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Editorial

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# A novel model for retinal imaging in the diagnosis of Alzheimer's disease



**Alzheimer's disease is the fifth-leading cause of death for adults over the age of 65. Retinal imaging has emerged to find more accurate diagnostic tool for Alzheimer's Disease. This paper highlights Hao et al.'s development of a new deep learning tool, EyeAD, which studies Optical Coherence Tomography Angiography (OCT-A) of patients with Alzheimer's. Integrating this model into clinical workflows may offer novel insights into the progression of this disease.**

## Background

As the fifth-leading cause of death among Americans above 65 years of age, Alzheimer's disease incurs an unrelenting burden on patients as well as on their caregivers and clinicians[1]. In 2022, an estimated 18 billion hours of unpaid caregiving for Alzheimer's was recorded in the United States[1]. Further, the management of this illness is frequently complicated by its late diagnosis[2].

To that end, retinal imaging has emerged as an area of interest to neurologists and neuroscientists. Retinal imaging studies have found that diffuse pathological changes in the cerebrum also affect the retinal microvascular, particularly in the progression of neurodegenerative diseases[3]. While other non-invasive techniques like neuroimaging, electroencephalogram, and cognitive testing reflect the function of the nervous system, retinal imaging remains unique in its ability to capture microvasculature of the central nervous system directly. Furthermore, brain imaging traditionally used to identify changes associated with Alzheimer's remains time consuming and costly[4]. Accordingly, retinal imaging offers a more efficient alternative to costly brain imaging in diagnosing Alzheimer's disease[5,6]. In addition, diagnosing Alzheimer's Disease by retinal imaging bypasses the cultural, educational, and class- based confounders embedded in neuropsychiatric screening tools like the Montreal Cognitive Assessment[7].

Hao et al.'s study, "Early detection of dementia through retinal imaging and trustworthy AI" uses data from 611 participants, who were diagnosed with Early Onset Alzheimer's Dementia before the age of 65, and 611 controls, who have no objective impairment concerning for dementia or cognitive impairment on neuropsychological assessment[8]. Hao et al. propose a new deep learning tool, EyeAD, to study microvasculature, vessel density, and choroidal thickness from Optical Coherence Tomography Angiography (OCT-A) and compare these findings between these two groups[5,9]. However, the lack of aged-matched controls limits the ability to rule-out age-related confounding factors entirely and limits the external validity of the study.

## Innovation

While deep learning algorithms have been validated for color fundus photography, their analysis cannot detect subtle vascular changes at the early stages of Alzheimer's Disease (i.e., mild cognitive impairment)[8]. In addition, algorithms for color fundus photography are not well- suited for OCT-A, which requires algorithms capable of processing its multi-layered data[10]. EyeAD addresses these limitations by utilizing an interpretable graph-based deep learning model. This study's results are consistent with findings from existing research: due to the neurodegenerative course of this disease, participants with Alzheimer's have less retinal macrovascular density relative to healthy controls that offers a rapid, noninvasive, and affordable method for the detection of dementia using OCTA-A[8].

## Continual areas of challenge

Replicating the results of this research in higher power studies with more control of confounding variables including age is a necessary step that may enable popularizing this tool in Alzheimer's diagnostics. In addition, as new diagnostic tools for Alzheimer's Disease become available, unifying findings across biomarkers remains an ongoing area of complexity. Interpreting different biomarkers of retinal vasculature in relation to results from traditional diagnostic brain imaging lacks standardization. As retinal imaging becomes relevant to several clinical applications, for example in the management of diabetic retinopathy, standardization of protocols for imaging and data gathering becomes increasingly necessary[11].

As opposed to the development of machine learning models, the development of deep learning models to analyze retinal vasculature requires significantly more raw data[12]. In addition, while OCT-A is becoming increasingly common in ophthalmology, it is still restricted to well- resourced research hospital settings due to consistently costly implementation[13]. One way to meet this significant need for raw data is to develop opt-in protocols for patients to share data collected from this deep learning tool as part of eye care completed at research hospitals. Such a partnership between clinicians and research teams could expand the pool of data available to train deep learning-based tools for OCT-A and thereby refine their analysis of retinal vasculature.

## Opportunities

EyeAD holds potential for both clinical practice and research. Hao et al.'s finding provide support for this deep learning tool in the diagnosis of cognitive impairment in a time- and cost- efficient manner. Further, longitudinal retinal imaging can also be used for risk stratification or prognostication of Alzheimer's disease progression. In research, this noninvasive tool may allow researchers to better understand the progression of Alzheimer's dementia, especially since participant attrition from longitudinal brain imaging studies of Alzheimer's disease is currently high[14]. Investigators of randomized control trials for novel therapeutics for Alzheimer's (such as trials of donanemab, monoclonal antibodies against beta-amyloid) could also more readily monitor changes in retinal vasculature as reliable proxies for treatment outcomes[15].

## Conclusion

EyeAD is a deep learning model that uses non-invasive retinal imaging in diagnosing Alzheimer's disease. Compared to existing screening and diagnostic tools for Alzheimer's, this model provides earlier and more cost-effective means to diagnosing this life-altering illness. The integration of this model into clinical workflow and therapeutic drug trial protocol could provide novel insights to the progression and treatment of this disease. Finding ways to bolster the

availability of retinal imaging will improve both the reliability of this deep learning tool and disease diagnosis.

## Data availability

No datasets were generated or analysed during the current study.

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## Author contributions

K.H. wrote the main manuscript; E.J.E., G.C.N., S.W., and J.C.K. provided timely feedback in further refining the manuscript. All authors reviewed the manuscript.

## Competing interests

J.C.K. is the editor-in-chief of NPJ Digital Medicine.