Two Stage Screening for Alzheimer's Disease Clinical Trial Recruitment Enrichment: Cognivue Clarity® and Plasma pTau217

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KEY TAKEAWAY: Cognivue *Clarity* could be used to establish whether there is (a) cognitive impairment with the Cognivue *Clarity* global score, and (b) a high likelihood of amyloid presence with the CARM. This could be followed by measuring a readily accessible AD biomarker such as plasma pTau217 as an *in vitro* diagnostic for amyloid.

INTRODUCTION

Clinical detection of amyloid-positive individuals is generally not possible without expensive biomarkers. This results in delays in diagnosis of Alzheimer's disease (AD) and Mild Cognitive Impairment due to AD (MCI-AD) reducing the window for treatment with amyloid-lowering therapies and missed opportunities for enrollment into clinical trials.

Preclinical Alzheimer's disease (pAD) is defined by amyloid positivity in the absence of cognitive impairment. pAD is generally not recognized clinically and is most often a post-mortem finding. With the advent of biomarkers, pAD is increasingly being recognized in research participants enrolled in longitudinal studies but otherwise are very difficult to identify in order to recruit in AD prevention studies.

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 previously demonstrated Cognivue *Clarity* can differentiate MCI from healthy controls and is sensitive to the presence of amyloid. We further demonstrated that Cognivue *Clarity* can detect pAD and that three subtests (Adaptive Motor Control, Visual Salience, and Shape Discrimination) explained most of the variability to detect amyloid. We used a machine learning paradigm to combine these three subtests and age to create the Cognivue Amyloid Risk Measure (CARM)

There is an unmet need for a brief but sensitive way to discriminate individuals who are likely to have amyloid from those who are less likely to have amyloid. This strategy, when combined with brief cognitive testing, could enrich recruitment into clinical trials for pAD, MCI-AD and AD; lower costs (e.g., time, effort, financial) related to expensive amyloid PET scans by prescreening individuals more likely to have an abnormal scan; and allow clinicians to intervene with amyloid-lowering therapies at the earliest possible stages.

Since Cognivue *Clarity* screens for cognitive impairment and the added value CARM metric, which is captured while completing Cognivue *Clarity*, screen for the likelihood of a positive amyloid PET scan, we tested whether a two-stage screening approach combining Cognivue *Clarity* and CARM with plasma pTau217 could sufficiently differentiate AD from non-AD processes to reduce the need for amyloid PET.

METHODS

Between April 2021 and November 2022, 1001 participants were enrolled, of which 887 completed both Cognivue *Clarity* and amyloid PET scans. Bio-Hermes inclusion criteria included age 60-85, fluency in English or Spanish, and a Mini-Mental State Examination (MMSE) score between 20-30 inclusive. Exclusion criteria included history of depression, strokes or seizures in the past year, or cancer within the past 5 years, or a negative amyloid PET scan in the past year. Written informed consent was obtained from all study participants. Bio-Hermes was reviewed and approved by Advarra, a central institutional review board (Reference Number Pro00046018) and registered on ClinicalTrials.gov (NCT04733989).

Participants were stratified into three clinical cohorts (Cognitively Normal, MCI, probable AD) using National Institute on Aging-Alzheimer Association (NIA-AA) consensus clinical criteria for MCI-AD and AD. Diagnostic characterization was based on the participants' performance on the MMSE, the Rey Auditory Verbal Learning Test (RAVLT) and the Functional Activities Questionnaire (FAQ). Participants underwent amyloid PET using 18F-Florbetapir (Eli Lilly and Company) and the standardized uptake value ratio (SUVR) was calculated. Amyloid status (elevated vs. not elevated) was established using a SUVR of 1.1 which is equivalent to a Centiloid Level of 24.1 consistent with thresholds used in recent AD clinical trials on amyloid-lowering monoclonal antibodies. Participants also had blood-based biomarkers collected and analyzed by C_2N Diagnostics laboratories (PrecivityAD) for Aβ40, Aβ42, Aβ42/Aβ40, ApoE ε4 and the Amyloid Probability Score (APS), Quanterix laboratories for pTau181, and Eli Lilly and Company for pTau217. The amyloid status for the cohort included 567 amyloid negative and 353 amyloid positive individuals.

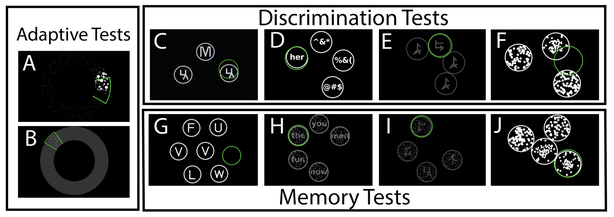
The clinical diagnosis was combined with amyloid status in 887 individuals who completed both Cognivue *Clarity* and amyloid PET to develop clinicopathologic groups consisting of True Controls (cognitively normal + the absence of amyloid, n=297), pAD (cognitively normal + the presence of amyloid, n=91), MCI-AD (cognitive impairment + the presence of amyloid, n=111), MCI due to a process other than AD (MCI-non-AD, cognitive impairment + the absence of amyloid, n=171), dementia due to AD (dementia + the presence of amyloid, n=130) and dementia due to a process other than AD (non-AD, dementia + the absence of amyloid, n=87).

A screening paradigm was developed using clinicopathologic groups, Cognivue *Clarity* scores, the CARM, and plasma pTau217. Statistical analyses were conducted using IBM SPSS v29 (Armonk, NY). Descriptive statistics were used to summarize overall sample characteristics. Independent sample t-tests or one-way analysis of variance (ANOVA) with Tukey-Kramer post-hoc tests were used for continuous data, and Chi-square analyses were used for categorical data.

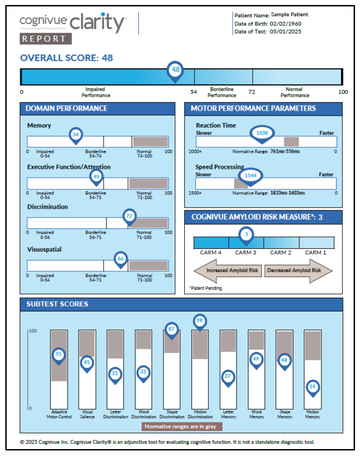
SAMPLE CHARACTERISTICS

	CARM 1/2	CARM 3/4	p-value
Clinical Variables			
Age, y	67.6 (5.3)	76.0 (5.1)	<0.001
Education, y	15.8 (2.6)	15.2 (2.8)	<0.001
Sex, % Female	60.3	52.7	0.023
Race, % NHW	78.6	79.2	0.772
MMSE	27.8 (2.1)	25.9 (2.9)	<0.001
FAQ	1.9 (3.6)	5.3 (6.0)	<0.001
RAVLT Total	43.1 913.5)	38.1 (14.2)	<0.001
Cognivue *Clarity*	73.2 (11.3)	54.6 (15.8)	<0.001
% Healthy Controls	71.0	29.0	<0.001
% pAD	50.5	49.5	
% MCI-AD	34.2	65.8	
% AD	16.3	83.7	
Plasma and Imaging Biomarkers			
ApoE4 carrier, %	35.9	38.9	0.373
pTau217	0.22 (0.15)	0.31 (0.22)	<0.001
pTau181	18.4 (11.3)	23.1 (14.2)	<0.001
Aβ42/40	0.099 (0.010)	0.095 (0.009)	<0.001
APS	23.8 (27.6)	40.9 (31.3)	<0.001
Amyloid PET SUVR	1.06 (0.2)	1.18 (0.3)	<0.001
Centiloid Level	16.8 (38.4)	40.0 (49.4)	<0.001
Mean (SD) or %			

COGNIVUE *CLARITY*®



- FDA-cleared Class II exempt medical device
- Computerized, self-administered 10-minute cognitive test
- Utilizes adaptive psychophysics to test baseline motor and visual skills to determine level of difficulty in subsequent tests
- Patient single point of interaction is via the CogniWheel, an easy-to-maneuver flywheel
- 130,000 data points collected per administration
- Video demonstration at https://Cognivue.com/videos/
- 10 subtests that include two validity performance measures (Adaptive Motor Control, Visual Salience) that are used to set the adaptive psychophysics profile. There are four discrimination tests (Letter, Word, Shape, Motion), and four memory tests (Letter, Word, Shape, Motion)
- Provides immediate results in a report and/or a comma-separated values file.
- Global, domain and subtest scores are scaled 0-100 with higher scores reflecting better performance.
- Score interpretations are provided as normal, borderline, or impaired performance
- CARM scores are provide as 4 levels with levels 1/2 representing low risk of amyloid and levels 3/4 representing high risk of amyloid

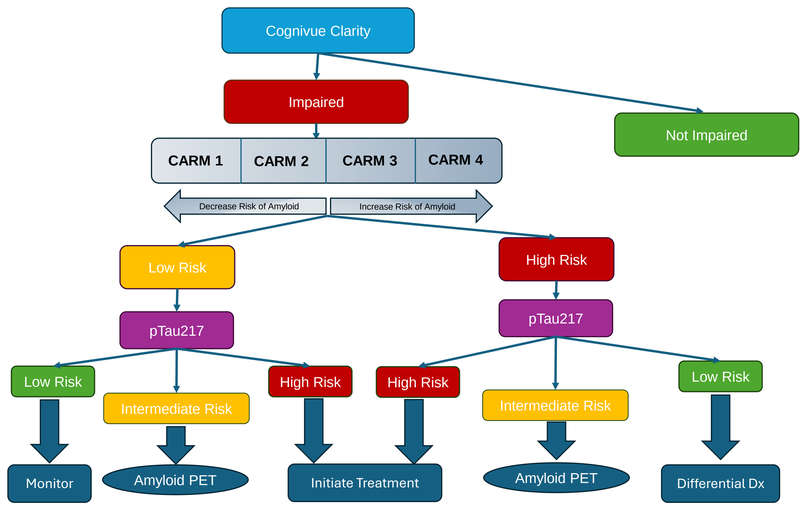


CONCEPTUAL MODEL

Schematic of Two Stage Screening

To increase the efficiency and cost-effectiveness of cognitive screening, a staged screening approach could improve diagnosis of cases for treatment or enrollment into clinical trials. We propose the following model:

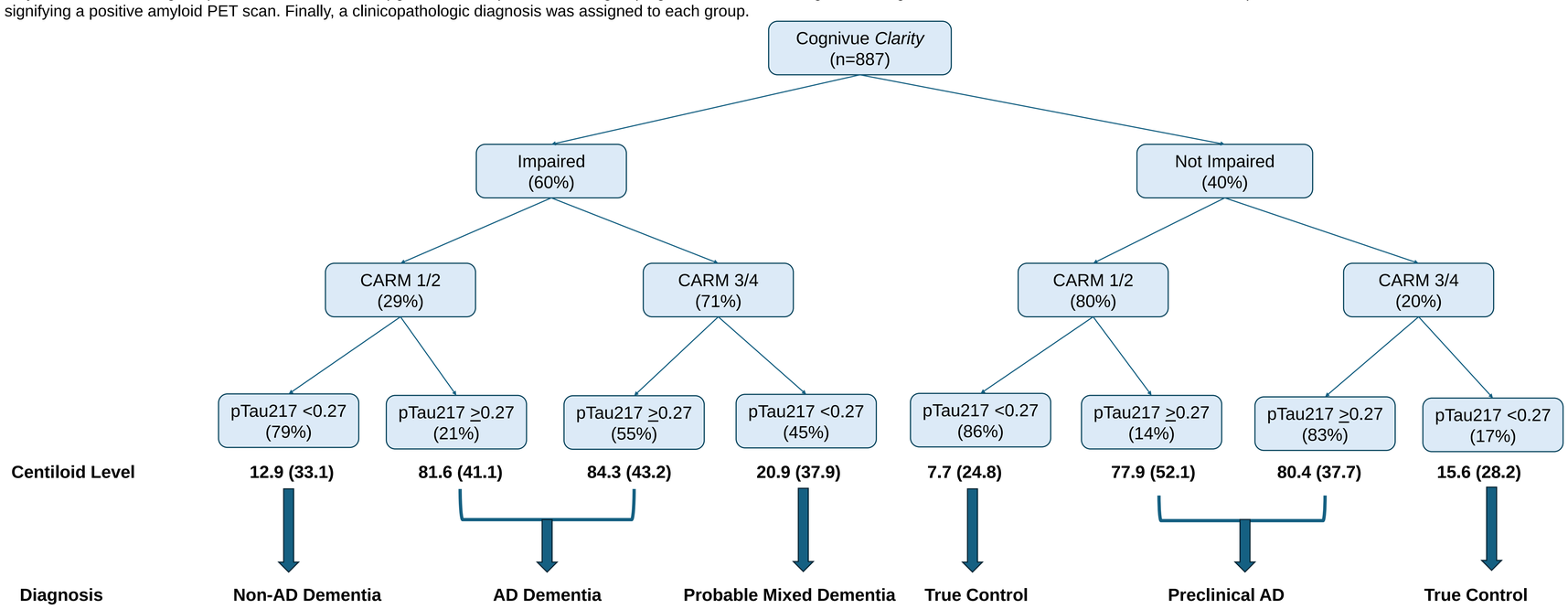
1. Cognivue *Clarity* can detect cognitive impairment
2. The CARM gives estimate on likelihood of elevated amyloid on PET scan
3. Plasma pTau217 used as a diagnostic for amyloid
4. Based on results of cognitive testing and plasma biomarker, improve clinical decision making



RESULTS

Implementation of the 2-Stage Screening with the Bio-Hermes Sample

We tested the 2-stage screening paradigm in 887 participants in Bio-Hermes to mimic who how individuals might be evaluated in clinical practice. We first only considered screening cognition with Cognivue *Clarity.* Based on a published cut-off global score of 69, the sample was divided into people with or without cognitive impairment. We then considered the CARM as to the likelihood of whether would have a positive amyloid PET scan with CARM 1/2 representing low risk and CARM 3/4 representing increased risk. Following an in-office cognitive test, a blood-based biomarker (pTau217) was examined as an *in vitro* diagnostic for a positive amyloid PET scan using the published cut-off of 0.027pg/ml. We compared the final groupings based on this 2-stage screening to the Centiloid level obtained from the Florbetapir PET scan with a threshold of 24.1 signifying a positive amyloid PET scan. Finally, a clinicopathologic diagnosis was assigned to each group.



Assignment of Diagnostic Groups with 2-stage Screening

Using this strategy, we were able to identify individuals with AD dementia as distinct from individuals that had a non-AD dementia or mixed dementia process. Further, we were able to discriminate True Controls from individuals that had Preclinical AD. This scheme provides an efficient way to determine individuals for treatment protocols with amyloid-targeting therapies or for enrollment into clinical trials. This scheme also provides a unique opportunity to identify individuals highly likely to have Preclinical AD for enrollment into prevention trials.

CONCLUSIONS

- With many AD prevention and treatment trials on-going, screening for individuals with cognitive impairment and amyloid is an expensive and labor-intensive proposition since neuropsychological testing alone cannot detect amyloid, and PET scans or CSF and Blood-based biomarkers cannot characterize cognitive performance.
- We tested a rapid screening paradigm for MCI-AD and AD combining Cognivue *Clarity* with a blood based pTau217 biomarker
- Cognivue *Clarity* could be used to establish whether there is (a) cognitive impairment with the Cognivue *Clarity* global score, and (b) a high likelihood of amyloid presence with the CARM.
- This could be followed by measuring a readily accessible AD biomarker such as plasma pTau217 as an *in vitro* diagnostic for amyloid
- Based on the results, patients can be directed to a treatment protocol, a clinical trial or other research protocol, be reassured and tested at a later time, or continue further search for etiology of the non-AD cause of cognitive impairment.
- This same screening paradigm could be used to potentially identify pAD in the clinic setting enabling enrollment into prevention trials.
- Employment of a 2-stage screening strategy (Cognivue *Clarity* + pTau217) could increase the likelihood of identifying early AD for treatment or trial enrollment, avoiding the cost of expensive PET scans in a brief, reliable, valid, and time- and cost-effective fashion.

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