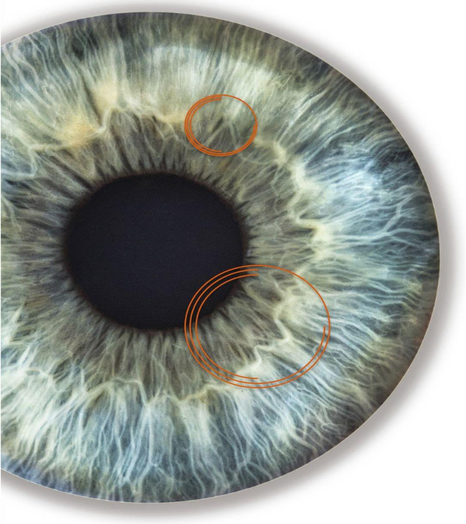

RetiSpec's Hyperspectral Imaging System: Results of a Validation Study in Preclinical AD and MCI

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BACKGROUND

Current technologies to detect the pathobiology of Alzheimer's disease (AD) are often invasive, expensive, and not widely available. The retina, a protrusion of the central nervous system, is a promising candidate for the non-invasive identification of various AD biomarkers. The retina shares developmental and biological similarities to the brain. High-resolution imaging of the retina enables quantification of many biophysical and biochemical properties.

By harnessing hyperspectral imaging technology and proprietary machine learning, RetiSpec's patented technology has the potential to provide rapid, simple and cost-effective identification of AD at early stages of the disease.

OBJECTIVES

The primary objective of this study was to evaluate the accuracy of RetiSpec's hyperspectral retinal imaging system in predicting individual brain amyloid beta (Aβ) status (Aβ+ or Aβ-), as compared to clinical gold standards of Aβ PET and/or CSF assessment.

A secondary goal of the study was to examine participant perceptions of RetiSpec's system in terms of comfort, duration, and acceptability.

METHODS

This study employed a cross-sectional study design. Participants were drawn from two study sites: Toronto Memory Program, Canada and the Joseph Sagol Neuroscience Center at Sheba Medical Center, Israel. Eligible individuals were adults between ages 50 and 90 years who were at risk for or who had preclinical AD or who had mild cognitive impairment (MCI)[1]. Aβ assessment via CSF and/or PET scan occurred within 12 months of retinal imaging. Those with a known history of advanced or severe ocular diseases were excluded. Individuals with mild-to-moderate conditions (e.g., cataract) were not excluded. An ophthalmologist reviewed participant images to assess retinopathies. The ophthalmologist and RetiSpec operator were blinded to Aβ status.

Participants were divided into two groups based on their PET or CSF amyloid results: (1) participants who were brain Aβ+, and (2) participants who were brain Aβ-.

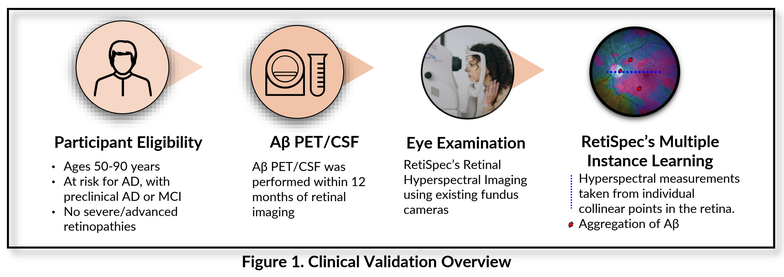

Figure 1. Clinical Validation Overview

For objective 1, the retinal recording system was based on a Topcon fundus camera and a commercially available hyperspectral camera. The system captured high resolution hyperspectral measurements across the retina in the wavelength range of 400-1000nm. Conventional images and spectral measurements for each of the retinal targets were located in recordings from each eye. Image quality was reviewed to make sure no stray light from iris reflection was present.

The spectra from each patient were then mapped to a single instance with the RetiSpec algorithm based on a Multiple Instance Learning (MIL) with discriminative mapping (MILDM) approach[2], which is a distance-mapped bag space method, and classified with a support vector machine. Unlike standard supervised machine learning methods, RetiSpec's MIL does not need to know the label for each and every measurement in the retina. Instead, it looks at a collection of measurements as a bag of *instances* (spectra) where some are positive (cross Aβ aggregation) and others are negative. It relies on the hypothesis that within the retinal spectral measurements of each brain Aβ+ patient (bag), it is possible to capture at least one spectrum (instance) of an Aβ aggregation, and that Aβ aggregations have a unique spectral signature.

To ensure the robustness of the model, all results were cross validated on 5 folds. The entire cross-validation was repeated 5 times with random 5-fold splitting. The model requires only ~20 spectral bands to achieve this result, which reduces the risk of overfitting. The number of support vectors was significantly smaller than the number of data points further reducing the chance of overfitting.

Additionally, participants from Toronto Memory Program completed a survey to report on their experience with the RetiSpec imaging procedure relative to comfort, duration, and acceptability.

RESULTS

Table 1. Sample Characteristics

		Aβ Positive	Aβ Negative	Total (%)
Total Participants (%)		72 (67%)	36 (33%)	108 (100%)
Mean Age (Range)		72 (51-89)	67 (54-81)	70 (51-89)
Sex	Female	38	19	57 (53%)
	Male	34	17	51 (47%)
Site	Toronto Memory Program	69	15	84 (78%)
	Sheba Medical Center	3	21	24 (22%)
Clinical Diagnosis	Healthy Control/Preclinical AD	42	33	75 (69%)
	MCI/Prodromal AD	30	3	33 (31%)
Aβ Comparator	Aβ-PET	20	28	48 (44%)
	Aβ -CSF	51	6	57 (53%)
	Both Aβ-PET and Aβ-CSF	1	2	3 (3%)
Education	Post Secondary/Graduate	63	14	77 (71%)
	High School	6	1	7 (7%)
	Unspecified	3	21	24 (22%)
Ethnicity	Caucasian	65	13	78 (72%)
	Asian	2	1	3 (3%)
	Black	1	0	1 (1%)
	Other	1	1	2 (2%)
	Unspecified	3	21	24 (22%)
Lens Replacement	Lens Replacement Surgery	21	4	25 (23%)
	Natural Lens	51	32	83 (77%)

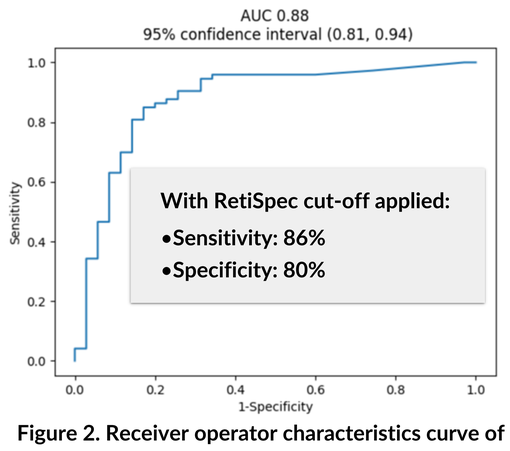

Figure 2. Receiver operator characteristics curve of algorithm performance compared to Aβ PET/ CSF

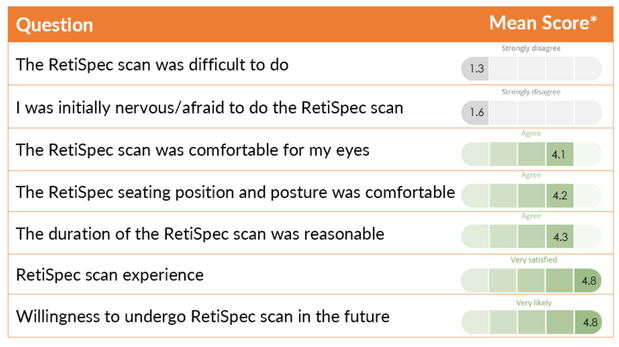

Figure 3. Results from participant experience survey

CONCLUSIONS

Results indicate that hyperspectral retinal imaging technology is effective in predicting brain Aβ status in individuals at risk for or with preclinical AD or who had MCI when compared to the clinical gold standards of Aβ PET and CSF assessment.

Additionally, participants reported an easy and comfortable experience of undergoing the RetiSpec scan and reported high willingness to undergo the scan in the future.

Our results suggest that if replicated in larger and diverse samples, retinal amyloid imaging may serve as a non-invasive, inexpensive, sensitive and specific biomarker for Alzheimer's disease in its earlier stages.

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ACKNOWLEDGMENTS

The authors thank the Centre for Aging + Brain Health Innovation for their financial support of this work. We also wish to thank the study participants for their time and commitment to this research -- it would not be possible without them. We further wish to thank the research and administrative staff who helped facilitate this study.

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