A multi-expert ensemble system for predicting Alzheimer transition using clinical features

Mario Merone, Sebastian Luca D’Addario, Pierandrea Mirino, Francesca Bertino, Cecilia Guariglia, Rossella Ventura, Adriano Capirchio, Gianluca Baldassarre, Massimo Silvetti and Daniele Caligiore

Abstract
Alzheimer’s disease (AD) diagnosis often requires invasive examinations (e.g., liquor analyses), expensive tools (e.g., brain imaging) and highly specialized personnel. The diagnosis commonly is established when the disorder has already caused severe brain damage, and the clinical signs begin to be apparent. Instead, accessible and low-cost approaches for early identification of subjects at high risk for developing AD years before they show overt symptoms are fundamental to provide a critical time window for more effective clinical management, treatment, and care planning. This article proposes an ensemble-based machine learning algorithm for predicting AD development within 9 years from first overt signs and using just five clinical features that are easily detectable with neuropsychological tests. The validation of the system involved both healthy individuals and mild cognitive impairment (MCI) patients drawn from the ADNI open dataset, at variance with previous studies that considered only MCI. The system shows higher levels of balanced accuracy, negative predictive value, and specificity than other similar solutions. These results represent a further important step to build a preventive fast-screening machine-learning-based tool to be used as a part of routine healthcare screenings.

Keywords: ADAS score, Cerebellar impairment, Clinical Dementia Rating Scale, Early diagnosis, Machine learning, Renal and genitourinary dysfunctions

1 Introduction
Alzheimer’s disease (AD) is the most worldwide diffused neurodegenerative disorder affecting elders [1, 2]. It causes progressive impairments of memory, language, visuospatial skills, and executive functions together with progressive reduction of functional autonomy in daily life. Depression and apathy are also frequent in the early and middle stages of the disease, whereas neurological signs and motor impairments (e.g., dystonia, tremor) could emerge in later stages [3]. AD diagnosis is commonly based on the analysis of the patient’s medical history, clinical tests, clinical and neurological exams, and brain imaging data. Usually, the diagnostic evaluations are started when the first clinical symptoms begin to manifest. However, the progressive neurocognitive diseases underlying AD starts 10–15 years before deficits become clinically noticeable and disease is diagnosed [4]; therefore the diagnostic process takes usually place when severe damages of brain are already present [5–8].

The early, pre-clinical identification of individuals at high risk for developing AD is fundamental to provide a critical time window for early clinical management, treatment, and care planning, thus also reducing healthcare costs. Indeed, when supplied at the earlier pre-clinical disease phases, treatments could produce more important benefits [9, 10]. Moreover, during the pre-clinical
stages lifestyle changes can be made that will slow or prevent AD development. For example, it could be possible to delay neurodegeneration by early modifying the exposure to certain risk factors such as hypertension, smoking, obesity, and diabetes [11, 12]. An early diagnosis and subsequent access to the proper services could help people live independently in their own homes for longer time and maintain a good quality of life for themselves, their families, and caregivers; also, it could allow people to plan and participate in their own legal, financial, and future support/care options and treatment when they still have the capacity to do so [13]. Early diagnosis gives patient’s relatives the time to adjust to the changes in function, mood, and personality that will occur when facing AD and their transition to a caregiver role, thus allowing them to feel more competent, acquire specific skills, reduce the stress and, as a consequence to suffer less from psychological problems such as anxiety and depression [14, 15].

Currently, MCI represents the earliest detectable stage of a potential ongoing progression toward AD. However, data indicate that only 20–40% of MCI individuals will convert to AD within 3 years from diagnosis [16, 17]. Researchers are investigating several promising biomarker candidates for AD onset anticipation, including brain imaging, proteins in cerebrospinal fluid (CSF), blood and urine tests, and genetic risk profiling [7, 8, 18]. Accuracy and timing are two critical aspects of these diagnostic approaches. While the literature shows that changes in biomarkers correlate with AD development, no single biomarker adequately predicts the conversion to AD of MCI patients and of healthy individuals, with an acceptable level of accuracy and well in advance with respect to the first manifestation of AD overt signs. Another critical aspect of current diagnostic approaches is that they require expensive tools (e.g., brain imaging), invasive clinical exams (amyloid-PET scan, CSF analysis), often also involving highly specialized personnel [13, 14].

Recent works support the use of Machine Learning (ML) tools into AD research and clinical practice to provide predictions with a certain degree of confidence, pivoting on information about the specific person (personalized medicine; [19–21]). These predictions support improved and more effective decision-making by researchers and clinicians [22, 23]. So far, many of these AI tools focus on predicting the AD conversion in MCI patients using different combinations of data from different sources, including genotyping, CSF biomarkers, brain imaging, demographic and clinical information, and cognitive performance ([18, 24–29]; see [30, 31], for recent reviews). Although some of these models could reach high levels of accuracy [32], consistency regarding what combination of features is more informative to predict AD as well as the translation into clinical practice are still lacking. One possible reason for this is that current AI algorithms still generally rely on expensive and invasive predictors, such as brain imaging or CSF biomarkers. As such, these studies only serve the purpose of a proof of concept, but do not represent a viable substitute of standard approaches with which they share application complexities and economic costs. To overcome these limitations, recent works proposed ML algorithms elaborating only non-invasive and easy-to-collect predictors (e.g., neuropsychological test scores, sociodemographic and clinical features, blood biomarkers) [20, 33].

In this paper, we developed, tested, and compared several ML algorithms and a weighted average rank ensemble ML system on the predictions provided by the various algorithms. The computer simulations show how the ensemble-based approach is a valuable AI tool for early detection of subjects at risk for developing AD. In particular, our system has four critical added values compared with similar approaches proposed in the literature. First, it extends the cohort of subjects by considering both healthy individuals and MCI patients drawn from the ADNI open dataset whereas previous studies mainly focused on MCI population; in this view, the system we proposed is aimed to provide a support for the early diagnosis in pre-clinical stages of AD in absence of MCI, that lacked in previous attempts. Second, it employs individuals whose diagnostic follow-up was available within 9 years after the baseline assessment. Most of the ML works proposed in literature focus on identifying biomarkers for early diagnosis starting from individuals whose diagnostic follow-up reached up to 3 years after the baseline assessment and mainly using a combination of neuroimaging, genetic and clinical data [34–36]. To the best of our knowledge, only few works investigated a greater time window to study the time point for conversion (from normal/MCI to AD) over 8 years using a combination of multi-scale genetic, neuroimaging and clinical data [37] or up to 5 years using MRI data [38]. The ML algorithm we proposed allows us to reach similar time windows (up to 9 years), but using only non-invasive and easily detectable clinical features. Third, it uses an optimized feature selection procedure to identify only five very easy-to-collect predictors based on neuropsychological test scores. This number of features is lower than that used by similar AI approaches [20, 33]. Finally, it shows higher balanced accuracy, negative predictive value, and specificity than previous similar approaches. Overall, these aspects make the AI system we propose here a clinically translatable early diagnostic tool to predict the conversion to AD within 9 years of healthy individuals and MCI patients, based on a low number of cost-effective, fast and easily collectable predictors.
2 Materials and methods

2.1 ADNI dataset

The data used in the preparation of this paper were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public–private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of the ADNI project has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. For the selection and extraction of the dataset, the data were imported into a MySQL database. In order to obtain the best possible dataset, the imported data were checked, cleaned from errors and missing data (such as checking for null values), and organized for the next stage of processing to eliminate redundant or incomplete data and select high-quality data. The database consisted of several tables, one table for each file downloaded from ADNI. The cleaned and selected data were collapsed into a single table through SQL and exported to a single CSV file for subsequent processing.

2.2 Cohort chosen for the study

For this study, we employed data from \( n = 525 \) participants, using identification numbers (RID; each uniquely assigned to a subject). The data were downloaded on Jan 30, 2021. We first manually select 69 features (i.e., test scores) from the ADNI database based on their availability and facility administration in the clinical context (most are already routinely assessed in clinical practice, see below). We used data chosen from ADNI 1 first exam date, then we extracted the data on the same patients (based on RID) in ADNI 2 collected at last 5 years apart. We indicate each feature with the same name used in ADNI. In particular, for each recording related to each patient, we combined demographic measures (sex, age, marital status, handedness, education) (Table 1), data from different neuropsychological tests such as:

- American National Adult Reading Test (ANARTER) which is used to estimate premorbid verbal levels of intelligence in dementing individuals [39].
- Boston Naming Test (BNTTOTAL) which is used to assess naming ability [40].
- Category Fluency Test (CATANIMSC,CATANINTR,CATANPERS) which is a test used to measure ability to spontaneously generate a set of semantically related words in 1 min [39].
- Clinical Dementia Rating (CDR) which is a five-point semi-structured interview between the patient and a reliable informant (e.g., caregivers) designed to stage the severity of dementia considering different aspects (memory (CDMEMORY), orientation (CDORIENT), judgment and problem solving (CDJUDGE), community affairs (CDCOMMUN), home and hobbies (CDHOME), personal care (CDCARE), global summary (CDGLOBAL)) [41, 42].
- Clock Drawing Test (CLOCKSCOR, COPYSCOR) in which subjects draw a clock and set the hands to 10 after 11 [43].
- Cognitive Subscale Alzheimer’s Disease Assessment Scale (ADAS14) (85 points including Q4 (Delayed Word Recall) and Q14 (Number Cancellation)) which is composed of two parts, the noncognitive subscale and the cognitive subscale, and returns a measure index of global cognition [44, 45].
- Geriatric Depression Scale (GDTOTAL) which is a self-report assessment used to identify mood changes in elderly patients [46].
- Neuropsychiatric Inventory Questionnaires, a short version of the Neuropsychiatric Inventory (NPI-SOCORE), which is a brief self-administered questionnaire [47].
- Mini Mental State (MMSCORE) which is a brief questionnaire measuring the global cognitive impairment [48].
- Rey Auditory Verbal Learning Test (RAVLT_forgetting_bl, RAVLT_immediate_bl, RAVLT_learning_bl, RAVLT_perc_forgetting_bl) that is a cognitive test used to evaluate verbal learning and memory [49].
- Trail Making Test (TRAASCOR, TRABSCOR), a test with two parts, the first is relative to psychomotor

| Variable | Value |
|----------|-------|
| Male     | 292   |
| Female   | 233   |
| Age (years) | [55 to 90]; mean 73 |
| Married  | 397   |
| Divorced | 43    |
| MCI      | 241 (EMCI = 55; LMCI = 186); conv. to AD 104 |
| NT       | 284 (SMC = 59); conv. to AD 20 |
| Right hand | 474 |
| Left hand | 51    |
| Education (years) | [6 to 20]; mean 16 |
| Evaluation time lap (years) | [5 to 13]; mean 9 |

EMCI: early MCI; LMCI: late MCI; SMC: subjective memory complaints; NT: normotypical
process, the second is relative to cognitive flexibility [50].

And other data such as:

- Family history (FHQMOM = mother, FHQ-DAD = father, FHQSIB = siblings) relative to dementia.
- Comorbidity with Parkinson’s disease (DXPARK).
- Medical history diseases (psychiatric (MHPSYCH), cardiovascular (MH4CARD), respiratory (MH5RESP), hepatic (MH6HEPAT), dermatological (MH7DERM), musculoskeletal (MH8MUSCL), endocrine-metabolic (MH9ENDO), gastrointestinal (MH10GAST), hematopoietic-lymphatic (MH11HEMA), renal (MH12RENA), allergies (MH13ALLE), alcohol abuse (MH14ALCH), smoking (MH16SMOK), malignancy (MH17MALI), other kind of problems (MH19OTHR)).
- Physical and neurological exams (general appearance (PXGENAPP), head general aspect (PXHEADEY), neck (PXNECK), chest (PXCHEST), heart (PXHEART), abdomen (PXABDOM), peripheral vascular (PXPERIPH), musculoskeletal (PXMUSCUL), visual (NXVISUAL) and auditory (NXAUDITO) impairment, tremor (NXTREMOR), cranial nerves (NXNERVE), motor strength (NXMOTOR), Cerebellar—Finger to Nose (NXFINGER), Cerebellar—Heel to Shin (NXHELL), sensory (NXSENSOR), deep tendon reflexes (NXTENDON), plantar reflexes (NXPLANTA), gait (NXGAIT)).

2.3 Data pre-processing
A logistic lasso regression method was applied as supervised feature selection method with $L1$ regularization [51, 52]. We used this regularization method because it has the effect of keeping in the final model only the most significant features, in particular the method forces the coefficients of less discriminating features toward zero. Furthermore, to face the dataset unbalance we applied the class weights technique modifying the training algorithm to take into account the different numerosity of the classes, giving different weights to the majority and minority classes [53]. Before applying the method all data were subject to standardization (null mean and standard deviation equal to one) in order to homogenize the feature scale. The classification used two classes, ‘convert to Alzheimer’ and ‘non convert to Alzheimer’, as indicated by the last test of each participant of her/his dataset after the evaluation time lapse. As shown in Eq. 1, the logistic regression estimates a binary decision function where the logit can be modeled as a linear function of features:

$$
\log \left( \frac{p(y_i|\mathbf{x}_i)}{1-p(y_i|\mathbf{x}_i)} \right) = \beta_0 + \sum x_{ij} \beta_j,
$$

where “$i$” is the index of sample, “$q$” the index of feature, and $\beta_0$ is the intercept and $\beta_j$ is coefficient of jth feature and $p(y_i|\mathbf{x}_i) = P(Y = 1|\mathbf{x}_i)$ with $Y \in \{0, 1\}$. The $L1$ penalty parameter is introduced into the model to reduce the estimates of the regression coefficients towards zero and to set some of them against the maximum likelihood estimates:

$$
\hat{\beta} = -L(\beta_0, \beta_j) + \lambda \|\beta\|_1,
$$

where $L$ is the log-likelihood function and $\lambda$ is the regularization parameter. We also perform standard statistical data analysis (Tables 2 and 3).

We selected the best parameter $C = 1/2$ weighting the effect of the regularization of the feature selection algorithm through a tenfold cross-validation grid search on

| Feature | Min | Max  | Mean  | Std. dev. |
|--------|-----|------|-------|-----------|
| ADAS14 | 1   | 40   | 15.79 | 8.64      |
| AGE    | 55  | 90   | 73.27 | 6.54      |
| ANARTERR | 0  | 47   | 10.78 | 8.39      |
| BNTOTAL | 11 | 30   | 27.61 | 2.83      |
| CATANIMSC | 6  | 38   | 19.39 | 5.35      |
| CATANINTR | 0  | 6    | 0.06  | 0.46      |
| CATANPERS | 0  | 13   | 0.74  | 1.25      |
| CDCARE | 0   | 1    | 0.01  | 0.12      |
| CDCOMMUN | 0  | 1    | 0.07  | 0.18      |
| CDGLOBAL | 0  | 0.5  | 0.23  | 0.25      |
| CDHOME | 0   | 1    | 0.07  | 0.18      |
| CDJUDGE | 0  | 1    | 0.16  | 0.25      |
| CDMEMORY | 0  | 2    | 0.25  | 0.29      |
| CODIENT | 0   | 2    | 0.10  | 0.22      |
| CLOCKSCOR | 1  | 5    | 4.59  | 0.71      |
| COPYSCOR | 0  | 5    | 4.81  | 0.50      |
| GDTOTAL | 0   | 6    | 1.13  | 1.29      |
| MMSCORE | 24  | 30   | 28.44 | 1.58      |
| NPISCORE | 0  | 17   | 1.25  | 2.23      |
| PTEDUCAT | 6  | 20   | 16.28 | 2.74      |
| RAVLT_forgetting_bl | 3  | 15   | 4.31  | 2.51      |
| RAVLT_immediate_bl | 13 | 70   | 40.72 | 11.24     |
| RAVLT_learning_bl | 0  | 11   | 5.15  | 2.58      |
| RAVLT_perc_forgetting_bl | 37.5 | 100  | 47.18 | 31.46     |
| TRAASCOR | 13 | 150  | 36.01 | 15.35     |
| TRABSCOR | 32 | 300  | 90.92 | 47.92     |

In bold the feature selected by the optimized procedure used for the features selection.
a range of the parameter described by the Python function logspace (0.1, 4, 20) that generates a row vector of 20 logarithmically spaced points between decades $10^{0.1}$ and $10^{4}$. Small values of $C$ imply a strong regularization which leads to find simple models underfitting the data. Large values of $C$ imply a low regularization which allows a higher complexity of the model overfitting the data.

The features selection process used a tenfold cross-validation method. To this purpose, we divided the data into tenfolds (sets). Out of the tenfolds, nine sets were used for training while the remaining set was used for testing; this process was then repeated 10 times using a different fold for each test. The score used in the test directed to isolate the best $C$ was based on the average recall of the two classes. To select only the most relevant features and implement a tighter dimensionality reduction on the method with the best parameter $C$, we selected only features with a coefficient greater than 0.5. In this way, we apply a stricter feature selection by selecting only those features that have an odds ratio greater than $e^{0.5} = 0.64$ and so a odds to have a discriminating impact greater of %60, in fact $(1.64 - 1) = 1.64$.

### 2.4 Classification model

To face the binary classification problem we used an Multi-Experts Ensemble model (MEE) composed of a random forest [54], a Neural Net [55], and a Support Vector Machine [56]. Ensemble methods usually produce more accurate solutions than single models do. This approach obtains the final prediction in the test phases by averaging the predictions of three classifiers with the hard majority voting rule. In developing the assembled classifier in addition to preliminary results, we chose a combination of classifiers that would allow us to analyze three different feature representation spaces based on the main learning paradigms Decision Tree (RF), Kernel Method (SVM) and Deep Learning (NN). To train the system and evaluate its performance we used the 10-Repeated-Nested-10-Fold-Cross-Validation procedure. In particular, we used this method to select the hyperparameters of each model of the ensemble classifier, and to achieve the average performance of ensemble method [57, 58]. In this way, we avoid model overfitting and optimistically biased estimates of model performance.

This procedure was composed of two cross-validation (CV) loops, each implementing a tenfold stratified CV:

- In the outer CV loop designed to obtain an unbiased estimate of model performance, the dataset was partitioned into the ‘Model Development Set’ and the

| Table 3 | Descriptive statistics for the nominal data of all subjects (S25) |
|---------|--------------------------|
| Feature | Mode | Min | Max |
| DXPARK  | 0    | 0   | 1   |
| FHQDAD  | 0    | 0   | 2   |
| FHQMOM  | 0    | 0   | 2   |
| FHQSIB  | 1    | 0   | 1   |
| MHPSCYCH| 0    | 0   | 1   |
| MH2NEURL| 0    | 0   | 0   |
| MH3HEAD | 1    | 0   | 1   |
| MH4CARD | 1    | 0   | 1   |
| MH5RESP | 0    | 0   | 1   |
| MH6HEPAT| 0    | 0   | 1   |
| MH7DERM | 0    | 0   | 1   |
| MH8MUSCL| 1    | 0   | 1   |
| MH9ENDO | 0    | 0   | 1   |
| MH10GAST| 0    | 0   | 1   |
| MH11HEMA| 0    | 0   | 1   |
| MH12RENA| 0    | 0   | 1   |
| MH13ALLE| 0    | 0   | 1   |
| MH14ALCH| 0    | 0   | 1   |
| MH16SMOK| 0    | 0   | 1   |
| MH17MALI| 0    | 0   | 1   |
| MH19OTH-R| 0    | 0   | 1   |
| NXVISUAL| 1    | 1   | 2   |
| NXLIMDIT| 1    | 1   | 2   |
| NXTREMOR| 1    | 1   | 2   |
| NXXNERVE| 1    | 1   | 2   |
| NXXMOTOR| 1    | 1   | 2   |
| NXXFINGER| 1    | 1   | 2   |
| NXHEEL  | 1    | 1   | 2   |
| NXSENSOR| 1    | 1   | 2   |
| NXTENDON| 1    | 1   | 2   |
| NXPLANT  | 1    | 1   | 2   |
| NXGAIT  | 1    | 1   | 2   |
| PTGENDER | 1    | 1   | 2   |
| PTHAND  | 1    | 1   | 2   |
| PTMARRY | 1    | 1   | 5   |
| PXGENAPP | 1    | 1   | 2   |
| PXHEADEY| 1    | 1   | 2   |
| PXNECK  | 1    | 1   | 2   |
| PXCHEST | 1    | 1   | 2   |
| PXHEART | 1    | 1   | 2   |
| PXABDOM | 1    | 1   | 2   |
| PXPERIPH| 1    | 1   | 2   |

In bold the feature selected by the optimized procedure used for the features selection.
‘Test Set’. This is schematized in the upper left part of Fig. 1;

- For each iteration of outer CV loop, an entire inner CV loop was performed. The inner CV loop was designed to select the optimal hyperparameters for the final model through a Grid Search technique with the accuracy on validation set as selection score [59]. The ‘Model Development Set’ was further partitioned into the ‘Training Set’ and ‘Validation Set’. This is schematized in the upper right part of Fig. 1.

The above reported whole procedure was repeated 10 times to verify the robustness of the method and the low influence of the initial random choice of the samples in the tenfolds. The completed procedure is outlined in the lower part of Fig. 1. Table 4 shows details of the three

---

**Table 4** Hyperparameters of the three models forming the MEE, and their range used by the grid search method

| Models                  | Hyperparameters | Range                                             |
|-------------------------|-----------------|---------------------------------------------------|
| Ensemble proposed Neural Net | Optimizer       | {'SGD', 'Adagrad', 'Adadelta', 'Adam', 'Adamax', 'Nadam'} |
|                         | Batch size      | {10, 20, 40, 60, 80, 100}                          |
|                         | Epochs          | {10, 50, 100}                                     |
|                         | Number of hidden units | {2:2:50}                                       |
| Random Forest           | Max depth       | {5, 20, 50, 80, 110}                              |
|                         | Min samples for leaf | {3, 4, 5, 10}                               |
|                         | Min samples for split | {8, 10, 12, 24, 32}                             |
|                         | Number of estimators | {30, 200, 300, 1000}                             |
| Support Vector Machine  | C parameter     | {0.1, 1, 10}                                     |
|                         | γ parameter     | {1, 0.1, 0.01, 0.001}                             |
|                         | Kernel          | {'linear', 'poly', 'rbf', 'sigmoid'}              |
models forming the ensemble as well as the ranges of the hyperparameters used for the grid search. The neural network we used was composed of one hidden layer with rectified linear units, and one output layer with 2 logistic units. The network size was set small due to the small size of the input patterns and to avoid overfitting.

3 Results and discussion
All tests were developed in Python and used Scikit-learn and Keras as main libraries [60]. The first key result of our study comes from the optimized procedure used for the features selection. This isolated only five critical features (on 69 initially considered, see Sect. 2.2) for very early prediction of AD development: one from the CDR, one from the ADAS14, two from the medical history questionnaires (MH3HEAD for Head, Eyes, Ears, Nose and Throat problems, and MH12RENA for Renal-Genitourinary problems), and one from neurological exams (NXHELL Cerebellar Heel to Shin, for cerebellar dysfunction). CDR and ADAS14 are two of the most common tests used in clinical practice for AD diagnosis and evaluation. CDR is a global clinical scale to evaluate different cognitive performances through six specific subscales with established diagnostic and severity-ranking utility and used for research in epidemiological studies and clinical trials as well as for patient evaluation in clinical practice [41, 61]. In particular, the optimized feature selection procedure described in Sect. 2 identified the CDR memory subscale (CDMEMORY) as one of the most relevant features to predict AD development. This result agrees with data suggesting that early episodic memory impairments related to pathologic changes in the hippocampus and entorhinal cortex are common AD initial symptoms. Several data show that memory impairment could be a good predictor for the conversion of MCI in AD [62], and memory dysfunctions could appear up to 7 years before AD diagnosis [63]. Aside from CDMEMORY, the features selection procedure underlined how the ADAS14 score is another critical feature to predict AD development. This result is in line with the crucial role that ADAS14 plays as a gold standard for assessing the efficacy of antidementia treatments [44, 45].

The optimized feature selection procedure also evidenced how some impairments (apparently) far from traditional AD neurodegenerative processes, like head injury and renal and cerebellar dysfunctions, could be critical features to predict AD development. Several studies support this result. Head injuries could lead to long-term problems with cognitive functioning and increase the risk of cognitive decline, which progresses faster in older individuals who suffer from head injuries than in those who did not [64, 65]. In addition, traumatic brain injuries could contribute to AD development, and if present in early or middle life, could increase the risk of late-life AD occurring [66–69].

There is complex pathophysiology of cognitive decline in chronic kidney disease (see [70] for a review). Kidney dysfunctions could contribute to impairments in semantic, episodic, and working memory. Furthermore, a lower estimated glomerular filtration rate at baseline was associated with a more rapid rate of cognitive decline [71].

Genetic mutations in Presenilin-1 protein have been described both in patients with cerebellar ataxia and in early AD onset [7, 72, 73]. In addition, MCI patients show lower cerebellar grey matter volumes compared with age-matched individuals, and total cerebellar grey matter volume decreases as the disease evolves. Furthermore, the decrease of cerebellar grey matter volume appears to be a predictable pattern to cerebellar grey matter atrophy in AD. This cerebellar impairment first affects the vermis

### Table 5 Performance of the ML algorithms

| Classifier models | Sensitivity (%) | Specificity (%) | Precision (%) | NPV (%) | BA (%) | F1-score |
|-------------------|----------------|-----------------|--------------|---------|--------|----------|
| MEE proposed      | 73.5           | 88.3            | 68.3         | 91.5    | 80.9   | 70.8     |
| AdaBoost          | 54.2           | 93.3            | 73.8         | 87.0    | 73.7   | 62.5     |
| MLP               | 76.3           | 78.4            | 54.4         | 91.6    | 77.4   | 63.5     |
| NB                | 48.5           | 90.0            | 61.1         | 85.4    | 69.4   | 54.1     |
| DT                | 59.1           | 87.0            | 66.0         | 87.5    | 73.1   | 62.4     |
| KNN               | 52.8           | 93.5            | 73.4         | 87.4    | 74.6   | 61.4     |
| LR                | 75.0           | 79.5            | 55.2         | 91.3    | 77.3   | 63.6     |
| RF                | 68.6           | 86.0            | 63.1         | 89.9    | 77.3   | 65.7     |
| SVM               | 65.6           | 89.0            | 66.9         | 89.4    | 77.3   | 66.2     |

Sensitivity: ratio between the AD converter subjects correctly labeled by the algorithm and all subjects that actually converted; Specificity: ratio between the non-AD converter subjects correctly labeled by the algorithm and all subjects that have not actually converted; Precision: ratio between the correctly AD converter subjects labeled by the algorithm and the AD converters; Negative predictive value (NPV): the proportion of predicted negatives which are real negatives. It reflects the probability that a predicted negative is a true negative; Balanced accuracy (BA): the average between sensitivity and specificity; F1-score: the harmonic average of the sensitivity and precision.
and the posterior lobe and then the anterior lobe (for a review see [74]). Overall, these results suggest framing AD according to a system-level perspective, where the interactions between brain–body dysfunctions could be critical for early diagnosis [19, 75].

The second interesting result of the present study comes from the analysis of the predictive power of the ML algorithms. The first row of Table 5 reports the performance achieved by the proposed system in terms of sensitivity, specificity, accuracy, negative predictive value, balanced accuracy, and F1-score. To develop a complete comparison, we tested and optimized other classifiers belonging to different learning paradigms, including a Multi-Layer Perceptron (MLP) as a neural network, a k-Nearest Neighbor (kNN) as an instance-based classifier, a Support Vector Machine (SVM) as a kernel machine, a Naive Bayes (NB) as a Bayesian classifier, a Decision Tree (DT) as a non-parametric classifier model, a Logistic Regression (LR) as a probabilistic regression model for classification, and finally a Random Forest (RF) and a Adaptive Boosting (AdaBoost) as a classification ensemble. All these systems were tested and trained with the same technique described in Sect. 2.4.

Table 6 reports for each method the average score obtained during Grid Search and values of hyperparameters most frequently selected during k-fold nested-cross-validation.

| Classifier models | Average score on validation set (%) | Best hyperparameters |
|-------------------|-------------------------------------|----------------------|
| Ensemble          | 78.5                                | Optimizer: Adam      |
| proposed          |                                     | Batch size: 60       |
| NN                |                                     | Epochs: 100          |
|                   |                                     | Number of hidden units: 32 |
| RF                | 81.7                                | Max depth: 80        |
|                   |                                     | Min samples for leaf: 3 |
|                   |                                     | Min samples for split: 12 |
|                   |                                     | Number of estimators: 100 |
| SVM               | 83.5                                | C: 0.1;               |
|                   |                                     | γ: 1;                 |
|                   |                                     | Kernel: radial basic function |
| AdaBoost          | 80.6                                | Algorithm: SAMME     |
|                   |                                     | Learning rate: 0.1   |
|                   |                                     | Number of estimators: 250 |
| MLP               | 72.3                                | Activation: identity |
|                   |                                     | Batch size: 20       |
|                   |                                     | Epochs: 80           |
|                   |                                     | Optimizer: Adam      |
|                   |                                     | Number of hidden units: 16 |
| NB                | –                                   | –                    |
| DT                | 78.3                                | Criterion of split: Gini |
|                   |                                     | Max depth: 2         |
|                   |                                     | Min samples for leaf: 5 |
|                   |                                     | Split method: best   |
| KNN               | 54.2                                | Distance metric: manhattan |
|                  |                                     | Number of neighbors: 19 |
| LR                | 78.6                                | C: 0.0885            |
|                   |                                     | Penalty: L1          |
|                   |                                     | Solver: Newton-cg    |

For all systems, the values of the hyperparameters that were most frequently found to be optimal during the optimization procedure and the average score obtained with the grid search are reported in Table 6, whereas their performance is reported in the remaining rows of Table 5.

Table 5 shows that the ensemble solution produces, on average, better predictive performances than the other algorithms we tested. In addition, compared with similar works that used only non-invasive and easily detectable clinical features [20], our system has a better negative predictive power. In particular, it can predict if a subject will not develop AD with higher performances in terms of specificity, negative predictive value, and balanced accuracy. This result could be critical for developing fast-screening protocols. The other metrics (sensitivity, precision, and F1-score) are similar to those obtained with similar approaches proposed in literature. These works, however, used a substantially larger number of features, prediction windows up to 3 years, and focused only on MCI patients. The ensemble-based ML algorithm proposed here can predict AD development within 9 years from first overt signs not only in MCI patients, but also in healthy individuals.

Despite these encouraging results, future improvements of our approach, for example in terms of generalization, could be obtained by enhancing the heterogeneity of the training set, and including data from different countries (e.g., Asia and Europe). In this way, it would be possible to detect different lifestyle and epigenetic elements that could act as risk or protective factors in AD development.

4 Conclusion
The current approaches for AD diagnosis often require invasive and expensive tools (e.g., brain imaging) and highly specialized personnel, and start at a time-point where the disorder has already caused severe brain damages, the underlying neuropathology may be less sensitive to treatment and the clinical signs are apparent [5, 6, 8].
A critical challenge of our years is to develop an artificial tool able to detect AD onset with many years of advances in order to limit or stop symptoms altogether ([36] for a review). Several works try to answer this question by integrating different aspects of AD pathophysiology, such as neuroimaging, plasma biomarkers, and genetic data [76–79]. The proposed approaches could be very accurate, but also expensive. This aspect could limit their use since another challenge is to make early diagnosis accessible to all [80]. Moreover, most of the ML works proposed in literature focus on identifying biomarkers for early diagnosis starting from individuals whose diagnostic follow-up reached up to 3 years [34, 35].

This article proposes an ensemble-based ML algorithm for predicting AD development within 9 years from first overt signs and using only five non-invasive and easily detectable clinical tests. The results we obtained represent a first important step towards building a preventive fast-screening machine-learning tool usable as part of a routine healthcare visit. In this way, it could help to identify individuals that might develop AD at an early pre-clinical stage and in cost-effective ways without raising undue anxiety associated with attending a specialized clinic [13].

Acknowledgements
This research was supported by the Advanced School in Artificial Intelligence (www.as-ai.org) and by AI2life s.r.l. (www.ai2life.com). Data collection and sharing for this project was funded by the ADNI (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer’s Association, Alzheimer’s Drug Discovery Foundation, Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmmun; F Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer’s Therapeutic Research Institute (www.alzther.org) and by AI2Life s.r.l. (www.ai2life.com). Data collection and sharing for this project was funded by the ADNI (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer’s Association, Alzheimer’s Drug Discovery Foundation, Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmmun; F Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer’s Therapeutic Research Institute (www.alzther.org) and by AI2Life s.r.l. (www.ai2life.com).

Author details
1. Wolters FJ, Chibnik LB, Waziny R et al (2020) Twenty-seven-year-time trends in dementia incidence in Europe and the United States. Neurology 95:e519–e531. https://doi.org/10.1212/WNL.00000000000010022
2. Zhang XX, Tian Y, Wang ZT et al (2021) The epidemiology of Alzheimer’s disease modifiable risk factors and prevention. J Prev Alzheimer’s Dis 8:313–321
3. Scheltens P, Strooper BD, Kivipelto M et al (2021) Alzheimer’s disease. Lancet 397:1577–1590
4. Amieva H, Le Coff M, Millet X et al (2008) Prodromal Alzheimer’s disease: successive emergence of the clinical symptoms. Ann Neurol 64:492–498
5. Beason-Held LL, Goh JO, An Y et al (2013) Changes in brain function occur years before the onset of cognitive impairment. J Neurosci 33:18008–18014
6. Rajan KB, Wilson RS, Weuve J et al (2015) Cognitive impairment 18 years before clinical diagnosis of Alzheimer disease dementia. Neurology 85:898–904
7. Reiman EM, Quroz YT, Fleisher AS et al (2012) Brain imaging and fluid biomarker analysis in young adults at genetic risk for autosomal

References
1. Wolters FJ, Chibnik LB, Waziny R et al (2020) Twenty-seven-year-time trends in dementia incidence in Europe and the United States. Neurology 95:e519–e531. https://doi.org/10.1212/WNL.00000000000010022
2. Zhang XX, Tian Y, Wang ZT et al (2021) The epidemiology of Alzheimer’s disease modifiable risk factors and prevention. J Prev Alzheimer’s Dis 8:313–321
3. Scheltens P, Strooper BD, Kivipelto M et al (2021) Alzheimer’s disease. Lancet 397:1577–1590
4. Amieva H, Le Coff M, Millet X et al (2008) Prodromal Alzheimer’s disease: successive emergence of the clinical symptoms. Ann Neurol 64:492–498
5. Beason-Held LL, Goh JO, An Y et al (2013) Changes in brain function occur years before the onset of cognitive impairment. J Neurosci 33:18008–18014
6. Rajan KB, Wilson RS, Weuve J et al (2015) Cognitive impairment 18 years before clinical diagnosis of Alzheimer disease dementia. Neurology 85:898–904
7. Reiman EM, Quroz YT, Fleisher AS et al (2012) Brain imaging and fluid biomarker analysis in young adults at genetic risk for autosomal
dominant Alzheimer’s disease in the presenilin 1 E280A kindred: a case-control study. Lancet Neurol 11:1048–1056
8. Younes I, Albert M, Moghekar A et al (2019) Identifying changepoints in biomarkers during the preclinical phase of Alzheimer’s disease. Front Aging Neurosci 11:74. https://doi.org/10.3389/FAGNE.2019.00074
9. Isaacs R, Ganzar C, Hirota H et al (2018) The clinical practice of risk reduction for Alzheimer’s disease: a precision medicine approach. Alzheimer’s & Dementia 14:1663–1673
10. Yiannopoulou KG, Papageorgiou SG (2020) Current and future treatments in Alzheimer disease: an update. J Cent Nervous Syst Dis. https://doi.org/10.1177/1759795320952079
11. Matthews FE, Stephan BCM, Robinson L et al (2016) A two decade dementia incidence comparison from the Cognitive Function and Ageing Studies I and II. Nat Commun 7:1–8. https://doi.org/10.1038/ncomms11398
12. Norton S, Matthews F, Barnes D et al (2014) Potential for primary prevention of Alzheimer’s disease: an analysis of population-based data. Lancet Neurol 13:788–794
13. Rasmussen J, Langerman H (2019) Alzheimer’s disease—why we need early diagnosis. Degener Neurol Neuromuscul Dis 1:92–130
14. De Vugt ME, Verhey FR (2013) The impact of early dementia diagnosis and intervention on informal caregivers. Prog Neurobiol 110:54–62
15. Frias CE, Cabrera E, Zabalgue A (2020) Informal caregivers’ roles in dementia: the impact on their quality of life. Life (Basel) 10:251. https://doi.org/10.3390/life10010251
16. Petersen R, Parisi J, Dickson D et al (2006) Neuropathologic features of amnestic mild cognitive impairment. Arch Neurol 63:665–672
17. Roberts R, Knopman D, Mielke M et al (2014) Higher risk of progression to dementia in mild cognitive impairment cases who revert to normal. Neurology 82:317–325
18. Ducat J, Sambaturo F, Bertolino A (2015) Accurate prediction of conversion to Alzheimer’s disease using imaging, genetic, and neuropsychological biomarkers. J Alzheimer’s Dis 49:1143–1159
19. Caligore D, Silvetti M, D’Amelio M et al (2020) Computational modeling of catecholamines dysfunction in Alzheimer’s disease at pre-plaque stage. J Alzheimer’s Dis 77:275–290
20. Grassi M, Roulleaux N, Caldirona D et al (2019) A novel ensemble-based machine learning algorithm to predict the conversion from mild cognitive impairment to Alzheimer’s disease using socio-demographic characteristics, clinical information, and neuropsychological measures. Front Neurol 10:756. https://doi.org/10.3389/fneur.2019.00756
21. Moustafa AA (2021) Alzheimer’s disease: understanding biomarkers, big data, and therapy. Academic Press, London. ISBN 978-0-12-821334-6
22. Hampel H, Vergallo A, Perry G et al (2019) The Alzheimer precision medicine initiative. J Alzheimer’s Dis 68:1–24
23. Perna G, Grassi M, Caldirona D et al (2018) The revolution of personalized psychiatry: will technology make it happen sooner? Psychol Med 48:705–713
24. Liu M, Cheng D, Wang K et al (2018) Multi-modality cascaded convolutional neural networks for Alzheimer’s disease diagnosis. Neuroinformatics 16:295–308
25. Long X, Chen L, Jiang C et al (2017) Prediction and classification of Alzheimer’s disease based on quantification of MRI deformation. PLOS ONE 12:e0173352. https://doi.org/10.1371/JOURNAL.PONE.0173352
26. Pan D, Zeng A, Ja L et al (2020) Early detection of Alzheimer’s disease using magnetic resonance imaging: a novel approach combining convolutional neural networks and ensemble learning. Front Neurosci 14:259. https://doi.org/10.3389/fnins.2020.00259
27. Platero C, Lin L, Tobar MC (2019) Longitudinal neuroimaging hippocampal markers for diagnosing Alzheimer’s disease. Neuroinformatics 17:43–61
28. Gruose S, Viejo-Sobera R (2021) Machine learning methods for predicting progression from mild cognitive impairment to Alzheimer’s disease dementia: a systematic review. Alzheimer’s Res Ther 13:1–29
29. Pradhan N, Singh AS, Singh A (2021) Alzheimer disease early diagnosis and prediction using deep learning techniques: a survey. In: Recent trends in communication and electronics, pp 590–593
30. Odusami M, Maskelilus R, Damaseliucis R et al (2021) Analysis of features of Alzheimer’s disease: detection of early stage from functional brain changes in magnetic resonance images using a Finetuned ResNet18 Network. Diagnostics 11:1071. https://doi.org/10.3390/diagnostics11061071
31. Beltran J, Wahba B, Hose N et al (2020) Inexpensive, non-invasive biomarkers predict Alzheimer transition using machine learning analysis of the Alzheimer’s Disease Neuroimaging (ADNI) database. PLoS ONE 15:e0235663
32. Camnissi DM, Cipriani G, Castelnuovo G (2022) Technological solutions for diagnosis, management, and treatment of Alzheimer’s disease-related symptoms: a structured review of the recent scientific literature. Int J Environ Res Public Health. https://doi.org/10.3390/IJERPH19053122
33. Odusami M, Maskelilus R, Damaseliucis R (2022) An intelligent system for early recognition of Alzheimersdisease using neuroimaging. Sensors. https://doi.org/10.3390/s22030740
34. Silva-Spinola A, Baldeiras I, Arrais JP et al (2022) The road to personalized medicine in Alzheimer’s disease: the use of artificial intelligence. Biomedics. https://doi.org/10.3390/Biomedicines10020315
35. Khanna S, Domingo-Fernández D, Iyappan A et al (2018) Using multi-scale genetic, neuromaging and clinical data for predicting Alzheimer’s disease and reconstruction of relevant biological mechanisms. Sci Rep. https://doi.org/10.1038/541598-018-29433-3
36. Moscoso A, Silva-Rodriguez J, Aldrey JM et al (2019) Prediction of Alzheimer’s disease dementia with MRI beyond the short-term: implications for the design of predictive models. NeuroImage: Clin. https://doi.org/10.1016/j.nicl.2019.101837
37. Battista P, Salvatore C, Castiglioni I (2017) Optimizing neuropsychological assessments for cognitive, behavioral, and functional impairment classification: a machine learning study. Behav Neural. https://doi.org/10.1155/2017/1850909
38. Kaplan E, Goodglass H, Weintraub S (1983) Boston naming test. Lea & Febiger, Philadelphia
39. Hughes CP, Berg L, Danziger WL et al (1982) A new clinical scale for the staging of Dementia. Br J Psychiatry 140:566–572
40. Morris JC (1993) The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 43:2412–2414
41. Pinto E, Peters R (2009) Literature review of the Clock Drawing Test as a tool for cognitive screening. Dementia Geniatr Cognit Disord 27:201–213
42. Kuerer JK, Speckley M, Montero-Idoso M (2018) The Alzheimer’s Disease Assessment Scale-Cognitive Subscale (ADAS-Cog): modifications and responsiveness in pre-dementia populations. A narrative review. J Alzheimer’s Dis 63:423–444
43. Rosen W, Mohs R, Davis K (1984) A new rating scale for Alzheimer’s disease. Am J Psychiatry 141:1356–1364
44. Yesavage JA, Brink TL, Rose TL et al (1982) Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatri Res 17:37–49
45. Cummings JL, Mega M, Gray K et al (1994) The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 44:2308–2314
46. Folstein MF, Robins LN, Helzer JE (1983) The mini-mental state examination. Arch Gen Psychiatry 40:812
47. Rey A (1964) The clinical psychological examination. Presses Universitaires de France, Paris
48. Reitan RM (1971) Trail making test results for normal and brain-damaged children. Percept Motor Skills 33:575–581
49. Fonti V, Belfiore E (2017) Feature selection using lasso. In: VU Amsterdam Research Paper in Business Analytics 30:1–25
50. Muthukrishnan R, Rohini R (2016) Lasso: a feature selection technique for multivariate analysis. Int J Data Mining Knowl Manag Process 3:15–33
51. Fonti V, Belfiore E (2017) Feature selection using lasso. In: VU Amsterdam Research Paper in Business Analytics 30:1–25
52. Forni V, Belfiore E (2017) Feature selection using lasso. In: VU Amsterdam Research Paper in Business Analytics 30:1–25
55. Goodfellow I, Bengio Y, Courville A (2016) Deep learning. MIT Press, Cambridge
56. Svensén M, Bishop CM (2007) Pattern recognition and machine learning. Springer, Berlin
57. Abdar M, Zomorodi-Moghadam M, Zhou X et al (2020) A new nested ensemble technique for automated diagnosis of breast cancer. Pattern Recogn Lett 132:123–131
58. Zhong Y, Chalise P, He J (2020) Nested cross-validation with ensemble feature selection and classification model for high-dimensional biological data. In: Communications in statistics-simulation and computation, pp 1–18
59. Ndlaye E, Le T, Fecq C et al (2019) Safe grid search with optimal complexity. In: International conference on machine learning, PMLR, pp 4771–4780
60. Kynäkides G, Margaritis KG (2019) Hands-on ensemble learning with python: build highly optimized ensemble machine learning models using scikit-learn and Keras. Packt Publishing Ltd, Birmingham
61. Lim WS, Chin JJ, Lam CX et al (2005) Clinical dementia rating experience of a multi-racial Asian population. Alzheimer Dis Assoc Disord 19:135–142
62. Lee YM, Park JM, Lee BD et al (2012) Memory impairment, in mild cognitive impairment without significant cerebrovascular disease, predicts progression to Alzheimer’s disease. Dementia Geriatr Cognit Disord 33:240–244
63. Grober E, CB Hall, Lipton RB et al (2008) Memory impairment, executive dysfunction, and intellectual decline in preclinical Alzheimer’s disease. J Int Neuropsychol Soc 14:266–278
64. Luukinen H, Viramo P, Koski K et al (1999) Head injuries and cognitive decline among older adults a population-based study. Neurology 52:557–557
65. Whitenecx GG, Gerhart KA, Cusick CP (2004) Identifying environmental factors that influence the outcomes of people with traumatic brain injury. J Head Trauma Rehabil 19:191–204
66. Plassman BL, Havlik RJ, Steffens DC et al (2000) Documented head injury in early adulthood and risk of Alzheimer’s disease and other dementias. Neurology 55:1158–1166
67. Rasmussen D, Brandt J, Martin D et al (1995) Head injury as a risk factor in Alzheimer’s disease. Brain Inj 9:213–219
68. Schofield P, Tang M, Mander K et al (1997) Alzheimer’s disease after remote head injury: an incidence study. J Neurol Neurosurg Psychiatry 62:119–124
69. Sivanandam TM, Thakur MK (2012) Traumatic brain injury: a risk factor for Alzheimer’s disease. Neurosci Biobehav Rev 36:1376–1381
70. Etgen T (2015) Kidney disease as a determinant of cognitive decline and dementia. Alzheimer’s Res Ther 7:29. https://doi.org/10.1186/s13195-015-0115-4
71. Buchman AS, Tanne D, Boyle PA et al (2009) Kidney function is associated with the rate of cognitive decline in the elderly. Neurology 73:920–927
72. Braga-Neto P, Pedroso JL, Alessi H et al (2013) Early-onset familial Alzheimer’s disease related to presenilin 1 mutation resembling autosomal dominant spinocerebellar ataxia. J Neurol 260:1177–1179
73. Testi S, Peluso S, Fabrici GM et al (2014) A novel PSEN1 mutation in a patient with sporadic early-onset Alzheimer’s disease and prominent cerebellar ataxia. J Alzheimer’s Dis 41:709–714
74. Jacobs HL, Hopkins DA, Mayrhofer HC et al (2018) The cerebellum in Alzheimer’s disease: evaluating its role in cognitive decline. Brain 141:37–47
75. Caligore D, Helmich RC, Hallert M et al (2016) Parkinson’s disease as a system-level disorder. NPJ Parkinson’s Dis 2:1–9. https://doi.org/10.1038/npjparkd.2016.25
76. Jo T, Nho K, Risacher SL et al (2019) Deep learning detection of informative features in tau PET for Alzheimer’s disease classification. BMC Bioinform. https://doi.org/10.1186/s12859-020-03848-0
77. Lin CH, Chiu SI, Chen TF et al (2020) Classifications of neurodegenerative disorders using a multiplex blood biomarkers-based machine learning model. Int J Mol Sci 21:1–15
78. Nguyen DT, Ryu S, Qureshi MN et al (2019) Hybrid multivariate pattern analysis combined with extreme learning machine for Alzheimer’s dementia diagnosis using multi-measure rs-fMRI spatial patterns. PLOS ONE. https://doi.org/10.1371/JOURNAL.PONE.0218826
79. Nunes A, Silva G, Duque C et al (2019) Retinal texture biomarkers may help to discriminate between Alzheimer’s, Parkinson’s, and healthy controls. PLOS ONE. https://doi.org/10.1371/JOURNAL.PONE.0218826
80. Clute-Reinig N, Jayadev S, Rhoads K et al (2021) Alzheimer’s disease diagnostics must be globally accessible. J Alzheimer’s Dis 84:1453–1455

**Publisher’s Note**
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.