# Ocular Biomarkers of Disease: Employing Routine Eye Exams to Promote Better Health Surveillance

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America's burden of disease will continue to rise over the next 40 years. In particular, the burden of vision impairment, Alzheimer's disease and related dementias (ADRD), and cardiovascular disease (CVD) will be higher for women, Hispanics, African Americans, and those with greater social barriers. A key challenge is to develop strategies to deny the organization of the pathologies that eventually lead to the manifestation of the disease. The development of appropriate tools and biomarkers can allow for early diagnosis of these diseases. Recent advances in optical coherence tomography angiography (OCTA) present a unique opportunity to examine the structural physiological features of the eyes that may mirror damaged vascular structures within the brain and heart, associated with aging, CVD, and diabetes (microvascular damage). Specifically, tracking of the vessel density and thickness of the nerve fiber layers of the eye provides valuable information regarding an individual's path toward not only visual impairment but also ADRD and CVD. Thus, OCTA can extend eye care beyond capturing those who are at risk for vision loss and include examination of imaging biomarkers that provide information concerning risk and possible trajectories of cerebral and cardiovascular health. Given loss of vision is perceived as "the worst ailment that could happen to a person" across all ethnic and racial groups, ophthalmologists and optometrists can not only provide a path toward improved eye health, but also serve as an innovative access point for early detection of individuals at risk for ADRD and CVD.

*Keywords*: ocular biomarkers, retinal imaging, OCTA, cardiovascular surveillance, neurovascular surveillance

Ocular Biomarkers of Disease

## Introduction

The number of Americans aged 65 years and older is projected to nearly double from 52 million in 2018 to 95 million by 2060, and that group's share of the total population will rise from 16 percent to 23 percent (U.S. Census Bureau, 2019). Although it is clear people are living longer, the quality of life during those extra years is not evident (Crimmins & Beltran-Sanchez, 2011). In fact, America's burden of vision loss, Alzheimer's disease and related dementias (ADRD), and cardiovascular disease (CVD) will continue to rise over the next 40 years. Diabetic retinopathy, cataracts, glaucoma, and age-related macular degeneration will double by 2050 (Teutsch, 2016). The projected rise in ADRD will more-than-triple over the same period, with projected growth from 5.8 million to 14 million individuals, or from 1.6% to 3.3% of the population (Matthews et al., 2019). The rise in these chronic diseases is typically greater for women, Hispanics, and African Americans (Matthews et al., 2019), as well as in those with significant social/behavioral barriers (Steenland et al., 2016). These findings provide compelling reasons for the United States to make eye health a population health imperative, to achieve the goals outlined in the 2016 National Plan to Address ADRD (U.S. Department of Health and Human Services, 2016). This plan describes the development of preventive interventions or treatment referral opportunities that may help to ensure these projections are never reached, potentially delaying the onset of the disease, and improving the quality of life for those individuals with these diseases (Steenland et al., 2016). The purpose of this report is to advocate a process for early identification of individuals at risk for the development of vascular and structural vision impairments, ADRD, and CVD.

## "Catch Me if You Can"

It is clear many eye pathologies, ADRD, and CVD are chronic diseases—diseases defined by their slow progression and persistence. An individual crosses a threshold called a ''clinical horizon'' to manifest (and be diagnosed with) a multifactorial chronic disease many years after the original causes of the disease have taken effect (Dorland, 1974). That is, the pathophysiological mechanisms underlying these diseases have usually been active long before a particular victim is outwardly affected or showing signs and symptoms of the disease (Booth et al., 1985). Thus, individuals with visual impairments, ADRD, and CVD experience a long asymptomatic (pre-clinical) phase, during which vascular and neural changes occur without significantly affecting health. This is followed by a symptomatic (prodromal) phase of progressive decline before the onset of functional impairment and overt disease (Amieva et al., 2008; Wilson et al., 2011; Harrison, 2013; Villemagne et al., 2013). A key challenge of preventing these conditions is to develop strategies to deny the organization of the pathologies that eventually lead to the manifestation of the disease. The development of appropriate tools and biomarkers can allow for early screening and evaluation. Within this quest, a common theme has emerged that suggests that a critical factor in the development of many eye conditions, ADRD,

Ocular Biomarkers of Disease

and CVD is vascular erosion (Hachinski, 2019). Although the precise mechanisms for vascular erosion are not fully understood, it is hypothesized that chronic assaults including inflammation, hypertension, smoking, dyslipidemia, hyperglycemia, blood chemistry, and hemodynamic forces damage endothelial cells and other vascular structures and contribute to a gradual breakdown and loss of vascular integrity. This loss of integrity eventually leads to altered or reduced blood flow to vital tissue structures and organs, including the eye, brain, and heart. This vascular damage extends to the loss of the integrity of the blood-brain barrier, leading to the gradual increase of extracellular plaque deposits including β-amyloid peptide (Aβ) and the microtubule binding protein tau (Hachinski, 2019).

Recent technological advances in optical coherence tomography angiography (OCTA), as utilized during the Eye Determinants of Cognition (EyeDOC) Study, presents a unique opportunity to examine the vasculature (i.e., vessel density and thickness) of the ocular tissue and nerve fiber layers of the eye, using 3D high-density scans of the retina and optic disc. Such an examination is particularly relevant because retinal neuronal and vascular structures can be observed and evaluated without resorting to more costly and potentially invasive procedures like computed tomography and MRI. In theory, tracking the vessel density and thickness of the nerve fiber layers of the eye may provide valuable information regarding an individual's path toward visual impairment, ADRD, and CVD.

**"Eye See Your Eye"**

Over the past decade, OCTA has shifted from older versions of time-domain to spectral-domain OCTA that allows 3D retinal imaging and higher axial resolution (~5–10 μm) in less time with lower measurement variability (Hwang et al., 2016). OCTA uses interferometry to examine vessel density and retinal nerve fiber layers and provides clinicians with precise information about specific diseases of the eye and optic nerve (e.g., diabetic retinopathy; see Figure 1), glaucoma, and macular degeneration. The entire retina is displayed as individual layers so that specific areas of interest can be isolated. High-resolution OCT scans are useful for visualizing both the microvasculature and anatomical changes that affect vision. Due to recent advances in software, sensitivity is enhanced so that volumetric imaging is now feasible and practitioners can clinically and objectively quantify vascular changes like capillary dropout, pathology, and abnormal angiogenesis. Therefore, OCTA measurements are objective metrics that can serve as biomarkers to detect and track progression of pathogenic processes of the eye.
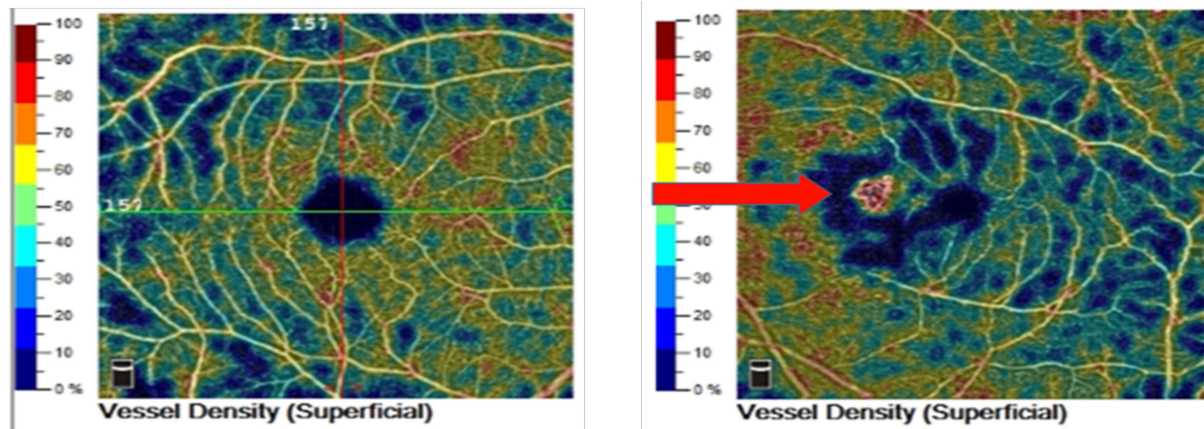
Ocular Biomarkers of Disease



*Figure 1.* Normal healthy control (left) compared to proliferative diabetic retinopathy with active bleed (right) indicated by the red arrow.

## "Eye See Your Brain"

The retina and optic nerve develop as a direct extension of the diencephalic tissue during embryonic establishment. The vessels within the microvasculature of the brain and eyes are the same in diameter (100–300 μm), end arterioles are without anastomoses, and barrier functions are consistent. Both areas are auto-regulated with low oxygen flow and high oxygen extraction (Cheung, 2017). The retina has intricate layers of specialized neurons called retinal ganglion cells (RGC) interconnected through synapses. This cell complex has a cell body, dendrites, and an axon with bipolar, amacrine, and horizontal cells making it typical to central nervous system neurons. Given the extent of this relationship, vascular- and neuro-degenerative processes in the eye may mirror changes in the brain. Indeed, retinal vascular pathology and cerebrovascular pathology are linked via autopsy (Cheung et al., 2017). Until recently, the consequences of microvascular pathology of the eye and brain were often not radiographically visible. With the advances in OCTA, the presence of reduced vessel density and microscopic infarcts of the eye are now clearly visible (see Figures 2 and 3), which could provide further information about the microvasculature and sensitive tissues of other organs.

Neuropathological changes in ADRD include amyloid plaques, neurofibrillary tangles, altered glial responses, and neuronal and synaptic loss (Serrano-Pozo, 2011). In addition to these molecular findings, ADRD has also been associated with a reduction in brain volume of the frontal subcortical region and temporal-parietal cortical structures. These changes are reflected by a reduction in eye neural volumes and nerve fiber layer thickness (Iadecola, 2013). Thus, examination of vascular markers, RGCs, and optic nerves using OCTA may be an effective strategy in screening patients and making appropriate clinical referrals for further assessment of microvascular and neuronal damage in other organs and tissues.
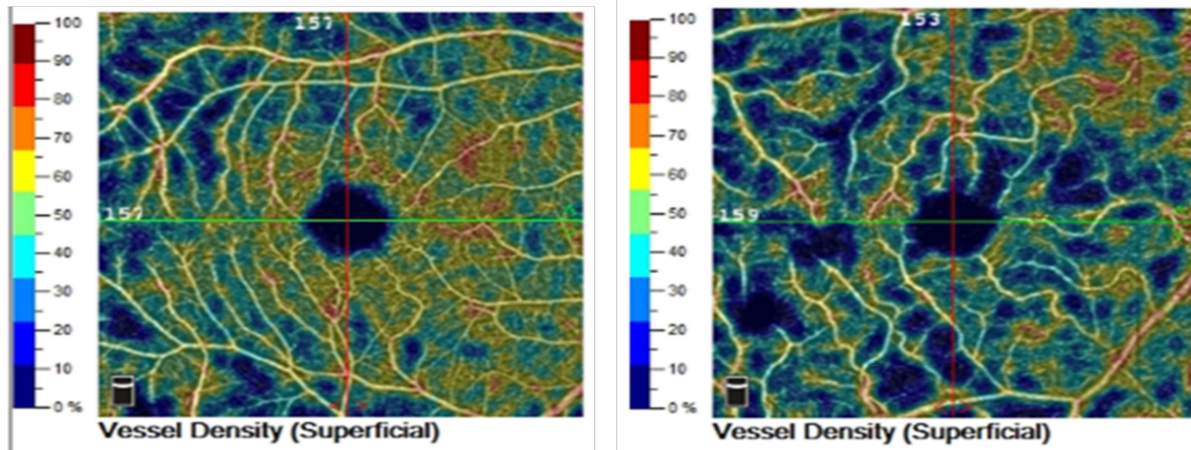
Ocular Biomarkers of Disease



*Figure 2.* Using OCTA, vascular density patterns can be compared. This is a representative example of imaging from two sex- and age-matched research study participants demonstrating a relatively normal retinal vascular pattern (left) and a retinal vascular pattern of a participant with known cognitive impairment (right).

**"Eye See Your Heart"**

Coronary heart disease is the leading cause of death for both men and women (CDC, 2019). A large portion of these deaths are attributed to coronary artery disease (CHD) of the epicardial arteries (Wang & Liew, 2011). However, recent evidence also implicates the presence of coronary microvascular dysfunction, often classified as Cardiac Syndrome X, in subgroups of patients (Agrawal et al., 2014).

As with the vasculature of the brain, the microcirculation of the eyes and the heart are similar. In addition, both micro-circulatory systems are often exposed to the same intrinsic and environmental effects (Flammer et al., 2013). Thus, examination of the vascular beds of the retina may present a window to the heart. Atherosclerosis Risk in Communities (ARIC) was one of the first studies to quantitatively measure the arteriolar and venular calibers of the eye and reported that narrower arterioles, represented as lower arteriole-to-venule ratio, predicted three-year risk of CHD events (Wong et al., 2002). Although further research is necessary, a summary of available literature suggests that arteriolar narrowing is reflective of a person's hypertensive risk profile, whereas venular widening is most associated with a poor metabolic profile (e.g., endothelial dysfunction, hyperglycemia, and inflammation; see Figure 3; Wang & Liew, 2011). Consequently, a more vigilant monitoring of cardiovascular risk profiles in patients with mild to moderate retinopathy is recommended. This level of monitoring and intervention could be initiated by ophthalmologists and optometrists, who have the opportunity to provide monitoring of retinal vascular markers (Wang & Liew, 2011).
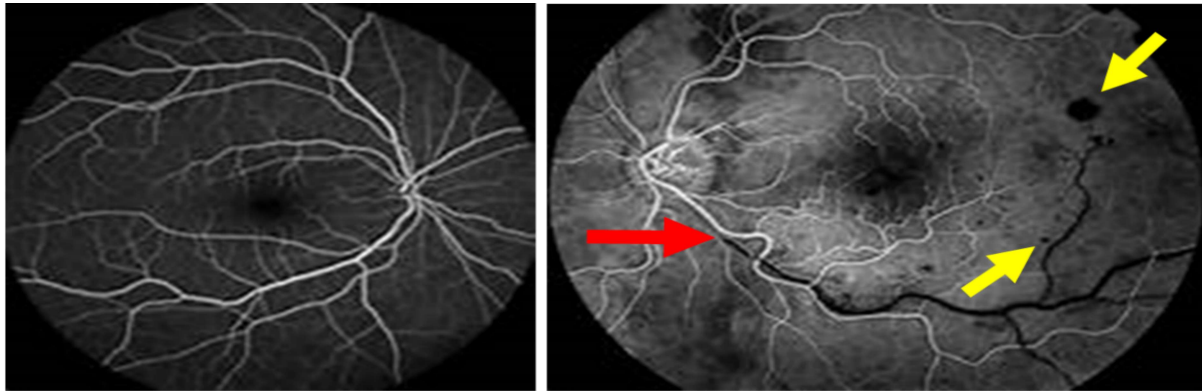
Ocular Biomarkers of Disease



*Figure 3.* Normal healthy control (left) compared to blocked perfusion (right) indicated by the red arrow and infarcts indicated by the yellow arrows.

**"Eye See Increased Access and Opportunity"**

Mississippi's Alzheimer's disease age-adjusted death rate in 2018 was 49.5 per 10,000, compared to 31 per 10,000 for the United States. This ranks Mississippi as the worst state in the country for ADRD mortality. Mississippi's high mortality rate from heart disease, kidney disease, cancer, diabetes, influenza/pneumonia, and septicemia indicates a significant need to identify at-risk groups at pre-clinical stages of disease.

Recognizing the influence of biology and genetics on an individual's health, the burden of disease in Mississippi is further compromised through the presence of social and behavioral determinants of health, or "the conditions in which people are born, grow, live, work, and age" (World Health Organization, 2013). The makeup of Mississippi's populace is such that many citizens, through lack of access (e.g., quality of education, food security, health insurance, safe and affordable housing, clean water and air, and physical activity) or increased exposure (e.g., social isolation, concentrated poverty, crime and violence, and insufficient access to quality healthcare providers), are at significantly greater risk for health disparities and health inequities. The consequences of these many health disparities and health inequities are such that, by the time individuals seek medical assistance, they have long since passed a "clinical horizon," allowing the original causes of the disease to have become organized into their full effects.

Interestingly, in a nationwide poll, respondents across all ethnic and racial groups described loss of eyesight as the worst ailment that could happen to them relative to losing memory, speech, hearing, or a limb (Scott, 2015). These findings, and the fact that 61 million adults in the United States are at high risk for serious vision loss, led to the recent launching of the nation's first Vision and Eye Health Surveillance System (VEHSS). The VEHSS is designed to help healthcare professionals, researchers, policymakers, and state health department professionals

Ocular Biomarkers of Disease

better understand the scope of vision loss, eye disorders, and eye care services in the United States. Given the concern for eye health across all ethnic and racial groups, the advances in OCTA can extend eye care beyond capturing those who are at risk for vision loss. The examination of biomarkers, like those obtained with OCTA, may provide helpful information concerning overall vascular and neuronal health, making it possible for patients to be referred to appropriate healthcare providers much earlier in the course of a disease rather than when the disease is more established.

EYE EXAM TO IDENTIFY PRECLINICAL BIOMARKERS OF DISEASE → PRESENT FINDINGS & DEVELOP TREATMENT PLAN → EXPLANATION, EDUCATION, & REFERRAL → IMPROVE HEALTH OUTCOMES AND QUALITY OF LIFE

*Figure 4.* Plan of action for early identification of individuals at risk for the development of vision loss, ADRD, and CVD.

**Summary**

OCTA is a non-invasive tool that can yield high-quality, live photography of both the structure and function of the blood vessels, nerves, and connecting tissues. Given that the eye presents an unobstructed view of these tissues and given the similarities between the tissues of the eye and other organs with respect to neuronal and vascular health, new opportunities exist to further develop the capabilities of OCTA as a screening tool that has the potential to provide valuable information regarding an individual's path toward vision loss, ADRD, and CVD.

Loss of eyesight is considered the worst ailment that could happen to an individual, independent of race and ethnicity. Thus, the likelihood for an individual with vision problems to seek medical attention, even in the face of social barriers, is considerably higher than for other health conditions. Thus, ophthalmologists and optometrists may represent an innovative access point to extend eye care beyond capturing those who are at risk for vision loss and include examination of retinal biomarkers to inform their patients' other healthcare providers concerning risks and possible trajectories of cognitive and cardiovascular health. Currently, there is a void of long-term investment in the surveillance of the most at-risk populations. Granted, we are unable to diagnose conditions like Alzheimer's, cerebrovascular disease, or CVD based on OCTA biomarkers, but OCTA could prove to be a very useful tool in identifying those at a higher risk of microvascular and neuronal conditions in a cost-effective manner. These efforts and opportunities using OCTA could lead to earlier referral to healthcare providers for appropriate evaluations, expanding access to care points.

Ocular Biomarkers of Disease

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Ocular Biomarkers of Disease

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Ocular Biomarkers of Disease

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