 (0/3)** [0, 0, 0, 0]
	$10 \sim 15$	1.000 (1/1) [1, 0, 0, 0]	1.000 (1/1) [0, 0, 0, 1]
ANXSEV	1	1.000 (20/20) [19, 0, 0, 1]	**0.650 (13/20)** [10, 1, 0, 2]
	2	0.933 (14/15) [11, 2, 0, 1]	**0.600 (9/15)** [5, 0, 0, 4]
	3	1.000 (4/4) [3, 1, 0, 0]	**0.750 (3/4)** [3, 0, 0, 0]
ANX	0	0.958 (68/71) [48, 3, 0, 17]	**0.859 (61/71)** [54, 0, 0, 7]
	1	0.974 (38/39) [33, 3, 0, 2]	**0.641 (25/39)** [18, 1, 0, 6]
SEX	1	0.938 (60/64) [44, 5, 0, 11]	**0.797 (51/64)** [42, 1, 0, 8]
	2	1.000 (51/51) [40, 1, 0, 10]	**0.765 (39/51)** [34, 0, 0, 5]
MEMTIME	$0 \sim 10$	1.000 (1/1) [1, 0, 0, 0]	1.000 (1/1) [1, 0, 0, 0]
	$10 \sim 20$	0.929 (39/42) [28, 3, 0, 8]	0.929 (39/42) [31, 0, 0, 8]
	$20 \sim 30$	0.974 (37/38) [30, 2, 0, 5]	**0.737 (28/38)** [25, 0, 0, 3]
	$30 \sim 40$	1.000 (13/13) [8, 1, 0, 4]	**0.846 (11/13)** [10, 0, 0, 1]

5. Discussion

5.1 Limitations

Although our best model can outperform clinicians, there are still some limitations of this work. Firstly, in NACC dataset, there is no explicit clinician diagnostic label for pure AD, pure LBD, Mix AD + LBD and other subtypes. Thus, we only defined clinician diagnosis based on separate diagnosis for AD and LBD, which is more rough. However, this will improve clinician performance compared to the case if real clinicians are requested to diagnose for the refined subtypes discussed in the work. The reason is that once AD symptoms appears, the clinician label is 1, so when clinician assign positive for AD, patients could have pure AD or Mix AD+LBD. Therefore, our model can still beat clinicians at least on the mixed type. Secondly, for our particular task, after selecting qualified patients, the number of samples in the dataset become relatively small. Because of this and individual variations for dementia symptoms, our best model may be overfitting to this specific dataset. Therefore, to test its generalization, a larger dataset for this task needs to be collected and evaluated on.

5.2 Future Works

To improve our model performance and also simplify the patient examination process, some possible ideas will be explored in the future: (1) only keep those input features which can be measured at home so that patients can predict dementia subtypes on their own. (2) change the way to define labels for data augmentation: using the clinician diagnosis of each patient's last visit as the label for all previous visits of this patient. The reason is

that later diagnosis is more accurate since symptoms will be more obvious for clinicians to distinguish subtypes. (3) Based on aggregated test scores like CDRSUM, the model may not be able to differentiate subtypes confidently. So expanding test scores which compose those aggregated ones may help if that will not lead to overfitting. (4) change the way to train the model using transfer learning: train the model on samples who only have clinician labels, then fine-tune it using samples with neuropathological results.

6. Conclusion

In conclusion, in this work we examined Multiclass Logistic Regression and Multilayer Perceptron to diagnose pure Alzheimes's disease, pure Lewy body dementia, the Lewy body variant of Alzheimer's disease and other subtypes at the first time patients manifest very mild or mild coginitive impairment. Multiclass Logitstic Regression is the best model on the validation set. It outperforms clinicians on the more severe mixed subtype, while performs worse on pure Lewy body dementia. We also investigate top features of each subtype for clinical interpretability and also calculated misdiagnosed probability for each group. To our best knowledge, this is the first work to use machine learning and only structured data to predict such refined dementia subtypes at the first early stage visit.

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Supplementary Material

Table 14: Clinical features used in this paper from NACC dataset

NACC Form	Feature Name	Descriptions
A1 Subject Demographics	NACCID	Subject ID number
	DATE	Visit Date, derived from VISITMO, VISITDAY, VISITYR
	SEX	Subject's sex
	HISPANIC	Hispanic/Latino ethnicity
	HIPOR	Hispanic origins
	PRIMLANG	Primary language
	EDUC	Years of education
	NACCAGEB	Subject's age at initial visit
	NACCNIHR	Subject's race
	NACCAGE	Subject's age at visit
A2 Co-participant Demographics	INSEX	Co-participant's sex Original
	NACCNINR	Co-participant's race
	INEDUC	Co-participant's years of education
	INRELTO	Co-participant's relationship to subject
A3 Subject Family History	NACCFAM	Indicator of first-degree family member with cognitive impairment
A4 Subject Medications	ANYMEDS	Subject taking any medications
	NACCAAAS	Reported current use of an antiadrenergic agent
	NACCAANX	Reported current use of an anxiolytic, sedative, or hypnotic agent
	NACCAC	Reported current use of an anticoagulant or antiplatelet agent
	NACCACEI	Reported current use of an angiotensin converting enzyme (ACE) inhibitor
	NACCADEP	Reported current use of an antidepressant
	NACCAHTN	Reported current use of any type of an antihypertensive or blood pressure medication
	NACCAMD	Total number of medications reported at each visit
	NACCANGI	Reported current use of an angiotensin II inhibitor
	NACCAPSY	Reported current use of an antipsychotic agent
	NACCBETA	Reported current use of a betaadrenergic blocking agent (Beta-Blocker)

A4 Subject Medications	NACCCCBS	Reported current use of a calcium channel blocking agent
	NACCDBMD	Reported current use of a diabetes medication
	NACCDIUR	Reported current use of a diuretic
	NACCEMD	Reported current use of estrogen hormone therapy
	NACCEPMD	Reported current use of estrogen + progestin hormone therapy
	NACCHTNC	Reported current use of an antihypertensive combination therapy
	NACCLIPL	Reported current use of lipid lowering medication
	NACCNSD	Reported current use of nonsteroidal anti-inflammatory medication
	NACCVASD	Reported current use of a vasodilator
A5 Subject Health History	TOBAC30	Smoked cigarettes in last 30 days O
	TOBAC100	Smoked more than 100 cigarettes in life
	SMOKYRS	Total years smoked cigarettes
	PACKSPER	Average number of packs smoked per day
	QUITSMOK	If the subject quit smoking, age at which he/she last smoked (i.e., quit)
	ALCOCCAS	In the past three months, has the subject consumed any alcohol?
	ALCFREQ	During the past three months, how often did the subject have at least one drink of any alcoholic beverage such as wine, beer, malt liquor, or spirits?
	CVHATT	Heart attack/cardiac arrest
	HATTMULT	More than one heart attack/cardiac arrest?
	CVAFIB	Atrial fibrillation
	CVANGIO	Angioplasty/endarterectomy/stent
	CVBYPASS	Cardiac bypass procedure
	CVPACDEF	Pacemaker and/or defibrillator
	CVPACE	Pacemaker
	CVCHF	Congestive heart failure
	CVANGINA	Angina
	CVHVALVE	Heart valve replacement or repair
	CVOTHR	Other cardiovascular disease
	CBSTROKE	Stroke
	STROKMUL	More than one stroke reported as of the Initial Visit
	CBTIA	Transient ischemic attack (TIA)

	TIAMULT	More than one TIA reported as of the Initial Visit
	SEIZURES	Seizures
	NACCTBI	History of traumatic brain injury (TBI)
	TBI	Traumatic brain injury (TBI)
	TBIBRIEF	Traumatic brain injury (TBI) with brief loss of consciousness
	TRAUMBRF	Brain trauma — brief unconsciousness
	TBIEXTEN	TBI with extended loss of consciousness — 5 minutes of longer
	TRAUMEXT	Brain trauma — extended unconsciousness
	TBIWOLOS	TBI without loss of consciousness — as might result from military detonations or sports injury
	TRAUMCHR	Brain trauma — chronic deficit
	NCOTHR	Other neurological condition
	DIABETES	Diabetes
	DIABTYPE	If Recent/active or Remote/ inactive diabetes, which type?
	HYPERTEN	Hypertension
	HYPERCHO	Hypercholesterolemia
	B12DEF	Vitamin B12 deficiency
	THYROID	Thyroid disease
	ARTHRIT	Arthritis
	ARTHTYPE	Type of arthritis
	ARTHUPEX	Arthritis, region affected — upper extremity
	ARTHLOEX	Arthritis, region affected — lower extremity
	ARTHSPIN	Arthritis, region affected — spine
	ARTHUNK	Region affected — unknown
	INCONTU	Incontinence — urinary
	INCONTF	Incontinence — bowel
	APNEA	Sleep apnea history reported at Initial Visit
	RBD	REM sleep behavior disorder (RBD) history reported at Initial Visit
	INSOMN	Hyposomnia/insomnia history reported at Initial Visit
	OTHSLEEP	Other sleep disorder history reported at Initial Visit
	ALCOHOL	Alcohol abuse — clinically significant occurring over a 12-month period manifested in one of the following areas: work, driving, legal, or social

	ABUSOTHR	Other abused substances — clinically significant impairment occurring over a 12-month period manifested in one of the following areas: work, driving, legal, or social
	PTSD	Post-traumatic stress disorder (PTSD) O
	BIPOLAR	Bipolar disorder
	SCHIZ	Schizophrenia
	DEP2YRS	Active depression in the last two years
	DEPOTHR	Depression episodes more than two years ago
	ANXIETY	Anxiety
	OCD	Obsessive-compulsive disorder (OCD)
	NPSYDEV	Developmental neuropsychiatric disorders (e.g., autism spectrum disorder [ASD], attention-deficit hyperactivity disorder [ADHD], dyslexia)
	PSYCDIS	Other psychiatric disorder
B1 Physical	NACCBMI	NACCBMI
	BPSYS	Subject blood pressure (sitting), systolic
	BPDIAS	Subject blood pressure (sitting), diastolic
B4 CDR score	CDRSUM	CDR sum of boxes
B5 Neuropsychiatric Inventory Questionnaire (NPI-Q)	NPIQINF	NPI-Q co-participant
	DEL	Delusions in the last month
	DELSEV	Delusions severity
	HALL	Hallucinations in the last month
	HALLSEV	Hallucinations severity
	AGIT	Agitation or aggression in the last monthv
	AGITSEV	Agitation or aggression severity
	DEPD	Depression or dysphoria in the last month
	DEPDSEV	Depression or dysphoria severity
	ANX	Anxiety in the last month
	ANXSEV	Anxiety severity
	ELAT	Elation or euphoria in the last month
	ELATSEV	Elation or euphoria severity
	APA	Apathy or indifference in the last month
	APASEV	Apathy or indifference severity
	DISN	Disinhibition in the last month
	DISNSEV	Disinhibition severity
	IRR	Irritability or lability in the last month
	IRRSEV	Irritability or lability severity
	MOT	Motor disturbance in the last month
	MOTSEV	Motor disturbance severity
	NITE	Nighttime behaviors in the last month
	NITESEV	Nighttime behaviors severity

	APP	Appetite and eating problems in the last month
	APPSEV	Appetite and eating severity
B6 Geriatric Depression Scale (GDS)	NACCGDS	Total GDS Score
B7 Functional Activities Questionnaire (FAQ)	BILLS	In the past four weeks, did the subject have any difficulty or need help with: Writing checks, paying bills, or balancing a checkbook
	TAXES	In the past four weeks, did the subject have any difficulty or need help with: Assembling tax records, business affairs, or other paper
	SHOPPING	In the past four weeks, did the subject have any difficulty or need help with: Shopping alone for clothes, household necessities, or groceries
	GAMES	In the past four weeks, did the subject have any difficulty or need help with: Playing a game of skill such as bridge or chess, working on a hobby
	STOVE	In the past four weeks, did the subject have any difficulty or need help with: Heating water, making a cup of coffee, turning off the stove
	MEALPREP	In the past four weeks, did the subject have any difficulty or need help with: Preparing a balanced meal
	EVENTS	In the past four weeks, did the subject have any difficulty or need help with: Keeping track of current events
	PAYATTN	In the past four weeks, did the subject have any difficulty or need help with: Paying attention to and understanding a TV program, book, or magazine

	REMDATES	In the past four weeks, did the subject have any difficulty or need help with: Remembering appointments, family occasions, holidays, medications
	TRAVEL	In the past four weeks, did the subject have any difficulty or need help with: Traveling out of the neighborhood, driving, or arranging to take public transportation
MMSE Score	NACCMMSE	Total MMSE score (using D-L-R-O-W)
C1 Neuropsychological Battery Summary Scores	LOGIMEM	Total number of story units recalled from this current test administration
	MEMUNITS	Logical Memory IIA — Delayed — Total number of story units recalled
	MEMTIME	Logical Memory IIA — Delayed — Time elapsed since Logical Memory IA — Immediate
	UDSBENTC	Total score for copy of Benson figure
	UDSBENTD	Total score for 10- to 15-minute delayed drawing of Benson figure
	UDSBENRS	Recognized original stimulus from among four options
	DIGIF	Digit span forward trials correct
	DIGIFLEN	Digit span forward length
	DIGIB	Digit span backward trials correct
	DIGIBLEN	Digit span backward length
	ANIMALS	Animals — Total number of animals named in 60 seconds
	VEG	Vegetable — Total number of vegetables named in 60 seconds
	TRAILA	Trail Making Test Part A — Total number of seconds to complete
	TRAILARR	Part A — Number of commission errors
	TRAILALI	Part A — Number of correct lines
	TRAILB	Trail Making Test Part B — Total number of seconds to complete
	TRAILBRR	Part B — Number of commission errors
	TRAILBLI	Part B — Number of correct lines
	WAIS	WAIS-R Digit Symbol
	BOSTON	Boston Naming Test (30) — Total score
	UDSVERFC	Number of correct F-words generated in 1 minute

	UDSVERFN	Number of F-words repeated in 1 minute
	UDSVERNF	Number of non-F-words and rule violation errors in 1 minute
	UDSVERLC	Number of correct L-words generated in 1 minute
	UDSVERLR	Number of L-words repeated in 1 minute
	UDSVERLN	Number of non-L-words and rule violation errors in 1 minute
	UDSVERTN	Total number of correct F-words and L-words
	UDSVERTE	Total number of F-word and L-word repetition errors
	UDSVERTI	Total number of non-F/L-words and rule violation errors
MoCA score	MOCATOTS	MoCA Total Raw Score — uncorrected
C2 Neuropsychological Batery Scores	CRAFTVRS	Craft Story 21 Recall (Immediate) — Total story units recalled, verbatim scoring
	CRAFTURS	Craft Story 21 Recall (Immediate) — Total story units recalled, paraphrase scoring
	DIGFORCT	Number Span Test: Forward — Number of correct trials
	DIGFORSL	Number Span Test: Forward — Longest span forward
	DIGBACCT	Number Span Test: Backward — Number of correct trials
	DIGBACLS	Number Span Test: Backward — Longest span backward
	CRAFTDVR	Craft Story 21 Recall (Delayed) — Total story units recalled, verbatim scoring
	CRAFTDRE	Craft Story 21 Recall (Delayed) — Total story units recalled, paraphrase scoring
	CRAFTDTI	Craft Story 21 Recall (Delayed) — Delay time
	CRAFTCUE	Craft Story 21 Recall (Delayed) — Cue (boy) needed
	MINTTOTS	Multilingual Naming Test (MINT) — Total score
	MINTTOTW	Multilingual Naming Test (MINT) — Total correct without semantic cue
	MINTSCNG	Multilingual Naming Test (MINT) — Semantic cues: Number given

	MINTSCNC	Multilingual Naming Test (MINT) — Semantic cues: Number correct with cue
	MINTPCNG	Multilingual Naming Test (MINT) — Phonemic cues: Number given
	MINTPCNC	Multilingual Naming Test (MINT) — Phonemic cues: Number correct with cue
Genetic Data (RDD-Gen)	NACCNE4S	Number of APOE e4 alleles
	NACCAPOE	APOE genotype
CSF Biomarker Data	CSFABETA	$A\beta_{1-42}$ reported value/concentration (pg/mL)
	CSFPTAU	$P-tau_{181P}$ reported value/concentration (pg/mL)
	CSFTTAU	T-tau reported value/concentration (pg/mL)
	CSFABMD	$A\beta_{1-42}$ assay method
	CSFPTMD	$P-tau_{181P}$ assay method
	CSFTTMD	T-tau assay method