Combining Cognivue Clarity and LucentAD Complete for a Time and Cost Efficient Two Stage Screening for Alzheimer's Disease Clinical Trial Recruitment Enrichment and Treatment Protocols

James E. Galvin,[*1] Lindsey Mette,[2] Zachary Fernandes,[2] David Wilson,[2] Heather M. Harris,[3] and Paul Estes[3]

[1]Comprehensive Center for Brain Health, Department of Neurology, University of Miami Miller School of Medicine, 7700 W Camino Real, Boca Raton FL, 33433;
[2]Lucent Diagnostics 900 Middlesex Turnpike, Billerica, MA 01821 ,[3]Cognvue Inc, 7911 Rae Blvd, Victor, NY 14564

KEY TAKEAWAYS: Two-stage screening with Cognivue *Clarity* and LucentAD Complete classifies individuals into those likely to have Alzheimer's disease vs those who do not. Cost effective approach limiting need for amyloid PET, enriching sample selection in low prevalence screening settings.

INTRODUCTION

For patients living with Alzheimer's disease and Mild Cognitive Impairment due to AD (MCI-AD), there can be a long delay in getting a correct diagnosis. This may reduce the window for treatment with amyloid-lowering therapies and missed opportunities for enrollment into clinical trials. The advent of sensitive computerized cognitive tests such as Cognivue *Clarity* and blood-based biomarkers of AD pathology such as Lucent*AD Complete* offer unique opportunities to hasten screening and identification of patients with early-stage AD outside of specialty centers and expensive and invasive biomarkers. For individuals with preclinical Alzheimer's disease (pAD), defined by amyloid positivity in the absence of cognitive impairment, recognition in the clinical setting has been nearly impossible. With the advent of amyloid PET being used more frequently in clinical trials and longitudinal research, pAD is increasingly recognized in research participants enrolled in these studies but otherwise pAD is very difficult to identify in order to recruit in AD prevention studies.

Cognivue *Clarity* is a 10-minute self-administered computerized cognitive assessment. A cut-off score of <69 can differentiate individuals with MCI from healthy controls. Cognivue *Clarity* is also sensitive to the presence of amyloid potentially allowing the rapid identification of early-stage AD and pAD. A machine learning paradigm to combine three Cognivue *Clarity* subtests and age was used to create the Cognivue Amyloid Risk Measure (CARM) as an added value metric for the likelihood of a positive amyloid PET scan.

Lucent*AD Complete* is a highly sensitive multi-biomarker blood test for assessing the presence of AD pathology using an algorithm to combine SIMOA ultrasensitive analysis of pTau217, Ab42/40 ratio, NfL, and GFAP into a single score ranging from 0-100 and uses a two-threshold cutoff with 0-44 representing low risk, 45-70 representing intermediate risk, and 70-100 representing high risk of a positive amyloid PET scan.

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. To increase the likelihood of screening for early-stage AD, we combined the Cognivue *Clarity* with Lucent*AD Complete* in a two-stage screening approach to (a) identify individuals with early-stage AD, (b) differentiate AD from non-AD processes, and (c) screen for pAD among cognitive normal controls.

METHODS

The Bio-Hermes Study,[6] 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 in 1,001 participants were enrolled, of which 964 completed Cognivue *Clarity,* Lucent*AD Complete,* and amyloid PET scans. Participants were stratified into three clinical cohorts (Cognitively Normal, MCI, probable AD) using National Institute on Aging-Alzheimer Association criteria for MCI-AD and AD. Participants underwent amyloid PET using 18F-Florbetapir as the Gold Standard.

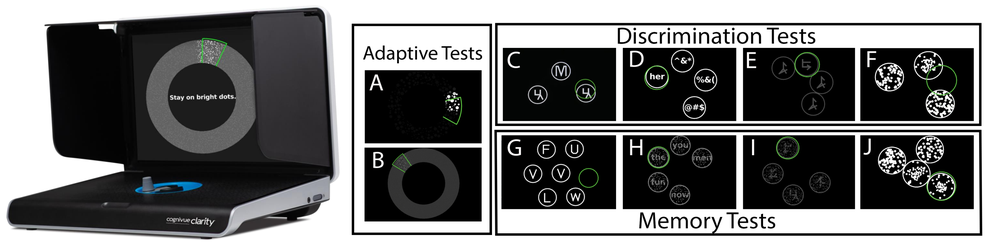
The clinical diagnosis was combined with amyloid status to develop clinicopathologic groups consisting of 297 True Controls, 91 pAD, 111 MCI-AD, 171 MCI due to a process other than AD (MCI-non-AD), 130 dementia due to AD, and 87 dementia due to a process other than AD (non-AD). Statistical analyses were conducted using IBM SPSS v29. Independent sample t-tests or one-way ANOVA with Tukey-Kramer post-hoc tests were used for continuous data, and Chi-square analyses were used for categorical data.

SAMPLE CHARACTERISTICS

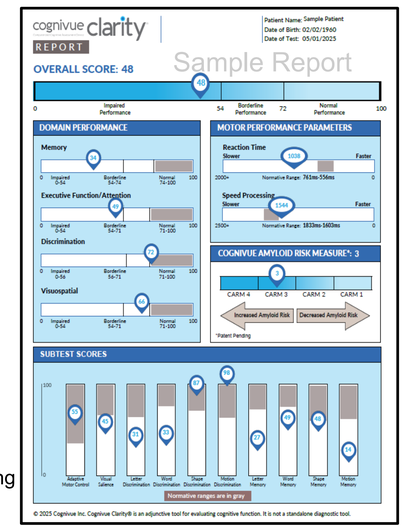
Table 1: Sample Characteristics by Amyloid Status (N=887)

	Negative	Positive	p-value
Clinical Variables			
Age, y	70.5 (6.6)	74.2 (6.1)	<0.001
Education, y	15.5 (2.5)	15.4 (3.0)	0.733
Sex, % Female	58.9	53.0	0.077
Race, % NHW	76.5	79.6	0.594
MMSE	27.4 (2.3)	25.7 (3.3)	<0.001
FAQ	2.6 (4.6)	5.9 (6.1)	<0.001
RAVLT Total	41.9 (14.5)	36.9 (13.7)	<0.001
Cognivue *Clarity*	67.3 (15.3)	58.1 (17.4)	<0.001
Lucent*AD Complete*	0.36 (0.20)	0.78 (0.26)	<0.001
% Controls	52.4	26.9	<0.001
% MCI	30.9	32.0	
% Probable AD	16.8	41.1	
Plasma and Imaging Biomarkers			
ApoE4 carrier, %	22.3	62.2	<0.001
Aβ42/40	0.101 (0.009)	0.091 (0.008)	<0.001
APS	17.4 (20.7)	57.1 (28.5)	<0.001
pTau217	0.19 (0.11)	0.38 (0.23)	<0.001
pTau181	17.2 (9.2)	26.4 (15.6)	<0.001
Amyloid PET SUVR	0.96 (0.07)	1.39 (0.21)	<0.001
Centiloid Level	-1.10 (12.6)	78.6 (38.4)	<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; 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 score is provided as 4 levels with levels 1/2 representing low risk and levels 3/4 representing high risk of amyloid



Lucent*AD Complete*

- A multi-biomarker blood test for assessing Alzheimer's disease pathology
- Correlated with CSF measurements and amyloid PET scans
- Includes pTau217, Ab42/40, GFAP and NfL
- Algorithmic approach reduces diagnostic uncertainty associated with single biomarker tests
- Ultrasensitive detection using Simoa technology
- 90% Sensitivity, 90% Specificity, 87% Negative Predictive Value, 92% Positive Predictive Value

Interpreting Lucent*AD Complete*

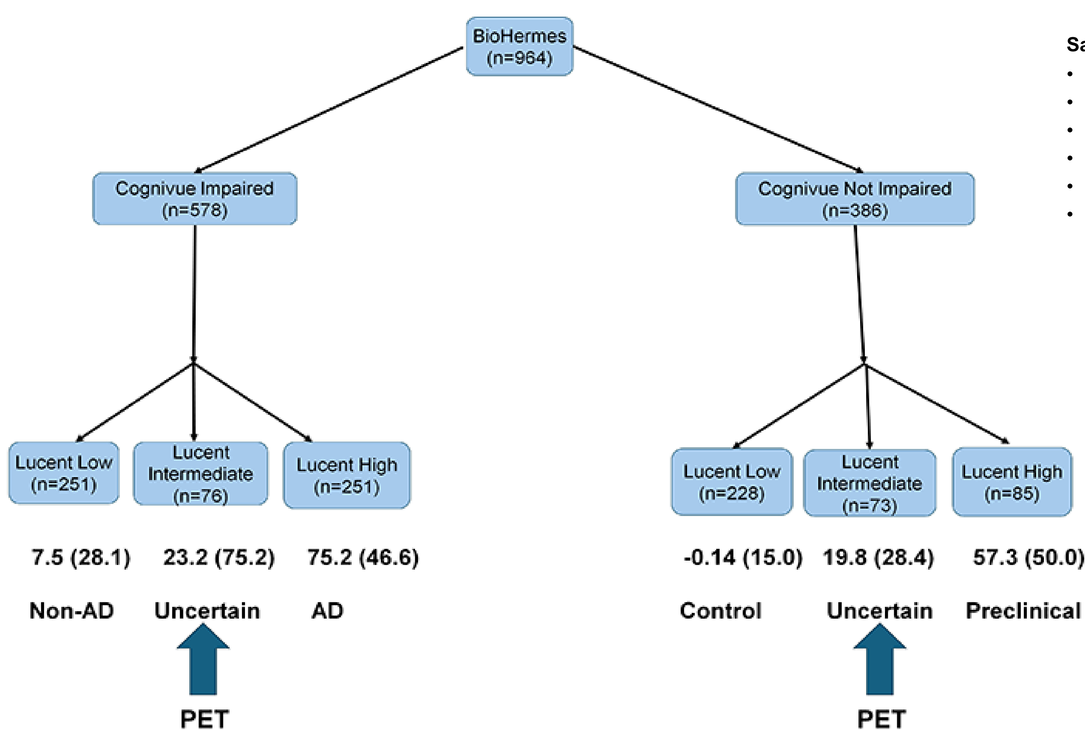
Result	<45	45—70	>70
Result Comment	Low likelihood of amyloid pathology.	Intermediate likelihood of amyloid pathology. If clinically indicated, consider confirmatory testing.	High likelihood of amyloid pathology.

- A negative result (<45) is consistent with the absence of amyloid by PET/CSF and reduces the likelihood of cognitive impairment due to AD. Alternative causes for the memory concerns should be investigated
- An elevated positive test result (>70) indicates a high likelihood of the presence of amyloid pathology. A positive results does not establish a diagnosis of AD or any other cognitive disorder
- A test result in the intermediate range (45-70) has increased uncertainty regarding amyloid status by PET/CSF. If clinically indicated, an intermediate result may require evaluation by other methods such as CSF or PET to confirm the presence or absence of amyloid pathology.

RESULTS

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

We tested the 2-stage screening paradigm to mimic how individuals might be evaluated in clinical practice. First, using screening cognition with Cognivue *Clarity,* the sample was divided into impaired (60%) and non-impaired individuals (40%). Lucent*AD Complete* was then used to classify individuals as low, intermediate, or high probability of amyloid pathology. Five classifications were derived matching 85% of BioHermes clinicopathological groups: True Controls (Cognitive Normal, Amyloid Negative), pAD (Cognitively Normal, Amyloid Positive), early-stage AD (Cognitive Impaired, Amyloid Positive), non-AD process (Cognitive Impaired, Amyloid Negative) and a small indeterminant group (15%) with mismatches between cognitive performance and amyloid status that would benefit from a confirmatory PET scan.



Sample Prevalence of Amyloid Positivity by PET Scan

- BioHermes Sample: 37.4%
- Cognivue *Clarity* Impaired: 47.1%
- Cognivue *Clarity* Not Impaired: 23.7%
- Lucent*AD Complete* Low Risk: 9.8%
- Lucent*AD Complete* Intermediate Risk: 32.7%
- Lucent*AD Complete* High Risk: 80.6%

Improvement of Classifying 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 and limits the potential number of amyloid PET scans. This scheme also provides a unique opportunity to identify individuals highly likely to have Preclinical AD for enrollment into prevention trials. The 2-stage approach can enrich a sample for amyloid prevalence, overcoming potential issues with poor positive predictive values in low prevalence screening settings.

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 biomarker (Lucent*AD Complete*).
- Cognivue *Clarity*, a 10-minute computerized battery, can detect individuals with cognitive impairment and with the CARM can identify individuals likely to have amyloid positivity.
- Using the staged screening approach (Cognivue *Clarity* + Lucent*AD Complete*), we classified 85% of the BioHermes sample into (a) True Controls who could be assured and reassessed at a later date, (b) non-AD processes that would direct towards a different work-up, or (c) early-stage AD and pAD that could be entered into a treatment protocol or enrolled in a clinical trial. We are testing this hypothesis is a follow-up study in a population-based sample.
- Only 15% of the sample would need a confirmatory amyloid PET scan.
- Employment of a 2-stage screening strategy (Cognivue *Clarity* + Lucent*AD Complete*) could increase the likelihood of identifying early AD for treatment or trial enrollment, avoiding the cost of expensive PET scans in a time- and cost-effective fashion.

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CONTACT

Heather M. Harris, Cognivue
Senior Vice President, Scientific Affairs & Partnerships
Email: **hharris@cognivue.com**

Lindsey Mette, Lucent Diagnostics
Director, Medical Affairs
Email: l**mette@lucentdiagnostics.com**

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