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REVIEW ARTICLE

Retinal imaging in Alzheimer's and neurodegenerative diseases

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Abstract

In the last 20 years, research focused on developing retinal imaging as a source of potential biomarkers for Alzheimer's disease and other neurodegenerative diseases, has increased significantly. The Alzheimer's Association and the *Alzheimer's & Dementia: Diagnosis, Assessment, Disease Monitoring* editorial team (companion journal to *Alzheimer's & Dementia*) convened an interdisciplinary discussion in 2019 to identify a path to expedite the development of retinal biomarkers capable of identifying

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biological changes associated with AD, and for tracking progression of disease severity over time. As different retinal imaging modalities provide different types of structural and/or functional information, the discussion reflected on these modalities and their respective strengths and weaknesses. Discussion further focused on the importance of defining the context of use to help guide the development of retinal biomarkers. Moving from research to context of use, and ultimately to clinical evaluation, this article outlines ongoing retinal imaging research today in Alzheimer's and other brain diseases, including a discussion of future directions for this area of study.

KEYWORDS
Alzheimer's disease, biomarkers, early detection, eye, neurodegeneration, retina, retinal imaging

1 | INTRODUCTION

Decades before individuals develop clinical symptoms that lead to a diagnosis of Alzheimer's disease (AD) dementia, neuropathological evidence of the disease may be detectable through the use of amyloid positron emission tomography (PET) imaging or by cerebrospinal fluid (CSF) assays.[1,2] This preclinical stage of AD, before the occurrence of substantial and irreversible brain damage, represents a window to intervene with potential therapies to stop or slow the disease progression.[3-5] According to a recent model of the course of AD disease severity, 38% of U.S. adults over the age of 50 years are at high risk for preclinical AD,[6] although most of them will not develop dementia during their lifetimes.[7]

Because clinical research has focused increasingly on the development of treatments and strategies to reduce risk, or stop or slow the disease progression, there remain unmet needs for identifying and validating sensitive, reliable, cost-effective, and widely available clinical assessment and diagnostic tools, especially in the earliest stages of the disease, where interventions to stop or slow disease progression are being developed. Amyloid PET neuroimaging and CSF testing are among the diagnostic biomarker tests most commonly used in clinical trials and some clinical practice, and they provide satisfactory sensitivity and specificity to be considered useful tools in increasing the certainty of an individual's diagnosis.[8] However, these tools are limited in their availability, and they can be invasive and/or time-consuming and have high cost. These barriers hamper widespread use of these approaches for population-level use. Blood-based biomarkers offer advantages in terms of cost, availability, and acceptance by both health care providers and their patients.[9] Substantial progress has been made over the past decade in addressing the many challenges to developing blood-based biomarkers, although issues related to replication and standardization remain.[9-11]

Although blood-based biomarkers increasingly appear to be viable tools for identifying and/or predicting individuals who are at increased risk for AD,[12] additional approaches are needed to effectively provide early detection of those who are at increased risk and to follow treatment response at the population level. The pathogenesis of dementia involves structures such as cerebral small vessels and cellular mechanisms that are too small or inaccessible to be visualized with current technologies. One emerging technology that may yield low-cost and non-invasive markers of early disease burden and progression is retinal imaging. The retina is a central nervous system (CNS) compartment that can be readily imaged with optical techniques, and retinal changes may reflect the pathological features in the brain early in the disease process. For example, some studies show that changes in retinal neuronal layers correspond to cerebral amyloid accumulation, as measured by amyloid PET, in preclinical AD.[71,72]

Since the turn of the century, interest in developing retinal imaging biomarkers for AD and other neurodegenerative diseases has exploded. A PubMed search using the terms "retina" and "Alzheimer" produced zero matches in 2000 and only seven in 2001, but 1283 in 2019. Since the Alzheimer's Association launched the journal *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring* (DADM) in 2015, it has included a regular section on retinal imaging within its table of contents. Continued interest in this topic prompted the Alzheimer's Association, in collaboration with the editorial team of DADM, to convene a think tank interdisciplinary meeting on May 22nd and 23rd, 2019 in Washington D.C., which attracted 90 registrants and speakers from nine countries and from academia, industry, professional and funding organizations, and governmental agencies.

The goal of this conference was to identify a path forward to expedite the development of retinal biomarkers capable of identifying biological changes associated with AD, and for tracking the progression of disease severity over time. Participants discussed multiple challenges, including the wide variety of imaging modalities available or in development; the likelihood that retinal markers of disease at one stage (eg, preclinical) may not be as sensitive at other stages or at different levels of disease severity; the possibility that optimal retinal biomarkers for disease progression versus staging versus response to treatment may differ; and the variability in methodologies, technologies, vendors, instrument limitations, and so on. These complications have resulted in studies with variable, inconsistent, and often contradictory results, making it difficult to draw firm conclusions about the reliability of various approaches. Most published studies thus far have also been cross-sectional in design, comparing individuals living with symptoms to cognitively unimpaired matched individuals, often lacking AD

biomarker confirmation; thus the natural course of retinal pathological changes over the course of clinical disease progression has not yet been established.

2 | THE RETINA AS A WINDOW TO THE BRAIN

The neurosensory retina is a developmental outgrowth of the brain and is the only (CNS) tissue not shielded by bone (eg, with the exception of the bony orbital floor and wall). Because of the eye's anatomy and transparency to light, the neurosensory retina is more accessible to non-invasive, repeated, high spatial resolution imaging. Moreover, the retina shares structural and pathogenic pathways with the CNS including the cerebral microvasculature and neural cells. Retinal cells are arranged in multiple layers: three layers of nerve and glial cell bodies and three layers of synapses. Photoreceptors capture visual information and transmit it via interneurons to retinal ganglion cells (RGCs). Extending from the inner retina, these cells make direct synaptic connections with the CNS through the optic nerve and optic pathways.[13]

Retinal changes have been observed across the continuum of AD and in other proteinopathies and neurodegenerative disorders, clearly establishing the importance of eye pathology in these diseases.[14] For example, the hallmark biomarkers of AD—amyloid beta (Aβ) plaques and neurofibrillary tangles (NFTs) composed of the protein *tau*—have been identified in the retina of individuals with AD[15] and may either trigger, or be otherwise associated with, a pathological cascade.[16,17] This cascade can lead to retinal degeneration, thinning of the retinal nerve fiber layer (RNFL), and other structural and functional changes observed in AD.[18] Although there is conflicting literature, several studies have corroborated findings by Koronyo-Hamaoui et al., pointing to the existence of Aβ_{40} and Aβ_{42} alloforms, Aβ deposits, (p)tau, NFTs, and inflammation in the retina of AD patients.[16,17,19-25] Aβ in the retina is also thought to cause microvascular changes similar to those observed in the cerebral microvasculature in AD.[26,27] Indeed, a recent study demonstrated in retinal tissue from mild cognitive impairment (MCI) and AD patients the accumulation of Aβ_{40} and Aβ_{42} in blood vessels, especially capillaries, and that this was associated with early and progressive loss of retinal vascular platelet-derived growth factor receptor-beta and pericytes, which are key components of the blood-retina and blood-brain barriers.[24]

More than one research group has shown, in both rodent and human neuropathological studies, similarities between Aβ plaques, including vascular Aβ deposits, in the retina and those in the brain of individuals with AD, although some plaques in the retina are smaller[16] than those in the brain[14,15,17] and larger ones differ in shape from those in the brain.[17,28] Moreover, the presence of amyloid pathology has been demonstrated also in melanopsin-containing retinal ganglion cells (mRGCs).[17] These cells, projecting to the suprachiasmatic nucleus of the hypothalamus, are crucial for circadian photoentrainment and they are lost in AD, possibly contributing to the occurrence of circadian and sleep disturbances in AD.[17] Still, in a cross-sectional study of cases with a clinical diagnosis of AD and neuropathological Braak staging ≥4, Den Haan et al. concluded that amyloid precursor protein and Aβ pathology in the retina differ from that seen in the cerebral cortex, and that no retinal differences were found between individuals with AD and those who did not have AD. They did observe diffuse phosphorylated or fibrillary or paired helical filament *tau* in AD retina, particularly in the peripheral retina of individuals with AD. In addition, they did not observe Aβ plaques in the AD retinas.[29] Contrariwise, Koronyo et al. have reported finding neurofibrillary tangles in human AD retina,[16] and this is a topic requiring further exploration.

RESEARCH IN CONTEXT

1. **Research in Context**: Because clinical research has focused increasingly on the development of treatments and strategies to reduce risk, or stop or slow the disease progression, there remain unmet needs in identifying and validating sensitive, reliable, cost-effective, and widely available clinical assessment and diagnostic tools. Emerging tools like retinal imaging may offer advantages in terms of cost, availability, and acceptance by both health care providers and their patients. The goal of this workshop was to identify a path forward to expedite the development of retinal biomarkers capable of identifying biological changes associated with Alzheimer's disease (AD), and for tracking progression of disease severity over time.
2. **Process**: The Alzheimer's Association and the editorial team of *Diagnosis, Assessment & Disease Monitoring* (the companion journal to *Alzheimer's & Dementia*), convened an interdisciplinary discussion in May 2019, to identify a path forward to expedite the development of retinal biomarkers capable of identifying biological changes associated with AD, and for tracking the progression of disease severity over time.
3. **Interpretation**: Moving from research to context of use and, ultimately, clinical evaluation, this article outlines the status of research today on retinal imaging in Alzheimer's and other brain diseases and provides a discussion on the future direction to move this work forward.
4. **Future Directions**: The Retinal Imaging in Alzheimer's and Neurodegeneration workshop participants identified a number of gaps in understanding the biological underpinnings, considerations for technology evaluation and validation, developing case of appropriate use, and comparisons between the emerging technologies.

3 | RETINAL IMAGING MODALITIES AND THEIR USE IN AD CLINICAL CARE AND RESEARCH

Different retinal imaging modalities provide different types of structural and functional information. An empirically derived combination

of both structural and functional retinal measures may be required to understand how this complex neurovascular/glial system is affected by AD.[30] Moreover, this is a rapidly evolving field, and the pace of engineering advances in these imaging modalities, like any other, outpaces needed advances in signal analyses and data interpretation. In addition, this provides a roadblock in moving retinal biomarkers from the discovery to the validation phase. In the sections below, we provide a cursory review of current work across several imaging modalities; see Alber et al., 2020, for a review and discussion of these technologies.[14]

3.1 | Optical coherence tomography to detect structural changes in the retina

Optical coherence tomography (OCT) provides two-dimensional cross-sectional images and three-dimensional (3D) volumetric measurements of retinal anatomy, and it is widely used for assessing retinal abnormalities in ophthalmologic and neurologic diseases such as glaucoma and multiple sclerosis.[31] OCT generates high-resolution images by measuring the time delay of reflected light. This type of imaging has high depth resolution and can image 2D and 3D volumes over a large field of view. Using interference data from multiple rapid scans, the OCT scanner generates 3D maps of the retina, which enable measurement of the thickness of the RNFL, the layer composed of axons; The ganglion cell layer (GCL) comprising primarily the neuron somata; the inner and outer plexiform layers (IPL and OPL) composed of microglia; and the outer retina where photoreceptors are found. OCT, first introduced clinically in the mid-1990s, has evolved over the years as the laser technology improved. An advanced technology called spectral-domain OCT (SD-OCT) was introduced in 2001.[32] SD-OCT produces faster imaging and is now a commonly used technology in clinical settings,[31] although advances with ultra-high-resolution and OCT-AO (adaptive optics) are promising too.

In a meta-analysis of 11 OCT studies in AD and MCI, Mahajan et al. concluded that AD was associated with thinning of the retina and loss of retinal ganglion cells, as well as decreased volume of the optic nerve. Similar but less-robust changes were seen in individuals with MCI.[33,34] A meta-analysis of 25 OCT studies found that individuals with AD and MCI had RNFL thinning compared to those without AD or MCI,[35] with glaucoma singled out as an important confounding factor to consider. In another review of 33 cross-sectional studies that compared OCT measures from individuals with and without AD, Santos et al. also found RNFL thinning in those individuals with AD compared to cognitively unimpaired individuals, but noted that although there is normal age-related thinning of the RNFL, most studies failed to control for the participants' age.[36] Several studies have shown that age-related loss is important to consider in assessment of RNFL changes in any chronic disease.[37] However, limitations to RNFL thickness as a marker include the lack of standardization in OCT studies, and this limits comparison across studies[38] and it is not specific for AD.

Santos et al. evaluated, within individuals, longitudinal relationships between retinal thickness and cognitive functioning, as well as AD brain changes among adults with preclinical AD. Participants with preclinical AD were selected based on evidence of Aβ burden as determined by amyloid PET imaging and reduced cognitive functioning in response to a challenge with very low-dose of scopolamine hydrochloride, a muscarinic anticholinergic agent. SD-OCT imaging was used to assess volume and thickness of all retinal neuronal layers and participants completed PET amyloid imaging at the beginning and end of the study period. Over a 27-month period, as compared with normal controls, participants in the preclinical stage of AD showed decreases in the macular RNFL, outer nuclear layer, and inner plexiform layer volume. Decreases in RNFL volume correlated with increased PET amyloid burden and reduced performance on a cognitive measure of audiovisual integration efficiency.[36,39]

OCT may also have predictive value according to two recent studies. Ko et al. demonstrated an association between lower RNFL thickness at baseline and cognitive decline over a 3-year period.[40] Mutlu et al. reported an association between thinner RNFL at baseline and an increased risk of developing dementia.[41]

3.2 | Imaging of retinal Aβ and other proteinopathies

The retinas of individuals with AD may exhibit specific pathological changes in addition to RNFL thinning. Some groups have identified Aβ plaques in the retina in living AD patients, using the food additive curcumin.[15-17,19,21-25,29,42] Curcumin, which has fluorescent properties and binds to fibrillary Aβ, has been studied for its diagnostic potential in AD by enabling non-invasive retinal fluorescent imaging.[15,16,43] The presence of amyloid plaques has been demonstrated in human retinas using curcumin and scanning laser ophthalmoscope (SLO).[15,16,44]

Non-invasive polarimetric imaging of retinal amyloid deposits (which also detects pure fibrillary Aβ) may provide a low-cost, non-invasive screening method for presymptomatic detection of AD Imaging, with polarized light correlating with fluorescent Aβ markers. Campbell et al. have shown that the number of Aβ deposits in human retinas *ex vivo* correlate with brain histopathology, even in early stages, and are now working to compare polarimetric markers with PET imaging of amyloid.[45,46]

Hyperspectral imaging of the retina may provide an alternative non-invasive method of measuring Aβ. The approach is based on the finding that Aβ has an influence on light scatter that varies with the wavelength of light. Hadoux et al. recently used retinal hyperspectral imaging in conjunction with machine-learning image analysis methods to distinguish between people with MCI and high brain Aβ burden on PET imaging from matched controls (Aβ PET negative).[21] The technique was also used to distinguish transgenic AD mice (5xFAD), known to accumulate Aβ in the brain and retina, from age-matched wild-type control mice. More et al. used a similar imaging method to distinguish between people with clinically diagnosed AD and cognitive unimpaired participants.[47]

These retinal imaging modalities require replication and neuropathological validation to move from the biomarker discovery to the biomarker validation phase.

3.3 | Vascular imaging of the retina

Because the retina shares developmental, structural, and pathogenic pathways with the CNS, its microvascular system is also very similar to, and contiguous with, the vascular supply of the CNS. Changes in the condition of the retinal microvessels thus may provide information about various cerebrovascular and neurodegenerative disorders including AD. Like the brain, the retina does not have traditional lymphatic vessels. The drainage of interstitial fluid from the brain occurs along the basement membranes of capillaries and arteries as intramural periarterial drainage fails in cerebral amyloid angiopathy (CAA).[48] It remains to be seen if a similar mechanism for clearance exists in the eye and whether the accumulation of amyloid in retinal vessels may be an early biomarker for cerebral CAA.

Emerging technologies provide a larger perspective that allows peripheral vasculature of the retinal microcirculation to be evaluated, without the need for angiography and contrast dyes.[49] These technologies include OCT angiography (OCT-A) and dynamic vessel analyzer examination of the fundus. For example, among individuals with AD and MCI, OCT-A imaging has revealed loss of retinal microvascular density in some studies[50,51] although not in others.[52] Retinal microvascular abnormalities and structural alterations have also been observed using OCT-A in people with elevated Aβ PET imaging or by CSF protein assays, indicative of preclinical AD.[53] Although not explicitly discussed at the Retinal Imaging in AD (RIAD) meeting, there are several retinal vascular changes that have been examined in AD, including, but not limited to, fractal dimension, vessel caliber, vessel branching, blood flow velocity, and retinal oximetry. These techniques have shown mixed results when comparing AD patients to healthy controls (see Alber et al., 2020 for a review), and standardization of methods is necessary to determine the context of use for these potential retinal vascular biomarkers.

3.4 | Imaging neuroinflammation and metabolism in the retina

In retinal tissue of triple transgenic AD mice, astrocytes and microglia are found in association with Aβ in the RGC. Widefield autofluorescence (AF) in vivo imaging of the retina has been used in mice to demonstrate the presence of inflammatory microglial cells, which may reflect CNS inflammation.[54] Adaptive optics SLO has also been used to examine leukocyte-endothelial interactions in the retinae of mice. Further analysis revealed that retinal microglia express an anti-inflammatory phenotype in presymptomatic stages of AD but adopt a pro-inflammatory phenotype as the disease progresses.[20]

3.5 | Next-generation retinal imaging approaches

Changes in cellular metabolism are among the earliest signs of retinal disease[55] and can be detected using AF imaging approaches, since intracellular coenzymes involved in mitochondrial function and energy metabolism are naturally autofluorescent.[55,56] Fundus autofluorescence (FAF) imaging can be accomplished using several different imaging systems including the fundus camera, sSL orchestrator (sSLO), and ultrawide field (UWF) imaging devices.[57]

Fluorescent lifetime imaging ophthalmoscopy (FLIO) is one advanced retinal imaging method that measures the decay in fluorescence intensity over time for endogenous fluorophores.[58] The decay time of the fluorescence signal depends on the specific fluorophores present and may be affected by many factors, including age. In patients with AD, fluorescence lifetime parameters have been shown to correlate with cognition (Mini-Mental State Examination [MMSE] score) and CSF concentrations of Aβ_{42} and phosphorylated tau.[59] In a pilot study of individuals identified to have AD-related brain pathology and therefore identified as preclinical AD, FLIO parameters correlated not only with CSF AD biomarkers but also with GCL-inner plexiform layer (IPL) thickness on OCT, suggesting its use as a simple, non-invasive diagnostic and assessment tool to identify individuals defined as having preclinical AD.[60] Further studies in larger longitudinal cohorts are needed, however, to define the most important parameters for discrimination.

As well as novel imaging of amyloid deposits with polarized light mentioned earlier, another novel approach involves the detection of apoptotic retinal cells (DARCs). Neurodegenerative diseases including AD are characterized by loss of RGCs. Using fluorescently labeled Annexin, Cordeiro et al. have demonstrated the ability to visualize apoptosis of individual RGCs in experimental models of neurodegeneration and in humans with glaucoma.[61] DARCs may be able to register early stages of RGC pathology, although it is not well established whether DARCs can detect changes in RNFL thickness reliably earlier than OCT[62]; however, recent published findings from the Phase 2 DARC trial demonstrate it to predict RNF loss by 18 months in glaucoma eyes.[73]

Furthermore, studies in Parkinson disease (PD) models suggest that these retinal changes occur before pathological signs of PD in the CNS are apparent, raising the possibility that this may represent a biomarker of early PD as well as a biomarker of treatment efficacy.[63] The application of this technology for early detection of AD has not yet been well delineated, and further validation is needed.

An important caveat when examining these retinal imaging techniques is that their specificity to AD cannot be determined without within-subject, longitudinal studies including histology- and/or biomarker-confirmed diagnostic criteria. There are few studies that make these comparisons, most of which are cross-sectional in nature. Another potential confounder is the presence of multiple pathologies, including cardiovascular and cerebrovascular insults, which can affect retinal and cerebral pathology.

4 | DISCOVERY AND VALIDATION OF RETINAL IMAGING BIOMARKERS FOR CLINICAL USE

4.1 | Lessons learned from plasma biomarker development

The development of blood-based biomarkers for AD has progressed rapidly since 2012, when a think tank similar to this one was convened by the Alzheimer's Association in partnership with others.[64] That meeting led to the establishment of a blood-based biomarker professional interest area (PIA) within the Association's International Society to Advance Alzheimer's Research and Treatment (ISTAART), and the development of guidelines to enable moving from discovery to application.[9] This approach provides a model for the development of retinal imaging biomarkers of AD, which are currently in the very early stage discovery phase. Among the lessons learned in the development of blood-based biomarkers are the need for collaboration among academic and industry researchers and the importance of transparency in methods for replication and validation across institutions, cultures, and populations. Other essential considerations to enable rapid progress in the field include the generation of novel collaborative paradigms, and the creation of large cohorts to enable:

- Providing partners with improved access to raw data
- Harmonizing, standardizing, and replicating methods, such that comparable results can be obtained across other various imaging technologies produced by multiple vendors
- Ensuring that chosen methods are scalable
- Considering possible confounders, including other age-related diseases that affect the eye (ie, macular degeneration and glaucoma)
- Including sex differences and racial and ethnic variables that may affect results
- Accounting of clinical use parameters to ensure that the methods fit into existing medical infrastructure and practice patterns.

Defining the context of use (COU) will guide the development of retinal biomarkers. Possible COUs may be (1) Identifying AD-related changes as a component of regular optometric or ophthalmologic examinations; (2) retinal exams as part of a multi-step detection process beginning in primary care settings (eg, following blood-based screening and before PET or CSF amyloid assessment); or (3) retinal Aβ as a surrogate for cerebral Aβ positivity. Other potential COUs could include screening for clinical trials, distinguishing AD from other causes of dementia, determining AD disease subtypes, diagnosing CAA early, before the signs of the modified Boston criteria, or a surrogate outcome for trials.

4.2 | Regulatory issues

The U.S. Food and Drug Administration (FDA) and other regulatory agencies worldwide have demonstrated an interest in expediting the development of safe and effective medical devices. At the FDA, the Center for Devices and Radiological Health (CDRH) regulates all medical devices and has issued guidance to help developers and researchers navigate the regulatory pathway. One of these is a draft guidance on the breakthrough devices program.[65] A retinal imaging platform developed by Optina Diagnostics to help in the diagnosis of AD obtained breakthrough device designation from the FDA in May 2019. The platform combines a cerebral amyloid predictor retina scan (or CAPRS) with a metabolic hyperspectral retinal camera (MHRC) and uses artificial intelligence to assess the hyperspectral retinal images captured with MHRC.

CDRH has also advocated for the creation of collaborative communities to bring together all stakeholders in the development of innovative devices and has published a toolkit to help in establishing such a community.[66] In addition, the CDRH has established The Network of Experts, a vetted network of partner organizations and their member scientists, clinicians, and engineers who can provide CDRH and CDER staff with rapid access to expertise when it is needed to supplement existing knowledge and expertise within the centers.[71]

5 | NEXT STEPS

This first RIAD think tank meeting represented the first step in a process of building collaborations across academia and industry to address the challenges associated with developing and implementing retinal imaging biomarkers. Although research in this area is still in the early development stages, retinal imaging is promising not only as a tool for prevention and early diagnosis, but also for the sub-stratification of individuals to facilitate precision medicine approaches to treat AD. Any new retinal imaging biomarker—or any biomarker—put forward will require rigorous testing and validation by multiple clinics.

A wide spectrum of methods and perspectives were introduced at this meeting. Moving forward, it will be necessary to reach consensus on best approaches and metrics for retinal imaging–related technologies, which may vary over the course of disease progression. These approaches should include the opportunities and the challenges of each method individually and take into account, the methods in combination with other biomarkers. Multimodal approaches and novel analytical methods should provide rich information.[30] Layering multiple tools together from the outset and considering them in the context of other biomarkers (eg, blood assays) may lead to the identification of preclinical disease with desirable sensitivity and specificity.

OCT retinal imaging has already been included as a sub-study within the Anti-Amyloid in Asymptomatic Alzheimer's Disease (A4) study, a secondary prevention trial in asymptomatic individuals who are amyloid positive (NCT02008357)[67]; and in the Longitudinal Evaluation of Amyloid Risk and Neurodegeneration (LEARN) observational cohort of amyloid-negative individuals (NCT02488720). Retinal imaging was added to the A4 and LEARN protocols to determine whether pathological changes in the retina occur before, coincident with, or after onset of AD neuropathology in the brain. The Atlas of Retinal Imaging in Alzheimer's (ARIAS) study (NCT03862222) is also underway, which will include OCT, OCT-A, blue light autofluorescence, measurement of

macular pigment optical density, as well as vision and neuropsychological tests, apolipoprotein E gene (*APOE*) genotyping, and other assessments. ARIAS participants will span the AD continuum from cognitively normal to mild dementia, and participants will be followed for at least 36 months. Several other large retinal imaging trials in AD are either launching or in the planning stages, and we expect this line of investigation to progress rapidly. It will be important to include all stages of the cognitive aging continuum in future studies, from cognitively normal to high risk for AD to MCI to AD dementia, in order to fully appreciate which retinal biomarker targets provide high sensitivity and specificity at each stage of the disease. The majority of the studies investigating retinal AD biomarkers to date have compared the clinically symptomatic AD population to a group of cognitively normal older adults: it will be essential target the pre-clinical and MCI phases of the disease to determine which retinal biomarkers are useful to detect AD risk and progression. Moreover, inclusion of techniques such as electroretinography, will be helpful to understand localized functional retinal changes and how they related to retinal AD pathology.

As has been shown in the development of fluid and imaging biomarkers, standardization and ensuring data quality are key. This includes a need to fully understand differences between manufacturers and instruments and how these instrumental differences impact variability in measurements across labs. Not only is standardization of retinal imaging techniques required, but standardization of retinal histology techniques will be essential to resolve somewhat discrepant literature on the quantity, localization, and morphology of retinal amyloid and tau deposition. Standardization and harmonization of image-processing techniques is also needed to ensure interoperability of measurements across devices produced by varying vendors. These efforts will require development of standard references and the open sharing of data across labs. Translating standardized methods to the clinic will also require novel ways to display information to make it useful to providers.

Establishing research cores with leaders who will both champion and be expert in the associated technologies—a model that proved successful in the AD Neuroimaging Initiative—may provide the impetus for progress in standardization. At the National Institutes of Health (NIH), many institutes support research relating to the eye and should play a key role in helping to shape this effort. Although the field is not yet ready to reach consensus on methods, agreement on a standard "minimum data set" (eg, availability of biomarker data through CSF or PET imaging) may now be possible to allow for comparisons across labs and programs. It may also be valuable to consider integrating retinal imaging with other technologies that provide information on the physiology of the retina, for example, oximetry, macular pigment optical imaging, pupillometry, and functional assessment of vision. Of interest, chromatic pupillometry is a noninvasive technique that specifically addresses mRGC function, even in the pre-clinical stage of the disease, and can be used as a valuable tool for detecting mRGC dysfunction in AD.[68-70] Convening research teams from around the world in a shared environment, such as a PIA of ISTAART, would enable continued discussion on harmonization and standardization of research procedures for retinal AD projects to emerge together.

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CONFLICTS OF INTEREST

B. Bouma has patents related to OCT instrumentation and signal processing, which are assigned to Mass General Hospital and licensed to Heidelberg Engineering. M.C. Carrillo and H.M. Snyder are full time employees of the Alzheimer's Association. M. Campbell is a member of the board of directors of LumeNeuro, a shareholder in LumeNeuro, and holds related patents through the University of Waterloo. M. Dueñas was a full time employee of the American Optometric Association when this conference took place. B. Fernández is a full time employee of Heidelberg Engineering. M. Koronyo-Hamaoui is a co-founder, minor shareholder, and consultant of NeuroVision Imaging, Inc. C. La Morgia received speaker honoraria and meeting reimbursement from Santhera Pharmaceuticals and receives funding from the Italian Ministry of Health (GR-2013-02358026). S.R. Sadda received honoraria from Topcon, Nidek, Heidelberg, Centervue, Optos, Amgen, Allergan, Novartis, Roche/ Genentech, Oxurion, 4DMT, and Merck; and he also received research instruments from Topcon, Nidek, Carl Zeiss Meditec, Centervue, Heidelberg, and Optos. P. van Wijngaarden is a founder of Enlighten Imaging PTY LTD, a start-up company focused on developing novel retinal imaging solutions for neurological and retinal diseases.

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