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BIOMARKERS

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## Biomarkers (non-neuroimaging) / novel biomarkers

# Exploring retinal imaging as a novel biomarker of Alzheimer's disease

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## Abstract

**Background:** Alzheimer disease (AD) and frontotemporal dementias (FTD) exhibit distinct pathologies but are difficult to reliably differentiate on clinical grounds. Detailed neuropsychiatric evaluations, cerebrospinal fluid analysis, and anatomic or molecular imaging may improve diagnostic accuracy. Even so, these modalities are expensive, time-consuming, and often inaccessible. The retina is a developmental outgrowth of the brain, and visual dysfunction is well documented in dementia subjects. As such, the retina may be a useful surrogate for diagnosing and monitoring the progression of dementias. We explored the potential role of multimodal retinal imaging for identifying ocular biomarkers of dementia and correlated our findings with cerebral amyloid burden.

**Method:** We recruited 5 participants with mid-to-late stage AD, 2 participants with mid-to-late stage FTD, as well as 9 age-matched healthy controls. Each participant underwent comprehensive ophthalmologic examination and ocular imaging (Optical Coherence Tomography (OCT), OCT-angiography (OCTA), wide-field fundus photography, near-infrared imaging, and fundus autofluorescence). Ocular findings were then correlated with cerebral amyloid burden, as detected by [$^{11}$C]PiB PET.

**Result:** We did not observe significant differences in retinal layer thicknesses, retinal perfusion, or sizes of the superficial avascular zones between PET-confirmed AD, clinically diagnosed FTD, and control subjects. AD subjects consistently demonstrated higher autofluorescence signal intensity (18.5 au), as detected by fundus autofluorescence imaging compared to FTD (16.0 au) and age-matched control subjects (16.3 au). Near-infrared ocular imaging also revealed a 1.95 fold increase in retinal reflectance in AD subjects compared to FTD and control subjects.

**Conclusion:** Identification of novel dementia biomarkers is essential for accurate diagnosis and monitoring of dementia progression. Recent studies highlighted the potential use of OCT and OCT-A to identify retinal layer thickness changes in AD and FTD. Our pilot study suggests that autofluorescence and near-infrared reflectance, but not OCT or OCT-A, detect retinal imaging changes that correlate with cerebral amyloid burden. These modalities may thus serve as accurate dementia biomarkers to aid in diagnosis, assessing pathologic severity, and gauging response to therapy in AD and FTD.