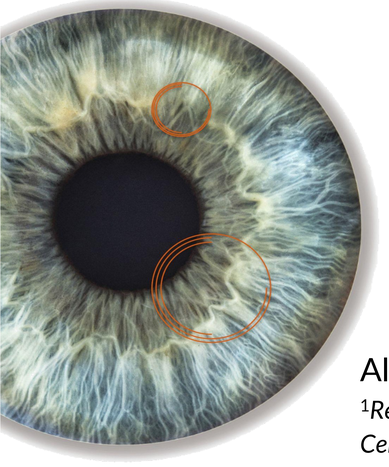

RetiSpec's AI-based retinal test: Results of a multi-site, prospective, validation study to predict brain AB pathology in a diverse population of adults with Preclinical, MCI, and Probable Alzheimer's disease

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BACKGROUND

With recently approved disease-modifying therapies, scalable Alzheimer's disease (AD) diagnostics are urgently needed. The retina shares developmental and biological similarities with the brain, which can be measured using non-invasive hyperspectral retinal imaging[1,2]. By combining hyperspectral imaging with artificial intelligence (AI), RetiSpec's technology may enable easy and efficient identification of AD markers across various AD stages.

OBJECTIVES

The primary objective of this multi-site prospective clinical validation study was to demonstrate the ability to predict brain amyloid beta (Aβ+ or Aβ–) status, as determined with positron emission tomography (PET) amyloid imaging with a non-invasive hyperspectral imaging of the retina.

METHODS

The Global Alzheimer's Platform Foundation® led a prospective, randomized, cohort study (Bio-Hermes) evaluating relationships between brain Aβ PET scans and AD diagnostics, including retinal, digital, and blood tests. This parent study enrolled 1000 participants between ages 60-85 and included a diversity target of 20% (Black/African American and Latino). A retinal imaging substudy evaluated the performance of RetiSpec's AI-based eye test to predict Aβ-PET status.

For the RetiSpec scan, participants were seated comfortably in front of a standard fundus camera (TRC-NW8, Topcon) equipped with a hyperspectral sensor (FireflEYE 185, Cubert-GmbH). Bilateral images were collected of various retinal regions (optic disc, fovea, superior retina, inferior retina). Image quality was scrutinized, with only those of acceptable quality being introduced into the AI model for analysis.

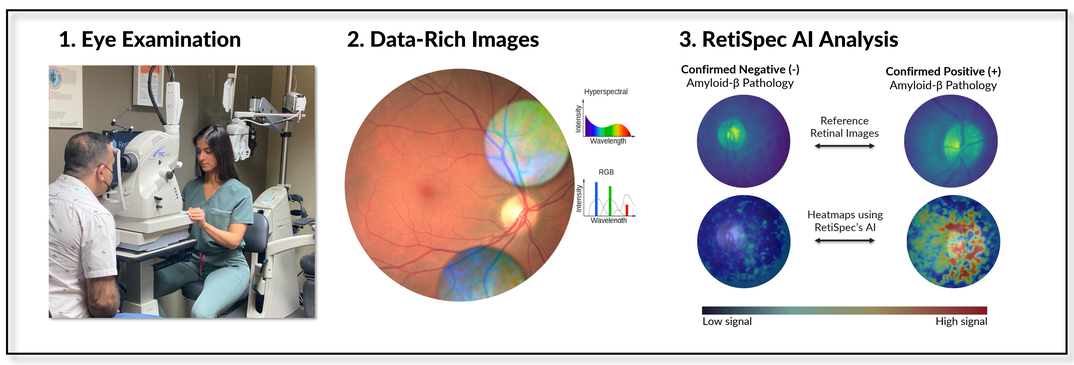

Figure 1. Illustration of RetiSpec's Imaging and analysis process

RetiSpec's AI is an ensemble model based on a 3-dimensional spectral-spatial architecture that scrutinizes retinal regions of the optic disc including the superior and inferior regions as compared to the spectral response from the fovea region. A portion of Aβ labels were unblinded for algorithm training while the remainder of data were blinded as a hold-out set for validation and held out externally (by GAP). Predictive performance on Aβ-PET status was assessed through receiver-operating characteristic (ROC) curve analysis. An Area Under the Curve (AUC) value of ≥0.7 was predefined as the threshold for overall success. ROC curves are reported for each sample group (blinded, unblinded, and total evaluable) using a predefined cut-off for predicting Aβ-PET status.

Exploratory analysis included: a logistic regression to obtain an APOE- and age-adjusted RetiSpec model, and comparison of performance between the RetiSpec model and blood plasma tests collected in the parent study (Aβ40/Aβ42 ratio, pTau181, pTau217). Test performance was evaluated by AUC with Aβ-PET status as the comparator.

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RESULTS

Table 1. Sample Characteristics

		Aβ Unblinded N (%)	Aβ Blinded N (%)	Total N (%)
Total Participants (%)		176	95	271
Age	Mean Age [Range]	71.7 [60-86]	72.1 [60-85]	71.9 [60-86]
Sex	Female	104 (59.1)	60 (63.2)	164 (60.5)
	Male	72 (40.9)	35 (36.8)	107 (39.5)
Aβ Status	PET- Aβ Positive	51 (29.0)	35 (36.8)	86 (31.7)
	PET- Aβ Negative	125 (71.0)	60 (63.2)	185 (68.3)
Study Cohort	Cohort 1 (Healthy)	95 (54.0)	40 (42.1)	135 (49.8)
	Cohort 2 (MCI)	47(26.7)	27 (28.4)	74 (27.3)
	Cohort 3 (Probable AD)	34 (19.3)	28 (29.5)	62 (22.9)
Years of Education	Mean [Range]	15.2 [8-23]	15.6 [9-24]	15.4 [8-24]
Cognitive Assessment	MMSE Score [Range]	27.4 [17-30]	26.4 [18-30]	27.1 [17-30]
Race	Asian	1 (0.6)	1 (1.1)	2 (0.7)
	Black or African American	20 (11.4)	15 (15.8)	35 (12.9)
	Unknown	4 (2.3)	-	4 (1.5)
	White	151 (85.8)	79 (83.2)	230 (84.9)
Ethnicity	Hispanic or Latino	16 (9.1)	1 (1.1)	17 (6.3)
	Not Hispanic or Latino	153 (86.9)	94 (98.9)	247 (91.1)
	Not Reported	7 (4.0)	-	7 (2.6)
Suspected Eye Conditions	Cataracts	15 (8.5)	11 (11.6)	26 (9.6)
	Intraocular Lens (IOL) Replacement	19 (10.8)	5 (5.3)	24 (8.9)
	Mild Ophthalmic Conditions/Findings	121 (68.8)	60 (63.2)	181 (66.8)
	Severe Retinopathies (AMD/Glaucoma)	6 (3.4)	2 (2.1)	8 (2.9)
	Not Listed	65 (36.9)	25 (26.3)	90 (33.2)

N=271 participants (60.5% females) with a mean age of 71.9 (60-86) from 6 sites were imaged and analyzed. Cohort distribution included, Healthy: N=135, MCI: N=74, Probable AD: N=62. Mean MMSE score was 27.1 (17-30). N=176 participants were unblinded and N=95 remained blinded with a total of N=86 Aβ positive and N=185 Aβ negative. Modest differences in ethnicity (p=0.009) and cohort status (p=0.0001) were attributed to a healthier substudy population and slightly lower proportion of Hispanic/Latino participants; nevertheless, the substudy met the participant target of 20% from underrepresented minority populations.

RetiSpec's model obtained an AUC of 0.77 (95%CI=0.70-0.83) on the total evaluable sample (sensitivity 80%; specificity 64%). The unblinded and blinded samples showed similar performance to the total sample: AUC=0.78 (95%CI=0.70-0.86) and AUC=0.73 (95%CI=0.62-0.83), respectively.

The APOE/Age-adjusted RetiSpec model on N=264 demonstrated an AUC of 0.80. When compared with N=187 substudy participants who were commonly evaluable with plasma biomarkers, all tests performed within 0.1 AUC: RetiSpec AUC=0.76; pTau181 AUC=0.79; Aβ40/Aβ42 AUC=0.80; pTau217 AUC=0.86.

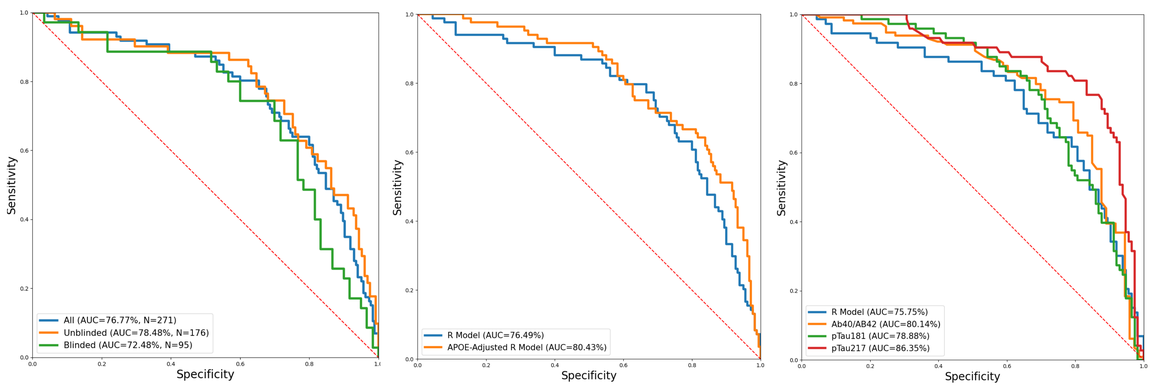

Figure 2. Receiver operator characteristics curve of algorithm performance compared to Aβ PET (left), performance compared to Aβ PET with APOE/Age-adjustment (center), performance of RetiSpec model and plasma biomarkers to predict Aβ PET (right)

DISCUSSION & CONCLUSIONS

In this prospective multi-site validation study, RetiSpec's AI-based retinal test demonstrated strong performance for its ability to predict brain Aβ-PET status across healthy, MCI and probable AD cohorts on a blinded dataset that was held by an external party (GAP) with results revealed only after providing predictions.

Non-invasive retinal imaging can be acquired from ethnically and clinically diverse populations with strong RetiSpec AI-model performance for prediction of Aβ-PET status across healthy, MCI and probable AD cohorts, when blinded. Notably, added clinical data can enhance predictive performance.

While further analysis is needed, these results demonstrate how the RetiSpec model may hold potential to aid in the evaluation of AD by providing decision support at the point-of-care and enabling more timely access to disease-modifying therapies.

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For more information on RetiSpec's technology:

RetiSpec