The Cognivue Amyloid Risk Measure (CARM): A Novel Method to Detect the Presence of Amyloid in Clinical Samples with Cognivue Clarity®

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KEY TAKEAWAY: Cognivue Clarity could be used to help screen older adults for treatment protocols with anti-amyloid therapies, enrich clinical trial recruitment before obtaining expensive biomarkers, and identify individuals likely to have pAD for prevention studies in a valid, brief, and cost-effective fashion

BACKGROUND

- Detection of the early stages of Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI) in the community has been challenging, and in clinical practice, many patients first come to medical attention at the moderate stage.
- Preclinical Alzheimer's disease (pAD) is defined by amyloid positivity in the absence of cognitive impairment.
- Clinical detection of individuals who have amyloid in their brain at the present time is not possible without first completing a biomarker assessment.
- The Bio-Hermes Study, funded by the Global Alzheimer's Platform Foundation, investigated the relationship between emerging blood-based and digital biomarkers and the presence of amyloid measured by PET scan.
- We explored the ability of Cognivue Clarity® (Cognivue, Inc, USA) [2] to detect the presence of amyloid in individuals with and without cognitive impairment.
- We identified through preliminary analysis that three components of Cognivue Clarity (Adaptive Motor, Visual Salience, Shape Discrimination; **Figure 1**) are statistically significantly different between true controls (cognitively normal/biomarker negative) and pAD (cognitively normal/ biomarker positive).
- Here, we describe the development and validation of the Cognivue Amyloid Risk Measure (CARM).

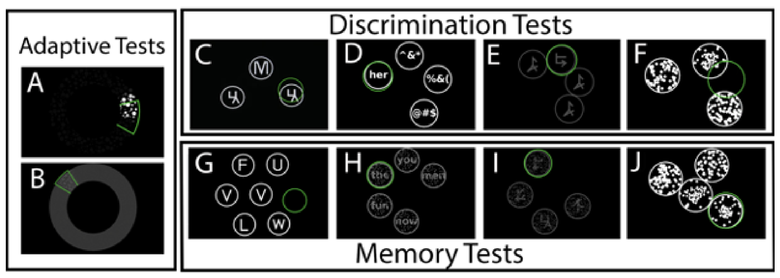


Figure 1: Representative views of Adaptive Motor Control, Visual Salience, and Shape Discrimination tests.

METHODS

- Bio-Hermes recruited 1001 individuals who completed Cognivue Clarity and had amyloid PET scan and plasma biomarkers (ptau181, ptau217, Ab42/40 ratio, and amyloid probability score or APS).
- Three Cognivue Clarity subtests (Adaptive Motor Control, Visual Salience, Shape Discrimination) were statistically significantly different between cognitively normal biomarker-positive (pAD) and True Control individuals and between cognitive impairment due to AD pathology from cognitive impairment due to non-AD processes [3].
- This finding was leveraged to determine whether an amyloid-specific marker could be developed.
- Initial exploration was conducted through statistical analysis with visual exploration revealing a small but present discrimination between amyloid negative and amyloid positive individual (defined by SUVR threshold of 24.1), see **Figure 2**.
- The 3 subtests plus age were combined and used to train gradient boosted regression of amyloid PET Centiloid levels, which was then thresholded based on specificity, sensitivity, and Youden J metrics to create the 4-point Cognivue Amyloid Risk Measure (CARM).
- Thresholds were recalibrated to report 80% specificity, Youden's J (best mix of sensitivity and specificity), and 80% sensitivity, which makes the CARM values easier to explain to clinicians and stakeholders.
- The addition of age into the model significantly increased accuracy in the detection of amyloid positivity.

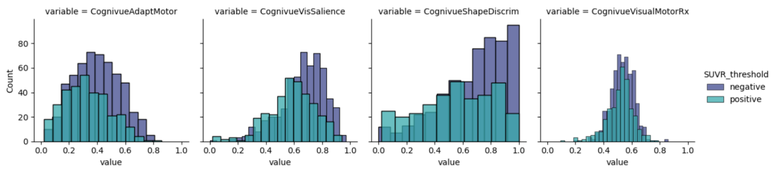


Figure 2. Histograms of each of the four identified significance Cognivue components separated by amyloid positivity based on SUVR threshold.

Developing the CARM

- *Primary target output* is an indicator of likelihood of a patient exhibiting amyloid positivity as defined by SUVR threshold. A continuous score ranging from 1 to 10 and/or a risk ranking using either 3 or 5 ranks, indicating low/moderate/high or very- low/low/moderate/high/very-high risk were targeted.
- Primary strategy was to explore the utility of five methodologies:
  1) a standardized mean strategy, with scoring based on number of SDs separated from the mean with and without weighting for each measure;
  2) linear modeling of centiloids (derived from SUVR, with scores thresholded to between 0 and 100) using regression models (linear regression, random forest regression, supper vector regression, gradient boosted machine regression) with evaluation metrics defined by either the standard SUVR threshold or an alternate threshold;
  3) classification modeling of amyloid positivity (meeting SUVR threshold) using random forest (RF) classification, logistic regression, support vector (SVM) classification, and gradient boosted machine (GBM) classification;
  4) hyperplane separation using support vector classification coefficients;
  5) ensemble modeling of the combined above models that perform best, with and without weighting of each model.

Refining the CARM

After the original CARM was developed, additional tweaking was performed that attempted to better fine-tune the sensitivity, specificity, and overall accuracy of the model and output with regards to determining amyloid positivity. Three additional versions were created:

- Version 2 examined the differing effects of scaling the original centiloid values as well as different methods of calculating the centiloids. Unscaling the data entirely (allowing negative values and values over 100) resulted in worse performance, but allowing negative values but not values over 100 was better than the original scaled model.
- Version 3 explored adding additional variables to the model (age, sex, race, ethnicity, education), with age identified as the best performing variable for determining amyloid positivity.
- Version 4 recalibrated the CARM to be a 4-point instead of a 3-point scale, with a score of 1 indicating a low specificity (below 80% sensitivity), a score of 2 indicating good specificity but low sensitivity (above 80% sensitivity but below Youden's J), a score of 3 indicating below 80% specificity but above Youden's J, and a score of 4 indicating high specificity (above 80%).

RESULTS

- The validation set (1/3 of training set used for validating models) indicated that the ensemble model was the best performing model with sensitivity of 72.6%, specificity of 63.4%, and a diagnostic odds ratio (DOR) of 4.59. However, running all models on the holdout test set revealed that the ensemble model was likely overfit, resulting in the lowest available DOR and F1 score. Instead, the best performing model on the final test set was the GBM Regression model with a DOR of 3.28 (**Table 1**), which also achieved the second highest score in the validation set. While specificity was consistently lower than the ensemble model, sensitivity was higher which is potentially more useful for this type of paradigm. Thus, the GBM Regression model was used to calculate the CARM.

		Sensitivity	Specificity	PPV	NPV	F1 Score	DOR
Validation set	Linear Regression	0.74	0.60	0.52	0.80	0.61	4.29
	Random Forest Regression	0.75	0.50	0.47	0.78	0.58	3.11
	GBM Regression	0.81	0.52	0.50	0.82	0.62	4.57
	Hyperplane Separation	0.71	0.63	0.54	0.79	0.61	4.29
	Ensemble model	0.73	0.63	0.54	0.80	0.62	4.59
Holdout set	Linear Regression	0.64	0.59	0.48	0.73	0.55	2.51
	Random Forest Regression	0.68	0.54	0.47	0.74	0.55	2.47
	GBM Regression	0.73	0.55	0.49	0.77	0.59	3.28
	Hyperplane Separation	0.60	0.61	0.47	0.72	0.53	2.30
	Ensemble model	0.60	0.60	0.47	0.72	0.53	2.25

Table 1.

- As the risk of amyloid increases with increasing age, the next variation was to incorporate age into the model to test whether this would improve discrimination. New CARM raw scores did not match the same scale as previously, due to allowing the centiloid values to be negative (very low risk of amyloid deposition). New thresholds were developed based on specificity, sensitivity, and Youden's J metrics:
  - CARM 1 used a raw score cutoff of 5 or below, determined to be the threshold for 80% sensitivity
  - CARM 2 used a raw score cutoff of 11.7 or below, determined to be the Youden's J
  - CARM 3 used a raw score cutoff of 22.1 or below, determined to be the threshold for 80% specificity
  - CARM 4 was assigned to those with a raw score above 22.1
- When using CARM 3 as a cutoff, 68.3 of biomarker-positive patients were identified, including half of preclinical AD patients (**Table 2**).
- Independent samples ANOVAs with Bonferroni-corrected pairwise post-hoc tests revealed significant differences between groups in all comparisons except sex (**Table 3**).
- Of note, many regional cortical PET uptake were found to significantly differ between CARM 1 and CARM 3, likely a result of the placement of MCI and other cognitively impaired patients into this group.
- CARM 1 and 2 were the most similar to each other, potentially due to the predicted raw CARM values being significantly lower than the centiloid cutoff for amyloid positivity.
- However, it should be noted that the raw CARM scores, while designed to predict centiloid values, are not useful at directly estimating the centiloid values themselves and thus not useful at determining amyloid positivity. Only the thresholded CARM is powered to do so.

	CARM 1	CARM 2	CARM 3	CARM 4	CARM 3+
% A+	19.9%	11.8%	25.7%	42.6%	68.3%
% A-	44.0%	17.0%	19.1%	19.9%	39.0%
% Preclinical AD	35.2%	15.4%	24.2%	25.3%	49.5%
% MCI	14.2%	10.4%	26.3%	49.2%	75.4%
% Non-AD CI	34.6%	14.8%	23.3%	27.2%	50.6%
% Healthy control	52.2%	18.9%	15.5%	13.5%	29.0%

A+ = Amyloid positive; A- = amyloid negative; MCI = mild cognitive impairment, CI = cognitive impairment

Table 2.

	CARM 1	CARM 2	CARM 3	CARM 4	ANOVA p-val
% Cognitively Impaired	0.40 (0.49)	0.47 (0.50)	0.64 (0.50)	0.75 (0.50)	0.000[b]
Age	66.25 (4.86)	70.78 (4.86)	74.78 (4.86)	77.02 (4.86)	0.000[a]
% Female	0.61 (0.49)	0.58 (0.50)	0.51 (0.50)	0.54 (0.50)	0.120
Education	15.86 (2.50)	15.78 (2.74)	15.29 (2.74)	15.16 (2.74)	0.007[c]
MMSE	27.99 (2.06)	27.45 (2.27)	26.52 (2.27)	25.43 (2.27)	0.000[d]
FAQ	1.87 (3.60)	2.09 (3.78)	4.43 (3.78)	5.92 (3.78)	0.000[a]
Cognivue Avg Score	75.00 (10.28)	69.15 (12.50)	61.39 (12.50)	49.36 (12.50)	0.000[a]
Cerebral uptake	888.32 (929.57)	732.46 (931.14)	527.40 (931.14)	623.48 (931.14)	0.000[b,c]
Post Cingulate uptake	894.76 (948.65)	800.31 (1088.28)	600.33 (1088.28)	772.21 (1088.28)	0.020[b]
Medial Frontal uptake	822.09 (865.90)	699.75 (927.87)	521.65 (927.87)	688.46 (927.87)	0.004[b]
Precuneus uptake	958.54 (1006.26)	856.96 (1176.73)	642.32 (1176.73)	847.32 (1176.73)	0.022[b]
Parietal uptake	853.17 (907.36)	744.83 (989.58)	539.42 (989.58)	721.37 (989.58)	0.005[b]
Temporal uptake	970.32 (1019.75)	855.04 (1153.87)	619.45 (1153.87)	809.94 (1153.87)	0.005[b]
Anterior Cingulate uptake	933.05 (979.95)	818.93 (1105.30)	608.72 (1105.30)	809.65 (1105.30)	0.010[b]
Centiloid Level	0.34 (30.81)	7.56 (38.92)	16.13 (38.92)	29.59 (38.92)	0.000[b,c,e]
AB42/40 ratio	0.10 (0.01)	0.10 (0.01)	0.10 (0.01)	0.09 (0.01)	0.000[b,c,e]
APS	22.02 (27.00)	27.96 (28.69)	37.97 (28.69)	43.13 (28.69)	0.000[d]
pTau 217	0.22 (0.16)	0.22 (0.11)	0.27 (0.11)	0.35 (0.11)	0.000[d]
SUVR	1.05 (0.19)	1.09 (0.25)	1.14 (0.25)	1.22 (0.25)	0.000[b,c,e,f]

Mean (SD)

a = Significantly different between all groups
b = Significantly different between 1 and 3
c = Significantly different between 1 and 4
d = Significantly different between all except 1 and 2
e = Significantly different between 2 and 4
f = Significantly different between 3 and 4

Table 3.

Summary of Results

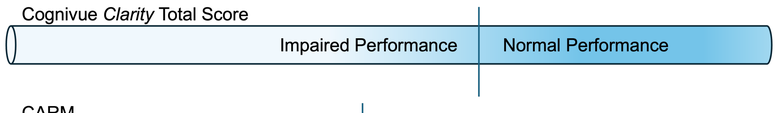
- Cognivue Clarity total scores discriminate cognitively normal from cognitively impaired individuals (p<.001, Cohen's d=0.732).
- The CARM discriminates individuals with amyloid from individuals without amyloid (p<.001, Cohen's d=0.618). Amyloid positivity increased across the 4 CARM thresholds (CARM1: 19%, CARM2: 12%, CARM3: 26%, CARM4: 43%, p<.001).
- Cognitive impairment also increased across CARM thresholds (CARM1: 40%, CARM2: 47%, CARM3: 64%, CARM4: 75%, p<.001).
- Dichotomizing the CARM into low likelihood of amyloid (CARM1, CARM2) and high likelihood of amyloid (CARM3, CARM4) provided excellent discrimination for amyloid positivity by PET (OR 3.67, 95%CI: 2.76-4.89).
- CARM thresholds also differentiated by increasing levels of plasma biomarkers: APS, Ab42/40 ratio, ptau181 and ptau217 (all ANOVA p<.001).
- CARM categories differentiated True Controls, pAD, MCI due to AD, AD, and cognitive impairment due to non-AD etiologies (c2=137.6, p<.001) with the majority of True Controls and non-AD etiologies being in CARM1 and CARM2, and the majority of pAD, MCI due to AD, and AD being in CARM3 and CARM4.

Combining CARM with Cognivue Clarity

- Combining the three Cognivue components of the CARM (Adaptive Motor, Visual Salience, Shape Discrimination) into a single score allowed us to also examine the efficacy of the CARM's centiloid prediction model compared to producing a simple mean.
- When predicting amyloid positivity, the mean score performed similarly to the raw CARM's centiloid model (Eta^2 0.826 vs 0.820), however the thresholded CARM performed significantly better than the thresholded mean score (using the same sensitivity, Youden's J, specificity strategy) at determining amyloid positivity; a Chi-squared test showed that the CARM produced a Cramer's V (a measure of power) of .301 (χ^2=79.98, p<.001) compared to the thresholded mean score's V of 0.234 (χ^2=48.32, p<.001).
- Additionally, the prediction of four-way diagnosis (healthy control, preclinical AD, AD MCI, non-AD MCI) was also more powerful when using the CARM with a binary cutoff of 3 (V=0.360, χ^2=114.7, p<.001) compared to a binary thresholded mean score (V=0.172, χ^2=26.4, p<.001).

CONCLUSIONS

- Cognivue Clarity detects individuals with cognitive impairment and a derivation of Cognivue scores was used to develop the CARM to predict the presence of amyloid.
- The generated CARM performed well at identifying amyloid positivity and moderately well at discriminating between preclinical Alzheimer's and cognitively normal individuals.
- Further refinement of the GBM regression model, including redetermination of risk thresholds, was examined using additional data. Age was added to the model to provide a more robust classification.
- The new thresholded CARM exhibits sensitivity to regional cortical amyloid levels.
- Combining the CARM and the Cognivue Clarity total score could help identify individuals with and without cognitive impairment due to AD or non-AD etiologies (See Scheme in **Figure 3**).
- Cognivue Clarity could be used to help screen older adults for treatment protocols with anti-amyloid therapies, enrich clinical trial recruitment before obtaining expensive biomarkers, and identify individuals likely to have pAD for prevention studies in a valid, brief, and cost-effective fashion.



	CARM Low	CARM High
Cognivue Normal	True Control	Preclinical AD
Cognivue Impaired	Non-AD Etiology	AD Etiology

Figure 3. Scheme for Maximizing Use of Cognivue Clarity.

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