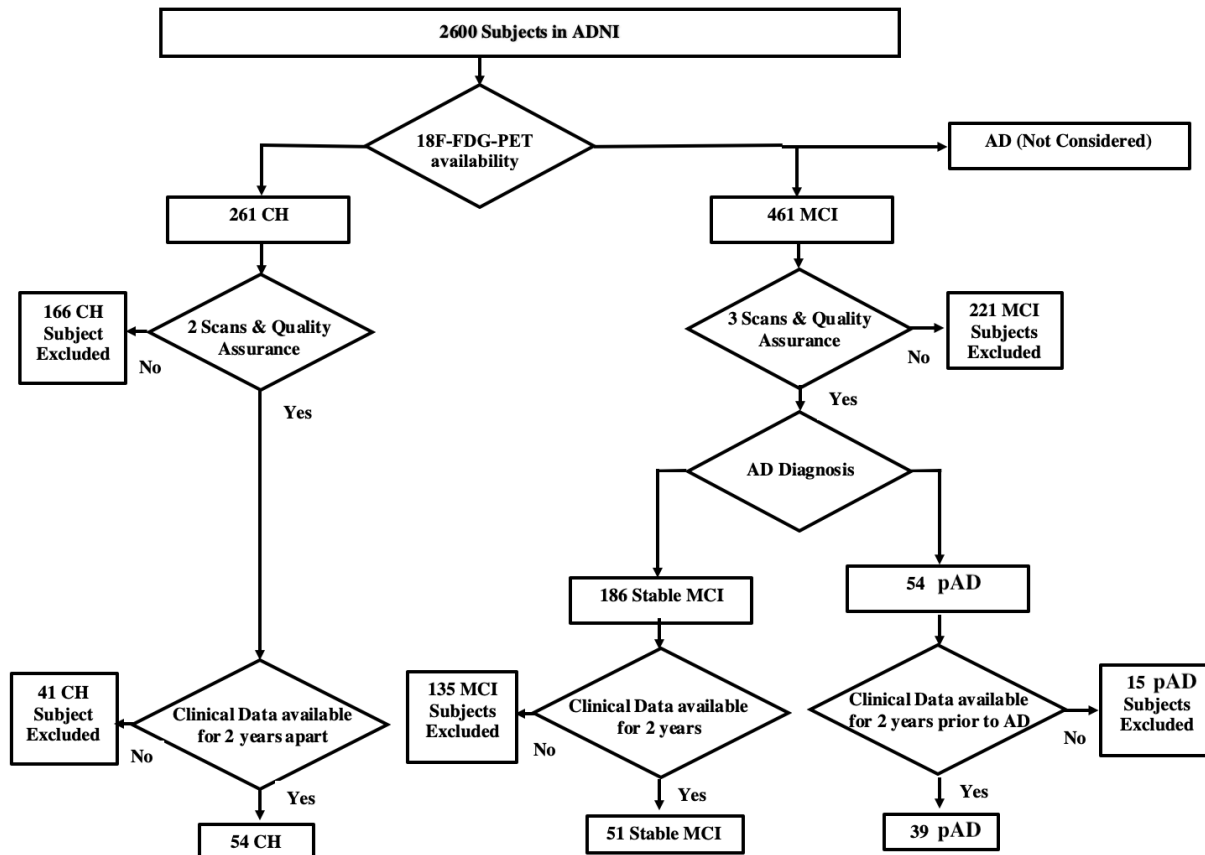


Supplementary Material

Monitoring Alzheimer's Disease Progression in Mild Cognitive Impairment Stage Using Machine Learning-Based FDG-PET Classification Methods



Supplementary Figure 1. Subject selection flowchart used in this study. The Alzheimer's Disease Neuroimaging Initiative (ADNI) database comprised over 2,600 subjects, including 452 patients with Alzheimer's disease (AD), 683 individuals with mild cognitive impairment (MCI), 185 late MCI, 340 early MCI, 115 significant memory concern, and 521 cognitively healthy (CH) subjects. For the purpose of this study, MCI, early MCI, and late MCI are merged. Based on availability of ^{18}F -FDG-PET scans, 261 CH and 461 MCI subjects were identified. Patients who were diagnosed with AD at baseline were not considered for the purpose of this study. Participants who were consecutively scanned (2 times for CH and 3 times for MCI) were included (CH, N = 95; MCI, N = 240). Due to a paucity of clinical data throughout the follow-up period, 41 CH participants were eliminated. As a result, 54 CH participants were considered in this study. Based on the follow-up diagnosis of MCI patients, we stratified them into stable MCI (n=186) and 54 MCI patients who converted to AD (prodromal AD; pAD). 221 MCI patients were excluded due to the unavailability of three consecutive FDG-PET scans and/or low quality of the images. 135 sMCI and 15 pAD patients were excluded due to lack of clinical data throughout the follow-up period, which resulted 51 sMCI, and 39 pAD in this analysis.

Supplementary Table 1. Different MAD scores according to the five different approaches in different groups and time.

		Different MAD scores				
Group	Time point	GLM	SSM/PCA1	SSM/PCA2	SVM-ISDA	SVM-SMO
CH	Year 0	-0.19 [-0.40, 0.03]	0.06 [-0.22,0.33]	0.05 [-0.22,0.32]	0.05 [-0.22,0.32]	0.04 [-0.22, 0.31]
	Year -1	n/a	n/a	n/a	n/a	n/a
	Year -2	-0.02 [-0.28, 0.24]	0.06 [-0.21,0.33]	-0.05 [-0.21,0.32]	0.06 [-0.20, -0.32]	0.06 [-0.20, 0.32]
MC	Year 0	-0.91 [-1.17, -0.64]	0.87 [0.51,1.23]	1.25 [0.88,1.61]	2.73 [1.95, 3.51]	3.68 [2.63,4.73]
	Year -1	-0.99 [-1.24, -0.74]	0.79 [0.41, 1.17]	1.08 [0.73,1.44]	2.39 [1.68, 3.10]	3.17 [2.22, 4.11]
	Year -2	-1.06 [-1.28, -0.85]	0.64 [0.29, 0.99]	0.94 [0.64,1.24]	2.21 [1.60, 2.83]	2.95 [2.12, 3.78]
pAD	Year 0	1.71 [1.30, 2.13]	2.72 [2.19,3.26]	3.12 [2.61,3.63]	5.98 [4.88, 7.08]	7.92 [6.49, 9.37]
	Year -1	1.25 [0.89, 1.61]	2.19 [1.74, 2.64]	2.57 [2.13, 3.01]	5.18 [4.11, 6.25]	6.90 [5.50, 8.31]
	Year -2	0.97 [0.65, 1.28]	1.96 [1.53, 2.39]	2.35 [1.84, 2.63]	4.17 [3.19, 5.15]	5.44 [4.11, 6.77]

CH, cognitively healthy; MCI, mild cognitive impairment; pAD, prodromal Alzheimer's disease; All data are based on z-score values generated by the MAD framework and presented based on mean and 95% confidence intervals (CI); n/a, not available.

Supplementary Table 2. Group comparison on longitudinal test sets with respect to different prediction models and timepoints in the clinical groups.

Algorithm	Group	Year -2 versus Year -1		Year -1 versus Year 0		Year -2 versus Year 0	
		MD	p	MD	p	MD	p
GLM	CH	n/a	n/a	n/a	n/a	0.16	0.025
	MCI	0.07	0.76	0.45	0.52	0.17	0.14
	AD	0.28	0.01	0.95	<0.001	0.73	<0.001
SSM/PCA1	CH	n/a	n/a	n/a	n/a	0.00	0.99
	MCI	0.16	0.29	0.07	1.00	0.23	0.17
	AD	0.22	0.18	0.54	<0.001	0.76	<0.001
SSM/PCA2	CH	n/a	n/a	n/a	n/a	0.00	0.92
	MCI	0.15	0.20	0.15	0.30	0.30	0.02
	AD	0.32	0.002	0.56	<0.001	0.88	<0.001
SVM-ISDA	HC	n/a	n/a	n/a	n/a	0.01	0.87
	MCI	0.17	1.00	0.34	0.14	0.51	0.04
	AD	1.02	<0.001	0.80	<0.001	1.82	<0.001
SVM-SMO	HC	n/a	n/a	n/a	n/a	0.01	0.84
	MCI	0.19	1.00	0.52	0.08	0.76	0.04
	AD	1.48	<0.001	1.02	<0.001	2.50	<0.001

MD is absolute value of mean difference between two time points. Adjustment for multiple comparisons: Bonferroni. Age at baseline and sex was used as covariates in the model. The effect of time in CH was evaluated using paired t-test.