

Testimony prepared for the United States Senate Special Committee  
on Aging:

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**“So much more than meets the eye”**

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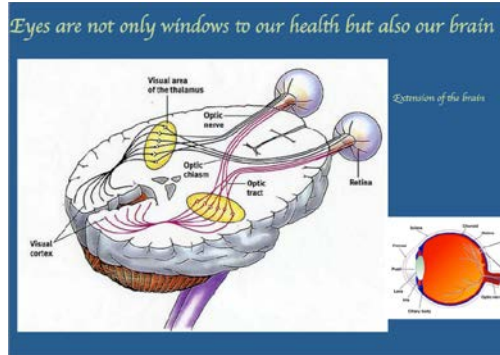
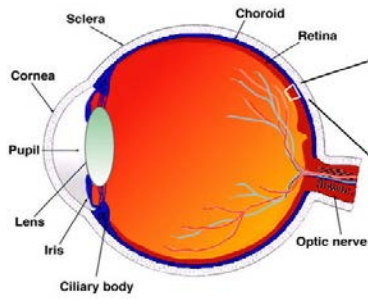
Thank you Chairman Collins, Ranking Member Casey and members  
of the Committee for the unmatched opportunity to testify today and

share some exciting multidisciplinary and collaborative work on one of the most important health issues of our time, Alzheimer's disease - the societal and cost impact of which you are well aware. My name is Dr. Sharon Fekrat and I am a retina surgeon and Professor of Ophthalmology and Associate Professor of Surgery at the Duke University School of Medicine and Associate Chief of Staff at the Durham VA Medical Center.

Alzheimer's disease is the leading cause of dementia worldwide, yet its early detection remains challenging. The high cost of MRI, the limited sensitivity and specificity of genetic and serum markers, and invasiveness of PET imaging and spinal fluid sampling limit our ability to detect Alzheimer's early. Because Alzheimer's has a 20-year relatively asymptomatic period of neuropathogenesis, there is growing interest in identifying Alzheimer's at asymptomatic stages for earlier clinical trial intervention to ultimately identify medications to delay the onset of, prevent, or even reverse Alzheimer's. We need rapid, easily accessible, inexpensive, noninvasive, yet accurate, diagnostic techniques to screen for Alzheimer's disease.

The task before us is not insurmountable. If a human being can walk on the moon or live in a space station, then we can find a means of diagnosing Alzheimer's earlier and subsequently identifying effective therapeutic interventions. This requires collaborative teamwork across disciplines and institutions, innovative critical thinking, and going out on a limb where the fruits are.

Look at the eyes of the person next to you. You see the colored iris, white sclera, and dark circular pupil. Yet there is so much more there than meets the eye. Behind the pupil, there is the wallpaper lining the inside of the eyeball called the retina.



The retina

wallpaper is the film of the camera, it is nerve tissue, and is a **direct extension** of our brain. In fact, the retina shares many structural and functional similarities with the brain and central nervous system. Spinal fluid biomarkers for Alzheimer's such as tau and amyloid beta have also been found in the vitreous gel behind the pupil and levels correlate with cognitive test scores. Amyloid has also been detected and imaged in the retina. Research has suggested that the neurodegenerative process in the brain may also occur in the retina with thinning of certain retinal layers. Changes in the retina and its small blood vessels may mirror, or even precede, detectable changes in the brain and its small blood vessels.

Imaging the retina in Alzheimer's disease however is not new. Color photographs of the retina in Alzheimer's show decreased retinal vein diameters, blood vessel branching complexity, and tortuosity. Recent imaging advances now allow us to evaluate the retinal microvasculature with unprecedented detail, on the order of **5 microns**- not even the width of a human hair, using new technology called optical coherence tomography angiography (OCTA) which takes ~70,000 scans per second to look at the very small retinal blood vessels. With this FDA approved retinal imaging technology, we are now able to take pictures of the retina through an undilated pupil quickly, noninvasively, inexpensively, and reproducibly at high resolution. Several research groups, including our group at Duke, are exploring how this new technology along with other retinal imaging methods can be used to diagnose preclinical Alzheimer's and stratify

the various stages. In fact, there is an Alzheimer's Association meeting on this topic next month.

We published imaging findings from 96-year-old identical twins, one had advanced Alzheimer's and one was cognitively normal. We found reduced retinal blood vessel density in the twin with Alzheimer's compared to her sister, indicating that marked loss of small retinal blood vessels does occur in Alzheimer's, independent of aging.

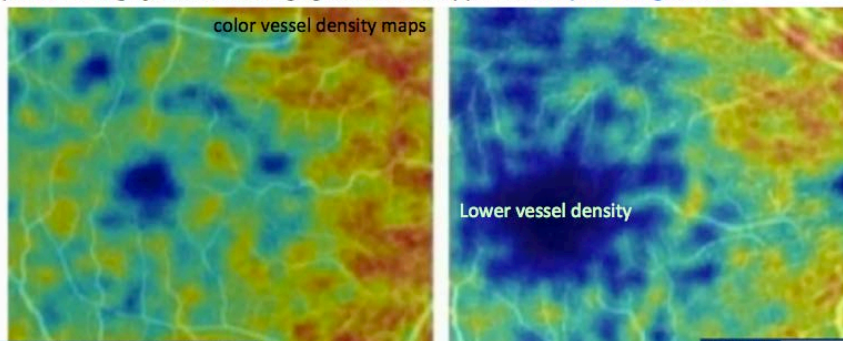
Ophthalmic Surgery, Lasers and Imaging Retina

CASE REPORT

**Assessment of Differences in Retinal Microvasculature Using OCT Angiography in Alzheimer's Disease: A Twin Discordance Report**

Dilraj S. Grewal, MD; Bryce W. Polascik; Gregory C. Hoffmeyer; Sharon Fekrat, MD

Ophthalmic Surgery, Lasers and Imaging Retina. 2018;49(6):440-444 <https://doi.org/10.3928>



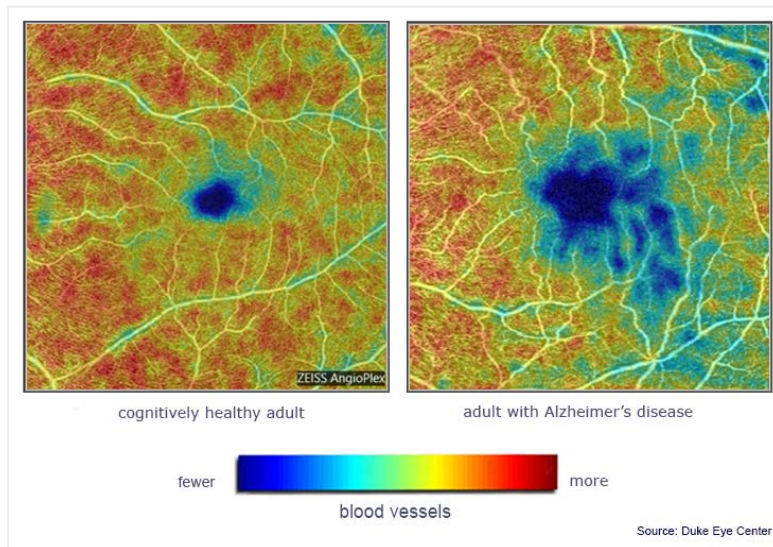
And it was these findings that spurred further research.

We recently completed the largest prospective study of 70 eyes with 39 individuals with Alzheimer's disease, 72 eyes of 37 persons with mild cognitive impairment (MCI), and 254 eyes from 133 cognitively healthy adult controls. We found decreased retinal blood vessel density and decreased perfusion density as well as decreased thickness in one of the retinal layers (ganglion cell – inner plexiform layer) in Alzheimer's disease compared to MCI and compared to

controls, even after adjusting for age, gender, and education. We did not find a difference in MCI compared to controls and it may be that we need a larger sample size to detect a difference between MCI and controls because of the varied spectrum of MCI individuals.

Our study adds to the published literature and improves our understanding of the smallest blood vessel changes in Alzheimer's. Right now, these eye tests cannot be solely used to diagnose Alzheimer's disease. However, this is the beginning of something big and more work needs to be done before these tests are ready for prime time because the findings must be validated in larger and diverse populations. The goal is to obtain multimodal retinal images that would result in a suite of biomarkers that could predict the risk of Alzheimer's and stratify the various stages of disease. Similar to getting a lipid panel and being able to determine your risk of heart disease.

The potential impact on early detection and clinical trial results is motivating. New treatments may be more effective earlier in the disease process. We are building multidisciplinary and multi-



institutional teams and forging relationships with industry to purposefully move forward. Our ongoing and future efforts keep us up at night and include collecting longitudinal data to assess changes over time, imaging genetically predisposed

asymptomatic persons, using images for deep learning artificial intelligence, and collecting retinal images globally to store in the Duke

Neurodegenerative Disease Retinal Imaging Repository for researchers to access.

Our eyes may indeed be windows to our brain health. Thank you for your efforts to support those working to find the way forward, which in turn supports those with Alzheimer's disease and their families. Time is of the essence.