

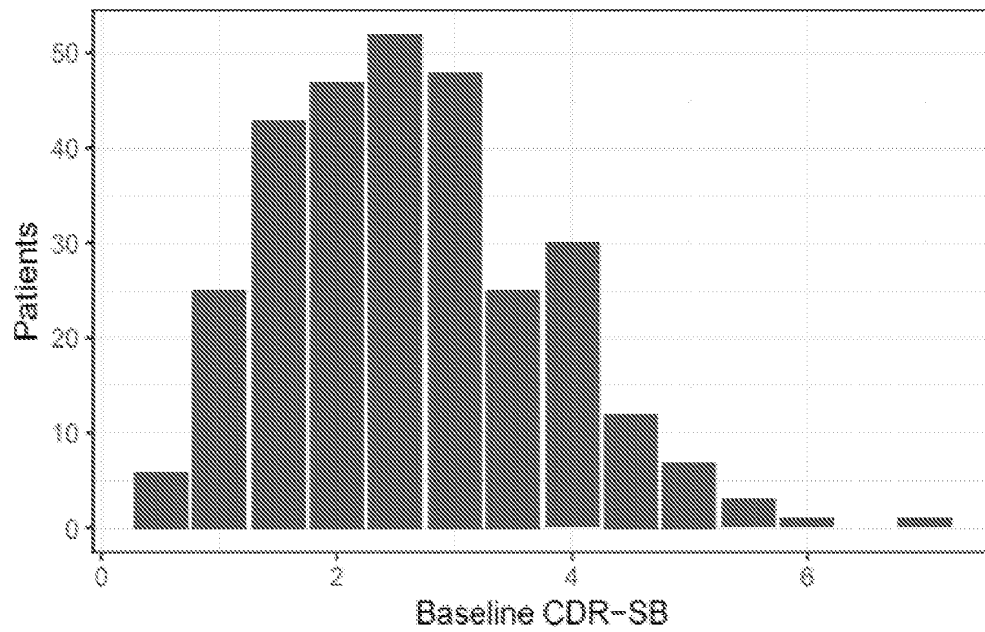


FIG. 1A

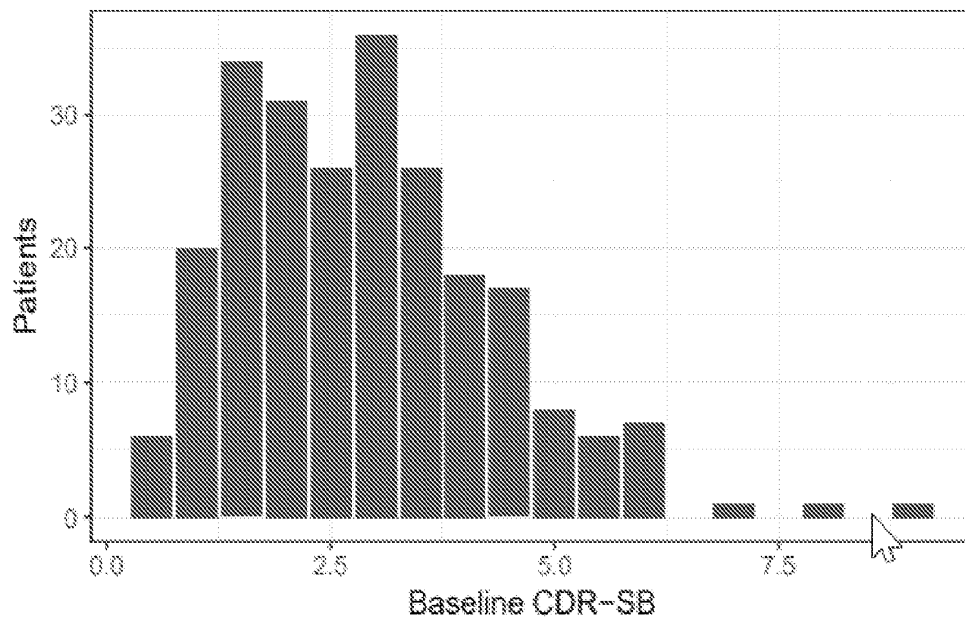


FIG. 1B

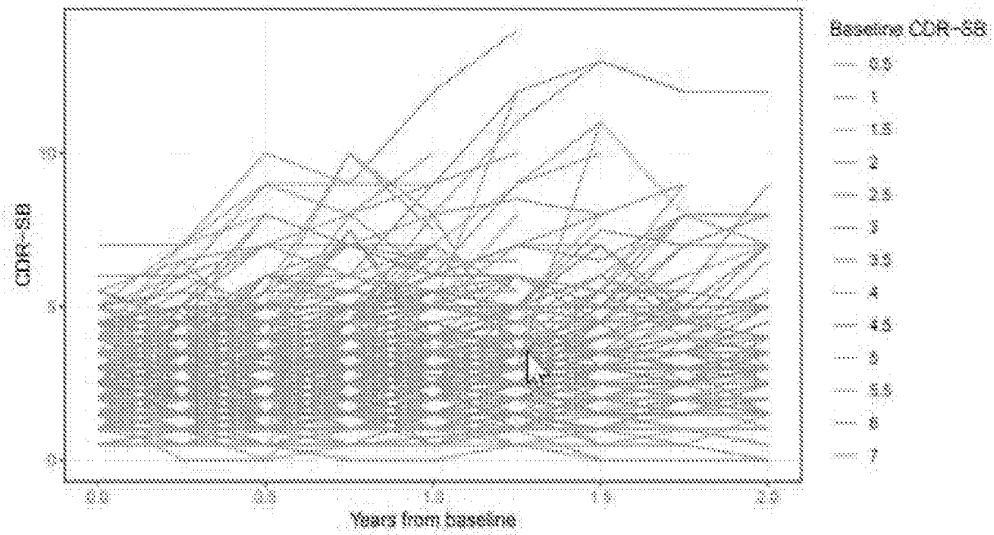


FIG. 1C

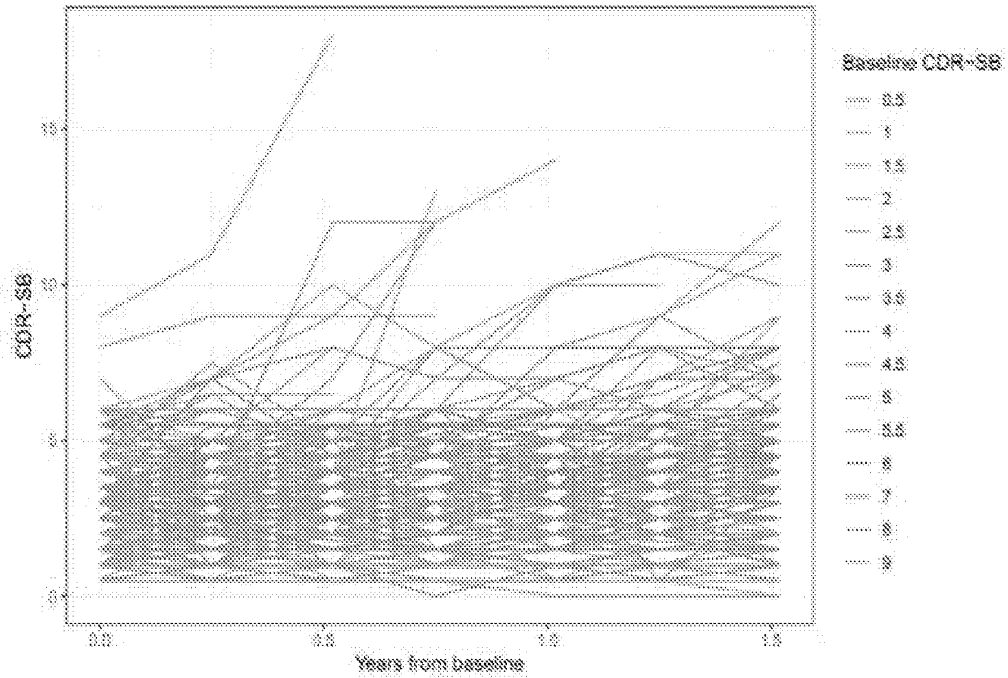
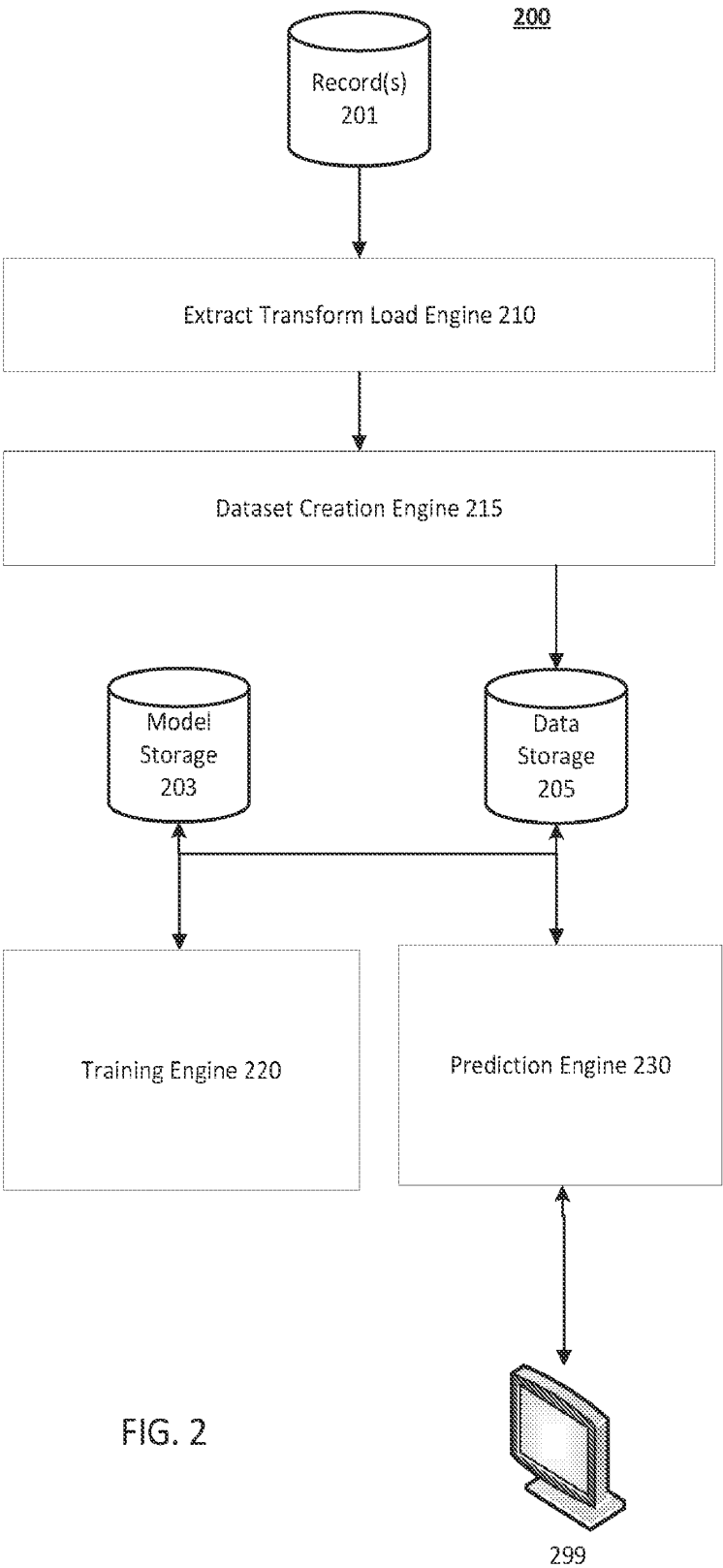


FIG. 1D



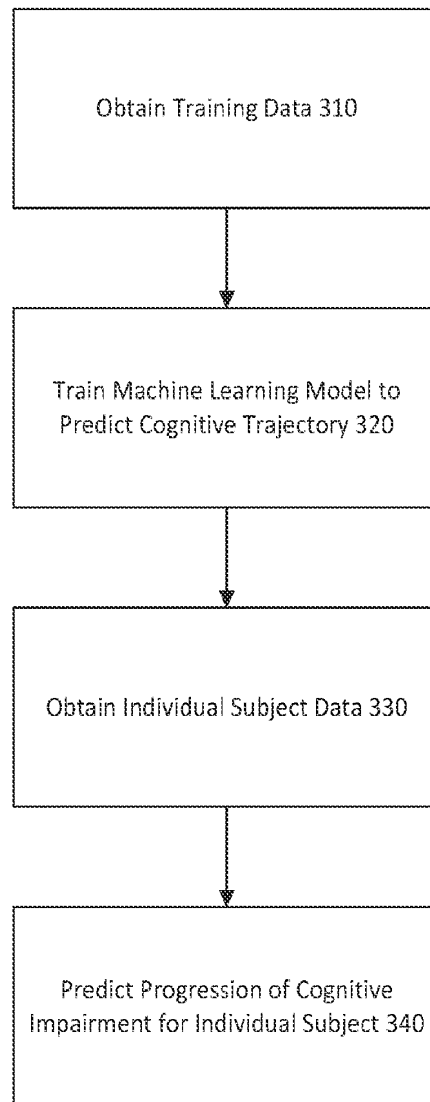
300

FIG. 3

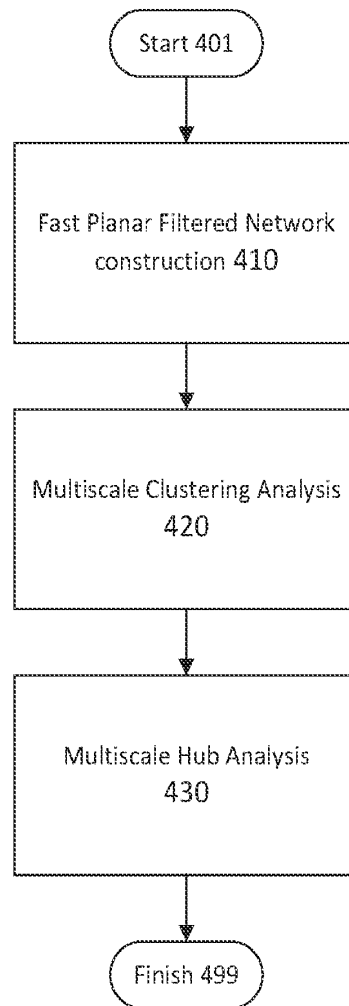
400

FIG. 4

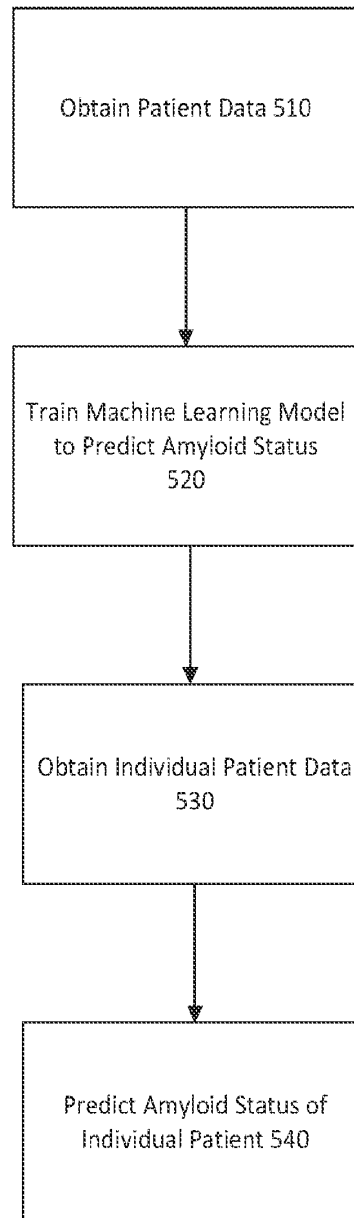
500

FIG. 5

		Training Cohort (TC)		Validation Cohort 1 (VC-1)		Validation Cohort 2 (VC-2)	
		Slower CD (N = 66)	Faster CD (N = 69)	Slower CD (N = 52)	Faster CD (N = 63)	Slower CD (N = 121)	Faster CD (N = 53)
Gender	F (%)	31 (47.0%)	34 (49.3%)	24 (46.2%)	40 (63.4%)*	59 (48.8%)	19 (35.9%)
ApoE	E4 (%)	39 (59.1%)	49 (71.1%)	37 (71.2%)	48 (76.2%)	83 (68.6%)	37 (69.8%)
Age	Mean (SD)	71.8 (6.7)	73.9 (6.9)*	71.1 (7.7)	71.3 (9.9)	71.9 (6.6)	73.2 (6.7)
BMI	Mean (SD)	27.9 (6.1)	25.3 (4.0)*	26.6 (3.8)	25.2 (3.2)*	28.0 (5.7)	27.0 (4.8)
MMSE	Mean (SD)	26.6 (2.7)	25.4 (2.8)*	27.4 (2.0)	26.0 (2.3)*	27.9 (1.8)	27.0 (1.8)*

*: $p < 0.05$; CD: 18-month cognitive decline; Faster CD: 18-month change in CDR-SB ≥ 1 ; Slower CD: 18-month change in CDR-SB < 1

FIG. 6A

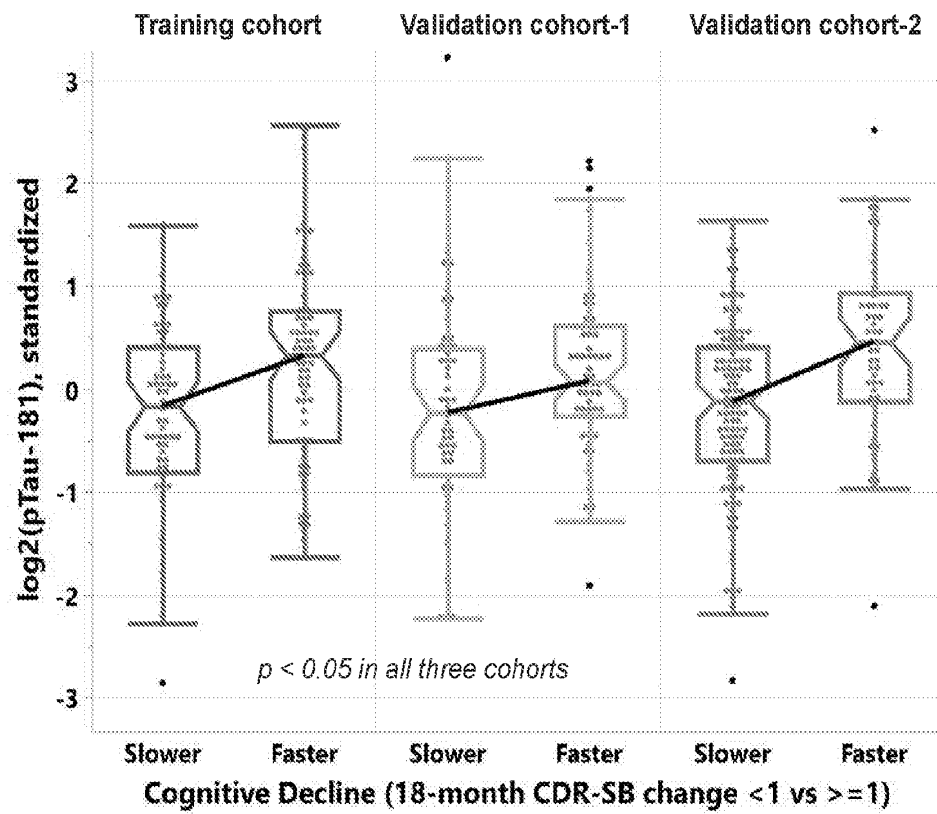


FIG. 6B

Prediction signatures	Validation Cohort-1 (VC-1; clinical trial)				Validation Cohort-2 (VC-2; ADNI)					
	18-month cognitive decline (CD)				18-month cognitive decline (CD)				36m MCI to AD prog.	
	Sens.	Spec.	ROC-AUC	p-value	Sens.	Spec.	ROC-AUC	p-value	ROC-AUC	p-value
p-Tau181	58.7%	59.6%	64.9%		74.2%	44.0%	65.3%		72.1%	
Cognitive	68.3%	65.4%	70.9%	0.002	71.2%	53.0%	66.7%	< 0.001	72.3%	< 0.0001
p-Tau181 + Cognitive	66.7%	67.3%	74.7%		74.2%	54.5%	71.1%		79.1%	
Cognitive + MRI	62.9%	76.9%	77.2%	0.18	48.8%	82.8%	76.1%	0.227	84.7%	0.0008
p-Tau181 + Cognitive + MRI	66.1%	75.0%	79.2%		63.4%	78.5%	77.2%		87.5%	

FIG. 6C

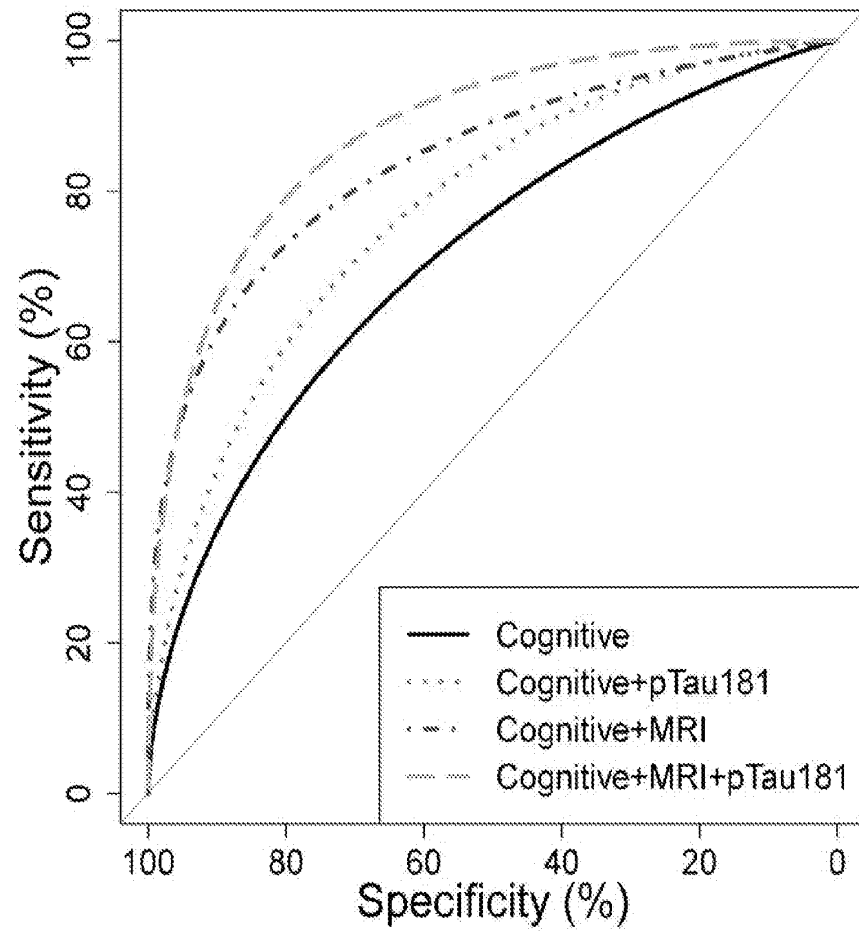


FIG. 6D

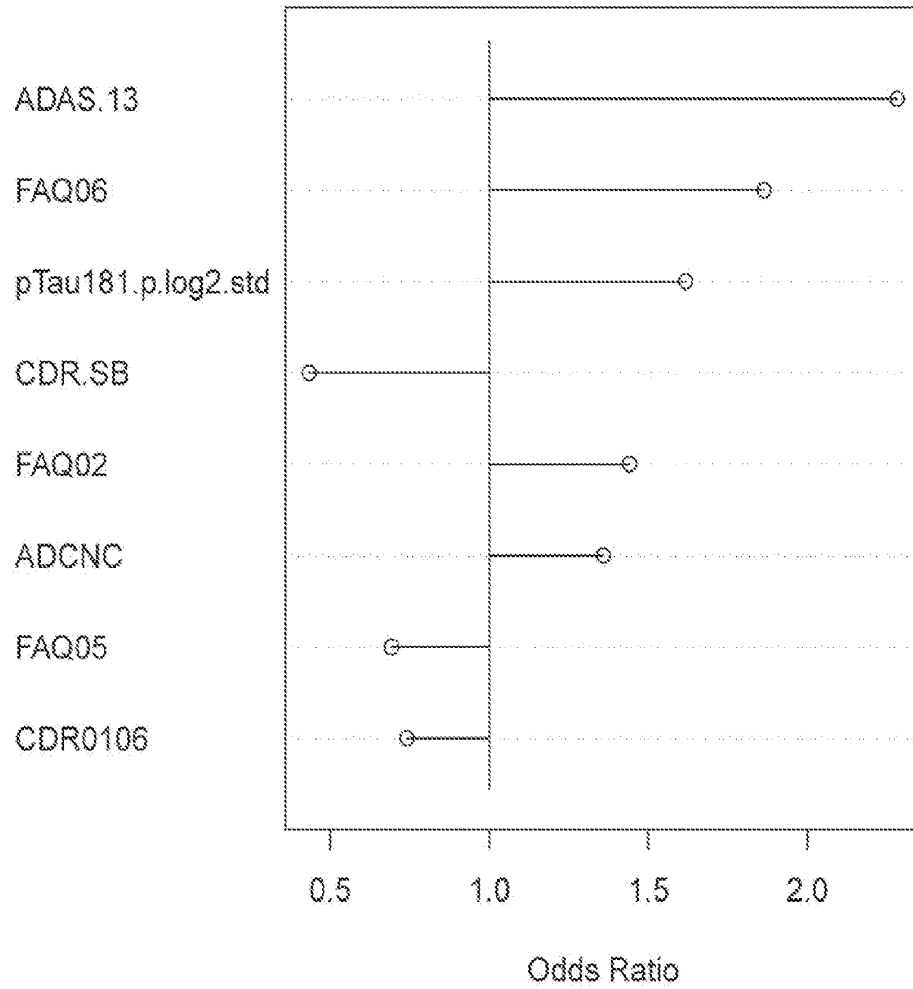


FIG. 6E

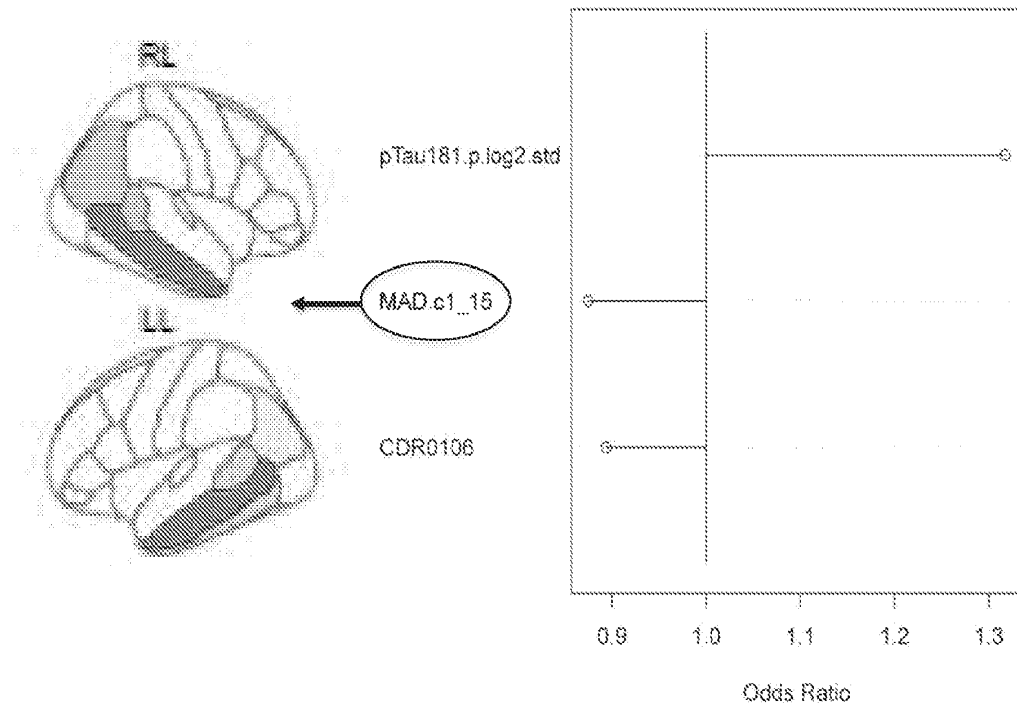


FIG. 6F

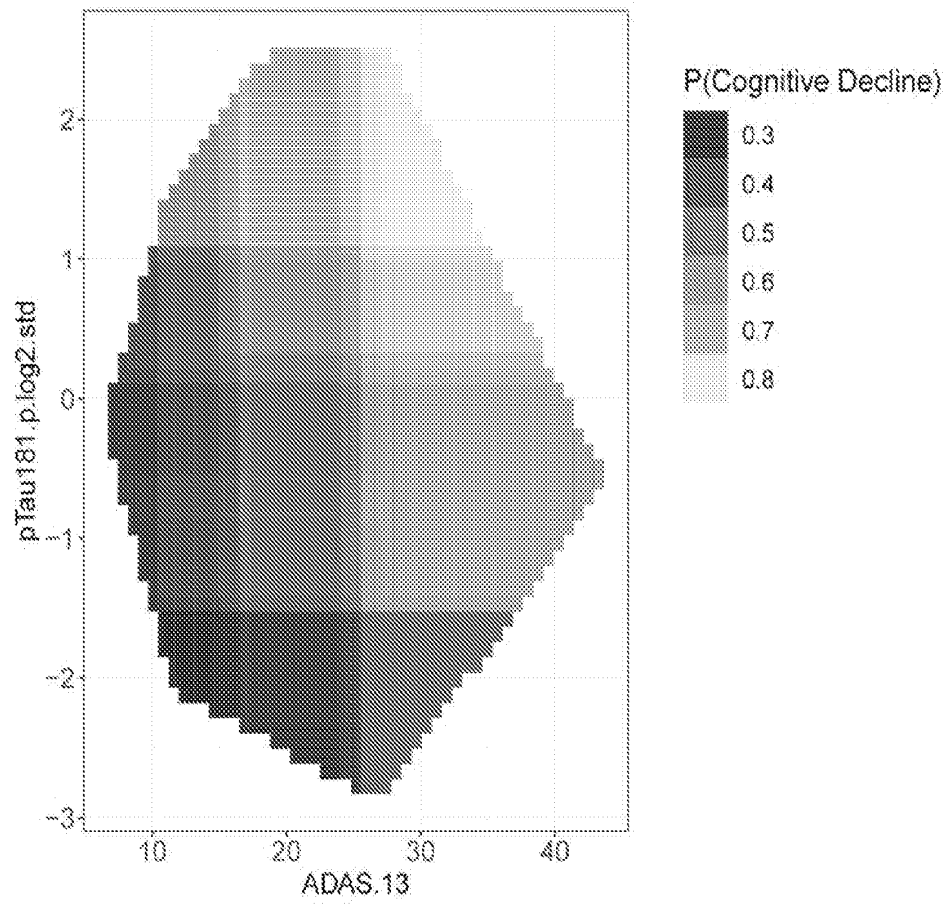


FIG. 6G

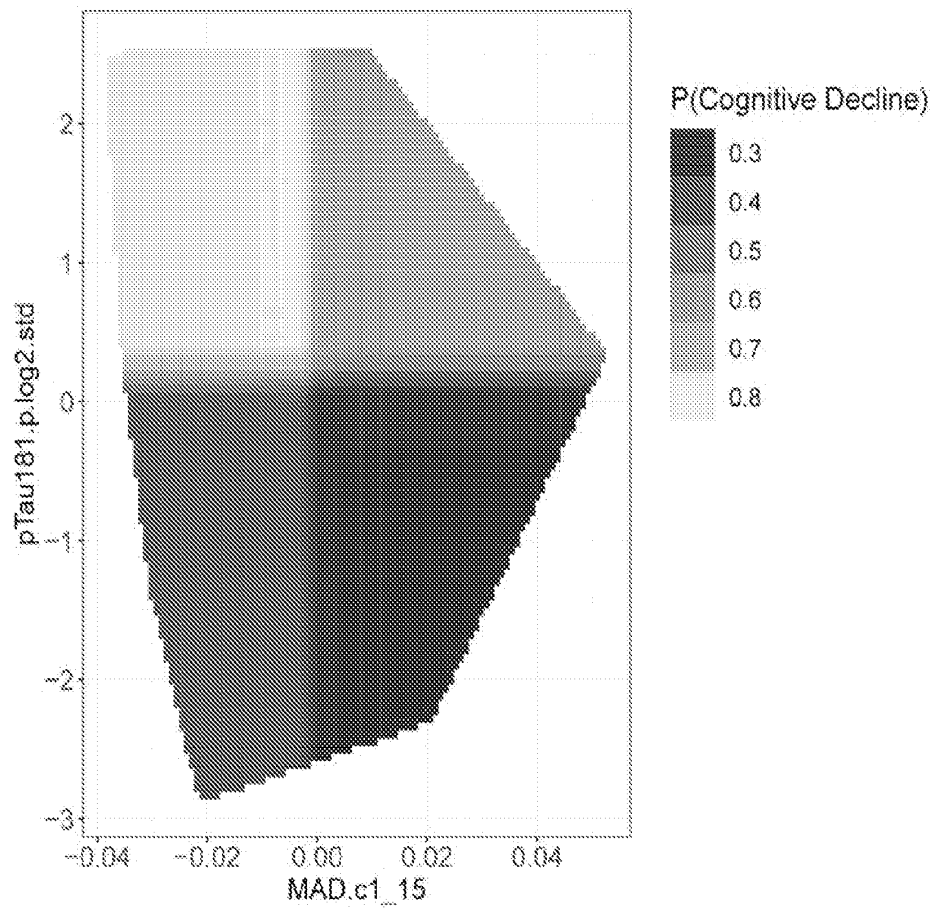


FIG. 6H

		Subjects with Plasma Aβ Data*		Subjects with Plasma pTau-181 Data†		Subjects with Plasma Aβ & pTau-181 Data‡	
		Amyloid Neg. (N=241)	Amyloid Pos. (N=272)	Amyloid Neg. (N=238)	Amyloid Pos. (N=160)	Amyloid Neg. (N=233)	Amyloid Pos. (N=60)
Gender	F (%)	127 (52.7%)	119 (43.8%)	127 (53.3%)	73 (45.6%)	125 (53.7%)	19 (47.5%)
ApoE	E4 (%)	84 (34.9%)	152 (55.9%)	78 (32.8%)	109 (68.1%)	78 (33.5%)	28 (65.0%)
Age	Mean (SD)	71.0 (6.7)	74.1 (6.3)	71.0 (6.7)	72.7 (6.6)	71.0 (6.7)	73.2 (6.3)
BMI	Mean (SD)	29.2 (5.0)	27.2 (4.6)	29.2 (5.1)	26.5 (4.8)	29.3 (5.0)	27.7 (5.4)
MMSE	Mean (SD)	26.3 (1.7)	26.3 (1.8)	26.3 (1.7)	26.6 (1.9)	26.3 (1.7)	27.0 (1.8)
		*Only MMSE is not significantly different		†Only BMI & Gender are not significantly different		‡Only ApoE status is significantly different	

FIG. 7A

Scenarios (data type)	Algorithm	Internal Cross-Validation Performance			Test Set Performance		
		BA	Sens.	Spec.	BA	Sens.	Spec.
ApoE	BEN	72.0%	67.4%	76.6%	73.8%	78.7%	68.9%
CogState	BEN	66.0%	66.5%	65.6%	65.9%	68.7%	63.2%
ApoE+ CogState	BEN	73.0%	71.0%	75.2%	75.4%	80.0%	70.7%
A β	MCL	75.6%	77.5%	73.7%	77.3%	74.1%	80.6%
A β + ApoE	MCL	75.2%	77.3%	73.1%	79.4%	85.2%	73.6%
A β + CogState	MCL	76.8%	78.8%	74.8%	76.2%	76.3%	76.1%
<i>Aβ+ CogState + ApoE</i>	<i>BEN</i>	<i>77.9%</i>	<i>79.5%</i>	<i>76.4%</i>	<i>77.8%</i>	<i>76.1%</i>	<i>79.4%</i>
A β + CogState + ApoE+ MRI	SGB	77.2%	80.1%	74.4%	72.6%	79.5%	65.7%
pTau	SGB	76.0%	76.8%	75.3%	77.9%	81.3%	74.6%
pTau+ ApoE	BEN	78.5%	77.7%	79.4%	78.8%	78.0%	79.5%
pTau+ CogState	BEN	78.2%	71.2%	85.3%	77.4%	75.0%	79.7%
<i>pTau+ CogState + ApoE</i>	<i>BEN</i>	<i>82.0%</i>	<i>82.0%</i>	<i>82.1%</i>	<i>81.5%</i>	<i>77.6%</i>	<i>85.5%</i>
pTau+ CogState + ApoE+ MRI	MCL	81.1%	78.1%	84.1%	81.8%	83.3%	80.3%
A β , pTau	SGB	77.9%	78.6%	77.2%	83.1%	83.3%	82.9%
A β , pTau+ ApoE	SGB	80.6%	82.1%	79.0%	80.8%	83.3%	78.3%
<i>Aβ, pTau+ CogState</i>	<i>SGB</i>	<i>81.4%</i>	<i>82.1%</i>	<i>80.6%</i>	<i>81.7%</i>	<i>75.0%</i>	<i>88.4%</i>
A β , pTau+ CogState + ApoE	SGB	82.6%	82.1%	83.1%	74.5%	66.7%	82.4%
A β , pTau+ CogState + ApoE+ MRI	SGB	76.8%	75.0%	78.7%	84.0%	83.3%	84.6%

FIG. 7B

Signature using plasma A β ₄₂ /
A β ₄₀, CogState & ApoE4

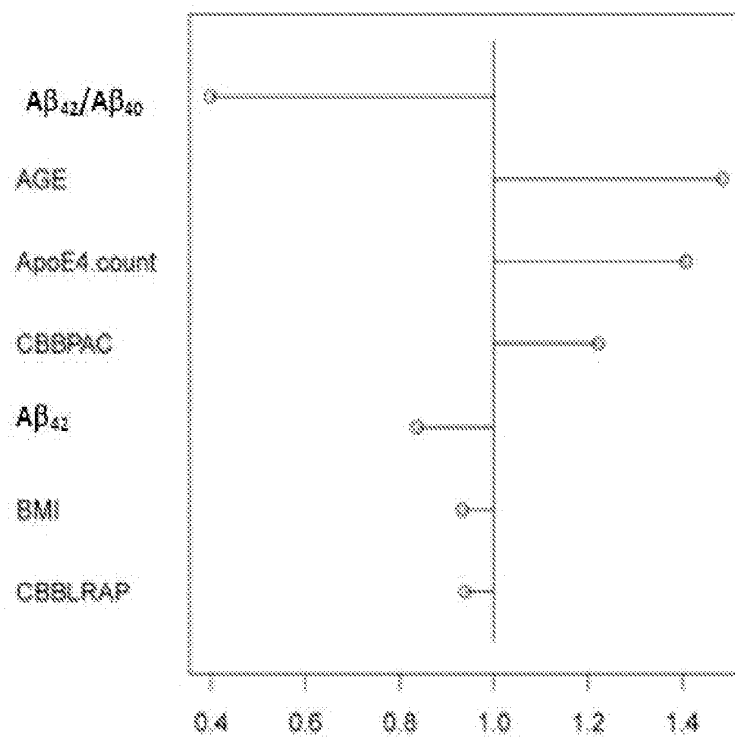


FIG. 7C

Signature using plasma pTau-181, CogState & ApoE4

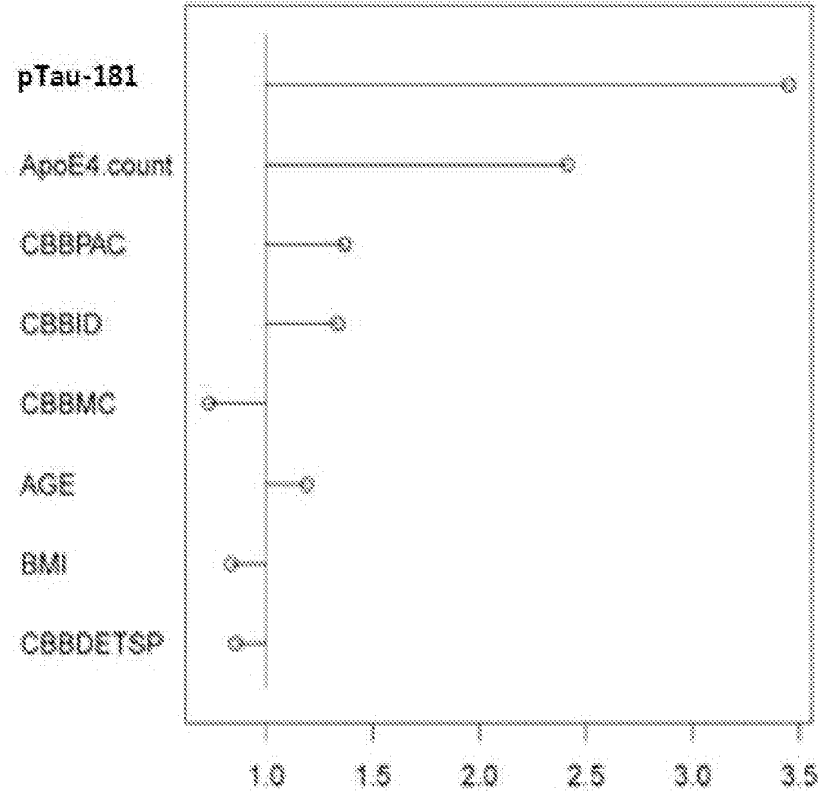


FIG. 7D

Signature using plasma A β 42 /
A β 40, pTau-181, CogState

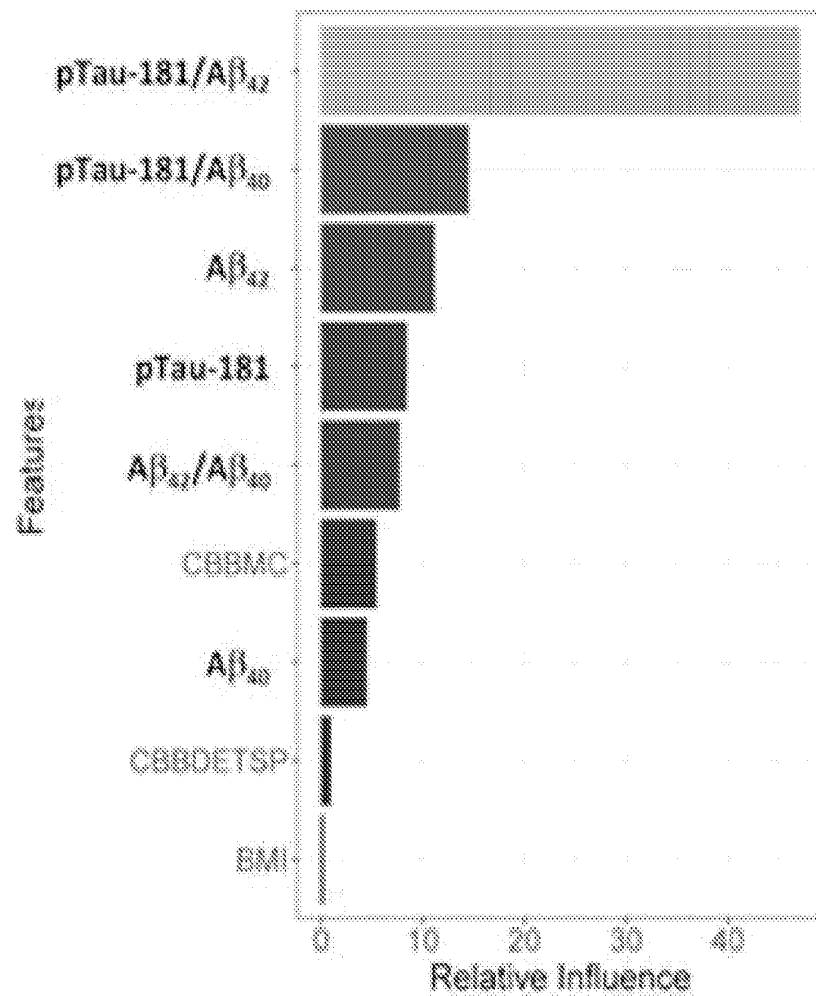


FIG. 7E

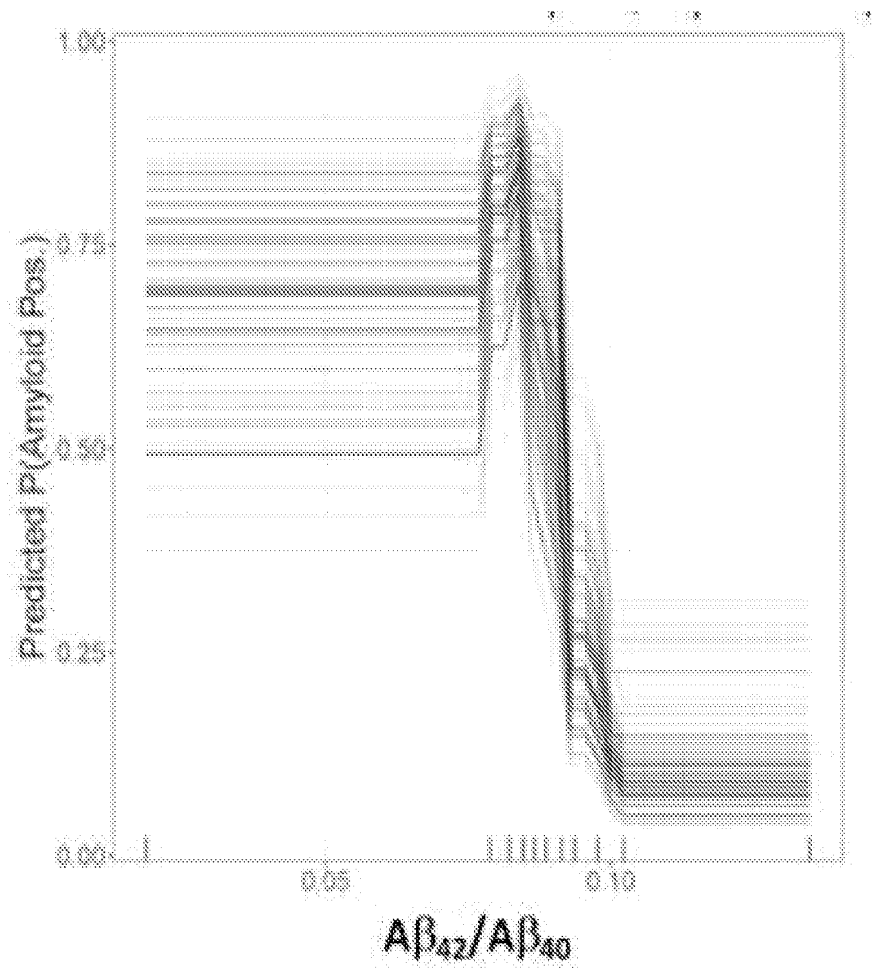


FIG. 7F

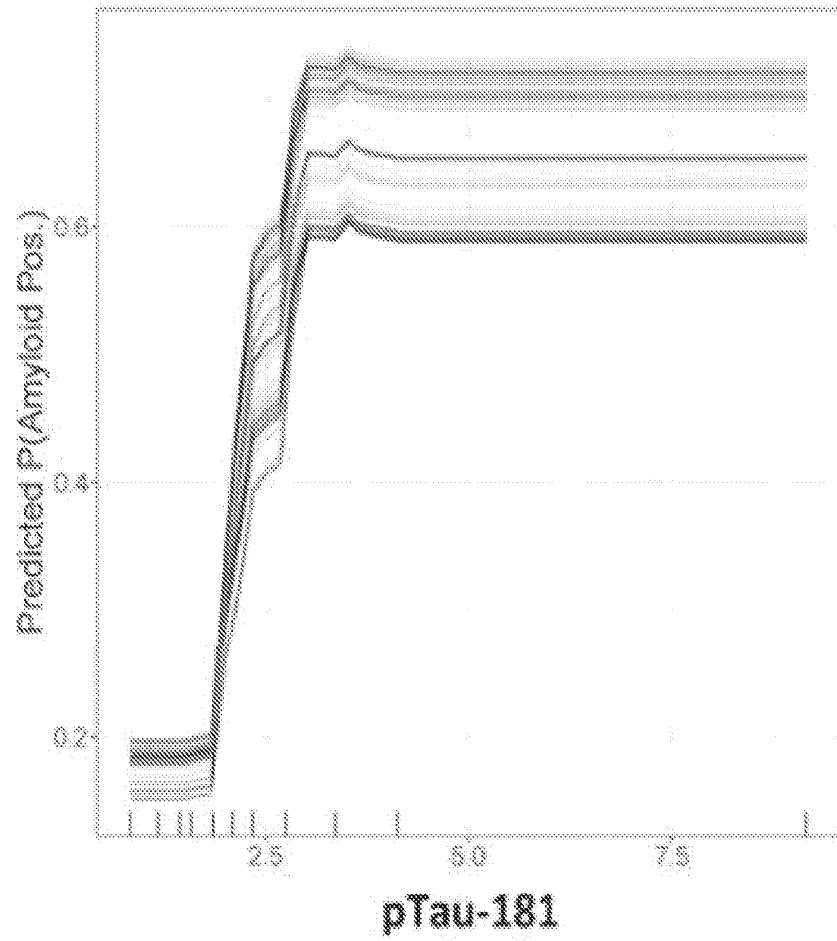


FIG. 7G

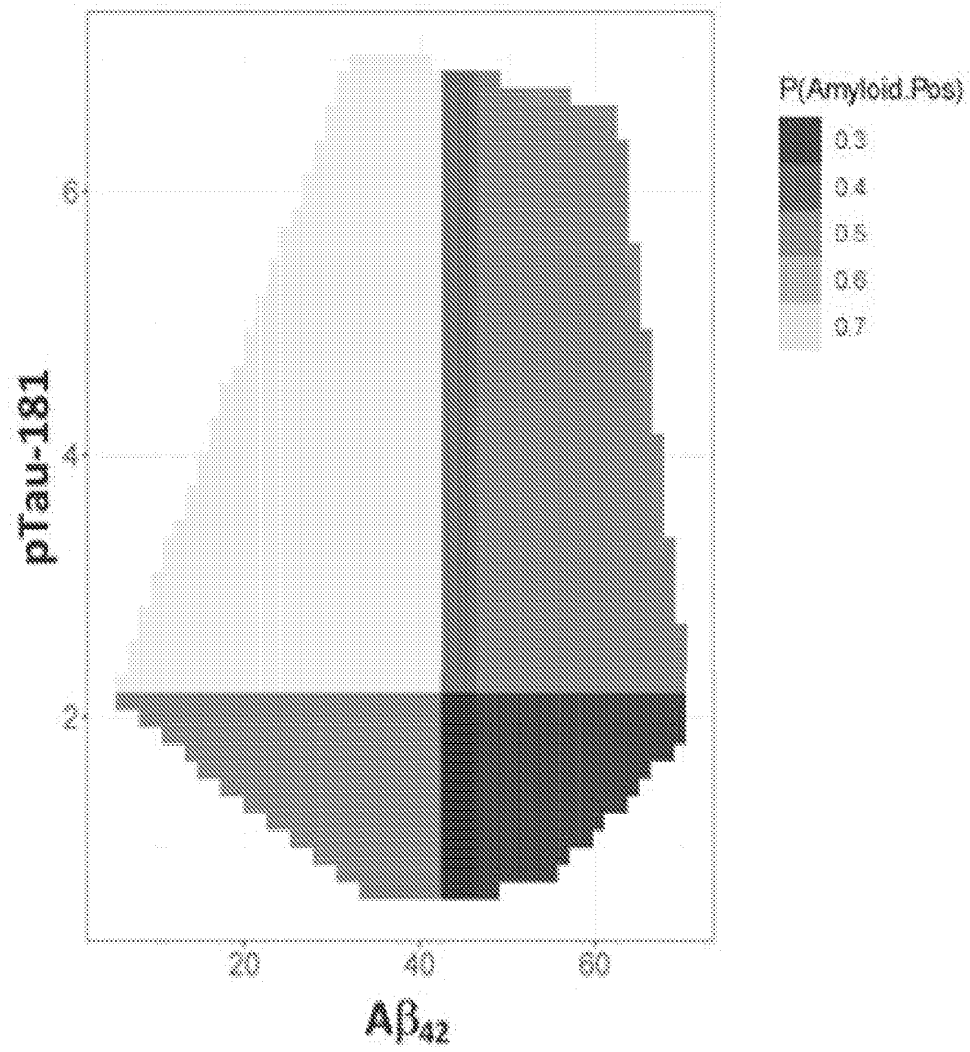


FIG. 7H

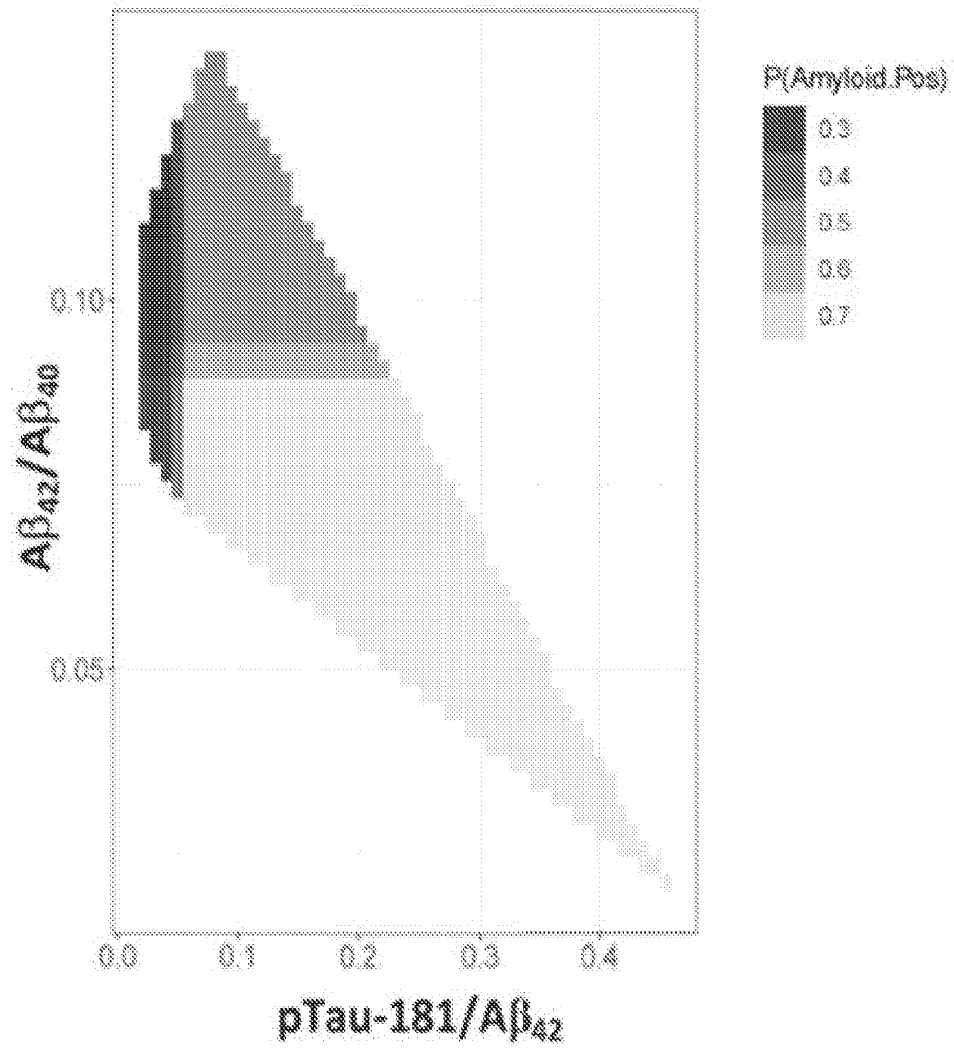


FIG. 7I

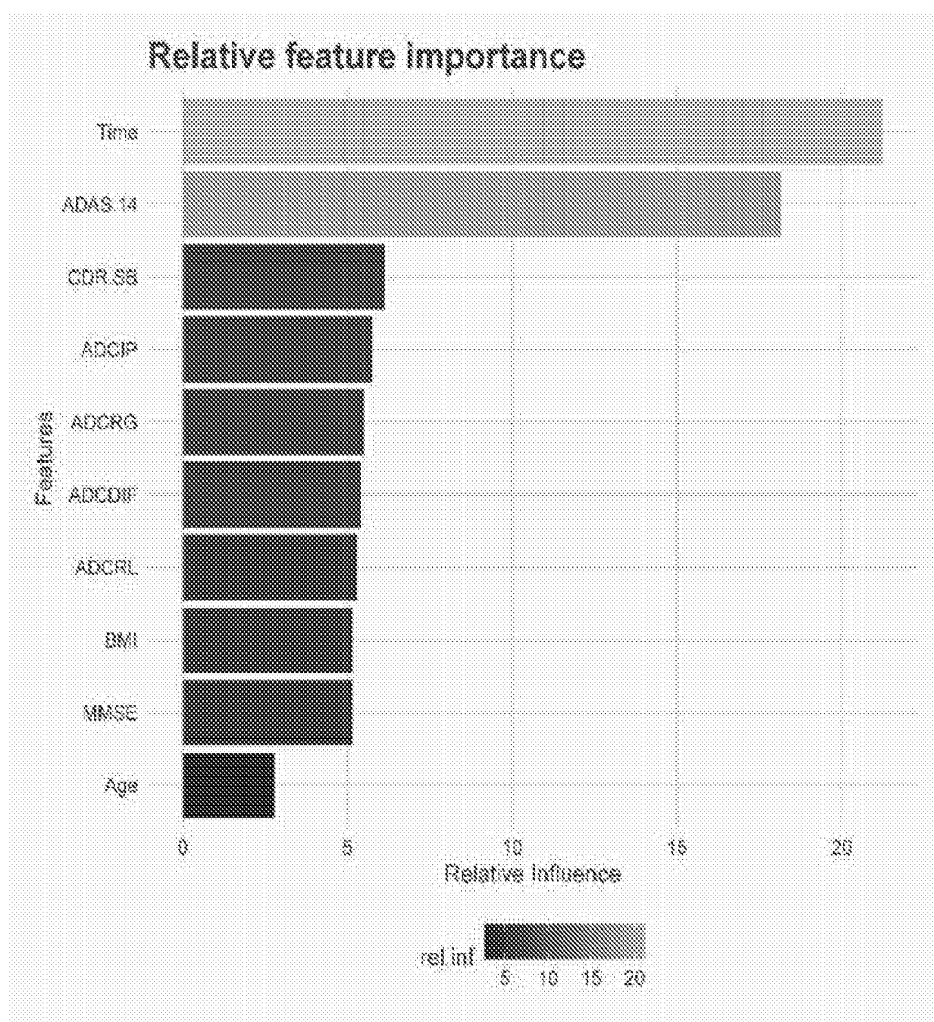


FIG. 8A

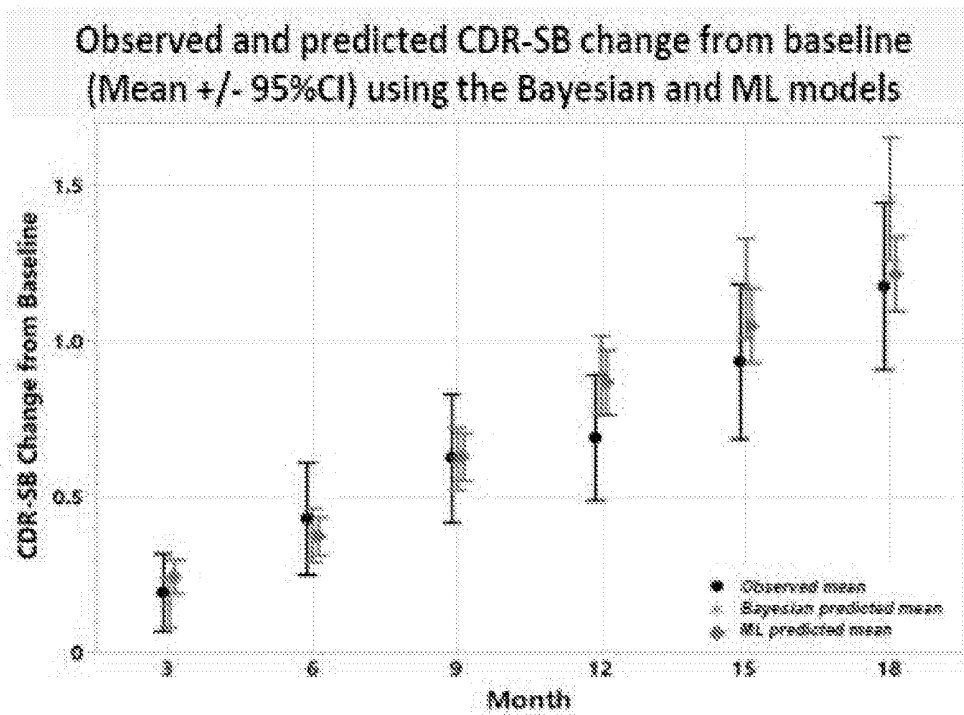


FIG. 8B

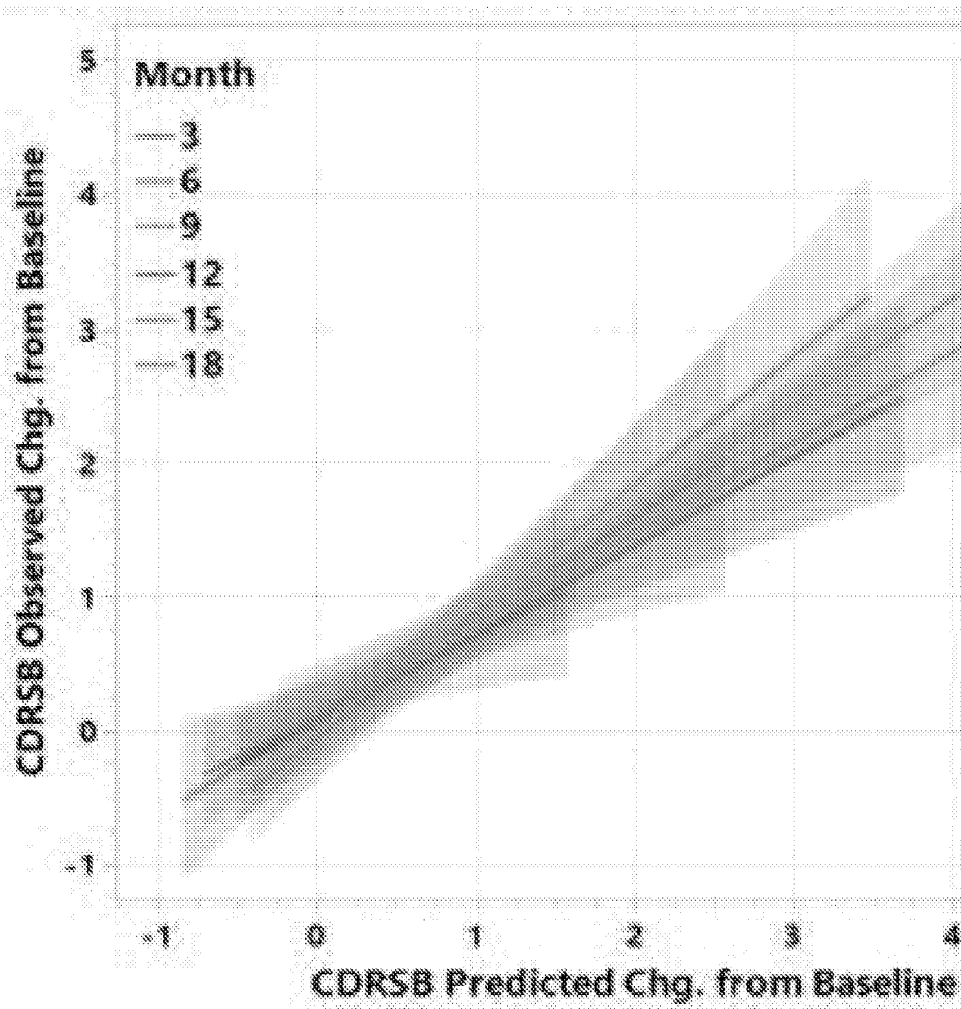


FIG. 8C

Correlation of observed vs. predicted		
Month	Bayesian nonlinear	Machine Learning
3	28.1%	28.3%
6	25.1%	33.8%
9	27.6%	41.9%
12	28.5%	43.4%
15	31.2%	44.5%
18	32.3%	47.9%

FIG. 8D

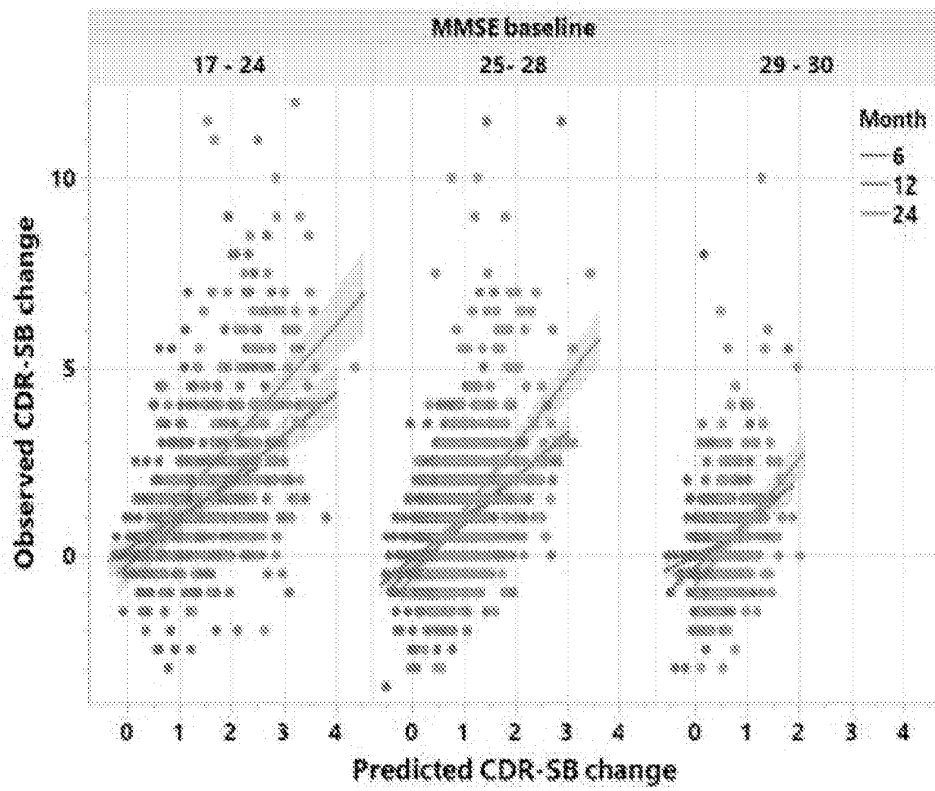


FIG. 8E

Correlation of observed vs. predicted CDR-SB change			
Month	MMSE baseline		
	17 - 24	25 - 28	29 - 30
6	34.5%	38.0%	25.1%
12	45.3%	43.3%	36.0%
24	51.3%	53.0%	40.1%

FIG. 8F

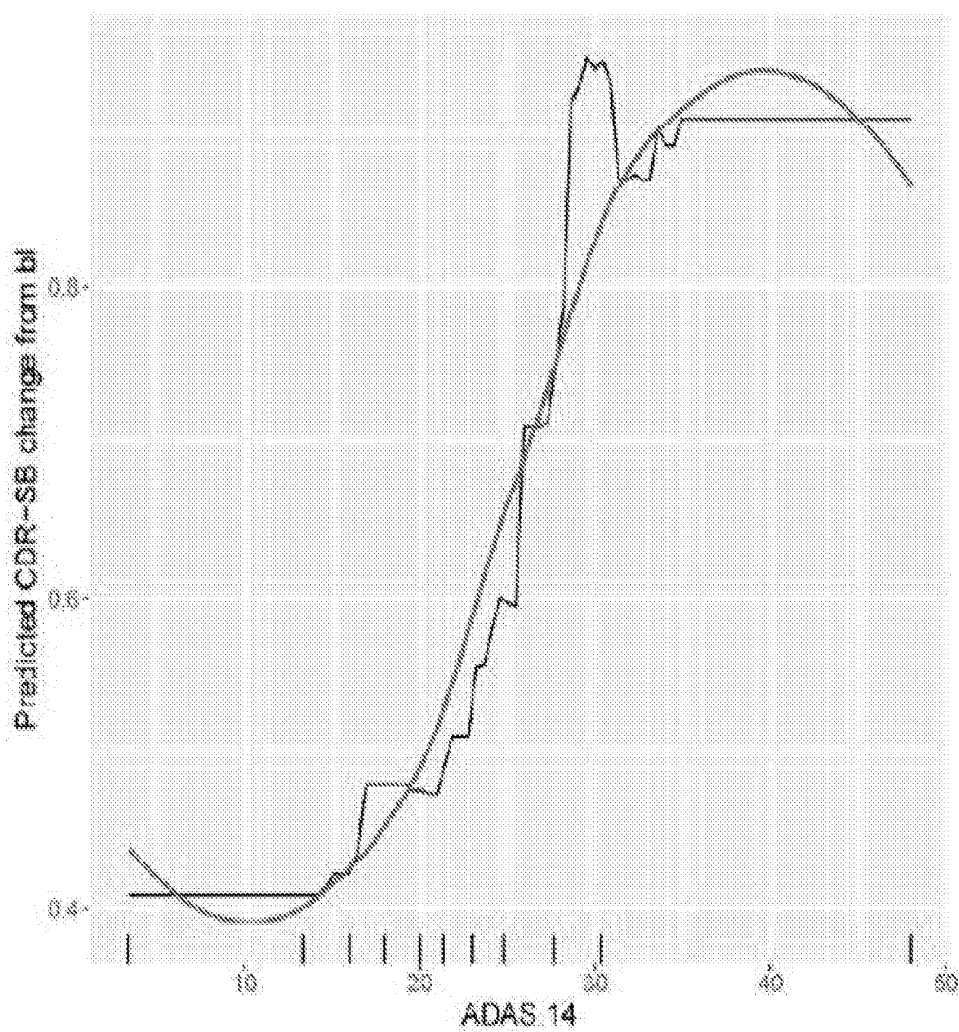


FIG. 8G

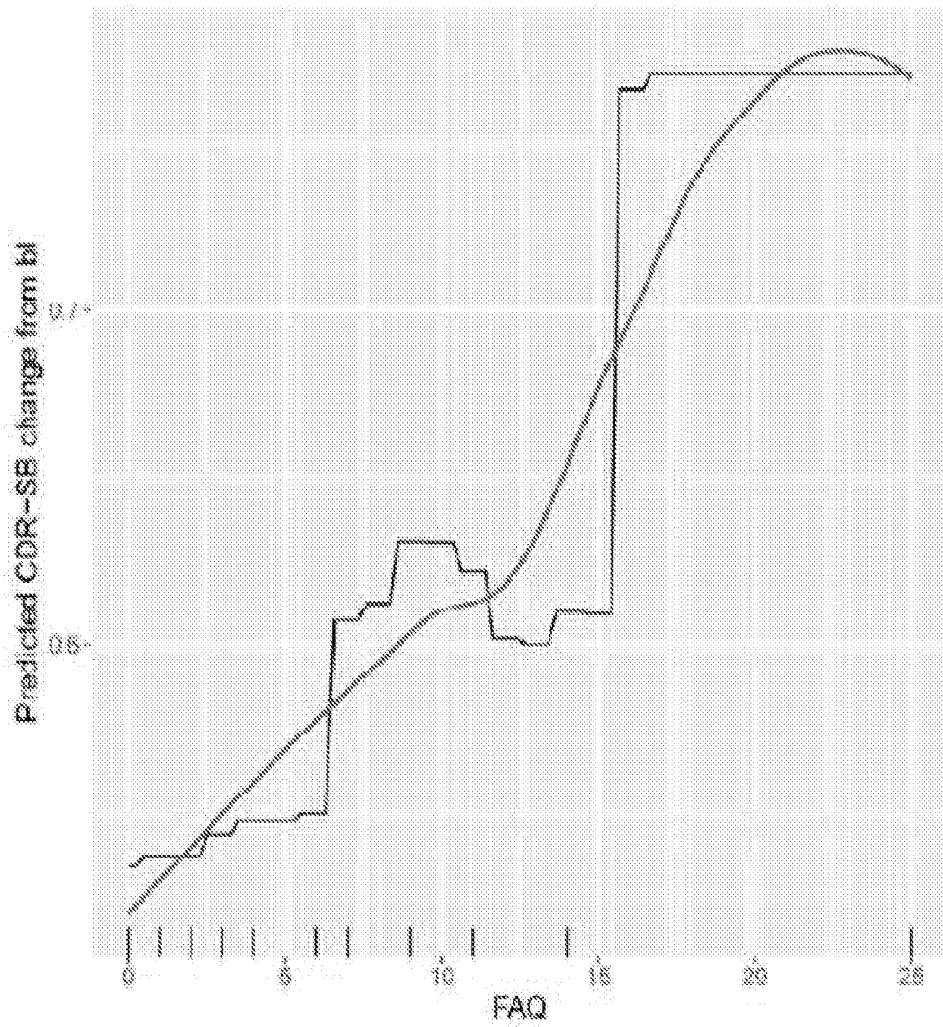


FIG. 8H

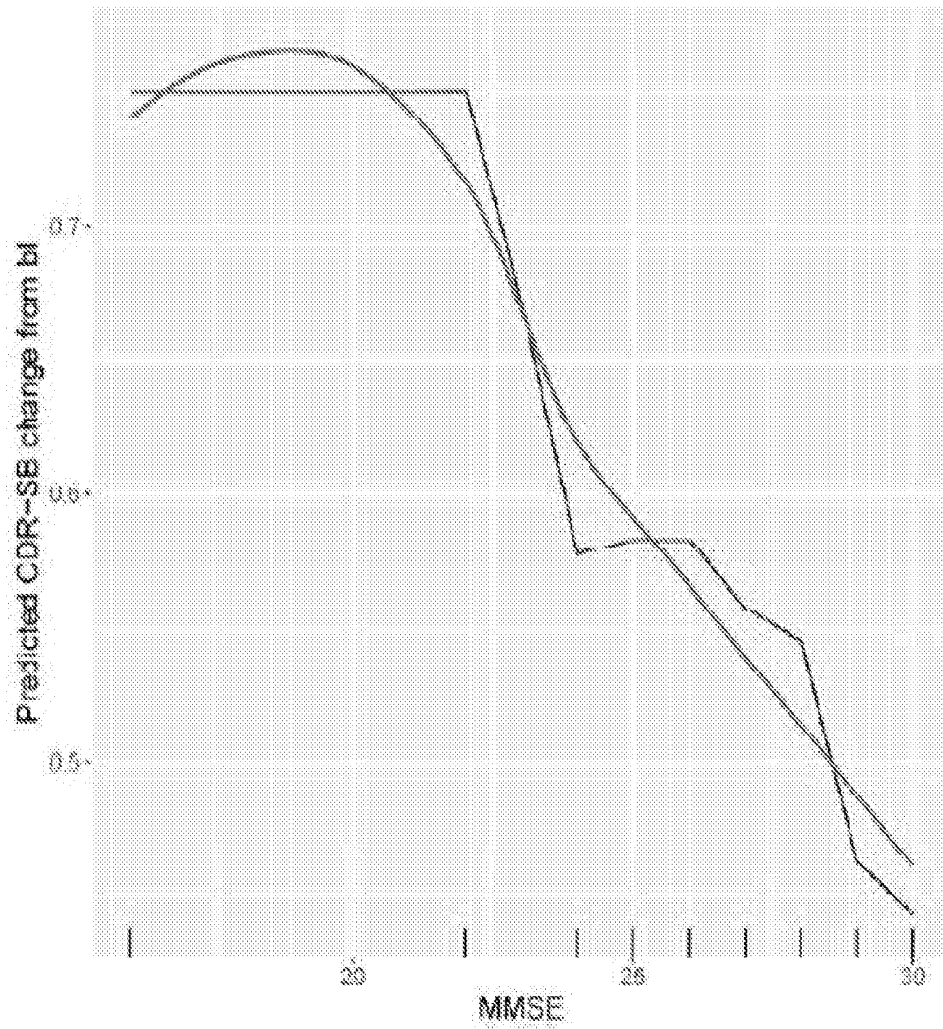


FIG. 8I

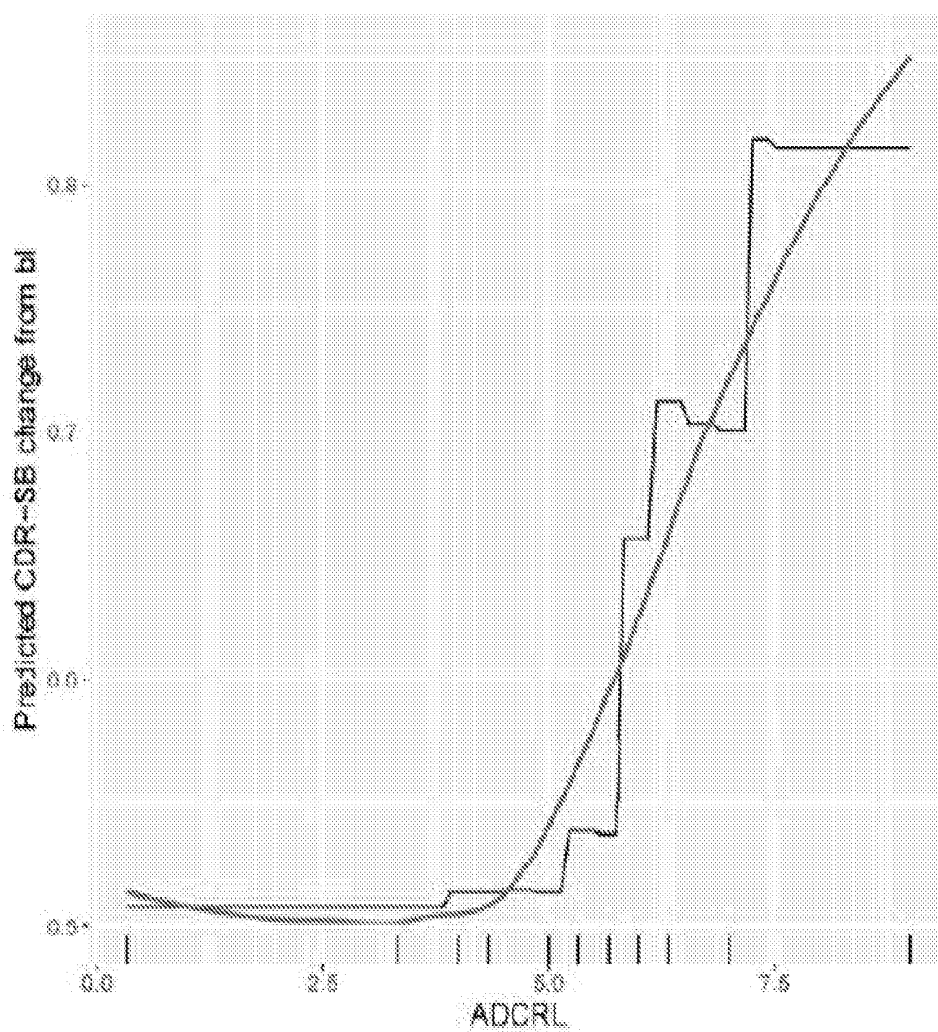


FIG. 8J

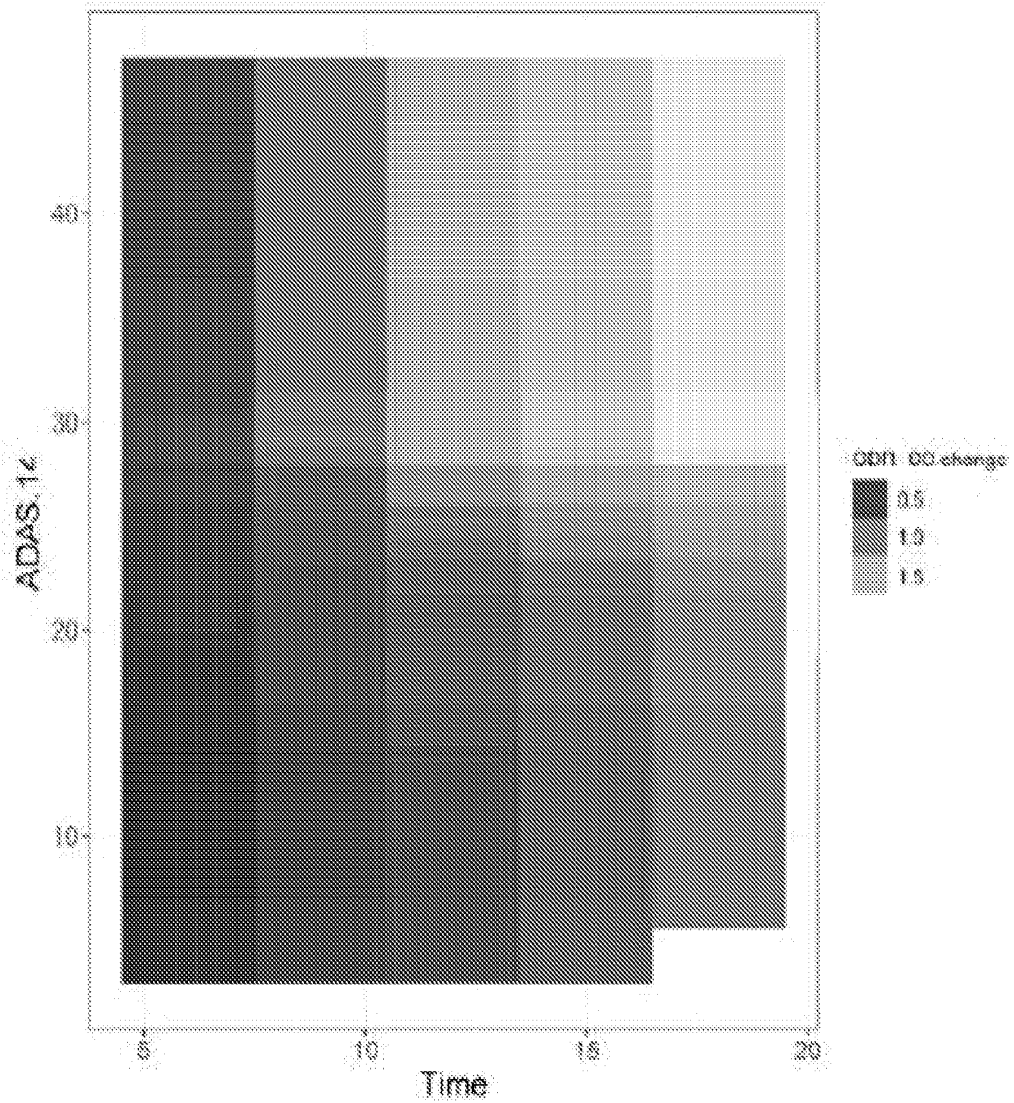


FIG. 8K

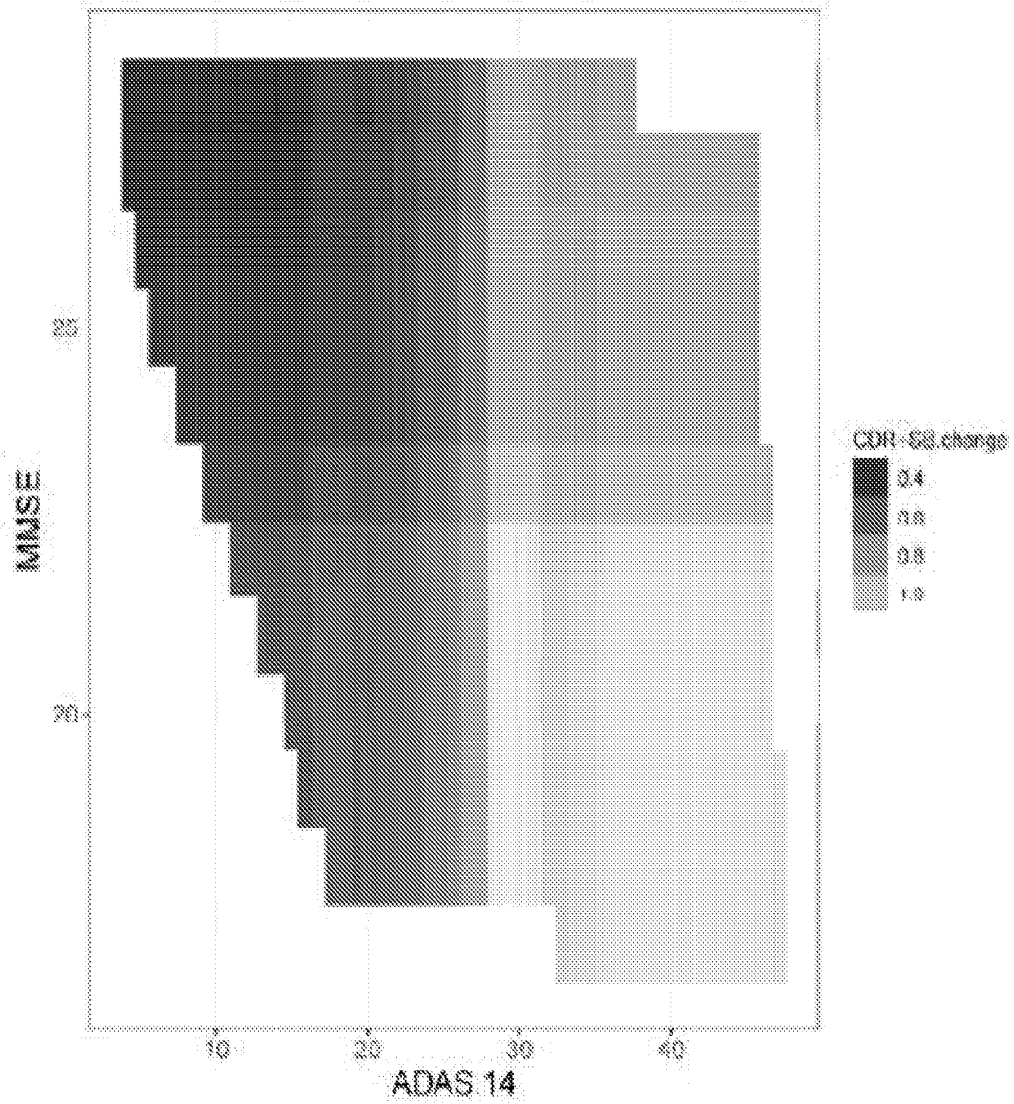


FIG. 8L

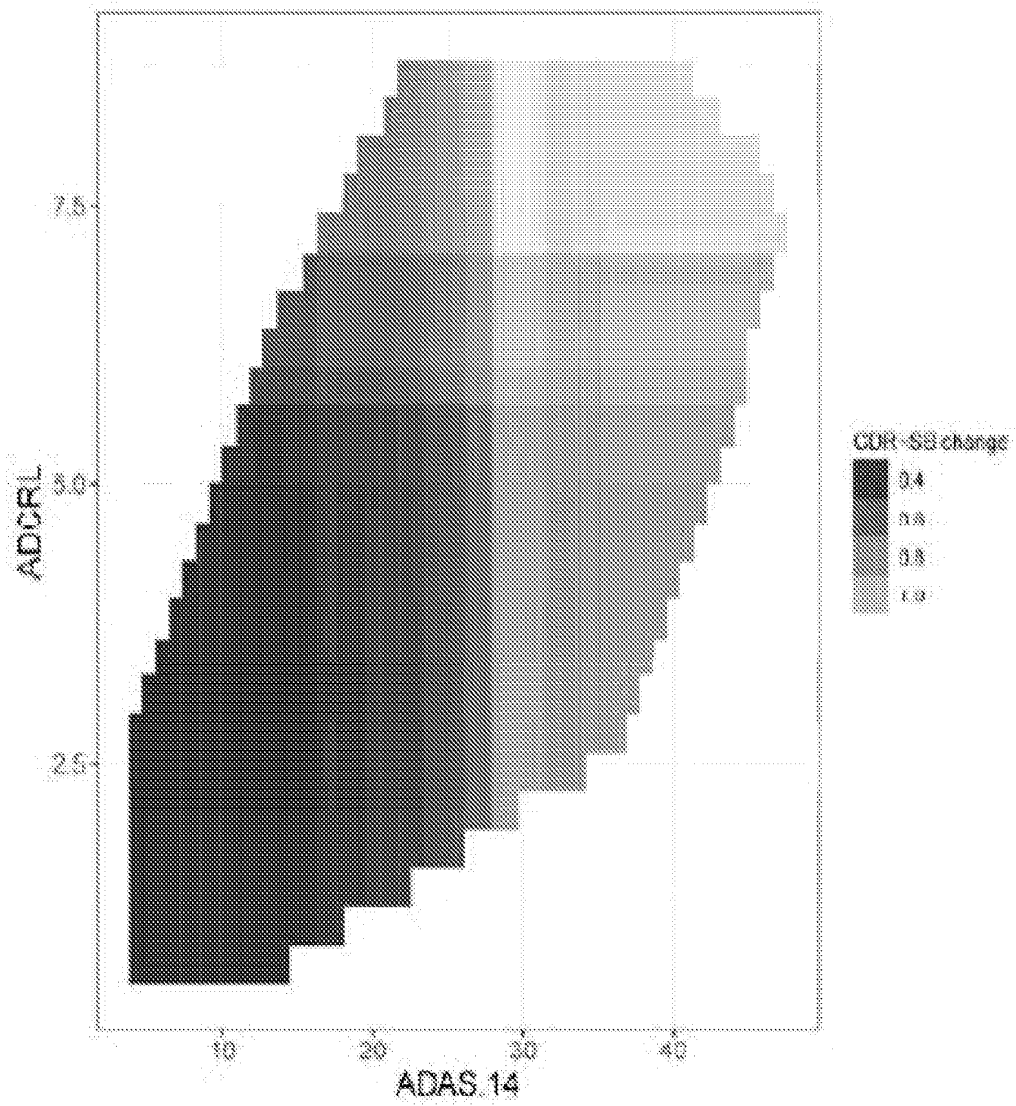


FIG. 8M

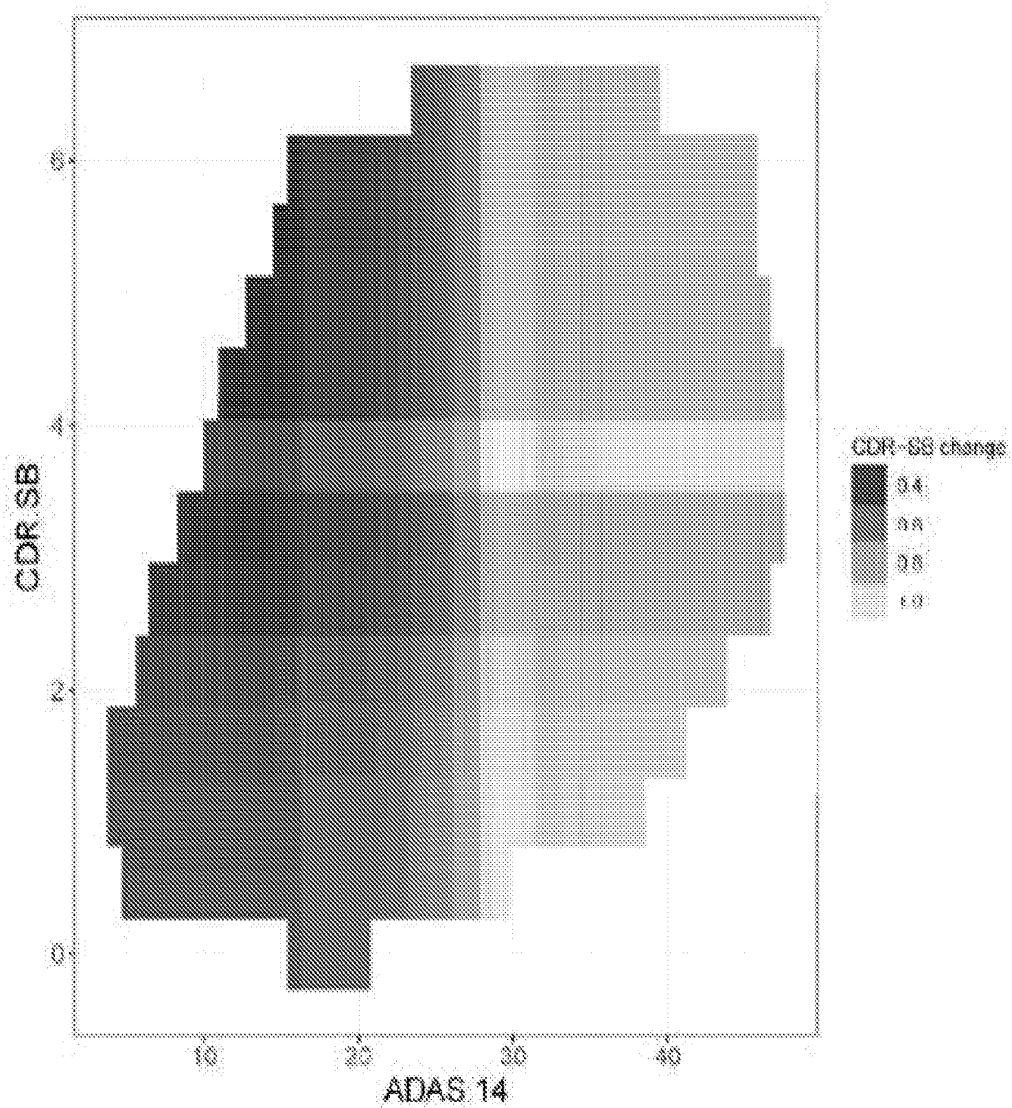


FIG. 8N

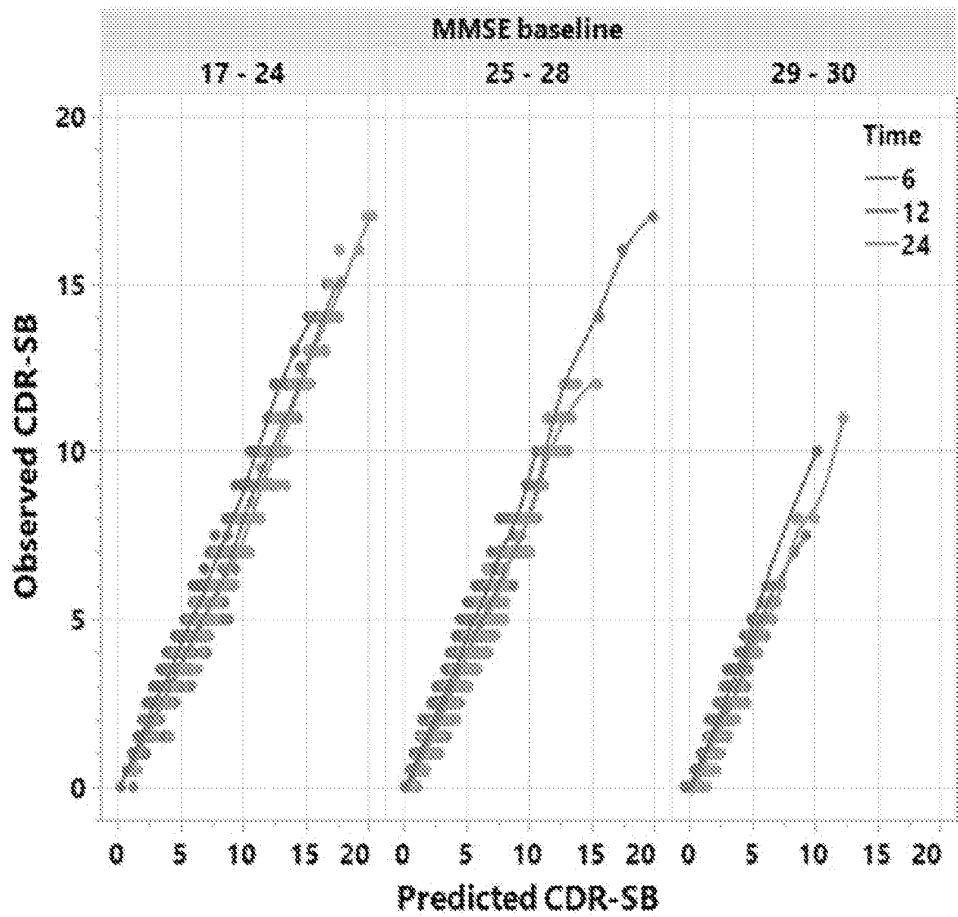


FIG. 80

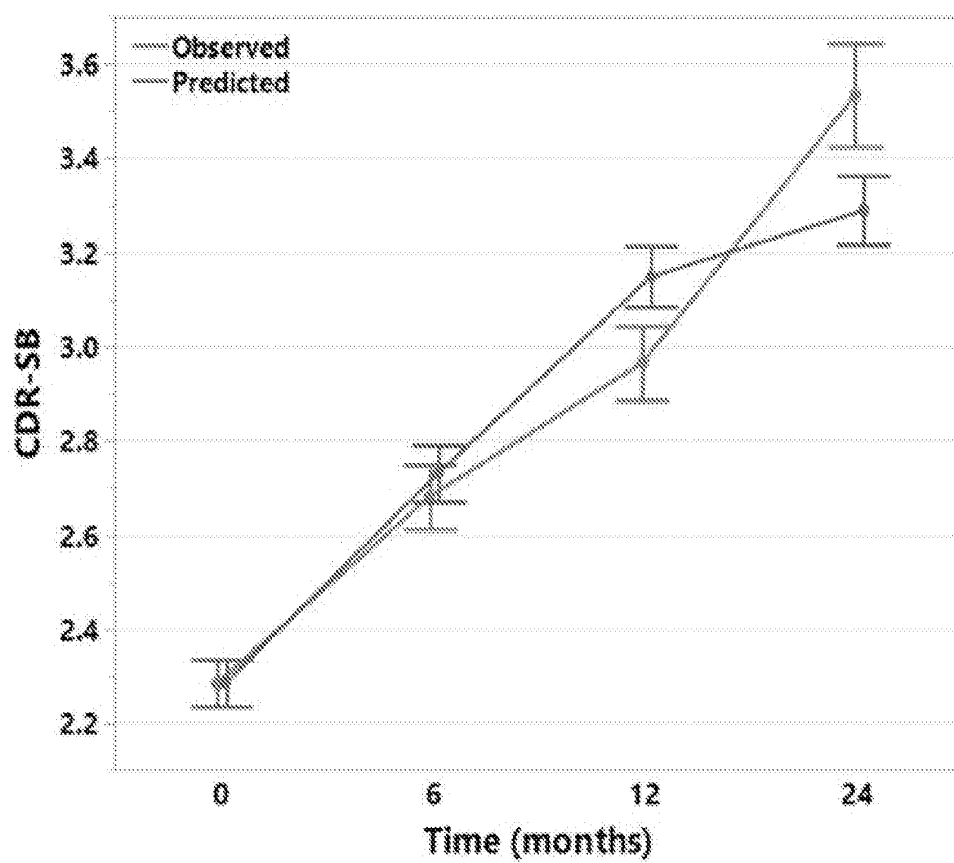


FIG. 8P

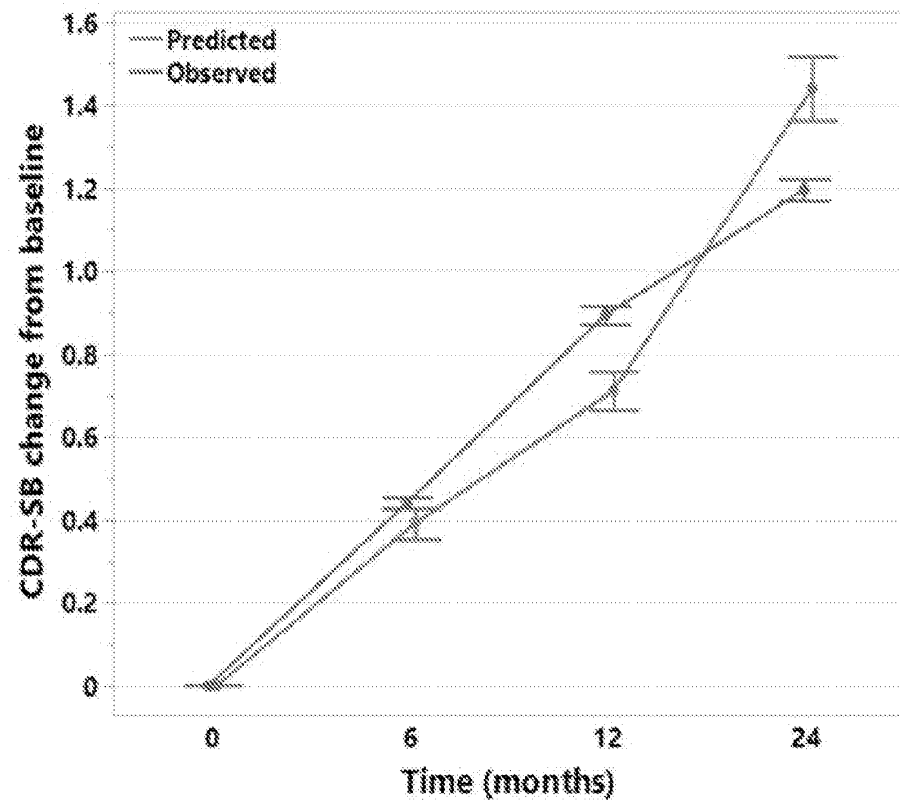


FIG. 8Q

		Training Cohort		Validation Cohort	
		MCI (N = 733)	Mild AD (N = 167)	MCI (N = 150)	Mild AD (N = 80)
Gender	F (%)	401 (54.3%)	85 (50.1%)	69 (46%)	29 (36.3%)
ApoE	E4 (%)	473 (64.1%)	106 (63.4%)	107 (71.3%)	56 (80.0%)
Age	Mean (SD)	72. (7.3)	72.1 (7.0)	71.4 (8.8)	70.9 (9.1)
BMI	Mean (SD)	25.8 (4.4)	26.3 (4.1)	25.6 (3.7)	26.3 (4.1)
MMSE	Mean (SD)	26.1 (2.5)	24.8 (2.7)	26.6 (2.3)	24.9 (2.1)
CDR-SB	Mean (SD)	2.4 (1.1)	3.4 (1.2)	2.3 (1.1)	4.0 (1.4)
CDR-SB 18-month change	Mean (SD)	1.1 (1.8)	2.0 (2.1)	1.0 (1.6)	1.5 (1.9)

FIG. 9A

Diagnosis	Time (month)	Training Cohort		Validation Cohort	
		Mean	SD	Mean	SD
MCI	3	0.22	0.99	0.13	0.86
	6	0.33	1.01	0.32	1.12
	9	0.46	1.31	0.56	1.35
	12	0.59	1.20	0.76	1.58
	15	0.85	1.45	0.86	1.76
	18	1.04	1.59	1.08	1.82
Mild AD	3	0.14	0.92	0.19	1.01
	6	0.63	1.89	0.52	1.41
	9	0.98	1.80	0.87	1.55
	12	0.92	1.76	1.22	1.74
	15	1.13	2.03	1.40	2.08
	18	1.49	1.91	2.01	2.09

FIG. 9B

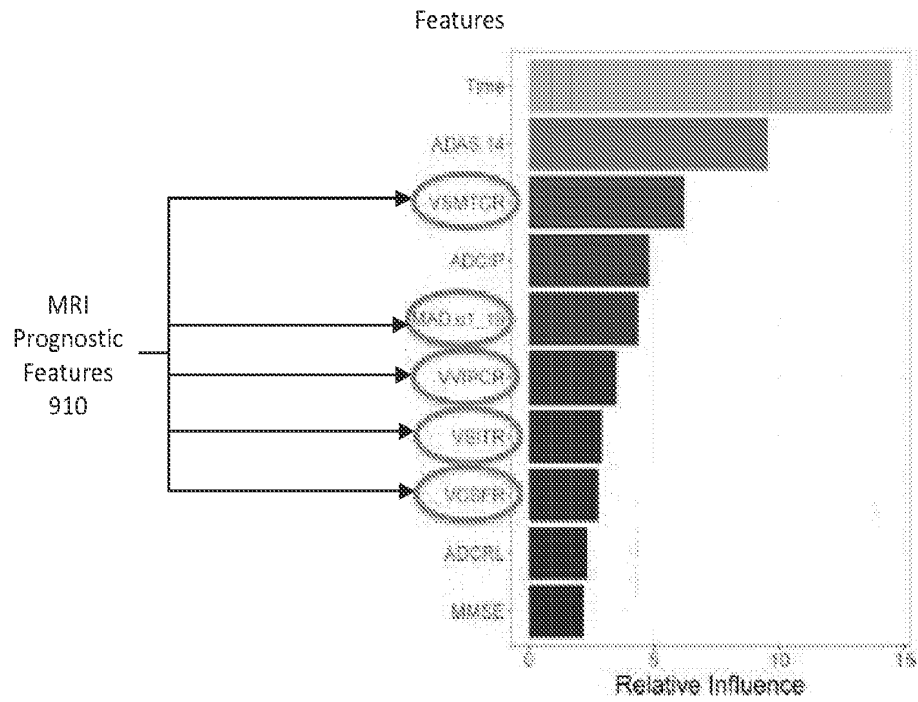


FIG. 9C

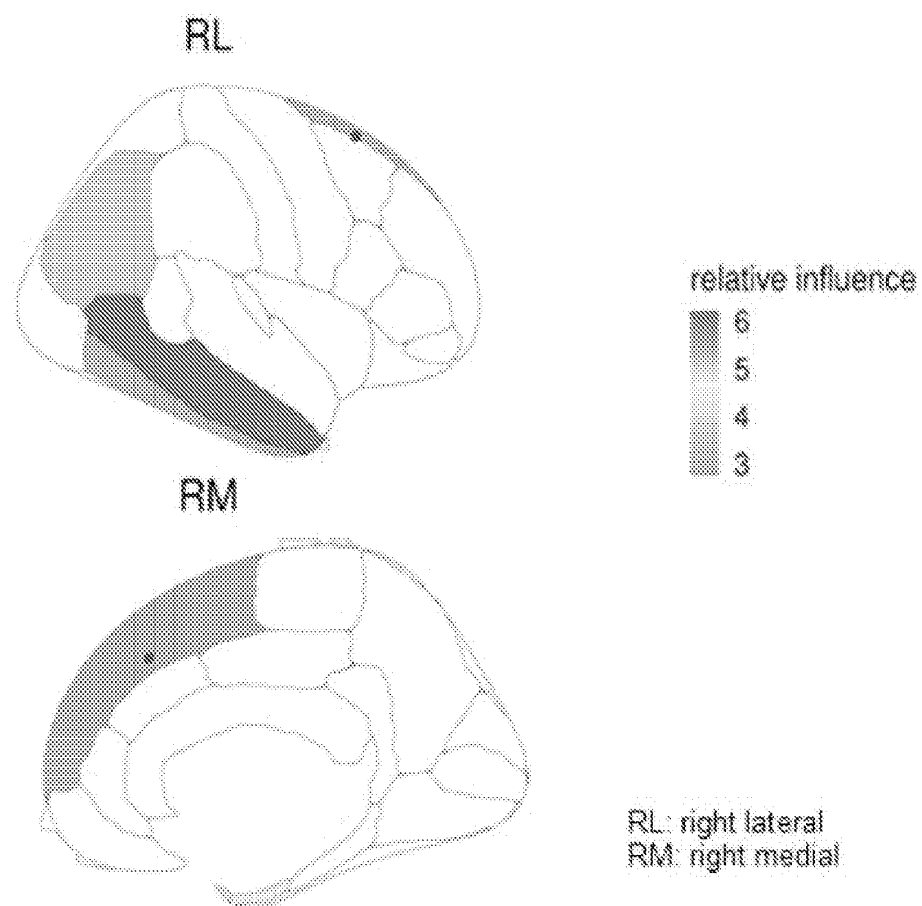


FIG. 9D

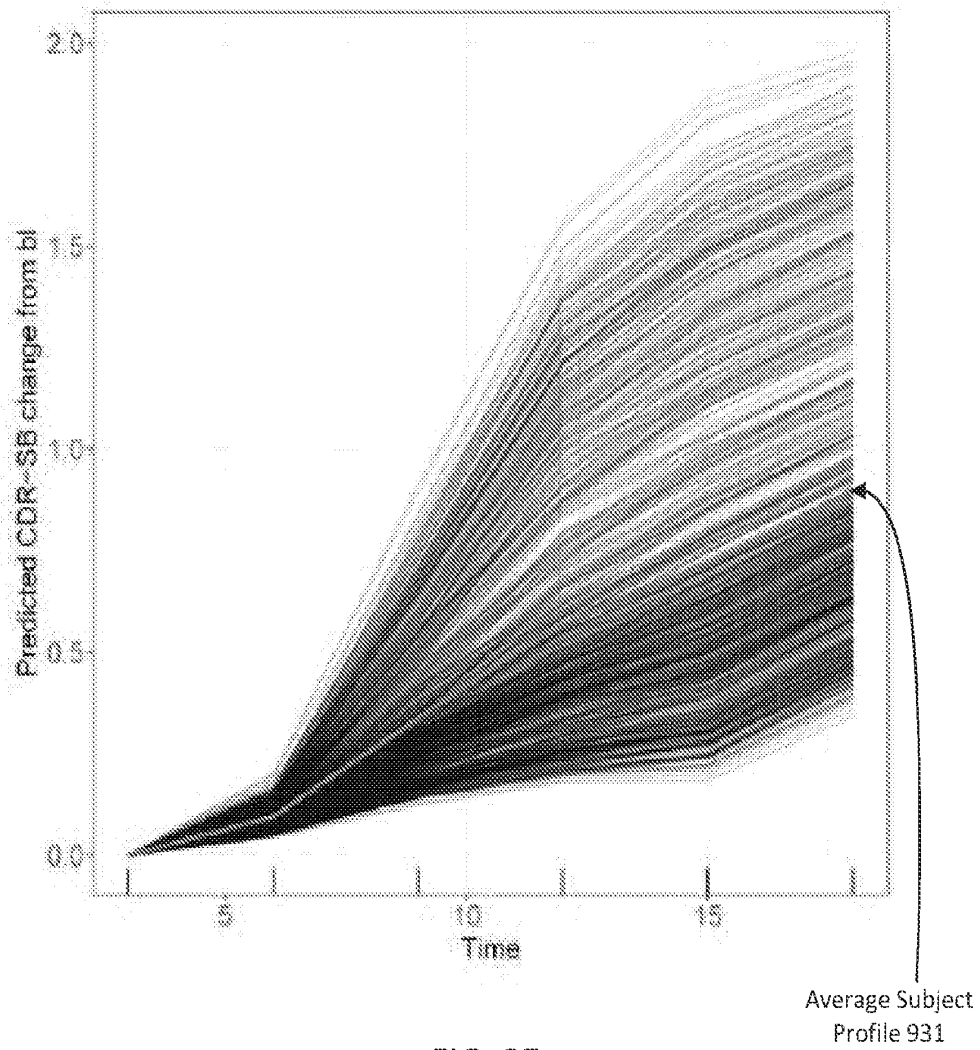


FIG. 9E

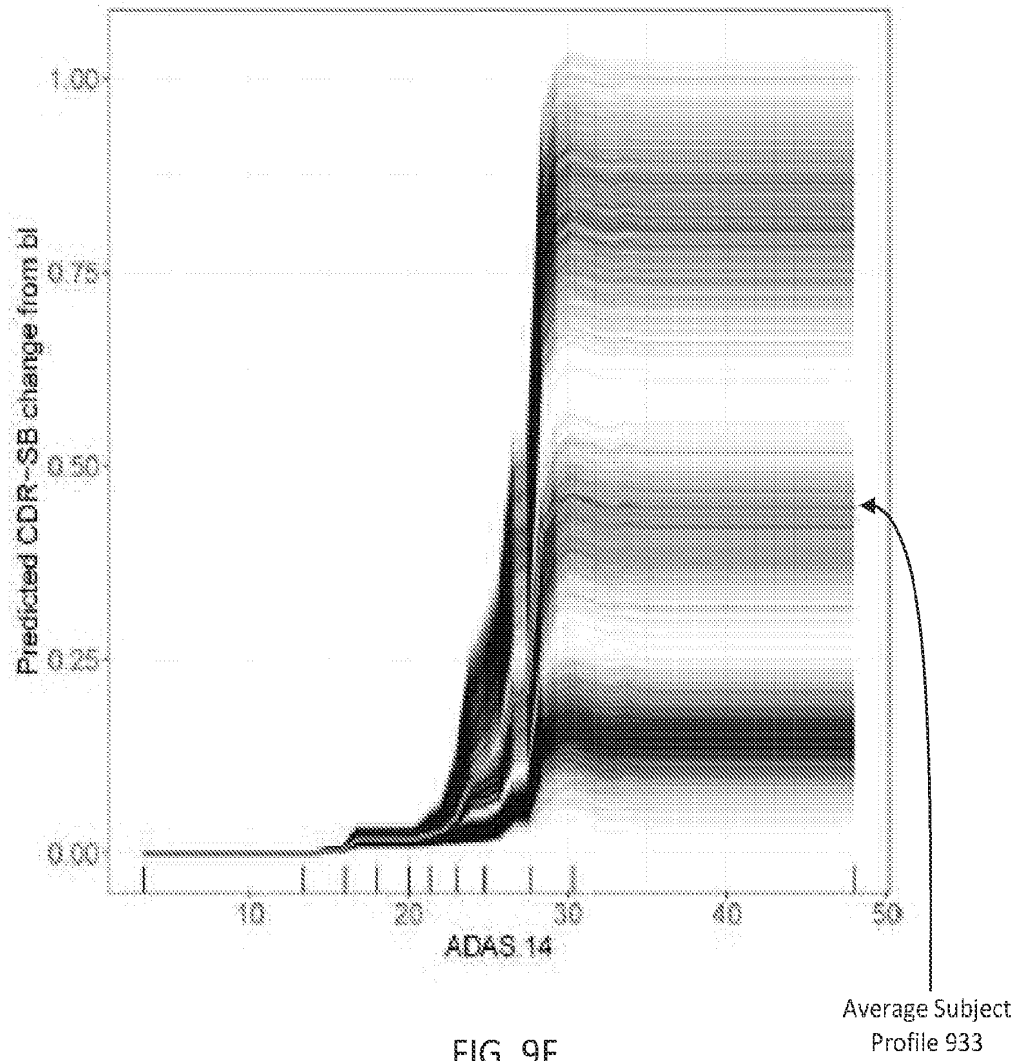
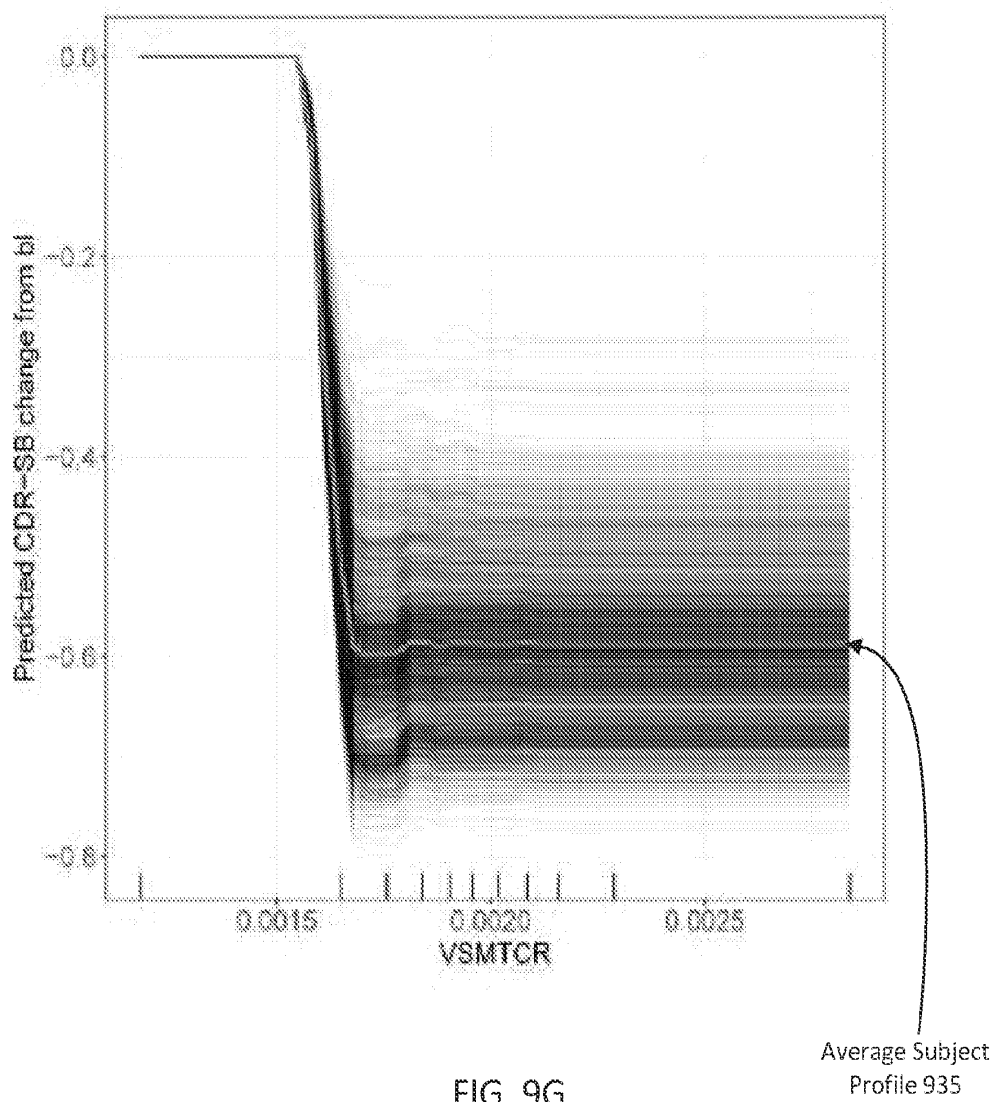


FIG. 9F



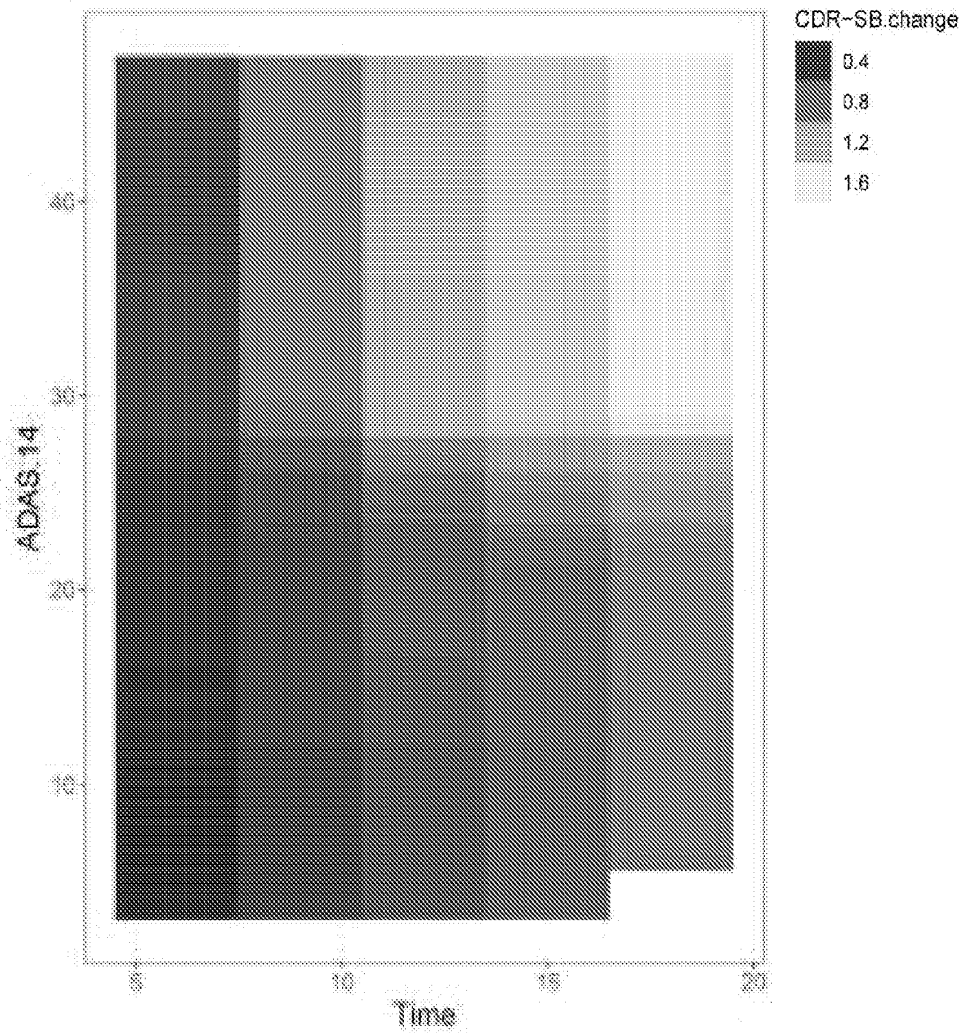


FIG. 9H

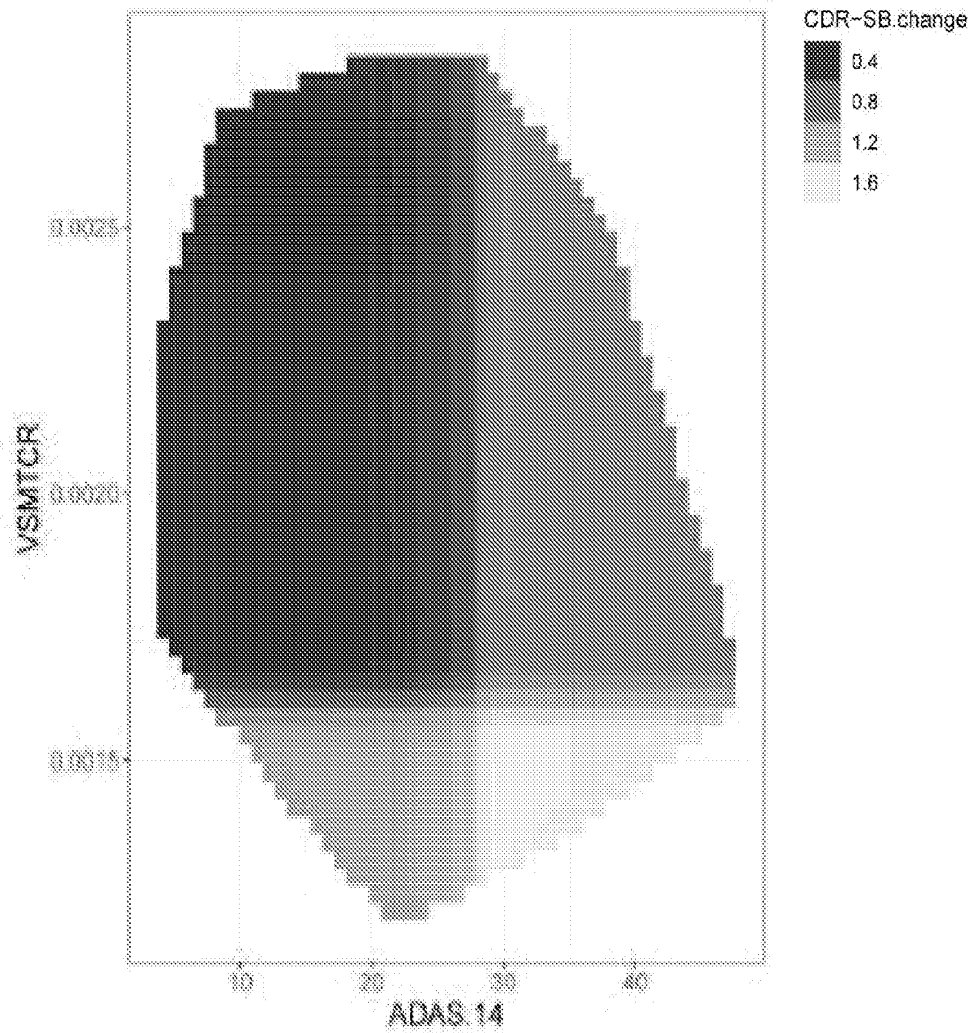


FIG. 9I

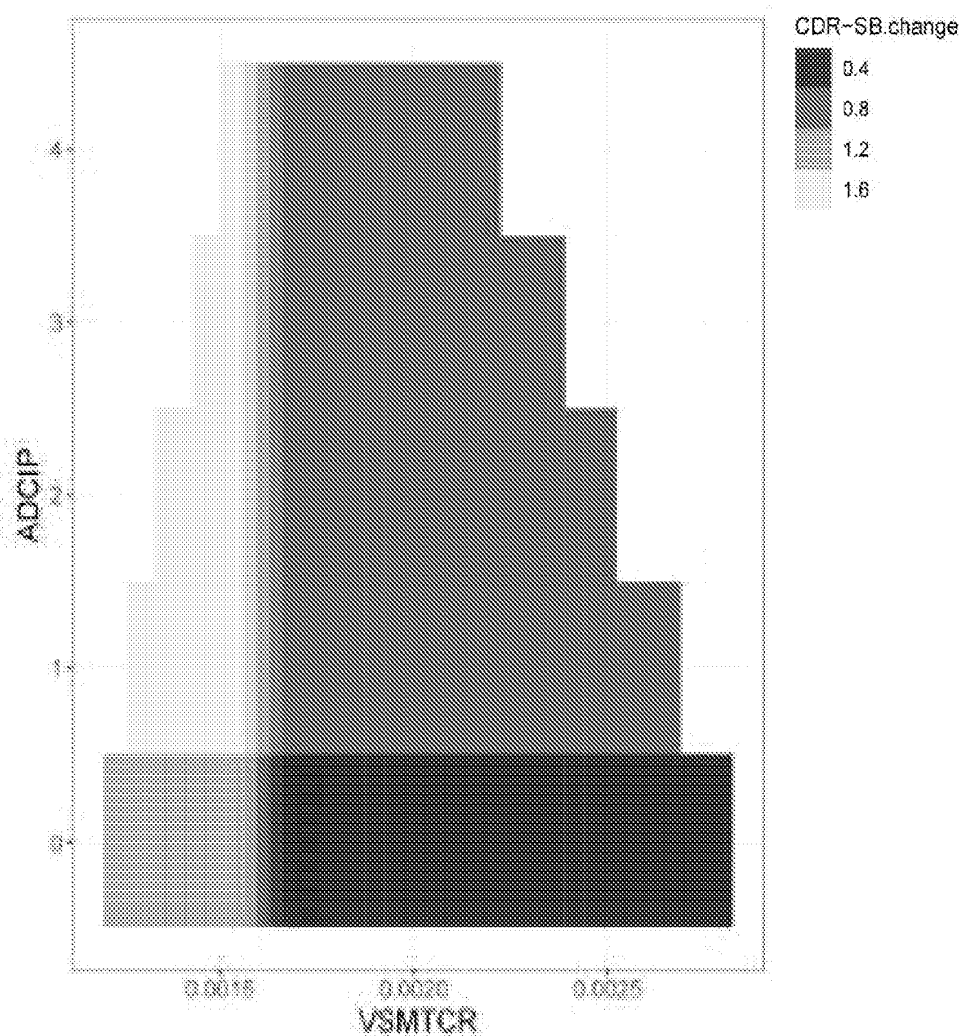


FIG. 9J

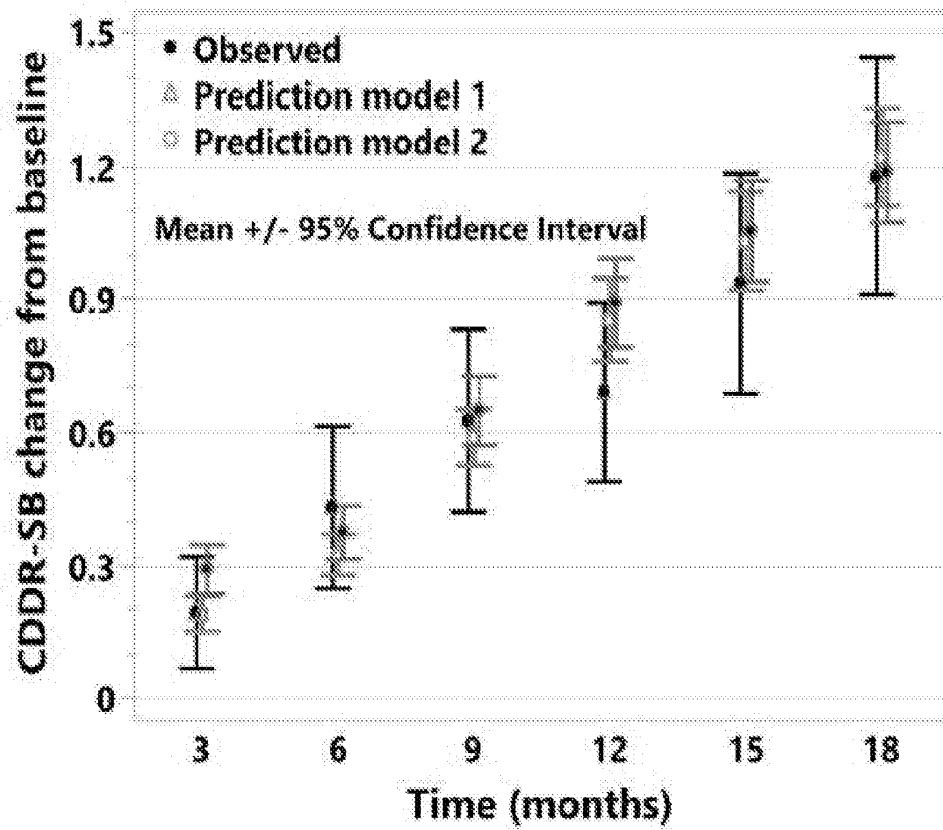


FIG. 9K

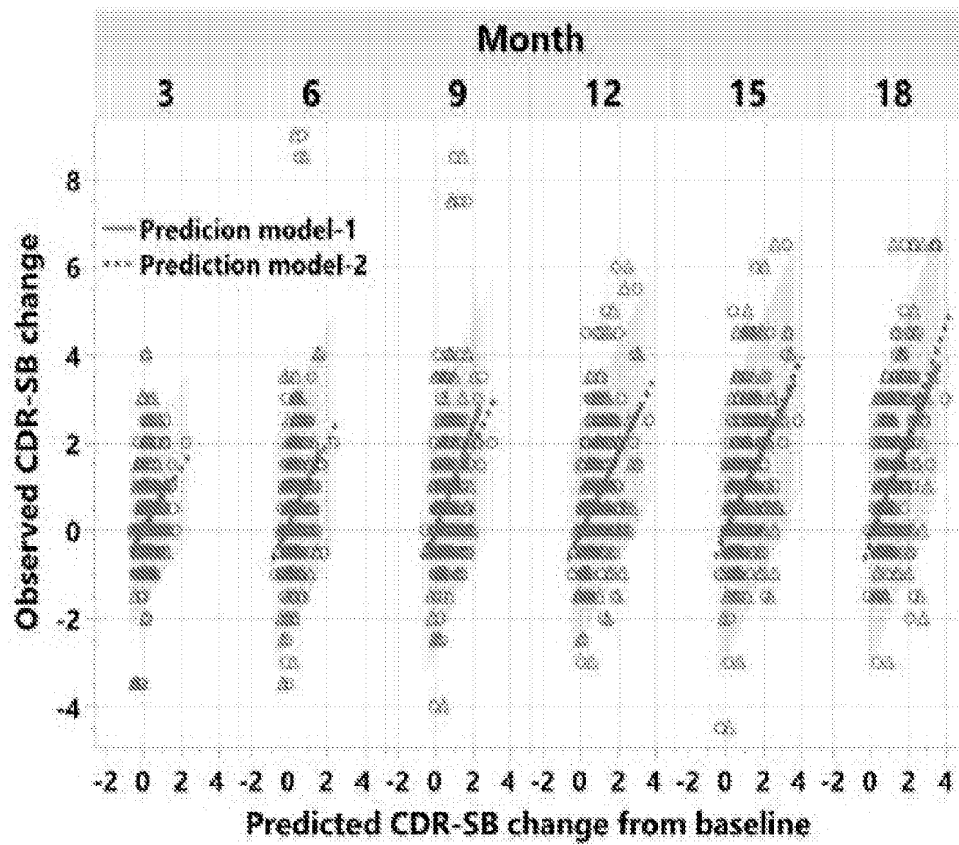


FIG. 9L

Month	Validation Cohort (VC)		
	Model-1	Model-2	p-value
3	0.243	0.330	0.075
6	0.269	0.324	0.205
9	0.381	0.340	0.783
12	0.434	0.463	0.254
15	0.409	0.445	0.185
18	0.415	0.497	0.036
Overall	0.385	0.429	0.010

FIG. 9M

Patient Characteristics		Training Cohort N = 934	Validation Cohort 1 N = 235	Validation Cohort 2 N = 421
Diagnosis	MCI; N (%)	761 (81%)	153 (65%)	286 (68%)
	Mild AD; N (%)	173 (19%)	82 (35%)	135 (32%)
Gender	Female; N (%)	431 (46%)	136 (58%)	189 (45%)
	Male; N (%)	503 (54%)	99 (42%)	232 (55%)
Race	White; N (%)	706 (76%)	213 (91%)	394 (94%)
	Non-White; N (%)	228 (24%)	22 (9%)	27 (6%)
ApoE4 status	E4 homozygous; N (%)	140 (15%)	39 (17%)	83 (20%)
	E4 heterozygous; N (%)	458 (49%)	127 (54%)	210 (50%)
	non-E4; N (%)	336 (36%)	69 (29%)	128 (30%)
Education	Mean (SD)	13.4 (3.6)	14.0 (3.7)	16.0 (2.7)
Age	Mean (SD)	72.1 (7.3)	71.2 (8.8)	73.4 (7.0)
BMI	Mean (SD)	25.9 (4.3)	25.7 (3.8)	26.6 (5.0)
MMSE	Mean (SD)	25.8 (2.5)	26.0 (2.3)	26.1 (3.0)
CDR-SB	Mean (SD)	2.6 (1.2)	2.9 (1.5)	2.5 (1.8)

FIG. 10A

Time (months)	Training Cohort			Validation Cohort 1			Validation Cohort 2		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
3	920	0.14	0.89	230	0.19	0.97			
6	888	0.36	1.19	219	0.43	1.37	319	0.44	1.14
9	823	0.61	1.39	205	0.63	1.50			
12	660	0.84	1.61	188	0.69	1.40	406	0.86	1.69
15	480	0.95	1.82	172	0.94	1.65			
18	335	1.23	1.88	161	1.18	1.70			
21	195	1.53	2.16						
24	90	1.72	2.18				261	1.43	2.14

FIG. 10B

Predictors	Description	% Relative Influence
Time	Time in months	24.48
ADAS.13	ADAS-Cog-13 composite	15.80
MMSE	MMSE composite	6.53
ADCRL	ADAS-Cog word recall	6.41
ADCIP	ADAS-Cog ideational praxis	6.08
ADCRG	ADAS-Cog word recognition	4.99
CDR.SB	CDR sum of boxes (composite)	4.82
BMI	Body mass index	4.63
ADCDF	ADAS-Cog word finding difficulty	4.47
Age	Age in years	3.12
CDR0106	CDR personal care	2.40
ADCCP	ADAS-Cog constructional praxis	2.24
ADCNC	ADAS-Cog number cancellation	1.95
Dx.bl	Baseline diagnosis (MCI or mild AD)	1.84
ADCOR	ADAS-Cog orientation	1.63
CDR0102	CDR orientation	1.53
CDR0103	CDR judgment and problem solving	1.19
ADCRL	ADAS-Cog delayed word recall	1.03
CDR0104	CDR community affairs	0.85
CDR0105	CDR home and hobbies	0.69
ADCRI	ADAS-Cog remembering test instructions	0.68
ADCOF	ADAS-Cog naming objects/fingers	0.53
ADCCMP	ADAS-Cog comprehension	0.43
Gender	Gender (female/male)	0.42
CDR0101	CDR memory	0.37
ADCCMD	ADAS-Cog commands	0.30
ApoE4.count	Number of ApoE4 alleles	0.27
CDR.global	CDR global scores	0.24
ADCSL	ADAS-Cog spoken language ability	0.09

FIG. 10C

Predictors	Description	% Relative Influence
Time	Time in months	17.52
ADAS_13	ADAS-Cog-13 composite	8.40
VSMTCR	Middle temporal cortex area; right (mm²)	6.27
ADCI_P	ADAS-Cog ideational Praxis	4.46
SBN_11	Structural brain network module #11	4.43
SBN_15	Structural brain network module #15	4.05
ADCL	ADAS-Cog word recall	2.96
MMSE	MMSE composite	2.75
SBN_3	Structural brain network module #3	2.42
VVPCB	Inferior parietal cortex volume; right (mm³)	2.04
ADCDIF	ADAS-Cog word finding difficulty	1.82
VLSFR	Superior frontal cortex thickness; right (mm)	1.76
VVFPL	Frontal pole volume; left (mm³)	1.67
CDRDL06	CDR personal care	1.65
VVPOCL	Postcentral cortex volume; left (mm³)	1.62
VVPRER	Precuneus volume; right (mm³)	1.56
SBN_8	Structural brain network module #8	1.43
VVLORL	Lateral orbitofrontal cortex volume; left (mm³)	1.39
VLCSTR	Superior temporal cortex thickness; right (mm)	1.38
VCFRCL	Precentral cortex thickness; left (mm)	1.09
VSTWR	Inferior temporal cortex area; right (mm²)	1.05
VVEL	Entorhinal cortex volume; left (mm³)	0.98
VVPREL	Praecuneus volume; left (mm³)	0.97
VVPCRR	Precentral cortex thickness; right (mm)	0.96
VVPOCR	Postcentral cortex volume; right (mm³)	0.94
SBN_12	Structural brain network module #12	0.92
SBN_4	Structural brain network module #4	0.91
SBN_10	Structural brain network module #10	0.92
ADCRG	ADAS-Cog word recognition	0.90
VSCUR	Cuneus area; left (mm²)	0.90
VCRATR	Rostral middle frontal cortex thickness; right (mm)	0.89
SBN_14	Structural brain network module #14	0.85
VSCACR	Caudal anterior cingulate area; right (mm²)	0.82
ADKNC	ADAS-Cog number cancellation	0.79
VVCACL	Caudal anterior cingulate volume; left (mm³)	0.76
SBN_9	Structural brain network module #9	0.75
CDR_SB	CDR sum of boxes (composite)	0.74
SBN_6	Structural brain network module #6	0.68
VSTTR	Transverse temporal cortex area; right (mm²)	0.65
VVSFR	Superior frontal cortex area; right (mm²)	0.60
SBN_18	Structural brain network module #18	0.60

ADCDR	ADAS-Cog orientation	0.59
VVPHR	Parahippocampal cortex volume; right (mm³)	0.53
CDRDL02	CDR orientation	0.55
VSRACL	Fusiform anterior cingulate cortex area; left (mm²)	0.54
VCLUR	Lateral orbitofrontal cortex thickness; left (mm)	0.52
VSCACL	Caudal anterior cingulate area; left (mm²)	0.50
Dx_M	Baseline diagnosis (MCI or mild AD)	0.49
SBN_2	Structural brain network module #2	0.49
VVCACR	Caudal anterior cingulate volume; right (mm³)	0.48
SBN_5	Structural brain network module #5	0.48
VCRML	Rostral middle frontal cortex thickness; left (mm)	0.42
BBB	Body mass index	0.41
CDRDL03	CDR judgment and problem solving	0.41
VSTL	Inferior temporal cortex area; left (mm²)	0.39
VVPRCL	Precentral cortex volume; left (mm³)	0.35
VSPERL	Perentorhinal cortex area; left (mm²)	0.38
SBN_1	Structural brain network module #1	0.37
VCPCL	Inferior parietal cortex thickness; right (mm)	0.35
VVPCCL	Posterior cingulate cortex volume; left (mm³)	0.34
SBN_13	Structural brain network module #13	0.34
Age	Age in years	0.33
VVSFL	Superior frontal cortex volume; left (mm³)	0.32
CDRDL05	CDR home and hobbies	0.32
VSLCR	Longist cortex area; right (mm²)	0.31
SBN_16	Structural brain network module #16	0.28
VSTL	Superior temporal cortex thickness; left (mm)	0.26
VCPCL	Inferior parietal cortex thickness; left (mm)	0.23
ADCLP	ADAS-Cog constructional praxis	0.23
SBN_7	Structural brain network module #7	0.20
SBN_17	Structural brain network module #17	0.15
VVFPL	Frontal pole; right (mm³)	0.10
CDRDL04	CDR social skills	0.07
ADCN	ADAS-Cog recognition test instructions	0.05
CDRDL04	CDR community affairs	0.05
CDRDL01	CDR memory	0.03
ADCCMP	ADAS-Cog comprehension	0.02
Gender	Gender (female/male)	0.00
AppE_novel	number of AppE labels	0.00
ADCCMD	ADAS-Cog commands	0.00
ADCSL	ADAS-Cog spoken language ability	0.00
ADGPRL	ADAS-Cog physical word recall	0.00
ADNCF	ADAS-Cog naming objects/figures	0.00

FIG. 10D

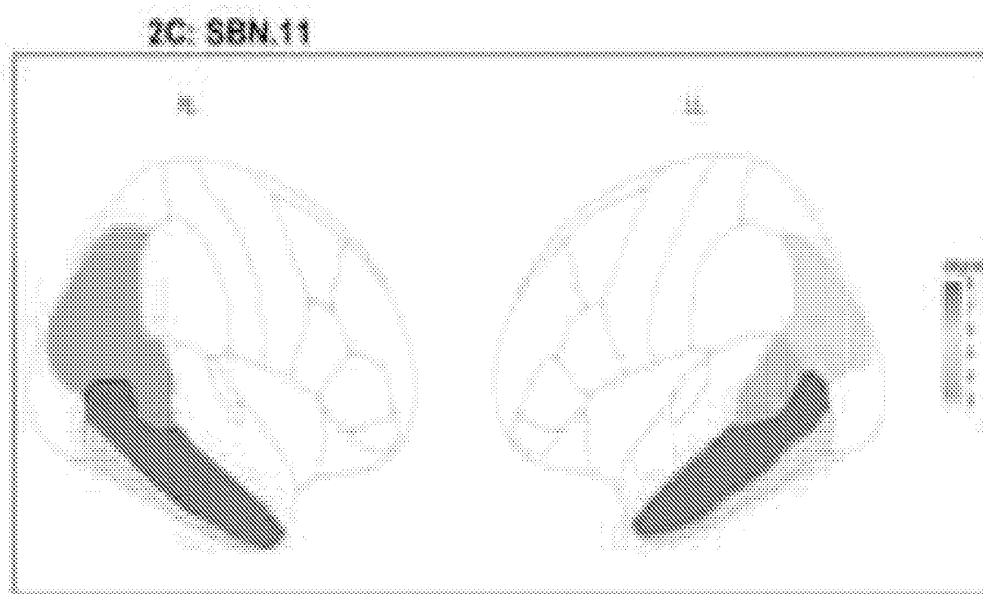


FIG. 10E

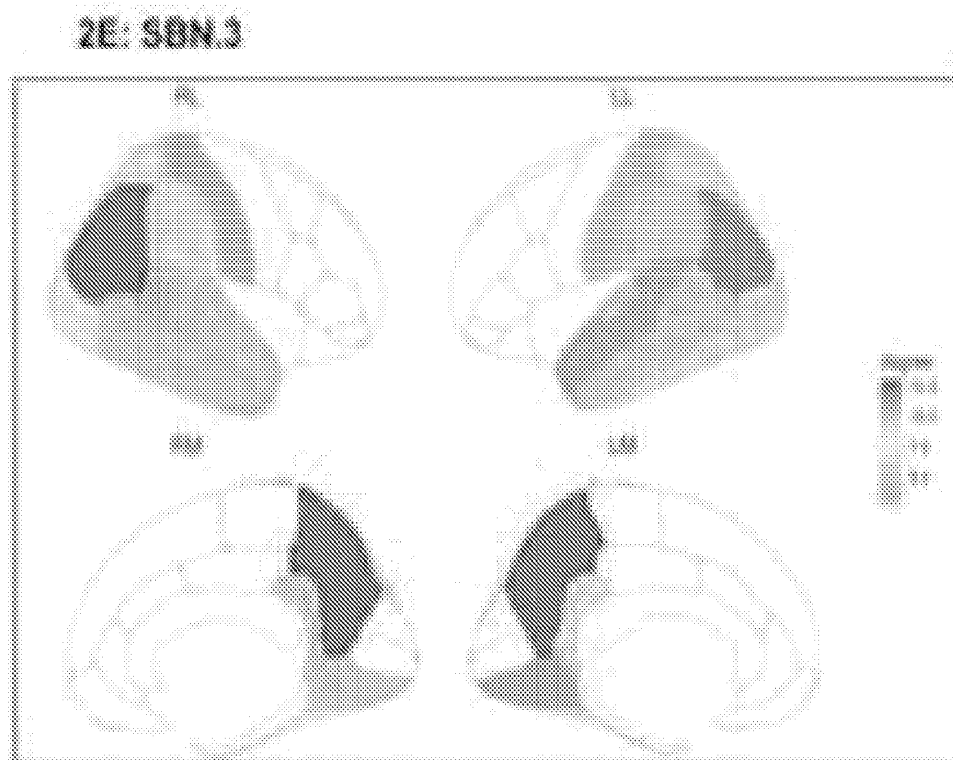


FIG. 10F

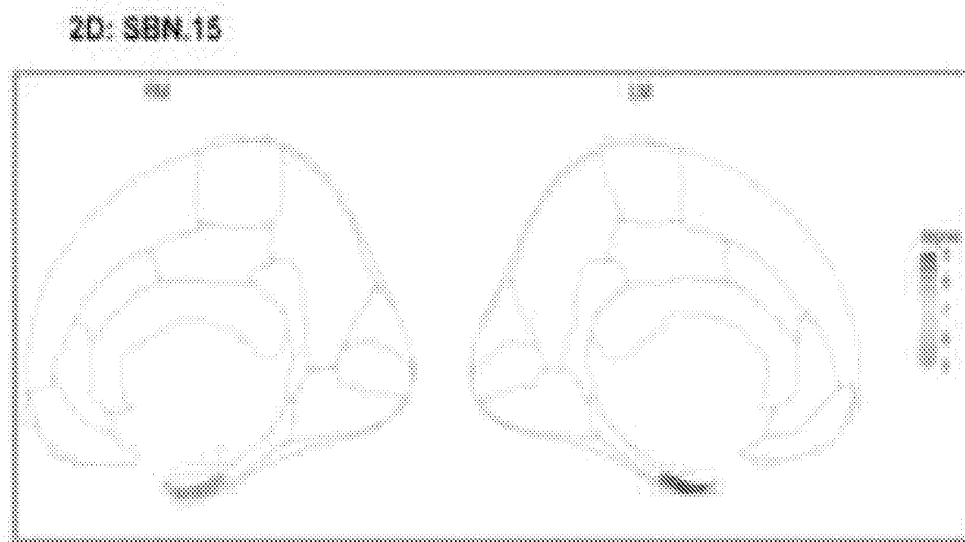


FIG. 10G

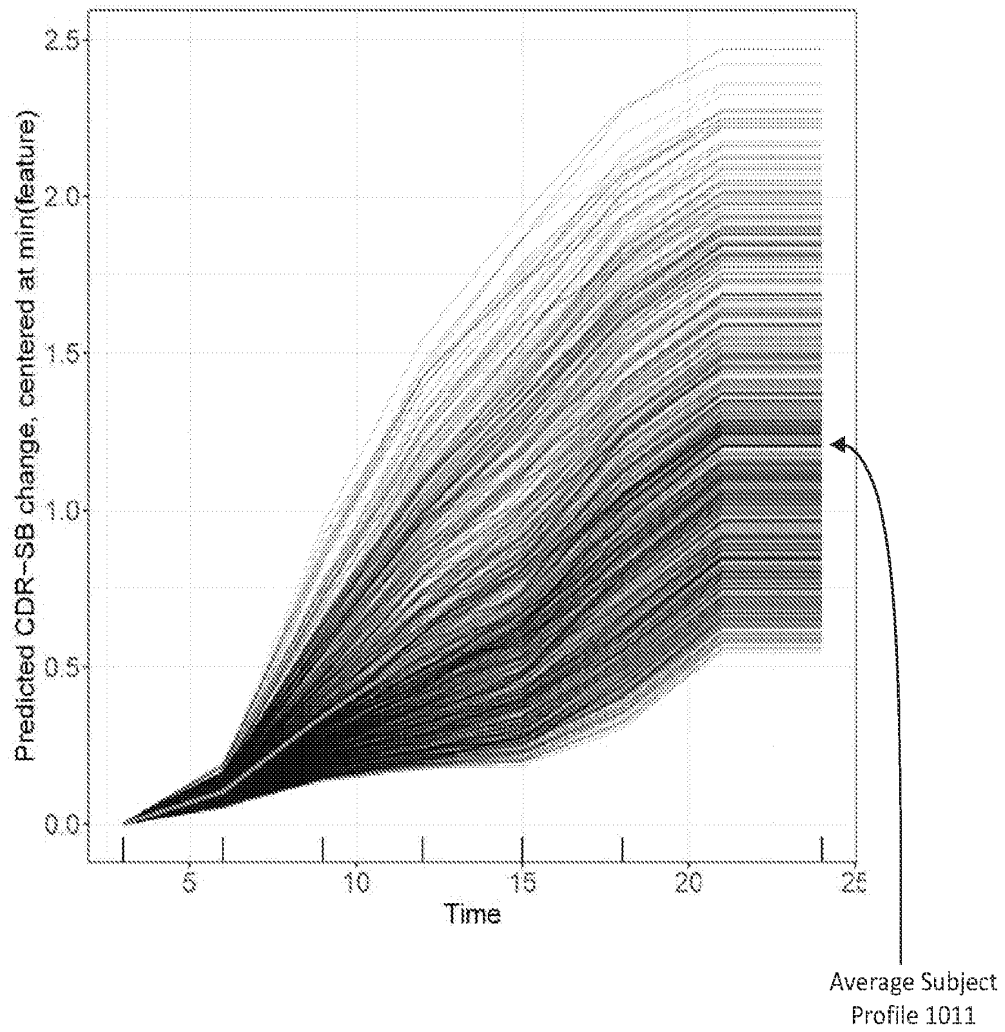


FIG. 10H

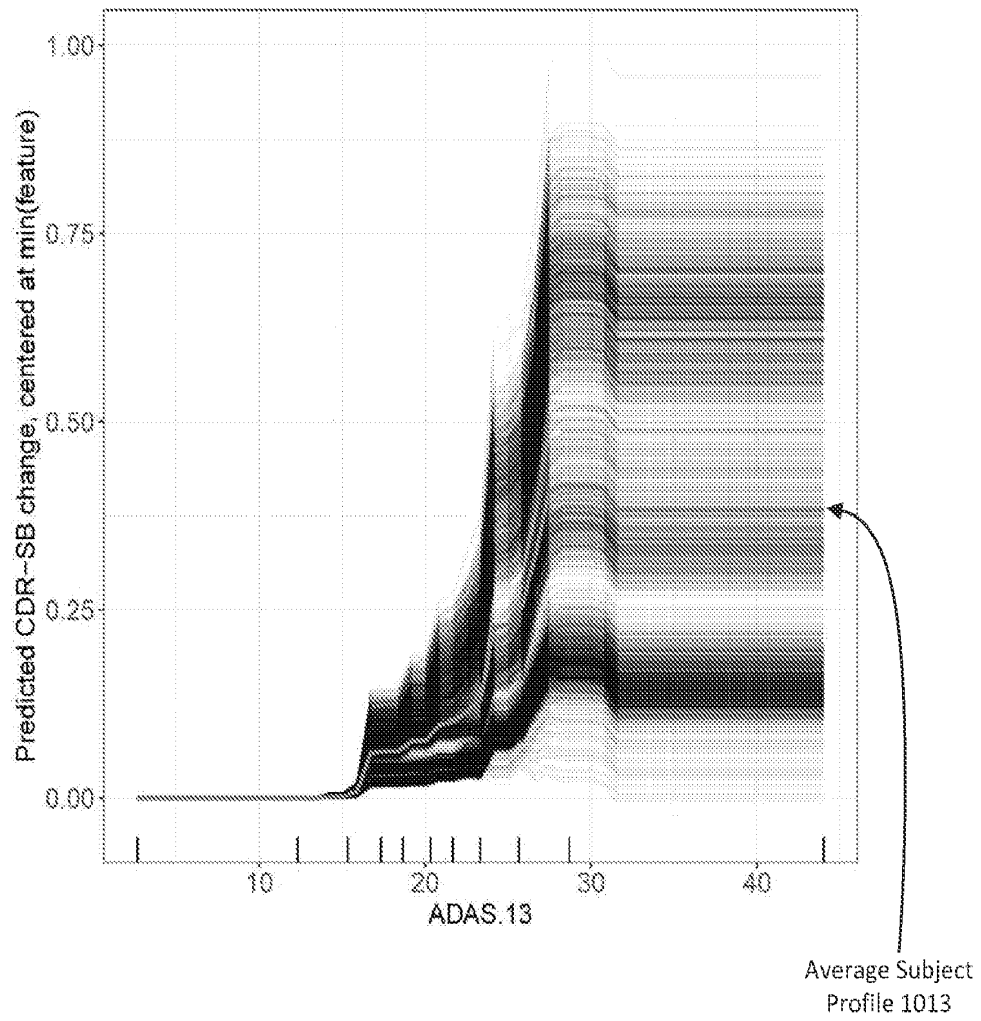


FIG. 10I

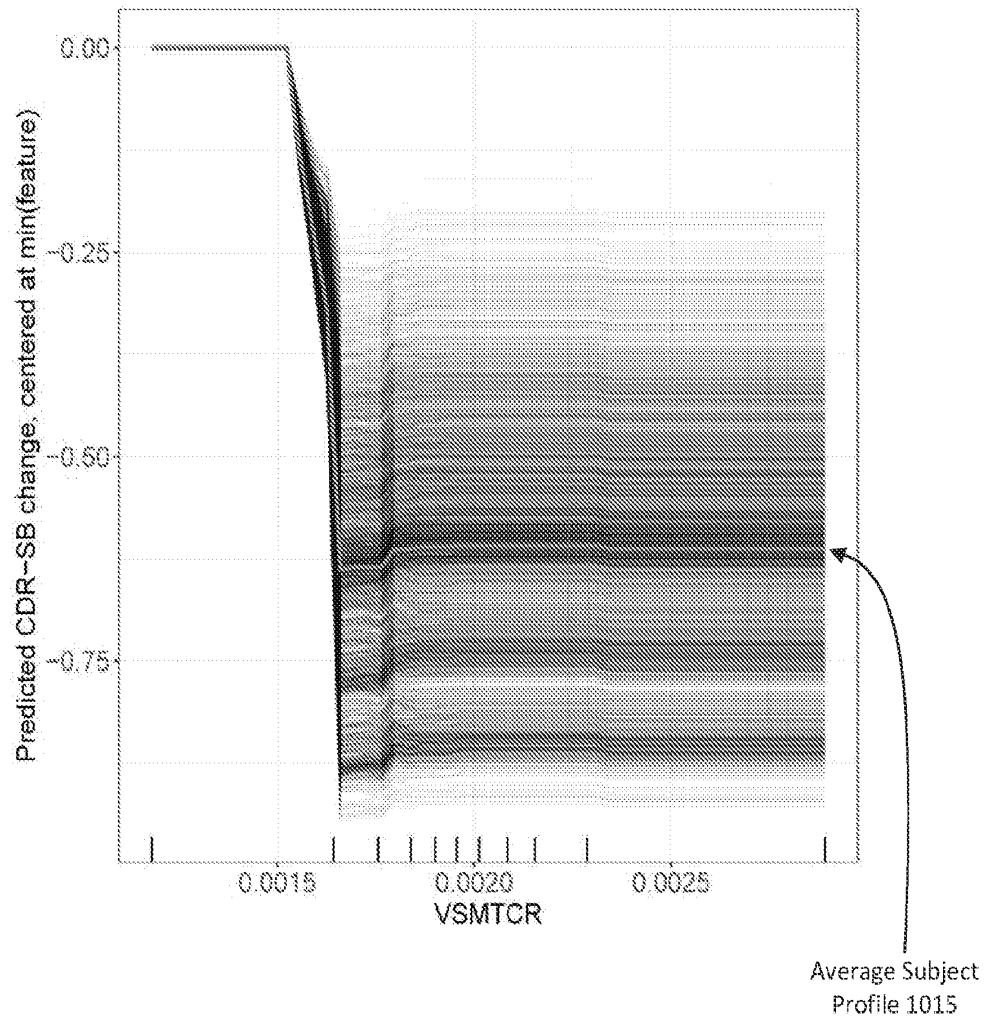
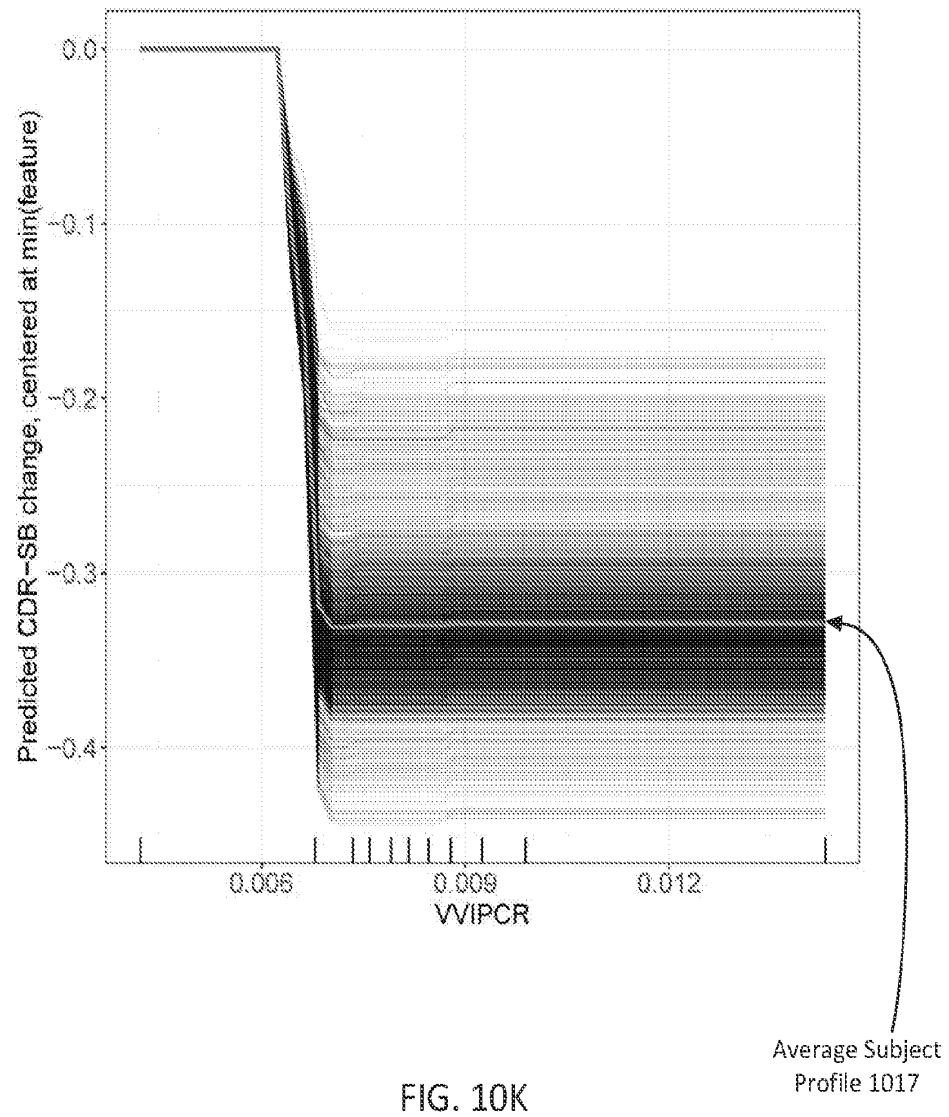


FIG. 10J



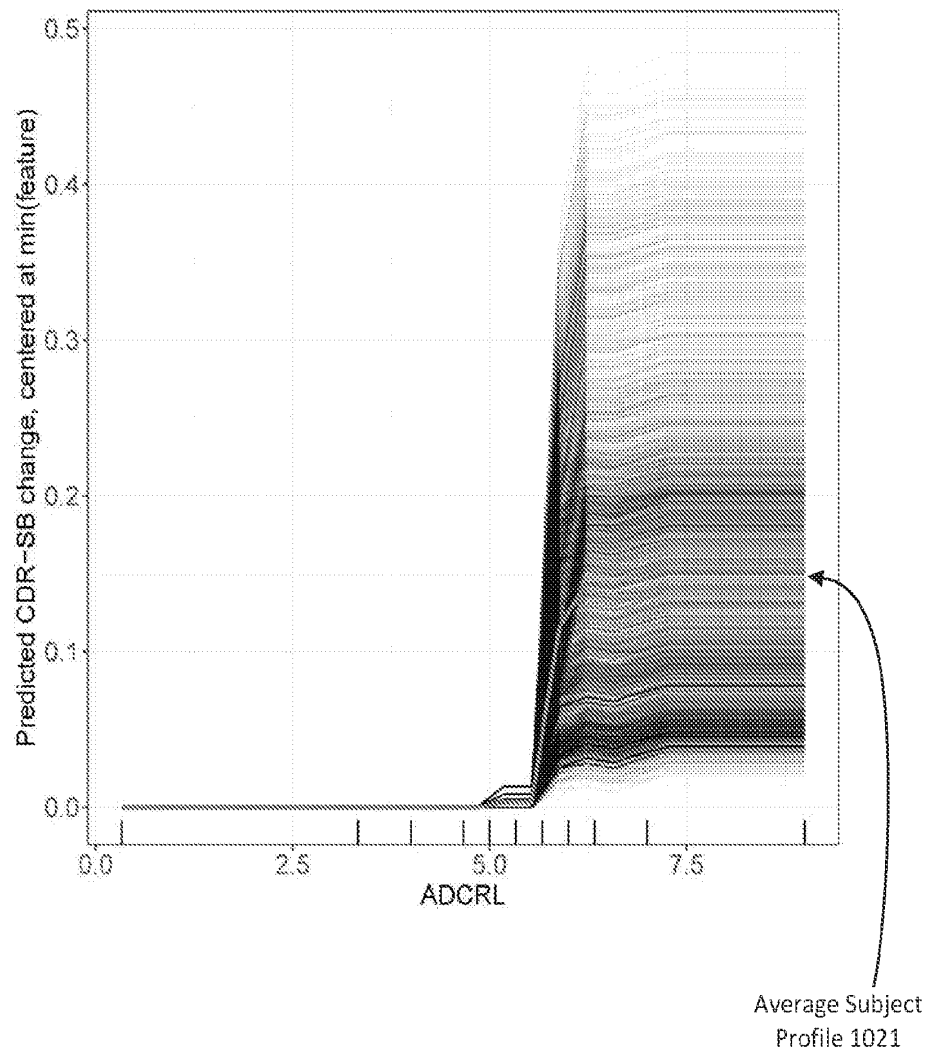


FIG. 10L

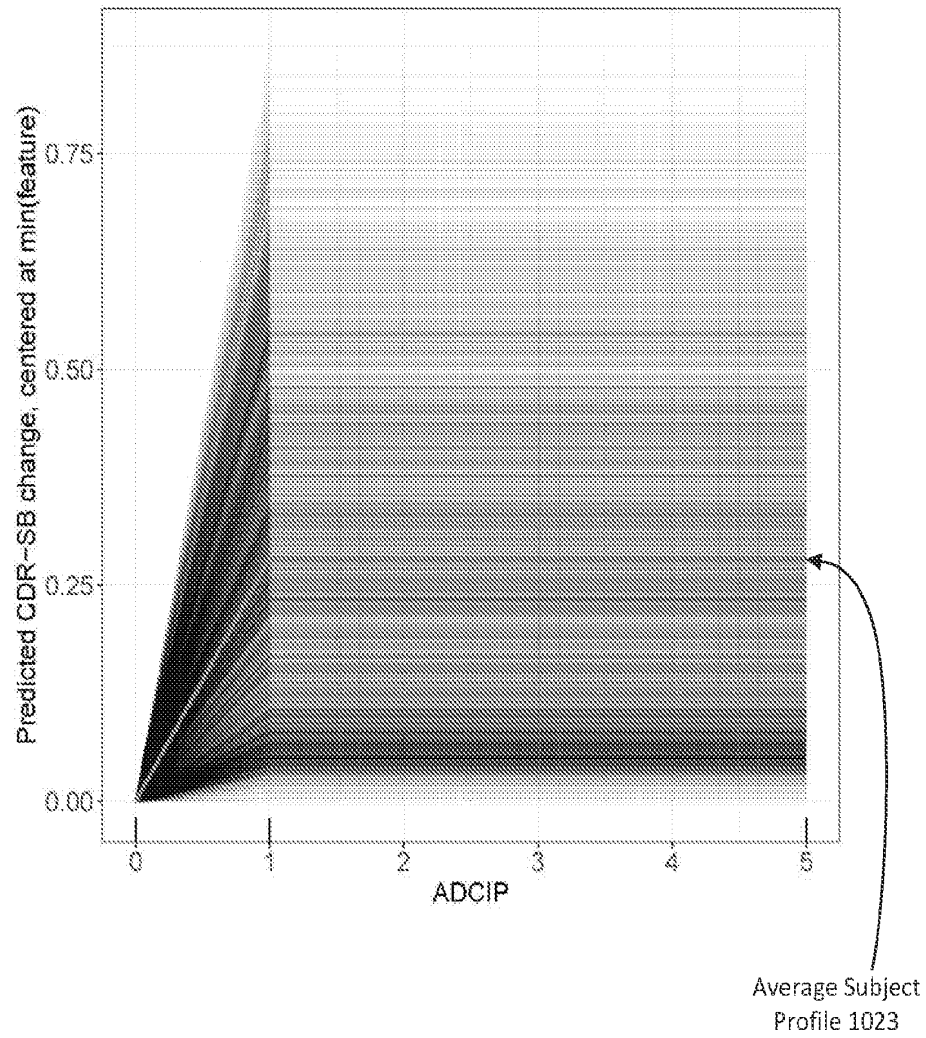


FIG. 10M

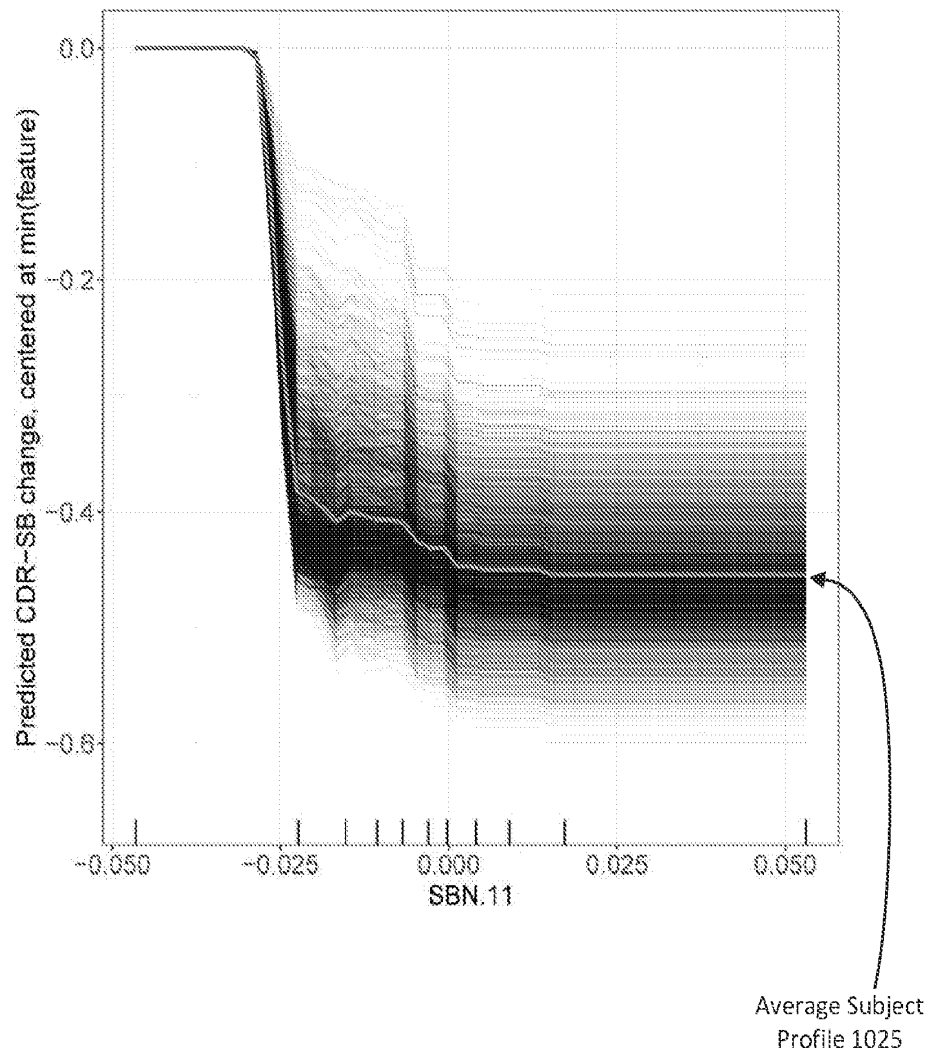


FIG. 10N

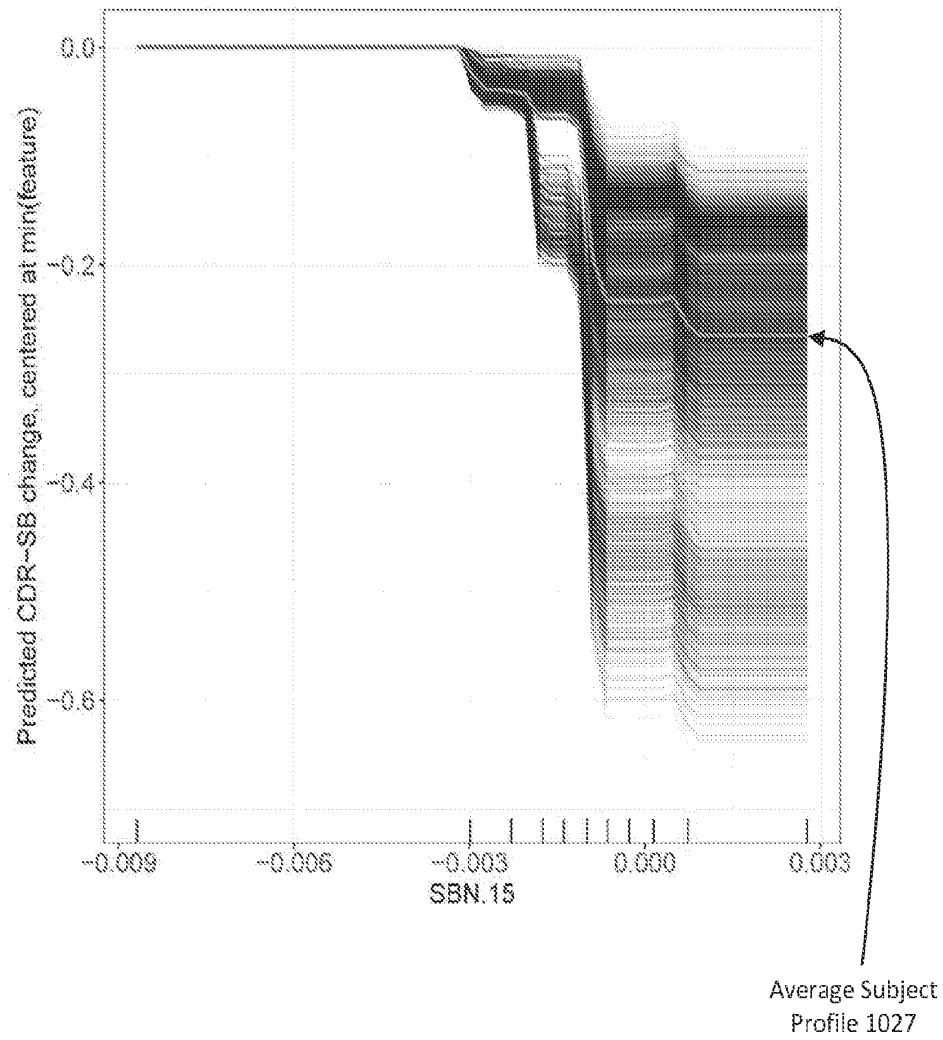


FIG. 100

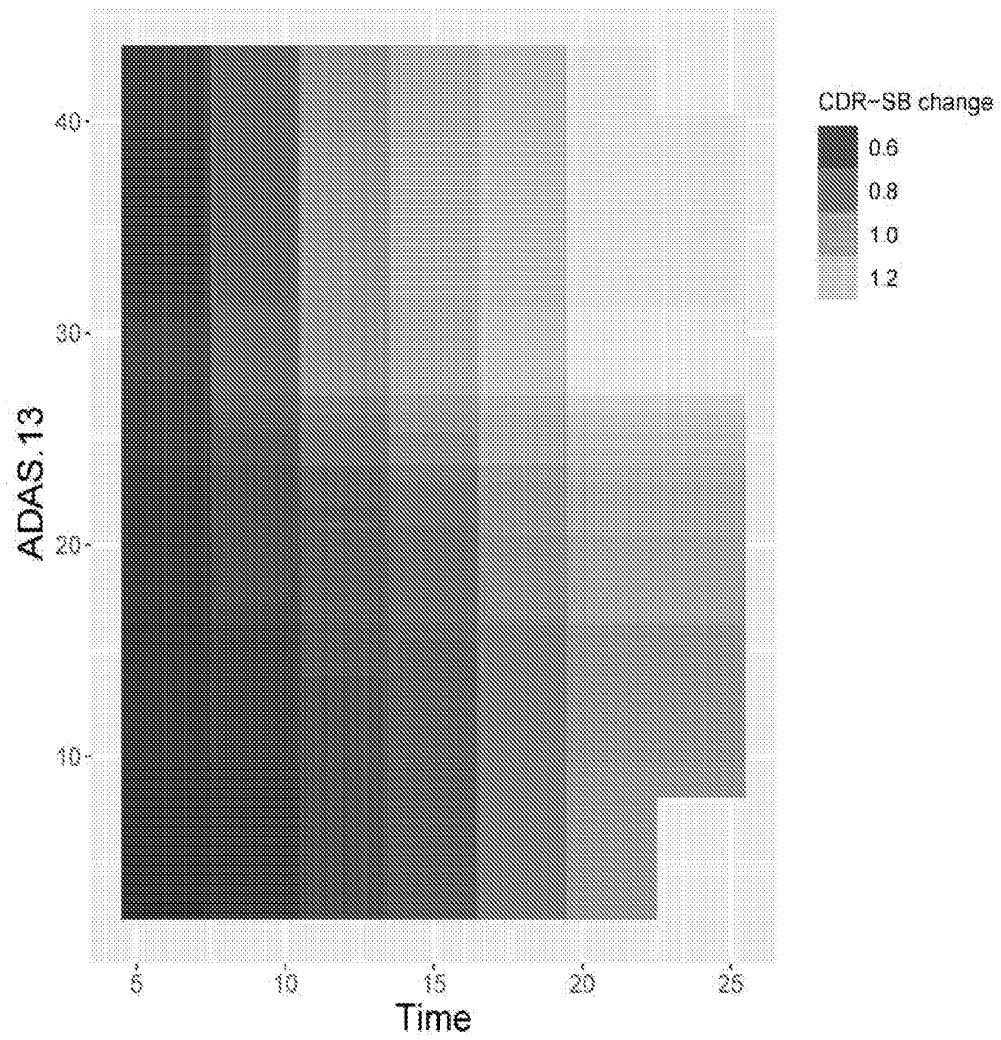


FIG. 10P

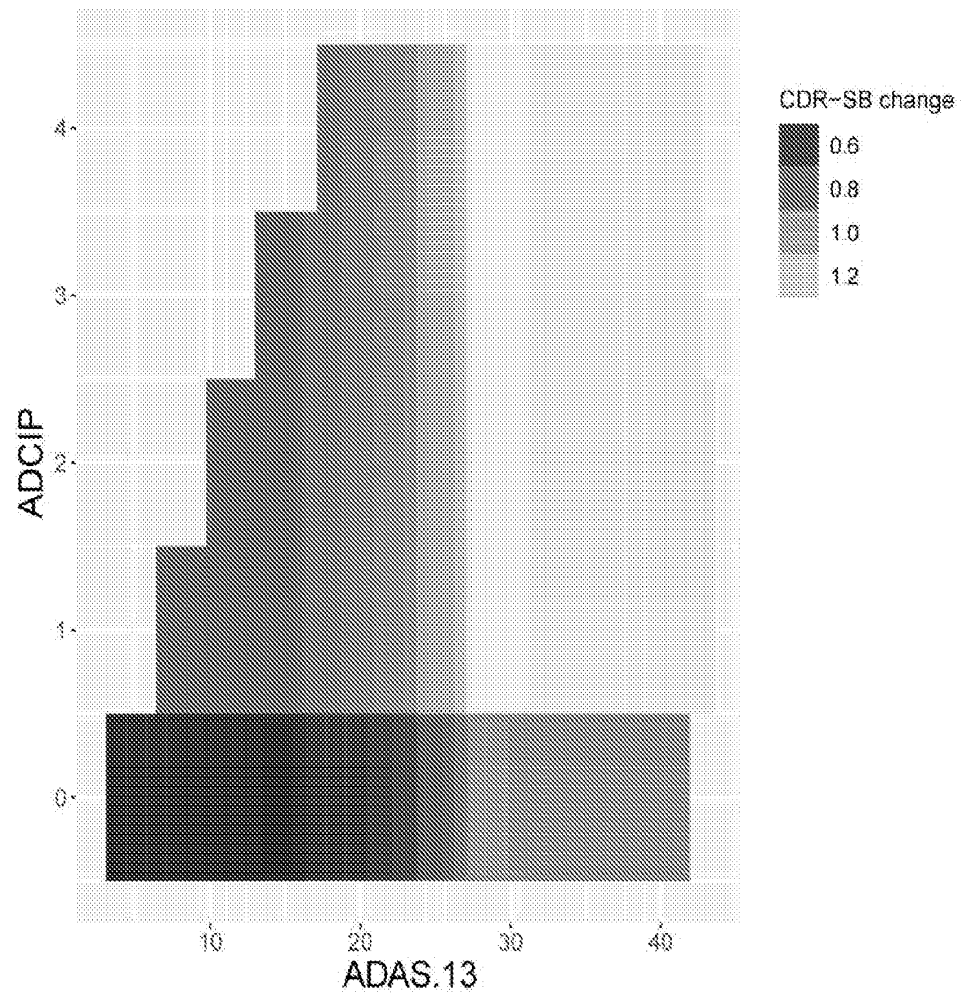


FIG. 10Q

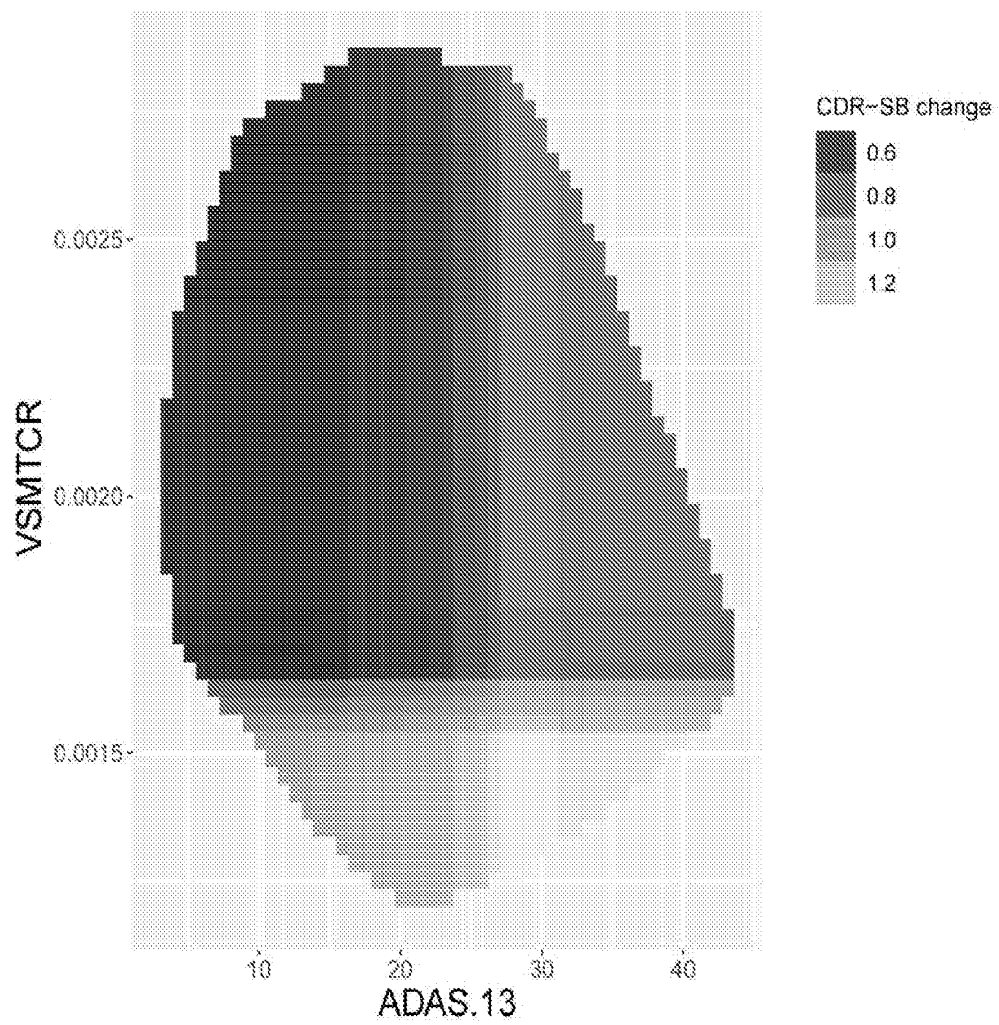


FIG. 10R

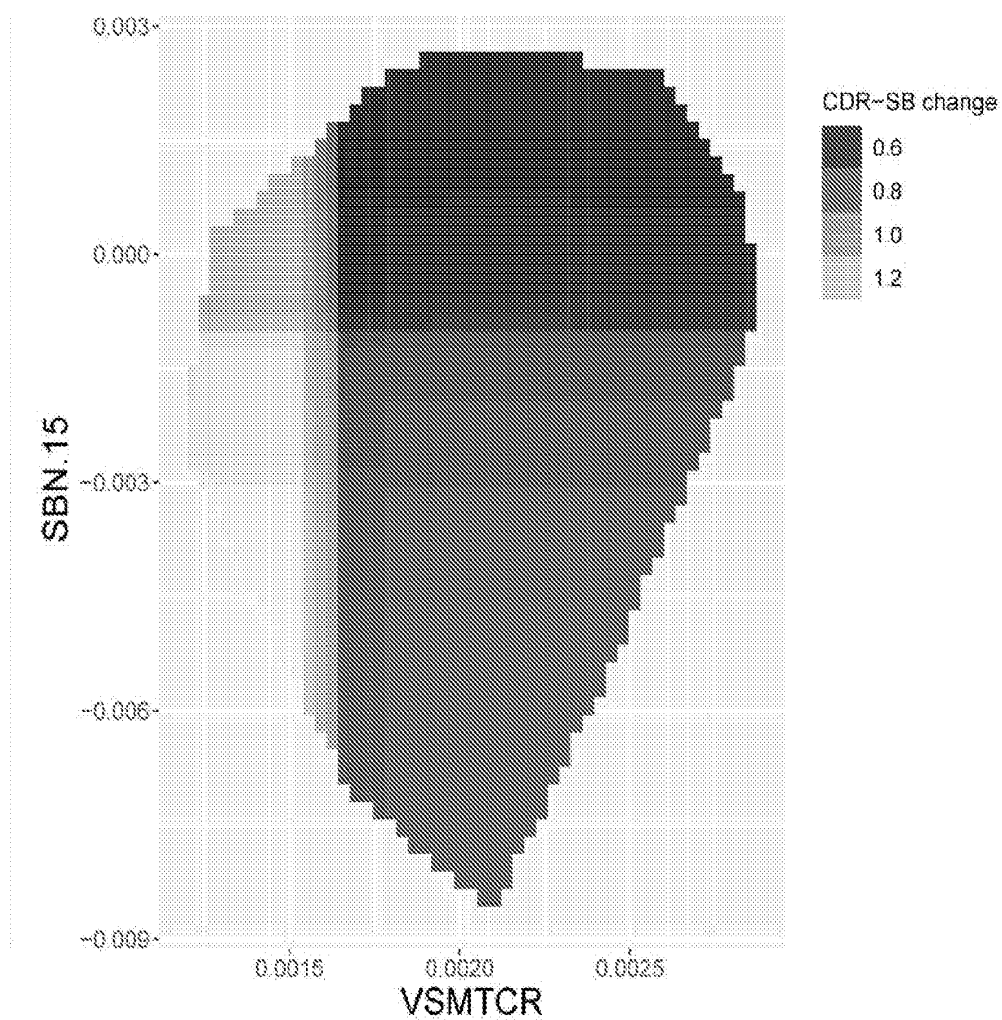


FIG. 10S

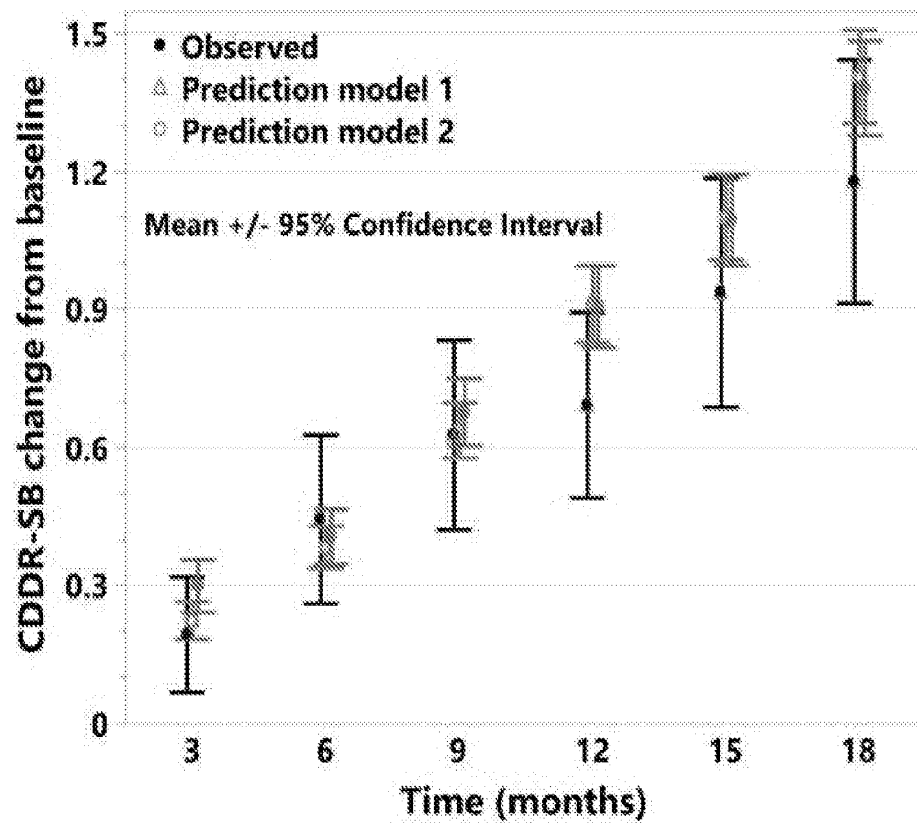


FIG. 10T

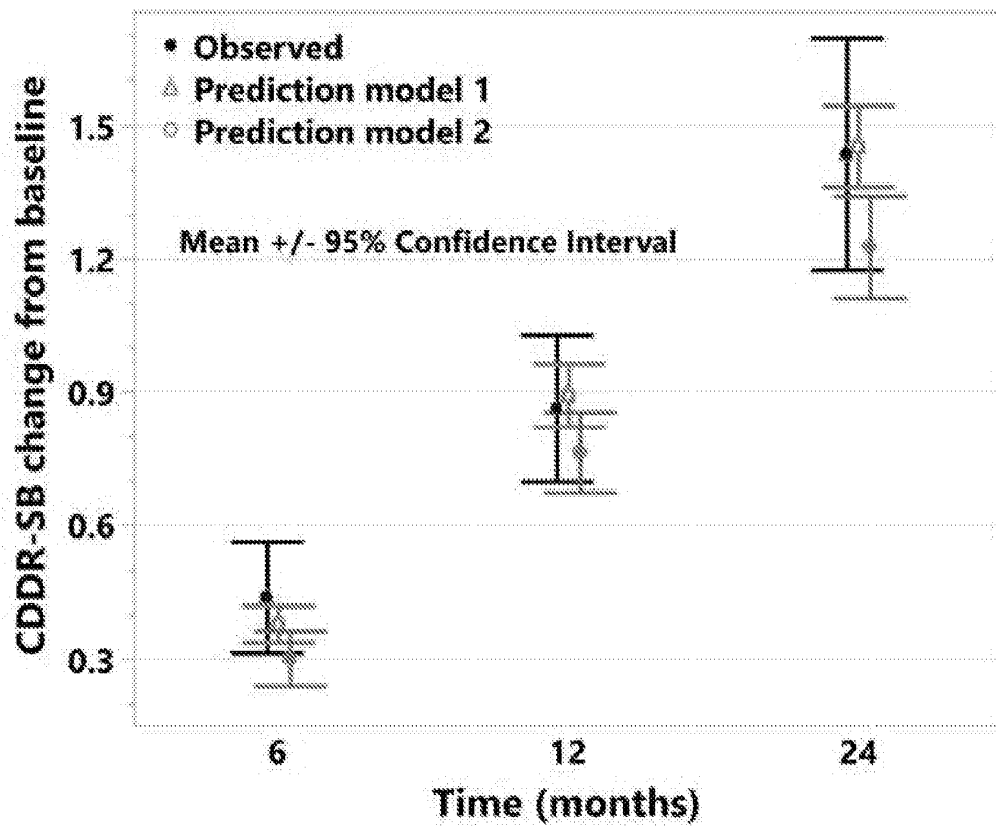


FIG. 10U

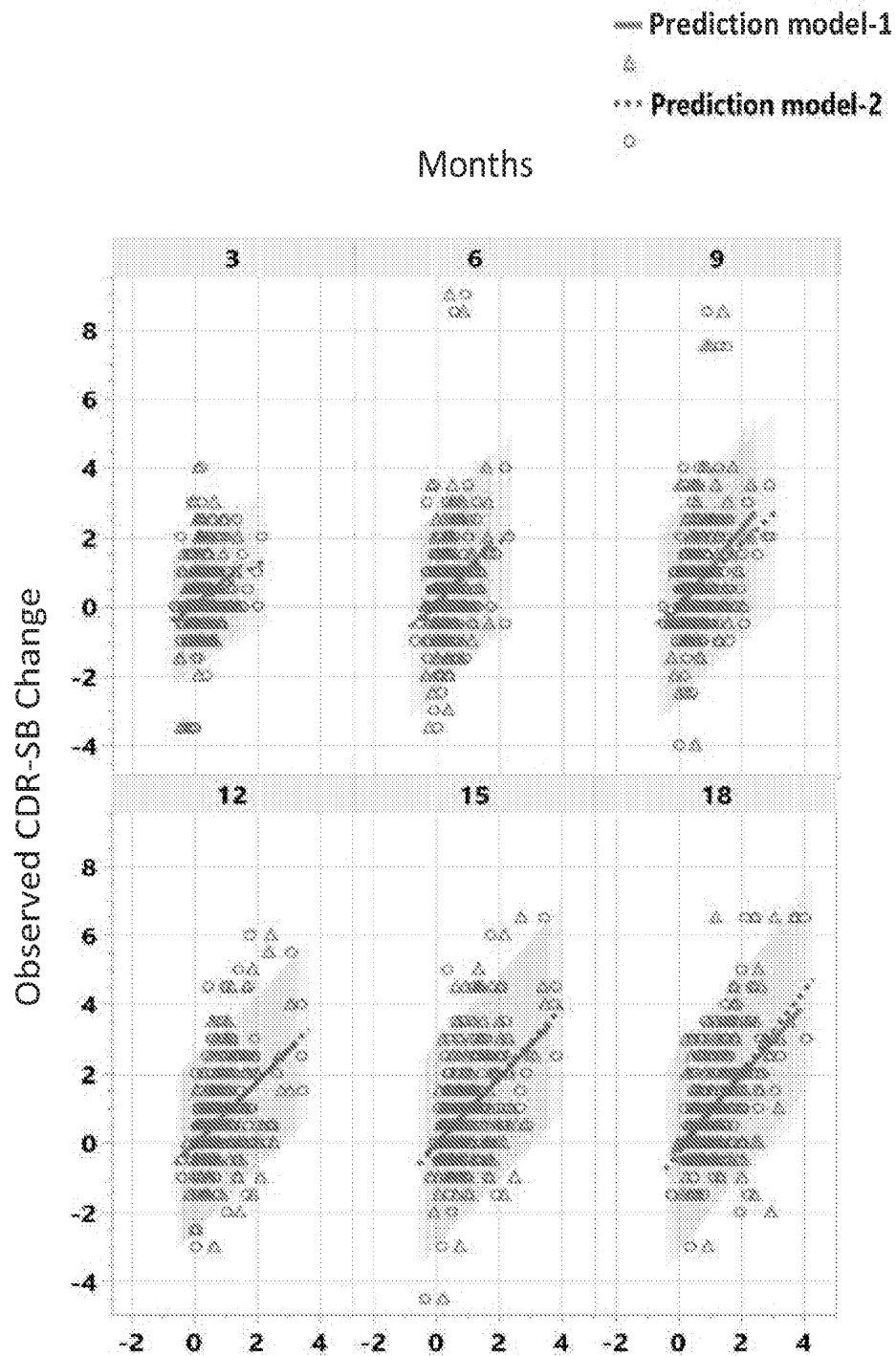


FIG. 10V

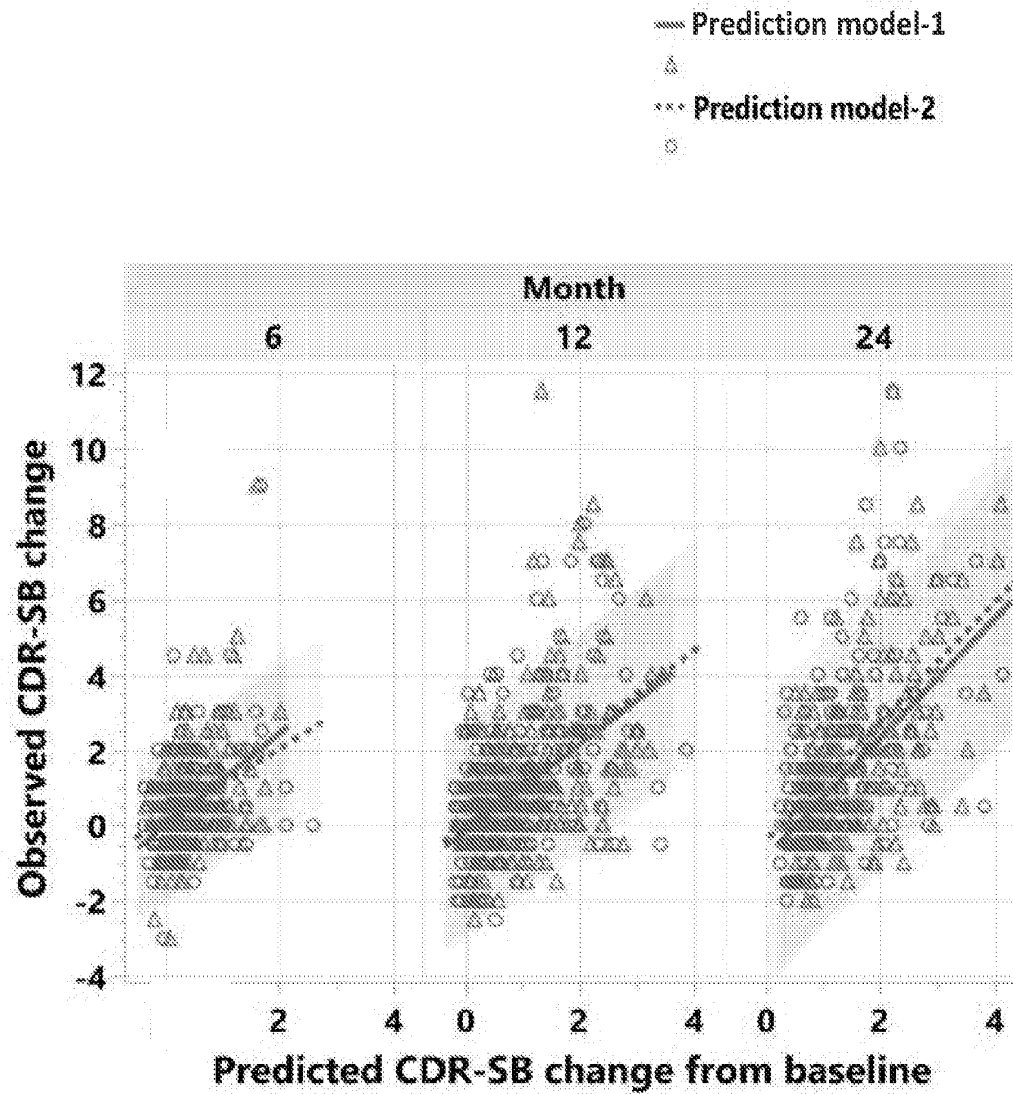


FIG. 10W

Month	VC-1					
	R^2		MSE		MAE	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
3	0.07	0.07	0.88	0.91	0.68	0.69
6	0.06	0.08	1.76	1.74	0.88	0.87
9	0.13	0.11	1.95	1.99	0.94	0.97
12	0.17	0.2	1.64	1.59	0.96	0.94
15	0.17	0.22	2.26	2.14	1.16	1.14
18	0.21	0.29	2.28	2.08	1.16	1.15
24	-	-	-	-	-	-

Month	VC-2					
	R^2		MSE		MAE	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
3	-	-	-	-	-	-
6	0.16	0.14	1.09	1.16	0.72	0.73
9	-	-	-	-	-	-
12	0.25	0.28	2.15	2.03	1.01	0.99
15	-	-	-	-	-	-
18	-	-	-	-	-	-
24	0.31	0.29	3.34	3.88	1.35	1.38

FIG. 10X

Month	VC-1		VC-2	
	Pearson Correlation		Pearson Correlation	
	Model 1	Model 2	Model 1	Model 2
3	0.26	0.26	-	-
6	0.24	0.28	0.4	0.37
9	0.36	0.33	-	-
12	0.41	0.45	0.5	0.53
15	0.41	0.47	-	-
18	0.46	0.54	-	-
24	-		0.56	0.54

FIG. 10Y

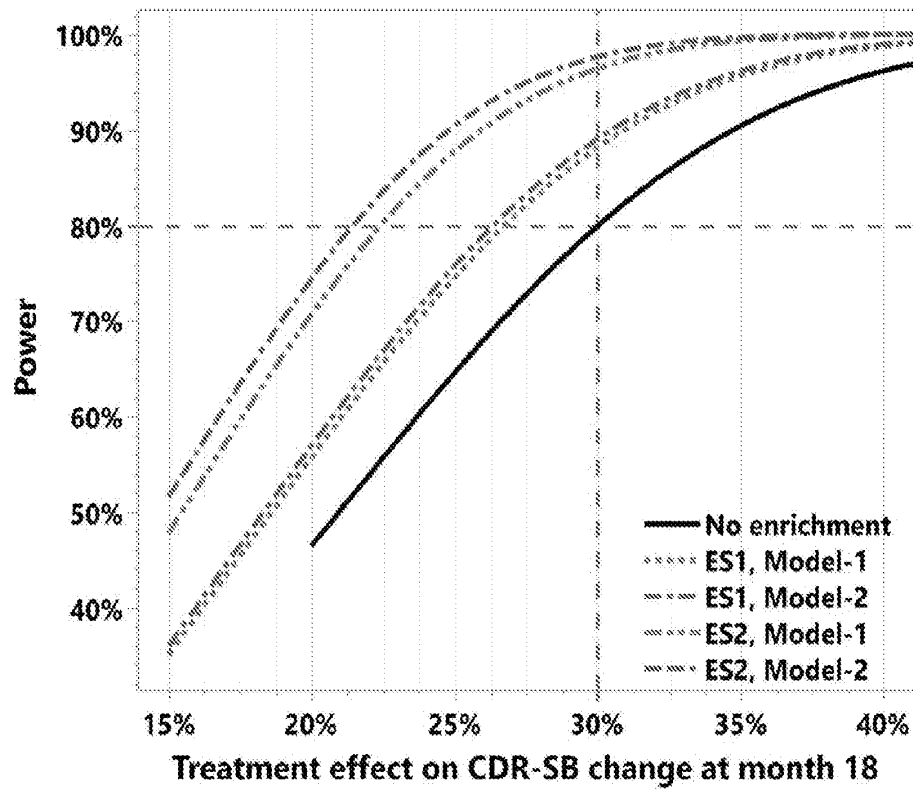


FIG. 10Z

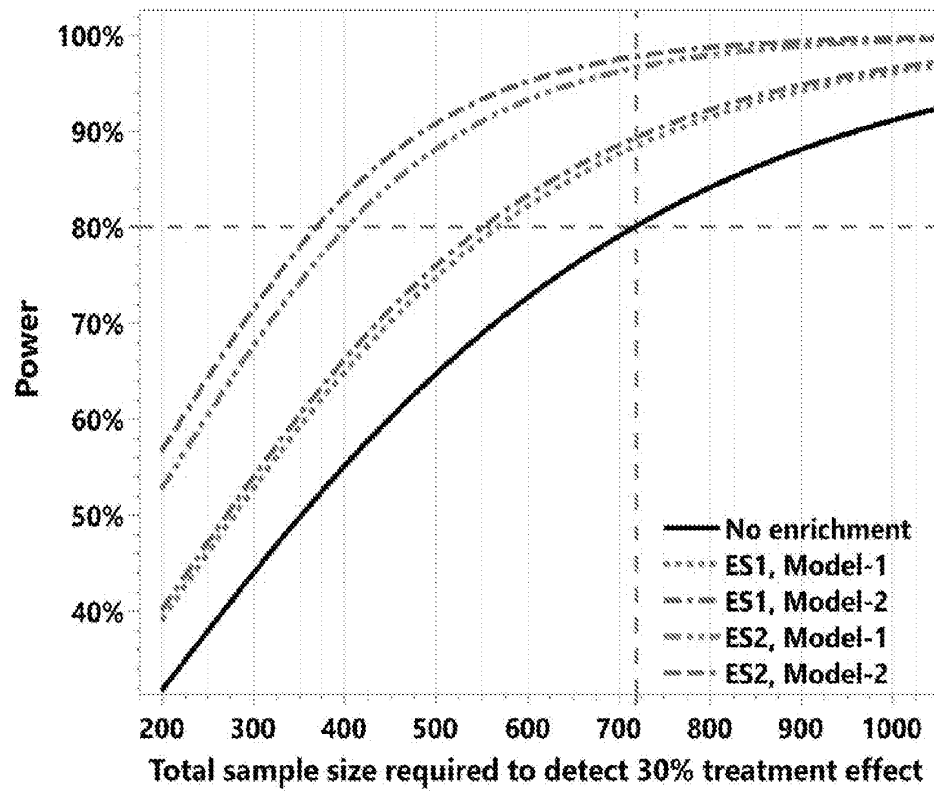


FIG. 10AA