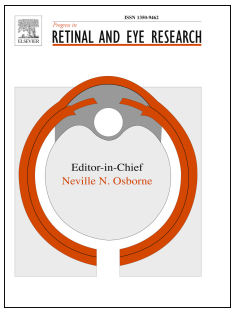
Journal Pre-proof



Value Proposition of Retinal Imaging in Alzheimer's Disease Screening: A Review of Eight Evolving Trends

Victor T.T. Chan, MBChB, An Ran Ran, PhD, Siegfried K. Wagner, FRCOphth, Herbert Y.H. Hui, Xiaoyan Hu, PhD, Ho Ko, PhD, Sharon Fekrat, FASRS, Yaxing Wang, PhD, Cecilia S. Lee, MD, Alvin L. Young, FRCOphth, Clement C. Tham, FRCOphth, Yih Chung Tham, PhD, Pearse A. Keane, FRCOphth, MD, Dan Milea, PhD, MD, Christopher Chen, PhD, MD, Tien Yin Wong, PhD, Vincent C.T. Mok, MD, Carol Y. Cheung, PhD

PII: S1350-9462(24)00055-7

DOI: https://doi.org/10.1016/j.preteyeres.2024.101290

Reference: JPRR 101290

To appear in: *Progress in Retinal and Eye Research*

Received Date: 18 May 2024

Revised Date: 13 August 2024

Accepted Date: 15 August 2024

Please cite this article as: Chan, V.T.T., Ran, A.R., Wagner, S.K., Hui, H.Y.H., Hu, X., Ko, H., Fekrat, S., Wang, Y., Lee, C.S., Young, A.L., Tham, C.C., Tham, Y.C., Keane, P.A., Milea, D., Chen, C., Wong, T.Y., Mok, V.C.T., Cheung, C.Y, Value Proposition of Retinal Imaging in Alzheimer's Disease Screening: A Review of Eight Evolving Trends, *Progress in Retinal and Eye Research*, https://doi.org/10.1016/j.preteyeres.2024.101290.

Value Proposition of Retinal Imaging in Alzheimer's Disease Screening: A Review of Eight Evolving Trends

Victor T.T. Chan[a,b] *MBChB*, **An Ran Ran**[a] *PhD*, **Siegfried K. Wagner**[c] *FRCOphth*, **Herbert Y.H. Hui**[a], **Xiaoyan Hu**[a] *PhD*, **Ho Ko**[d,e] *PhD*, **Sharon Fekrat**[f] *FASRS*, **Yaxing Wang**[g] *PhD*, **Cecilia S. Lee**[h] *MD*, **Alvin L. Young**[a,b] *FRCOphth*, **Clement C. Tham**[a] *FRCOphth*, **Yih Chung Tham**[i] *PhD*, **Pearse A. Keane**[c] *MD FRCOphth*, ***Dan Milea**[j] *MD PhD*, ***Christopher Chen**[k,l] *MD PhD*, ***Tien Yin Wong**[m] *PhD*, ***Vincent C.T. Mok**[d,e] *MD*, ***Carol Y Cheung**[a] *PhD*

[a] Department of Ophthalmology and Visual Sciences, the Chinese University of Hong Kong, Hong Kong SAR, China

[b] Department of Ophthalmology and Visual Sciences, Prince of Wales Hospital, Hong Kong SAR, China

[c] NIHR Biomedical Research Center at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London, UK.

[d] Division of Neurology, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong SAR China.

[e] Gerald Choa Neuroscience Institute, Margaret K.L. Cheung Research Centre for Management of Parkinsonism, Therese Pei Fong Chow Research Centre for Prevention of Dementia, Lui Che Woo Institute of Innovative Medicine, Li Ka Shing Institute of Health Science, Lau Tat-chuen Research Centre of Brain Degenerative Diseases in Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR China.

[f] Departments of Ophthalmology and Neurology, Duke University School of Medicine, Durham, North Carolina, USA

[g] Beijing Institute of Ophthalmology, Beijing Ophthalmology and Visual Science Key Lab, Beijing Tongren Hospital, Capital University of Medical Science, Beijing, China.

[h] Department of Ophthalmology, University of Washington, Seattle, WA, USA

[i] Department of Ophthalmology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

[j] Singapore National Eye Centre, Singapore

[k] Memory Aging & Cognition Centre, National University Health System, Singapore.

[l] Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore.

[m] Tsinghua Medicine, Tsinghua University, Beijing, China.

* These authors contributed equally as senior authors
Correspondence: Carol Y. Cheung
Email: carolcheung@cuhk.edu.hk
Address: Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, 4/F Hong Kong Eye Hospital, 147K Argyle Street, Kowloon, Hong Kong SAR; T: +852 3943 5831 / F: +852 2715 9490

Abstract

Alzheimer's disease (AD) is the leading cause of dementia worldwide. Current diagnostic modalities of AD generally focus on detecting the presence of amyloid β and tau protein in the brain (for example, positron emission tomography [PET] and cerebrospinal fluid testing), but these are limited by their high cost, invasiveness, and lack of expertise. Retinal imaging exhibits potential in AD screening and risk stratification, as the retina provides a platform for the optical visualization of the central nervous system in vivo, with vascular and neuronal changes that mirror brain pathology.

Given the paradigm shift brought by advances in artificial intelligence and the emergence of disease-modifying therapies, this article aims to summarize and review the current literature to highlight 8 trends in an evolving landscape regarding the role and potential value of retinal imaging in AD screening.

1. Introduction

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease of older adults. The recent Food and Drug Administration (FDA) approval of aducanumab and lecanemab for early-stage AD (i.e., mild cognitive impairment [MCI] or mild dementia due to AD) underscores a pivotal advance in AD treatment strategies (Cummings et al., 2023, 2021). In addition, around 40% of worldwide dementias could be prevented or delayed simply by addressing some modifiable risk factors, such as hypertension, diabetes, obesity, physical inactivity, and smoking (Kivipelto et al., 2020; Livingston et al., 2020). Nevertheless, many patients with early-stage AD attribute their cognitive complaints as part of normal aging and do not seek timely medical attention. The advent of disease-modifying therapies highlights the need for efficient, simple, and cost-effective screening methods to identify those with early-stage AD for timely intervention.

Current diagnostic modalities for AD primarily focus on detecting amyloid β (Aβ) overabundance and tauopathy in the brain, such as lumbar puncture or positron emission tomography (PET) imaging. These procedures are either expensive, invasive, not widely accessible, or demand significant expertise for their execution and interpretation, hence precluding their use for large-scale screening. While blood biomarkers for AD are gaining popularity, their application in large-scale AD screening is also not well-established due to a number of reasons (Mielke and Fowler, 2024).

In contrast, retinal imaging represents a plausible and non-invasive solution to assist the screening of early-stage AD among populations at risk (such as those with diabetes or a family history of AD) (Cheung et al., 2017; Kashani et al., 2021). The retina is the only part of the central nervous system (CNS) that allows direct, non-invasive, and high-resolution *in vivo* visualization. Furthermore, the retina exhibits findings that mirror those in the cerebrum (a.k.a. the oculome) (Cheung et al., 2021a; London et al., 2013; Wagner et al., 2020). It is increasingly evident that optical coherence tomography (OCT) reveals changes in retinal neuronal and axonal layers related to AD, while digital retinal fundus photography and OCT angiography (OCTA) capture AD-associated microvascular features (Chan et al., 2019; Cheung et al., 2019). A thinner retinal nerve fibre layer (RNFL) is also associated with an increased risk of AD-dementia (Mutlu et al., 2018), or cognitive decline in older adults (Kim et al., 2022).

In this article, we aim to review the current literature and outline the 8 major trends which shape the role and potential value of retinal imaging in AD screening.

2. Methods

References for this review were identified by searches of PubMed between January 2005 and January 2024. The search terms “artificial intelligence”, “deep learning”, “retinal imaging”, “Alzheimer’s disease”, “dementia” and “cognitive impairment” were used. Additional references were identified from Additional references were identified from the citations of the articles found. There were no language restrictions. The final reference list was generated based on relevance to the topics covered in this review.

3. Evolving Trends in the role and potential value of retinal imaging in AD screening

3.1. Emerging histopathological evidence for AD pathology in retina

The increasing body of histopathological research shows promising evidence to support the use of retinal imaging in AD screening (Gaire et al., 2024). Aβ accumulation has been demonstrated in the retina of patients with AD (Grimaldi et al., 2019; Koronyo et al., 2017; Qiu et al., 2020; Xu et al., 2022). In particular, Koronyo et al. in their studies utilized immunofluorescence, several Aβ-epitope labelling techniques, and a combination of monoclonal antibodies against various N’-, C’- and, centre Aβ sequences to measure amyloid burden (Koronyo et al., 2017). Their findings comprehensively validated Aβ accumulation in the AD retina in comparison to cognitively normal controls and showed a significant correlation between retinal and brain plaque burdens (Koronyo et al., 2017). Histopathological studies from the same group also revealed Aβ deposits within retinal blood vessels (Koronyo et al., 2017). Transmission electron microscopy analysis has also revealed the presence of $A\beta_{42}$ deposits and classical fibrils and protofibrils in the retina, which were identical in ultrastructure to their counterparts in the brain (Koronyo et al., 2023; Shi et al., 2020). Studies also demonstrated the presence of phosphorylated tau (pTau) in the retina (den Haan et al., 2018; Grimaldi et al., 2019; Gupta et al., 2008; Koronyo et al., 2017), and pTau in the retina might correlate with tauopathy in the AD brain (Hart de Ruyter et al., 2023). Noticeably, hyperphosphorylated tau (pTau) pathology may be more closely tied to cognitive impairment than Aβ pathology (Hanseeuw et al., 2019).

However, several challenges need to be adequately addressed to provide solid histopathological ground for adopting retinal imaging in AD. First, discrepancies exist between histopathological

studies with different staining and biochemical techniques (Alber et al., 2024; Jiang et al., 2016). For instance, several pathological studies failed to demonstrate the presence of extracellular retinal amyloid plaque-like structure (den Haan et al., 2018; Ho et al., 2014; Lee et al., 2020; Williams et al., 2017) or p-tau pathology in the retina (Ho et al., 2014). Also, in non-AD controls, various levels of p-tau pathology were observed (den Haan et al., 2018) and the molecular pattern of retinal tauopathy might be different from cerebral tauopathy (Walkiewicz et al., 2024). Furthermore, an experimental mouse model showed that chronic exposure to head trauma led to a retinal tauopathy, suggesting a non-specific, reactive nature of retinal tauopathy (Xu et al., 2015). Harmonization of histopathological methods will be essential to validate the pathological basis of retinal changes in AD. Future immunochemical studies using antibodies to identify Aβ material in the retina also need to exclude the possibility of non-specific staining and cross-reactivity with other proteins (Alber et al., 2024). Second, the linkage of retinal Aβ and p-tau pathologies with those in the AD brain has to be further clarified. For example, whether retinal changes are early versus late stage phenomena, and whether the retinal Aβ and p-tau pathologies originate from retrograde propagation versus simultaneous deposition in the retina and the brain (Alber et al., 2024).

3.2. Positioning of retinal imaging as a risk stratification tool (low risk or needs attention) for early AD

"All screening programmes do harm; some do good as well, and of these, some do more good than harm at reasonable cost" (Gray et al., 2008); not all individuals involved in screening benefit, and in fact, some can be harmed. The trade-offs include missing diagnosis (i.e. false negative) or subjecting an individual to unnecessary investigation and psychological stress (i.e. false positive). Apparently, there is no 'one size fits all' population-based screening strategy and the benefit-harm balance of any screening program could be improved by risk stratification, which identify only high-risk individuals for screening, rather than performing such screening across the entire population (Knoppers et al., 2021). For those with established AD-dementia, diagnosis is not a problem that requires a technological solution; as simple pen and paper cognitive tests have already achieved satisfactory performance (Creavin et al., 2016). Similarly, those high-risk individuals (such as a strong family history of AD) might also directly consider investigations with higher sensitivity and specificity (e.g. blood biomarkers or neuroimaging) for surveillance purposes. However, for those asymptomatic or mildly symptomatic individuals (e.g., MCI), an efficient and cost-effective risk stratification or triage tool (low risk vs. needs attention) is essential to improve the yield of any screening strategies.

Therefore, we propose that the clinical niche of retinal image analysis should focus on the risk stratification or triage of AD (low risk versus needs attention), when the patients are still asymptomatic or in the stage of AD-MCI (**Figure 1**). These patients might then be referred for further testing of early AD (such as blood biomarkers, PET imaging or CSF testing)(Cheung et al., 2019). Frankly, retinal image analysis does not provide certainty of the diagnosis of AD, but only a probability that an apparently well person at risk from AD who should then be individually tested for further confirmation. Also, the role of retinal imaging in AD screening is not to replace other pre-existing or potential screening strategies (such as blood biomarkers or neuroimaging), but to utilize retinal imaging as a risk stratification or triage tool and combine with other biomarkers in a synergistic manner to improve the benefit-harm balance for any potential screening strategies (**Figure 2**).

Although a number of qualitative (e.g., retinopathy signs) and quantitative (e.g., OCT neuronal thickness, retinal vessel calibres) retinal measures have been associated with AD (Chan et al., 2019), it should be recognized that no single definitive retinal image features at this stage are specific to the risk of AD. In practice, it is challenging to rely solely on a basket of retinal measures for AD detection. Also, instead of being specific to AD, these retinal changes often reflect a combination of aging together with systemic vascular (e.g., hypertension), neurological (e.g., multiple sclerosis, Parkinson's disease), metabolic (e.g., diabetes), and eye (e.g., glaucoma) diseases. Accordingly, retinal changes are yet to be regarded as biomarkers of AD as these changes might not directly related to the pathogenic process of AD. While the implementation of deep learning (DL) might improve the accuracy of retinal image analysis (Cheung et al., 2022a), these fundamental limitations of retinal image analysis should be recognized.

Meanwhile, further works are required to evaluate the retinal changes in AD-MCI as most of the previous studies mainly recruited subjects with AD-dementia (Chan et al., 2019). Also, to elucidate the retinal changes in AD, previous studies commonly excluded some concomitant ophthalmic and systemic conditions that are prevalent among senile populations. The next essential research gap to address is to evaluate the accuracy of these retinal features in AD screening when applied in the population with co-existing systemic and ophthalmic conditions.

3.3. Application of AI in retinal imaging for AD screening

With the emergence of DL, a form of artificial intelligence (AI), more powerful analytical tools are now available for retinal image analysis and pattern recognition. After inputting images labelled as abnormal (e.g., AD) and images labelled as normal, DL models can learn both known and unknown features from images for the detection of a condition, without the need to labelling specific features on the images manually. As a result, AI could greatly facilitate automated analyses of ophthalmic images, especially features that could not be readily quantifiable as human-defined variables. DL may also offer superior reproducibility, as some manual processing steps that are difficult to standardize, such as segmentation of retinal structures, may be bypassed. DL has achieved significant progress in recent years in ophthalmology and multiple systemic conditions could be detected through DL using ophthalmic images, such as cardiovascular disease (Cheung et al., 2021b), diabetes (Zhang et al., 2021), and chronic kidney disease (Sabanayagam et al., 2020). Given the advantages of AI in ophthalmic image analysis, it has been applied to the field of dementia as well. DL techniques have greater potential to facilitate the detection of AD and to differentiate AD from other non-AD conditions, by extracting features that are otherwise hard to be explicitly quantified.

Cheung et al. developed a DL model for risk stratification of AD using 12,132 fundus photographs from Hong Kong, Singapore, and UK (Cheung et al., 2022a). The DL algorithm adopted the technique of feature fusion to integrate information from multiple optic nerve head-centred and macula-centred retinal photographs of both eyes. The algorithm was also developed with unsupervised domain adaptation, which addresses the issue of domain shift and allows the algorithm to transfer to a new study site with inputs of retrospective data. In the internal validation, the model achieved 83.6% accuracy, 93.2% sensitivity, 82.0% specificity, and an AUROC of 0.93 for differentiation of patients with AD from cognitively normal subjects. Performance was similar in smaller external validation sets from Hong Kong, Singapore, and the USA (Cheung et al., 2022a). Of note, the algorithm retained a robust ability to differentiate AD without significant interference from concomitant eye diseases (e.g., age-related macular degeneration and glaucoma) and diabetes. Wisely et al. developed an AI model with multiple imaging modalities using convolutional neural network (CNN) DL from a total of 284 eyes from 159 subjects, of which 36 were clinically diagnosed with AD by experienced neurologists (Wisely et al., 2022). The retinal imaging inputs included ganglion cell inner plexiform layer (GCIPL) thickness maps, OCTA scans, ultra-widefield color and fundus autofluorescence scanning laser ophthalmoscopy images, and patient data inputs such as age, sex, and years of

education. Their best-performing model, including GCIPL maps, quantitative data and patient data achieved an AUROC of 0.841 on the test set. When used in isolation, the GCIPL thickness had the highest predictive value for AD, with an AUROC of 0.809. Using the same multi-modal CNN approach, Wisely et al. further developed another AI model capable of identifying MCI with OCT and OCTA images. This model achieved a sensitivity of 79% and specificity of 83% (Wisely et al., 2023). However, both models were developed with relatively small sample sizes and not validated externally with independent datasets. Tian et al. utilized data from the UK Biobank to develop a modular DL algorithm that enables automated image selection, vessel segmentation, and classification of AD, achieving an average classification accuracy of 82.44% (Tian et al., 2021).

Although retinal image-based DL shows promise for AD screening, it relies on vast amounts of data and complex model structures with millions of parameters. This complexity gives rise to the black-box nature of DL and makes clinicians struggle to understand how a model derives a given decision or prediction, limiting its acceptance in clinical settings. This issue is highly relevant to the application of AI in the field of dementia because, unlike other ocular pathologies, the ocular features related to AD are not readily observable by human eyes and hence it is difficult to determine whether the model performs properly to make predictions based on those "unseen" features. Existing studies generated heatmaps to highlight discriminative areas for the algorithm to make a decision which may be a first step (Cheung et al., 2022a). However, heatmaps are often challenging to interpret and might be falsely reassuring as the process of generating heatmaps is a post-hoc model and does not necessarily reflect the decision-making process of the algorithm. There is also growing interest in interpretable AI, which attempts to reveal the working mechanisms of complex AI models (Chaddad et al., 2023; Chen et al., 2022). Another plausible approach is an attention-guided CNN. Guan et al. developed a model for thorax disease classification using this approach, which allows clinicians to identify which features in the image contributed to the reasoning and conclusion of the model (Guan et al., 2020). This potentially bridges the interpretability gap between the AI models and physicians' decisions. An audit approach is also critical to evaluating an AI algorithm as this identifies the worst mistake a model could potentially make, instead of evaluating its best performance (Liu et al., 2022).

3.4. Retinal imaging could leverage pre-existing eye care infrastructure for opportunistic screening of early AD.

Vision is often regarded as the most valued sense (Enoch et al., 2019), and the probability of visiting an optician is 4 times higher than going to a general practitioner in the >40 age group (YouGovUK, 2018). Fundus photography and sometimes OCT are also readily available in community optometry clinics. Meanwhile, several countries have implemented national screening programmes for diabetic retinopathy (DR), including Iceland, the national screening program in the UK, the OPHDIAT in France, and the Risk Assessment and Management Programme (RAMP) in Hong Kong. These programmes serve as convenient routes for opportunistic screening of AD, especially since those with diabetes are at an increased risk of developing AD. For example, the GoDARTS study demonstrated that retinal vascular measures from diabetes retinal screening photographs could enhance stratifying patients with diabetes at increased risk of dementia (Doney et al., 2022). Consistently, a recent simulation model also suggested that enabling AD pre-screening in primary care and referring those testing positive to specialists would make the biggest impact on reducing wait times for specialists and increase the number of people treated with disease-modifying therapies from 2025 through 2044 (Liu et al., 2024). Advancements in telemedicine and portable fundus cameras could also further extend the incorporation of AI in these primary care infrastructures. For instance, the digital retinal images captured with portable fundus cameras can be uploaded to a cloud-based server for further processing from AI models, without the need to invest in AI infrastructure at every point of care.

Furthermore, ophthalmic conditions causing visual impairment are common among patients suffering from AD. Visual impairment is an important risk of developing dementia (Chen et al., 2017; Shang et al., 2021; Zheng et al., 2018), and cataract extraction is associated with a lower risk of developing dementia (Lee et al., 2022). This is because visual impairment may lead to psychosocial difficulties (Brenner et al., 1993), and a reduction in physical or cognitive activity (Varadaraj et al., 2021), all of which are associated with cognitive decline. Visual impairment might also reduce visual input and lead to reduced activation in central sensory pathways, which in turn accelerates the development of dementia (Roberts and Allen, 2016; Ward et al., 2018). In addition, a meta-analysis showed that age-related macular degeneration, glaucoma, DR, and cataract may be associated with an increased risk of all-cause dementia and AD (Feng et al., 2023).

Taken together, patients with visual complaints, who commonly present to optometrists or community eyecare infrastructure and receive retinal imaging, represent an excellent and immediately available channel for opportunistic screening of early-stage AD.

3.5. Increasing use of a multi-modal approach to AD screening

In a real-life clinical setting, a clinician takes different sources of information into account before arriving at a provisional diagnosis, including medical history, physical examination, and investigation results. Similarly, an ideal model for AD screening should combine information from different sources, including structured clinical information, to achieve more robust predictive capabilities.

Since each retinal imaging modality is particularly useful for capturing certain aspects of the retina, a multi-modal approach is a natural solution to capture most, if not all, AD-related manifestations in the retina. For example, fundus photographs reveal the status of retinal microvasculature, OCTA captures the status of retinal capillary networks, and OCT provides information on the retinal neuronal and axonal layers and choroids. With the advent of ultra-widefield imaging, we could now also assess a larger view of the retinal vasculature to uncover peripheral retinal changes in AD (Csincsik et al., 2018; Pead et al., 2023). Newer retinal imaging methods are also gaining attention in detecting the presence of Aβ in the retina, such as the use of orally administered curcumin (Koronyo et al., 2017), adaptive optics scanning laser ophthalmoscopy (AS-SLO) (Etebar et al., 2024), and hyperspectral imaging (Hadoux et al., 2019; More et al., 2016; Saeed et al., 2024). Therefore, a combination of different retinal imaging modalities might potentially increase the performance of risk stratification.

It is also possible to combine retinal imaging with other screening modalities, such as cognitive testing, to improve screening or risk stratification. Multidomain performance measures, such as the Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS- Cog), the Clinical Dementia Rating – Sum Of Boxes (CDR-SOB), and the Preclinical Alzheimer's Cognitive Composite (PACC) can improve detection of subtle- to- mild cognitive decline and potentially better reflect the cross-domain decline observed in early AD (Cedarbaum et al., 2013; Donohue et al., 2014).

Another particularly exciting direction is to combine retinal imaging with blood-based biomarkers, such as Aβ oligomers and plasma phosphorylated tau 217 (p-tau217). Aβ

oligomers could achieve up to 100% sensitivity and 92% specificity (Youn et al., 2020). However, there are a number of challenges in the clinical application of plasma Aβ, and the correlation of Aβ with the later phase of AD is poor (Huang et al., 2022). Phosphorylated tau in plasma has been explored as an alternative. Recent evidence evaluating plasma pTau supports its use in discriminating AD from non-AD pathologies with good diagnostic performance (Karikari et al., 2020; Palmqvist et al., 2020). pTau is also a potentially sensitive biomarker for early AD due to its elevated level in the early phase of AD (Lantero Rodriguez et al., 2020). Given that blood-based biomarkers are gaining popularity, it is appealing to complement blood-based biomarkers with retinal imaging. For example, patients suspicious of AD identified from retinal imaging can be referred for further blood-based biomarkers testing. Further studies are warranted to evaluate any additional values or benefits of combining retinal imaging and blood-based biomarkers in AD screening.

3.6. Downstream application: Integrating retinal imaging to assist AD screening

While there is emerging evidence supporting the role of retinal imaging in AD screening, questions still remain on whether it is more efficient and beneficial than the current screening strategy (e.g., Mini-Mental State Examination [MMSE] and Montreal Cognitive Assessment [MoCA]).

One key issue is the paucity of evidence assessing the health-economic outcomes of retinal imaging in AD screening since therapeutic intervention for AD was not available until the recent introduction of lecanemab and aducanumab. Hence, future health economic analyses should take into account the current changes in the circumstances. It is also essential to compare the public health impact of the increased demand for diagnostic resources to the cost and health effects of remaining undiagnosed. Careful modeling of potential insurance consequences is also equally important (Arias et al., 2024). This information would be of utmost importance to support any policy-level implementation.

To integrate retinal imaging into a routine screening workflow of AD at the point of care in primary care settings, it is also important to consider the following factors: (1) deployment mode: whether it is 1-tiered, 2-tiered, or 3-tiered starting from non-specialists to specialists; (2) whether to use AI as a fully autonomous tool or as a clinical decision assistive tool to neuropsychiatric testing; (3) public health impact of false positivity and false negativity. Each false positive case identified as having risks of AD would be directed to tertiary specialty care

for additional clinical assessment and investigation, resulting in significantly increased demand for downstream diagnostic and healthcare resources. On the other end, each false negative case would provide false reassurance to the patients, deferring them from timely diagnosis and treatment; (4) potential workflow and referral pathway.

3.7. The ATNV framework can be expanded to include retinal vascular features.

There is increasing recognition that cerebral small vessel disease plays a significant role in the pathogenesis of AD and predicts the risks of cognitive decline (Hilal et al., 2020), the Amyloid/Tau/Neurodegeneration (ATN) framework has included vasculopathy (V) to form the "ATNV" framework (Jack et al., 2018). Studies have suggested that the onset of clinical dementia might be preceded by cerebral vasculopathy (Govindpani et al., 2019). Cerebral vascular pathologies could contribute to neurodegeneration and cognitive decline by impairing energy supply, inducing oxidative stress and inflammatory cascades, and impeding amyloid clearance (Marchesi, 2011).

The retinal microvasculature shares many similarities with that of the brain and is also considered part of the CNS circulation. In particular, the blood-retinal barrier is similar to the blood-brain barrier (Baker et al., 2008), and the retinal microvasculature has similar physiological properties as the cerebral small vessels (Patton et al., 2005). Hence, it is not surprising that CNS vasculopathy can also be reflected in the retinal vasculature. Examples of retinal vascular abnormalities in AD include reduced vascular branching complexity (Cheung et al., 2014; Frost et al., 2013), increased vascular tortuosity (Cheung et al., 2014), venous narrowing (Cheung et al., 2014; Feke et al., 2015), reduced macular microvascular density (Bulut et al., 2018; O'Bryhim et al., 2018), and choriocapillaris reduction (Kwapong et al., 2024). Recently, Cheung et al. also demonstrated an association between DL-based measurement of retinal vessel calibre and the risk of cognitive decline and dementia (Cheung et al., 2022b). Despite these retinal vascular changes are not specific to AD and could represent neurodegeneration in general, they could be of significant value to reflect the vascular status in the cerebral counterpart.

The presence of DR lesions (e.g., microaneurysms, haemorrhages) are also associated with the early stage of cognitive impairment as well, independent of the effect of age (Chan et al., 2023). A study using an autopsy cohort also showed that DR is associated with a nearly 2-fold higher

risk of microinfarcts in the brain, a risk factor of AD, highlighting that vascular conditions of the retina are associated with vascular pathology in the brain (Lee et al., 2019).

Taken together, retinal vascular imaging might serve as a proxy for CNS vasculopathy and reflect the pathogenic vascular process in the CNS. Retinal vascular imaging features may be explored for utilization in the ATNV framework. Further works are required to evaluate how retinal vascular biomarkers can be integrated into the ATNV framework, including standardized analytic methods, sensitivity or specificity, and device specific cut-off.

3.8. International collaboration can address current challenges in retinal imaging as a tool for AD screening.

Moving forward, there is an urgent need for multi-centre collaboration to address the existing challenges and establish standardized consensus for retinal imaging-based screening programs for AD **(Table 1)**. For instance, the International Society to Advance Alzheimer's Research and Treatment (ISTAART) "The Eye as a Biomarker for AD" Professional Interest Area was established in 2020 to address the variability in the histopathological and *in vivo* retinal imaging studies (Alber et al., 2024). Similarly, the Deep Dementia Phenotyping (DEMON) Network also advocates collaborative dementia research across multiple institutions (Costanzo et al., 2023).

The development of a robust DL system is data intensive, requiring a large amount of data with representative variability (i.e., disease and normal) to improve robustness and generalizability – a *sine qua non* for DL. To address the data dependency of AI, the collection of a large dataset can also be achieved through collaborative multicentre studies. Traditionally, data from different sites of studies are pooled in a centralized location for model training and testing, which is referred to as "centralized learning". However, the data-sharing process across research centres raises several legal, societal, and ethical challenges. While anonymization of data is increasingly encouraged (Olatunji et al., 2022), such data may still be vulnerable to linkage attacks and re-identification (Akram et al., 2020). One possible solution is using privacy-preserving technologies such as federated learning (Aich et al., 2022). In federated learning, initial models are trained locally by contributing institutions using their own data, and the model parameters, instead of raw data, are then transferred to a central server for aggregation and refinement (Aich et al., 2022). This allows multiple research centres to collaboratively train AI models in a decentralized way without extensive data sharing (Rieke

et al., 2020). Another alternative would be swarm learning which provides blockchain-based peer-to-peer data security with complete data decentralization (Warnat-Herresthal et al., 2021). Generation of synthetic data (e.g. by generative adversarial network or latent diffusion models) is also a feasible way of creating plausible images for AI model development while maintaining data confidentiality, especially for multi-centre collaborative studies.

For a consortium to collaborate effectively, the issue of data heterogeneity and image standardization must be adequately addressed. The ophthalmic images captured in different research centres might highly vary due to the diversity of proprietary devices, imaging protocols, and acquisition techniques. This could be achieved through the standardization of retinal images according to the Digital Imaging and Communications in Medicine (DICOM) standard (Ting et al., 2021). DICOM is the standard for medical image communication and management that is widely adopted by different medical specialties for data storage, exchange, and transmission. In the field of radiology which also utilizes different imaging modalities, the wide application of the DICOM standard has enabled the sharing of medical data between different centres (Graham et al., 2005). Hence, standardization of ophthalmic images with DICOM standard could largely facilitate multi-centre collaborations in a large consortium for AI and machine learning (Lee et al., 2021). Compliance of AI studies reporting to validated standards, such as Consolidated Standards of Reporting Trials–Artificial Intelligence (CONSORT-AI) (Liu et al., 2020), could also facilitate critical appraisal and interpretation between different research institutes.

4. Future Trends

The above trends have showcased the roles and values of retinal imaging in AD screening. We envision one possible future trend is that patients with pre-symptomatic AD and AD-MCI, who often have visual complaints, could receive AI-assisted retinal image analysis when they attend optometrists, community eyecare infrastructure, or DR screening programs (**Figure 2**). The retinal images captured will be sent to a cloud-based server for subsequent analysis with a validated AI algorithm and generate a probability of having AD continuum disease. Patients identified with potential risk of AD are then referred to primary or secondary care for further testing, such as blood biomarkers, neurocognitive testing, neuroimaging, or CSF testing.

4.1 Advances in Digital Health

Digital health comprises overlapping areas ranging from the internet of things (IoT), and telemedicine to the use of big data. The advances in digital health will continue to revolutionize the landscape of retinal imaging. One key example is the development of the digital virtual clinic. In a UK proof-of-concept study, a cloud-based teleophthalmology platform that could be used across a range of devices could prevent more than 50% of would-be referrals into hospitals, allowing specialist care to be utilized in a more cost-efficient manner (Kern et al., 2020). The increasing popularity of smartphone optics would also help to improve the availability of retinal imaging (Banik et al., 2021). Current research has exhibited the application of smartphone optics in hemato-histological and microbiological examinations (Banik et al., 2021), which could be applied similarly for retinal imaging. The development of an algorithm and a user-friendly system that is compatible with mid-range smartphones is only a matter of time.

4.2 Retinal image-based foundation models

The advanced developments in the AI field, such as foundation models (Betzler et al., 2023; Thieme et al., 2023), could also enhance the application of AI-based retinal imaging for AD detection. With the aid of self-supervised learning, a foundation model could generate labelled data automatically and learn general-purpose feature representations that can adapt easily to generalizable disease detection from retinal images (Zhou et al., 2023). This could democratize access to AI in routine clinical practice, where an enormous volume of retinal imaging data accumulates daily. Foundation models could also raise the general quality of healthcare AI models by learning powerful representations from large volumes of data. Currently, there are existing foundation models trained on retinal images (retinal fundus photographs and OCT images) showing generalizability to cardiovascular and neurodegenerative diseases, such as ischaemic stroke, myocardial infarction, and Parkinson's disease, indicating its great potential for AD detection (Zhou et al., 2023).

4.3 Retinal imaging as markers for clinical trial recruitment

The potential usage of retinal imaging in other clinical aspects should not be overlooked. Given that the efficacy and risks of lecanemab and aducanumab are still in doubt (Tampi et al., 2021), further clinical trials are imperative for their wider use or the development of other treatments. Retinal imaging offers a unique edge over other test markers such as PET imaging or CSF analysis in terms of cost-effectiveness and invasiveness in the recruitment of appropriate study cohorts. Changes in the retina which mirrors vascular and neuronal changes associated with

AD could be used for the evaluation of clinical response to avant-garde medical treatments, both independently or synergistically with other markers from CSF or blood. For instance, Reid et al validated the use of retinal vascular imaging as a treatment outcome marker in the ENVIS-ion study, which aims to determine whether low-dose aspirin reduces the development of white matter hyper-intense lesions and silent brain infarction (Reid et al., 2012). More research should be performed to fully utilise its potential as a clinical outcome marker or similarly, as a disease biomarker, which can ultimately facilitate the prevention and prediction of AD respectively.

5. Conclusion

Retinal imaging should be positioned as a screening risk stratification tool for AD to facilitate the identification of patients with early-stage AD. The increasing body of clinical and histopathological research shows promising evidence to support the use of retinal imaging in AD screening. Vision loss and major eye diseases are common among AD patients, providing an opportunity for eyecare professionals to be involved in AD screening. Retinal imaging could also leverage pre-existing eye care infrastructure in the community and primary care setting. Since our retina could reflect the vasculopathy in the CNS, the ATNV framework can potentially be expanded to include retinal vascular features. The advancement of AI and multi-modal retinal imaging also greatly facilitated retinal image analysis. However, further downstream modelling of retinal imaging and additional research is still warranted to assess the practicality, accuracy, and generalizability of retinal imaging in AD screening, to fully capitalise on the technology in our joint battle against this debilitating disease.

Figure 1. Natural History of Alzheimer's Disease Continuum

The pathophysiology of Alzheimer's Disease (AD) continuum is characterized by the accumulation of abnormal amyloid and tau, followed by neurodegeneration of brain structure and subsequent decline in cognitive and clinical function. Subjects with pre-symptomatic AD allows us to investigate the pathophysiology of AD. The recently approved disease-modifying therapies target early AD, such as AD-mild cognitive impairment (MCI) and mild AD-dementia. Hence, any potential screening strategies should target patients with AD-MCI. With the advancement of retinal imaging, there is a chance of earlier detection of early AD, which might further extend the spectrum of patients who can benefit from any disease-modifying therapies. For patients with established AD-dementia, further studies are required to investigate whether we can predict the progression of dementia.

Figure 2. Potential Clinical Care Pathway

One possible future is that patients with pre-symptomatic Alzheimer's Disease (AD) and AD-mild cognitive impairment (MCI), who often have visual complaints, could receive artificial intelligence (AI)-assisted retinal image analysis when they attend optometrists, community eyecare infrastructure, or diabetic retinopathy screening programs. The retinal images captured will be sent to a cloud-based server for subsequent analysis with a validated AI algorithm and generate a probability of having AD continuum disease. Patients identified with a potential risk of AD are then referred to primary or secondary care for further testing, such as blood biomarkers, neurocognitive testing, neuroimaging, or cerebrospinal fluid testing.

478 **References**

479

480 Aich, S., Sinai, N.K., Kumar, S., Ali, M., Choi, Y.R., Joo, M. Il, Kim, H.C., 2022. Protecting
481 Personal Healthcare Record Using Blockchain Federated Learning Technologies, in:
482 International Conference on Advanced Communication Technology, ICACT.
483 https://doi.org/10.23919/ICACT53585.2022.9728772
484 Akram, M.U., Abdul Salam, A., Khawaja, S.G., Naqvi, S.G.H., Khan, S.A., 2020. RIDB: A
485 Dataset of fundus images for retina based person identification. Data Br.
486 https://doi.org/10.1016/j.dib.2020.106433
487 Alber, J., Bouwman, F., den Haan, J., Rissman, R.A., De Groef, L., Koronyo-Hamaoui, M.,
488 Lengyel, I., Thal, D.R., 2024. Retina pathology as a target for biomarkers for
489 Alzheimer's disease: Current status, ophthalmopathological background, challenges, and
490 future directions. Alzheimer's Dement. https://doi.org/10.1002/alz.13529
491 Arias, J.J., Manchester, M., Lah, J., 2024. Direct to Consumer Biomarker Testing for
492 Alzheimer Disease—Are We Ready for the Insurance Consequences? JAMA Neurol.
493 81, 107. https://doi.org/10.1001/jamaneurol.2023.4811
494 Baker, M.L., Hand, P.J., Wang, J.J., Wong, T.Y., 2008. Retinal signs and stroke: Revisiting
495 the link between the eye and brain. Stroke.
496 https://doi.org/10.1161/STROKEAHA.107.496091
497 Banik, S., Melanthota, S.K., Arbaaz, Vaz, J.M., Kadambalithaya, V.M., Hussain, I., Dutta, S.,
498 Mazumder, N., 2021. Recent trends in smartphone-based detection for biomedical
499 applications: a review. Anal. Bioanal. Chem. https://doi.org/10.1007/s00216-021-03184-
500 z
501 Betzler, B.K., Chen, H., Cheng, C.-Y., Lee, C.S., Ning, G., Song, S.J., Lee, A.Y., Kawasaki,
502 R., van Wijngaarden, P., Grzybowski, A., He, M., Li, D., Ran Ran, A., Ting, D.S.W.,
503 Teo, K., Ruamviboonsuk, P., Sivaprasad, S., Chaudhary, V., Tadayoni, R., Wang, X.,
504 Cheung, C.Y., Zheng, Y., Wang, Y.X., Tham, Y.C., Wong, T.Y., 2023. Large language
505 models and their impact in ophthalmology. Lancet Digit. Heal. 5, e917–e924.
506 https://doi.org/10.1016/S2589-7500(23)00201-7
507 Brenner, M.H., Curbow, B., Javitt, J.C., Legro, M.W., Sommer, A., 1993. Vision Change and
508 Quality of Life in the Elderly: Response to Cataract Surgery and Treatment of Other
509 Chronic Ocular Conditions. Arch. Ophthalmol.
510 https://doi.org/10.1001/archopht.1993.01090050114040
511 Bulut, M., Kurtuluş, F., Gözkaya, O., Erol, M.K., Cengiz, A., Akldan, M., Yaman, A., 2018.

Evaluation of optical coherence tomography angiographic findings in Alzheimer's type dementia. Br. J. Ophthalmol. https://doi.org/10.1136/bjophthalmol-2017-310476

Cedarbaum, J.M., Jaros, M., Hernandez, C., Coley, N., Andrieu, S., Grundman, M., Vellas, B., 2013. Rationale for use of the Clinical Dementia Rating Sum of Boxes as a primary outcome measure for Alzheimer's disease clinical trials. Alzheimer's Dement. https://doi.org/10.1016/j.jalz.2011.11.002

Chaddad, A., Peng, J., Xu, J., Bouridane, A., 2023. Survey of Explainable AI Techniques in Healthcare. Sensors. https://doi.org/10.3390/s23020634

Chan, R.N.F., Tang, Z., Chan, V.T.T., Chan, R.N.C., Cheng, E.T.W., Ng, N.C.Y., Cheung, C.Y., 2023. The cross-sectional and longitudinal relationship of diabetic retinopathy to cognitive impairment: a systematic review and meta-analysis. Eye. https://doi.org/10.1038/s41433-022-02033-2

Chan, V.T.T., Sun, Z., Tang, S., Chen, L.J., Wong, A., Tham, C.C., Wong, T.Y., Chen, C., Ikram, M.K., Whitson, H.E., Lad, E.M., Mok, V.C.T., Cheung, C.Y., 2019. Spectral-Domain OCT Measurements in Alzheimer's Disease: A Systematic Review and Meta-analysis. Ophthalmology. https://doi.org/10.1016/j.ophtha.2018.08.009

Chen, H., Gomez, C., Huang, C.M., Unberath, M., 2022. Explainable medical imaging AI needs human-centered design: guidelines and evidence from a systematic review. npj Digit. Med. https://doi.org/10.1038/s41746-022-00699-2

Chen, S.P., Bhattacharya, J., Pershing, S., 2017. Association of vision loss with cognition in older adults. JAMA Ophthalmol. https://doi.org/10.1001/jamaophthalmol.2017.2838

Cheung, C.Y., Chan, V.T.T., Mok, V.C., Chen, C., Wong, T.Y., 2019. Potential retinal biomarkers for dementia: What is new? Curr. Opin. Neurol. https://doi.org/10.1097/WCO.0000000000000645

Cheung, C.Y. lui, Ikram, M.K., Chen, C., Wong, T.Y., 2017. Imaging retina to study dementia and stroke. Prog. Retin. Eye Res. https://doi.org/10.1016/j.preteyeres.2017.01.001

Cheung, C.Y., Mok, V., Foster, P.J., Trucco, E., Chen, C., Wong, T.Y., 2021a. Retinal imaging in Alzheimer's disease. J. Neurol. Neurosurg. Psychiatry. https://doi.org/10.1136/jnnp-2020-325347

Cheung, C.Y., Ran, A.R., Wang, S., Chan, V.T.T., Sham, K., Hilal, S., Venketasubramanian, N., Cheng, C.Y., Sabanayagam, C., Tham, Y.C., Schmetterer, L., McKay, G.J., Williams, M.A., Wong, A., Au, L.W.C., Lu, Z., Yam, J.C., Tham, C.C., Chen, J.J., Dumitrascu, O.M., Heng, P.A., Kwok, T.C.Y., Mok, V.C.T., Milea, D., Chen, C.L.H.,

546 Wong, T.Y., 2022a. A deep learning model for detection of Alzheimer's disease based
547 on retinal photographs: a retrospective, multicentre case-control study. Lancet Digit.
548 Heal. https://doi.org/10.1016/S2589-7500(22)00169-8
549 Cheung, C.Y., Wong, W.L.E., Hilal, S., Kan, C.N., Gyanwali, B., Tham, Y.C., Schmetterer,
550 L., Xu, D., Lee, M.L., Hsu, W., Venketasubramanian, N., Tan, B.Y., Wong, T.Y., Chen,
551 C.P.L.H., 2022b. Deep-learning retinal vessel calibre measurements and risk of
552 cognitive decline and dementia. Brain Commun.
553 https://doi.org/10.1093/braincomms/fcac212
554 Cheung, C.Y., Xu, D., Cheng, C.Y., Sabanayagam, C., Tham, Y.C., Yu, M., Rim, T.H., Chai,
555 C.Y., Gopinath, B., Mitchell, P., Poulton, R., Moffitt, T.E., Caspi, A., Yam, J.C., Tham,
556 C.C., Jonas, J.B., Wang, Y.X., Song, S.J., Burrell, L.M., Farouque, O., Li, L.J., Tan, G.,
557 Ting, D.S.W., Hsu, W., Lee, M.L., Wong, T.Y., 2021b. A deep-learning system for the
558 assessment of cardiovascular disease risk via the measurement of retinal-vessel calibre.
559 Nat. Biomed. Eng. https://doi.org/10.1038/s41551-020-00626-4
560 Cheung, C.Y.L., Ong, Y.T., Ikram, M.K., Ong, S.Y., Li, X., Hilal, S., Catindig, J.A.S.,
561 Venketasubramanian, N., Yap, P., Seow, D., Chen, C.P., Wong, T.Y., 2014.
562 Microvascular network alterations in the retina of patients with Alzheimer's disease.
563 Alzheimer's Dement. https://doi.org/10.1016/j.jalz.2013.06.009
564 Costanzo, E., Lengyel, I., Parravano, M., Biagini, I., Veldsman, M., Badhwar, A., Betts, M.,
565 Cherubini, A., Llewellyn, D.J., Lourida, I., Macgillivray, T., Rittman, T., Tamburin, S.,
566 Tai, X.Y., Virgili, G., 2023. Ocular Biomarkers for Alzheimer Disease Dementia: An
567 Umbrella Review of Systematic Reviews and Meta-analyses. JAMA Ophthalmol.
568 https://doi.org/10.1001/jamaophthalmol.2022.4845
569 Csincsik, L., MacGillivray, T.J., Flynn, E., Pellegrini, E., Papanastasiou, G., Barzegar-
570 Befroei, N., Csutak, A., Bird, A.C., Ritchie, C.W., Peto, T., Lengyel, I., 2018. Peripheral
571 Retinal Imaging Biomarkers for Alzheimer's Disease: A Pilot Study. Ophthalmic Res.
572 https://doi.org/10.1159/000487053
573 Cummings, J., Aisen, P., Apostolova, L.G., Atri, A., Salloway, S., Weiner, M., 2021.
574 Aducanumab: Appropriate Use Recommendations. J. Prev. Alzheimer's Dis.
575 https://doi.org/10.14283/jpad.2021.41
576 Cummings, J., Apostolova, L., Rabinovici, G.D., Atri, A., Aisen, P., Greenberg, S., Hendrix,
577 S., Selkoe, D., Weiner, M., Petersen, R.C., Salloway, S., 2023. Lecanemab: Appropriate
578 Use Recommendations. J. Prev. Alzheimer's Dis. https://doi.org/10.14283/jpad.2023.30
579 den Haan, J., Morrema, T.H.J., Verbraak, F.D., de Boer, J.F., Scheltens, P., Rozemuller, A.J.,

Bergen, A.A.B., Bouwman, F.H., Hoozemans, J.J., 2018. Amyloid-beta and phosphorylated tau in post-mortem Alzheimer's disease retinas. Acta Neuropathol. Commun. https://doi.org/10.1186/s40478-018-0650-x

Doney, A.S.F., Nar, A., Huang, Y., Trucco, E., MacGillivray, T., Connelly, P., Leese, G.P., McKay, G.J., 2022. Retinal vascular measures from diabetes retinal screening photographs and risk of incident dementia in type 2 diabetes: A GoDARTS study. Front. Digit. Heal. https://doi.org/10.3389/fdgth.2022.945276

Donohue, M.C., Sperling, R.A., Salmon, D.P., Rentz, D.M., Raman, R., Thomas, R.G., Weiner, M., Aisen, P.S., 2014. The preclinical Alzheimer cognitive composite: Measuring amyloid-related decline. JAMA Neurol. https://doi.org/10.1001/jamaneurol.2014.803

Enoch, J., McDonald, L., Jones, L., Jones, P.R., Crabb, D.P., 2019. Evaluating Whether Sight Is the Most Valued Sense. JAMA Ophthalmol. https://doi.org/10.1001/jamaophthalmol.2019.3537

Etebar, F., Harkin, D.G., White, A.R., Dando, S.J., 2024. Non-invasive in vivo imaging of brain and retinal microglia in neurodegenerative diseases. Front. Cell. Neurosci. 18. https://doi.org/10.3389/fncel.2024.1355557

Feke, G.T., Hyman, B.T., Stern, R.A., Pasquale, L.R., 2015. Retinal blood flow in mild cognitive impairment and Alzheimer's disease. Alzheimer's Dement. Diagnosis, Assess. Dis. Monit. https://doi.org/10.1016/j.dadm.2015.01.004

Feng, J., Huang, C., Liang, L., Li, C., Wang, X., Ma, J., Guan, X., Jiang, B., Huang, S., Qin, P., 2023. The Association Between Eye Disease and Incidence of Dementia: Systematic Review and Meta-Analysis. J. Am. Med. Dir. Assoc. https://doi.org/10.1016/j.jamda.2023.06.025

Frost, S., Kanagasingam, Y., Sohrabi, H., Vignarajan, J., Bourgeat, P., Salvado, O., Villemagne, V., Rowe, C.C., Lance MacAulay, S., Szoeke, C., Ellis, K.A., Ames, D., Masters, C.L., Rainey-Smith, S., Martins, R.N., 2013. Retinal vascular biomarkers for early detection and monitoring of Alzheimer's disease. Transl. Psychiatry. https://doi.org/10.1038/tp.2012.150

Gaire, B.P., Koronyo, Y., Fuchs, D.-T., Shi, H., Rentsendorj, A., Danziger, R., Vit, J.-P.S., Mirzaei, N., Doustar, J., Sheyn, J., Hampel, H., Vergallo, A., Davis, M.R., Jallow, O., Baldacci, F., Verdooner, S.R., Barron, E., Mirzaei, M., Gupta, V.K., Graham, S.L., Tayebi, M., Carare, R.O., Sadun, A.A., Miller, C.A., Dumitrascu, O.M., Lahiri, S., Gao, L., Black, K.L., Koronyo-Hamaoui, M., 2024. Alzheimer's Disease Pathophysiology in

the Retina. Prog. Retin. Eye Res. 101273. https://doi.org/10.1016/j.preteyeres.2024.101273

Govindpani, K., McNamara, L.G., Smith, N.R., Vinnakota, C., Waldvogel, H.J., Faull, R.L.M., Kwakowsky, A., 2019. Vascular dysfunction in Alzheimer's disease: A prelude to the pathological process or a consequence of it? J. Clin. Med. https://doi.org/10.3390/jcm8050651

Graham, R.N.J., Perriss, R.W., Scarsbrook, A.F., 2005. DICOM demystified: A review of digital file formats and their use in radiological practice. Clin. Radiol. https://doi.org/10.1016/j.crad.2005.07.003

Gray, M., Patnick, J., Blanks, R., 2008. Maximising benefit and minimising harm of screening. BMJ. https://doi.org/10.1136/bmj.39470.643218.94

Grimaldi, A., Pediconi, N., Oieni, F., Pizzarelli, R., Rosito, M., Giubettini, M., Santini, T., Limatola, C., Ruocco, G., Ragozzino, D., Di Angelantonio, S., 2019. Neuroinflammatory Processes, A1 Astrocyte Activation and Protein Aggregation in the Retina of Alzheimer's Disease Patients, Possible Biomarkers for Early Diagnosis. Front. Neurosci. https://doi.org/10.3389/fnins.2019.00925

Guan, Q., Huang, Y., Zhong, Z., Zheng, Z., Zheng, L., Yang, Y., 2020. Thorax disease classification with attention guided convolutional neural network. Pattern Recognit. Lett. https://doi.org/10.1016/j.patrec.2019.11.040

Gupta, N., Fong, J., Ang, L.C., Yücel, Y.H., 2008. Retinal tau pathology in human glaucomas. Can. J. Ophthalmol. https://doi.org/10.3129/I07-185

Hadoux, X., Hui, F., Lim, J.K.H., Masters, C.L., Pébay, A., Chevalier, S., Ha, J., Loi, S., Fowler, C.J., Rowe, C., Villemagne, V.L., Taylor, E.N., Fluke, C., Soucy, J.P., Lesage, F., Sylvestre, J.P., Rosa-Neto, P., Mathotaarachchi, S., Gauthier, S., Nasreddine, Z.S., Arbour, J.D., Rhéaume, M.A., Beaulieu, S., Dirani, M., Nguyen, C.T.O., Bui, B. V., Williamson, R., Crowston, J.G., van Wijngaarden, P., 2019. Non-invasive in vivo hyperspectral imaging of the retina for potential biomarker use in Alzheimer's disease. Nat. Commun. https://doi.org/10.1038/s41467-019-12242-1

Hanseeuw, B.J., Betensky, R.A., Jacobs, H.I.L., Schultz, A.P., Sepulcre, J., Becker, J.A., Cosio, D.M.O., Farrell, M., Quiroz, Y.T., Mormino, E.C., Buckley, R.F., Papp, K. V., Amariglio, R.A., Dewachter, I., Ivanoiu, A., Huijbers, W., Hedden, T., Marshall, G.A., Chhatwal, J.P., Rentz, D.M., Sperling, R.A., Johnson, K., 2019. Association of Amyloid and Tau with Cognition in Preclinical Alzheimer Disease: A Longitudinal Study. JAMA Neurol. https://doi.org/10.1001/jamaneurol.2019.1424

Hart de Ruyter, F.J., Morrema, T.H.J., den Haan, J., Twisk, J.W.R., de Boer, J.F., Scheltens, P., Boon, B.D.C., Thal, D.R., Rozemuller, A.J., Verbraak, F.D., Bouwman, F.H., Hoozemans, J.J.M., 2023. Phosphorylated tau in the retina correlates with tau pathology in the brain in Alzheimer's disease and primary tauopathies. Acta Neuropathol. https://doi.org/10.1007/s00401-022-02525-1

Hilal, S., Tan, C.S., van Veluw, S.J., Xu, X., Vrooman, H., Tan, B.Y., Venketasubramanian, N., Biessels, G.J., Chen, C., 2020. Cortical cerebral microinfarcts predict cognitive decline in memory clinic patients. J. Cereb. Blood Flow Metab. https://doi.org/10.1177/0271678X19835565

Ho, C.Y., Troncoso, J.C., Knox, D., Stark, W., Eberhart, C.G., 2014. Beta-amyloid, phospho-tau and alpha-synuclein deposits similar to those in the brain are not identified in the eyes of Alzheimer's and Parkinson's disease patients. Brain Pathol. https://doi.org/10.1111/bpa.12070

Huang, S., Wang, Y.J., Guo, J., 2022. Biofluid Biomarkers of Alzheimer's Disease: Progress, Problems, and Perspectives. Neurosci. Bull. https://doi.org/10.1007/s12264-022-00836-7

Jack, C.R., Bennett, D.A., Blennow, K., Carrillo, M.C., Dunn, B., Haeberlein, S.B., Holtzman, D.M., Jagust, W., Jessen, F., Karlawish, J., Liu, E., Molinuevo, J.L., Montine, T., Phelps, C., Rankin, K.P., Rowe, C.C., Scheltens, P., Siemers, E., Snyder, H.M., Sperling, R., Elliott, C., Masliah, E., Ryan, L., Silverberg, N., 2018. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimer's Dement. https://doi.org/10.1016/j.jalz.2018.02.018

Jiang, J., Wang, H., Li, W., Cao, X., Li, C., 2016. Amyloid plaques in retina for diagnosis in Alzheimer's patients: A meta-analysis. Front. Aging Neurosci. https://doi.org/10.3389/fnagi.2016.00267

Karikari, T.K., Pascoal, T.A., Ashton, N.J., Janelidze, S., Benedet, A.L., Rodriguez, J.L., Chamoun, M., Savard, M., Kang, M.S., Therriault, J., Schöll, M., Massarweh, G., Soucy, J.P., Höglund, K., Brinkmalm, G., Mattsson, N., Palmqvist, S., Gauthier, S., Stomrud, E., Zetterberg, H., Hansson, O., Rosa-Neto, P., Blennow, K., 2020. Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. Lancet Neurol. https://doi.org/10.1016/S1474-4422(20)30071-5

Kashani, A.H., Asanad, S., Chan, J.W., Singer, M.B., Zhang, J., Sharifi, M., Khansari, M.M., Abdolahi, F., Shi, Y., Biffi, A., Chui, H., Ringman, J.M., 2021. Past, present and future

role of retinal imaging in neurodegenerative disease. Prog. Retin. Eye Res. https://doi.org/10.1016/j.preteyeres.2020.100938

Kern, C., Fu, D.J., Kortuem, K., Huemer, J., Barker, D., Davis, A., Balaskas, K., Keane, P.A., McKinnon, T., Sim, D.A., 2020. Implementation of a cloud-based referral platform in ophthalmology: Making telemedicine services a reality in eye care. Br. J. Ophthalmol. https://doi.org/10.1136/bjophthalmol-2019-314161

Kim, H.M., Han, J.W., Park, Y.J., Bae, J. Bin, Woo, S.J., Kim, K.W., 2022. Association Between Retinal Layer Thickness and Cognitive Decline in Older Adults. JAMA Ophthalmol. https://doi.org/10.1001/jamaophthalmol.2022.1563

Kivipelto, M., Mangialasche, F., Snyder, H.M., Allegri, R., Andrieu, S., Arai, H., Baker, L., Belleville, S., Brodaty, H., Brucki, S.M., Calandri, I., Caramelli, P., Chen, C., Chertkow, H., Chew, E., Choi, S.H., Chowdhary, N., Crivelli, L., Torre, R.D. La, Du, Y., Dua, T., Espeland, M., Feldman, H.H., Hartmanis, M., Hartmann, T., Heffernan, M., Henry, C.J., Hong, C.H., Håkansson, K., Iwatsubo, T., Jeong, J.H., Jimenez-Maggiora, G., Koo, E.H., Launer, L.J., Lehtisalo, J., Lopera, F., Martínez-Lage, P., Martins, R., Middleton, L., Molinuevo, J.L., Montero-Odasso, M., Moon, S.Y., Morales-Pérez, K., Nitrini, R., Nygaard, H.B., Park, Y.K., Peltonen, M., Qiu, C., Quiroz, Y.T., Raman, R., Rao, N., Ravindranath, V., Rosenberg, A., Sakurai, T., Salinas, R.M., Scheltens, P., Sevlever, G., Soininen, H., Sosa, A.L., Suemoto, C.K., Tainta-Cuezva, M., Velilla, L., Wang, Y., Whitmer, R., Xu, X., Bain, L.J., Solomon, A., Ngandu, T., Carrillo, M.C., 2020. World-Wide FINGERS Network: A global approach to risk reduction and prevention of dementia. Alzheimer's Dement. https://doi.org/10.1002/alz.12123

Knoppers, B.M., Bernier, A., Moreno, P.G., Pashayan, N., 2021. Of screening, stratification, and scores. J. Pers. Med. https://doi.org/10.3390/jpm11080736

Koronyo, Y., Biggs, D., Barron, E., Boyer, D.S., Pearlman, J.A., Au, W.J., Kile, S.J., Blanco, A., Fuchs, D.T., Ashfaq, A., Frautschy, S., Cole, G.M., Miller, C.A., Hinton, D.R., Verdooner, S.R., Black, K.L., Koronyo-Hamaoui, M., 2017. Retinal amyloid pathology and proof-of-concept imaging trial in Alzheimer's disease. JCI Insight. https://doi.org/10.1172/JCI.INSIGHT.93621

Koronyo, Y., Rentsendorj, A., Mirzaei, N., Regis, G.C., Sheyn, J., Shi, H., Barron, E., Cook-Wiens, G., Rodriguez, A.R., Medeiros, R., Paulo, J.A., Gupta, V.B., Kramerov, A.A., Ljubimov, A. V., Van Eyk, J.E., Graham, S.L., Gupta, V.K., Ringman, J.M., Hinton, D.R., Miller, C.A., Black, K.L., Cattaneo, A., Meli, G., Mirzaei, M., Fuchs, D.T., Koronyo-Hamaoui, M., 2023. Retinal pathological features and proteome signatures of

716 Alzheimer's disease. Acta Neuropathol. https://doi.org/10.1007/s00401-023-02548-2
717 Kwapong, W.R., Tang, F., Liu, P., Zhang, Z., Cao, L., Feng, Z., Yang, S., Shu, Y., Xu, H.,
718 Lu, Y., Zhao, X., Chong, B., Wu, B., Liu, M., Lei, P., Zhang, S., 2024. Choriocapillaris
719 reduction accurately discriminates against early-onset Alzheimer's disease. Alzheimer's
720 Dement. 20, 4185–4198. https://doi.org/10.1002/alz.13871
721 Lantero Rodriguez, J., Karikari, T.K., Suárez-Calvet, M., Troakes, C., King, A., Emersic, A.,
722 Aarsland, D., Hye, A., Zetterberg, H., Blennow, K., Ashton, N.J., 2020. Plasma p-
723 tau181 accurately predicts Alzheimer's disease pathology at least 8 years prior to post-
724 mortem and improves the clinical characterisation of cognitive decline. Acta
725 Neuropathol. https://doi.org/10.1007/s00401-020-02195-x
726 Lee, A.Y., Campbell, J.P., Hwang, T.S., Lum, F., Chew, E.Y., 2021. Recommendations for
727 Standardization of Images in Ophthalmology. Ophthalmology.
728 https://doi.org/10.1016/j.ophtha.2021.03.003
729 Lee, C.S., Gibbons, L.E., Lee, A.Y., Yanagihara, R.T., Blazes, M.S., Lee, M.L., Mccurry,
730 S.M., Bowen, J.D., Mccormick, W.C., Crane, P.K., Larson, E.B., 2022. Association
731 Between Cataract Extraction and Development of Dementia. JAMA Intern. Med.
732 https://doi.org/10.1001/jamainternmed.2021.6990
733 Lee, C.S., Larson, E.B., Gibbons, L.E., Latimer, C.S., Rose, S.E., Hellstern, L.L., Keene,
734 C.D., Crane, P.K., 2019. Ophthalmology-Based Neuropathology Risk Factors: Diabetic
735 Retinopathy is Associated with Deep Microinfarcts in a Community-Based Autopsy
736 Study. J. Alzheimer's Dis. https://doi.org/10.3233/JAD-181087
737 Lee, S., Jiang, K., McIlmoyle, B., To, E., Xu, Q., Hirsch-Reinshagen, V., Mackenzie, I.R.,
738 Hsiung, G.Y.R., Eadie, B.D., Sarunic, M. V., Beg, M.F., Cui, J.Z., Matsubara, J.A.,
739 2020. Amyloid Beta Immunoreactivity in the Retinal Ganglion Cell Layer of the
740 Alzheimer's Eye. Front. Neurosci. https://doi.org/10.3389/fnins.2020.00758
741 Liu, J.L., Baker, L., Chen, A., Wang, J., Girosi, F., 2024. Modeling Early Detection and
742 Geographic Variation in Health System Capacity for Alzheimer's Disease?Modifying
743 Therapies. RAND Corporation, Santa Monica, CA. https://doi.org/10.7249/RRA2643-1
744 Liu, X., Cruz Rivera, S., Moher, D., Calvert, M.J., Denniston, A.K., Chan, A.W., Darzi, A.,
745 Holmes, C., Yau, C., Ashrafian, H., Deeks, J.J., Ferrante di Ruffano, L., Faes, L., Keane,
746 P.A., Vollmer, S.J., Lee, A.Y., Jonas, A., Esteva, A., Beam, A.L., Chan, A.W., Panico,
747 M.B., Lee, C.S., Haug, C., Kelly, C.J., Mulrow, C., Espinoza, C., Fletcher, J., Paltoo, D.,
748 Manna, E., Price, G., Collins, G.S., Harvey, H., Matcham, J., Monteiro, J., ElZarrad,
749 M.K., Ferrante di Ruffano, L., Oakden-Rayner, L., McCradden, M., Keane, P.A.,

Savage, R., Golub, R., Sarkar, R., Rowley, S., 2020. Reporting guidelines for clinical trial reports for interventions involving artificial intelligence: the CONSORT-AI extension. Nat. Med. https://doi.org/10.1038/s41591-020-1034-x

Liu, X., Glocker, B., McCradden, M.M., Ghassemi, M., Denniston, A.K., Oakden-Rayner, L., 2022. The medical algorithmic audit. Lancet Digit. Heal. https://doi.org/10.1016/S2589-7500(22)00003-6

Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., Brayne, C., Burns, A., Cohen-Mansfield, J., Cooper, C., Costafreda, S.G., Dias, A., Fox, N., Gitlin, L.N., Howard, R., Kales, H.C., Kivimäki, M., Larson, E.B., Ogunniyi, A., Orgeta, V., Ritchie, K., Rockwood, K., Sampson, E.L., Samus, Q., Schneider, L.S., Selbæk, G., Teri, L., Mukadam, N., 2020. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet. https://doi.org/10.1016/S0140-6736(20)30367-6

London, A., Benhar, I., Schwartz, M., 2013. The retina as a window to the brain - From eye research to CNS disorders. Nat. Rev. Neurol. https://doi.org/10.1038/nrneurol.2012.227

Marchesi, V.T., 2011. Alzheimer's dementia begins as a disease of small blood vessels, damaged by oxidative-induced inflammation and dysregulated amyloid metabolism: implications for early detection and therapy. FASEB J. https://doi.org/10.1096/fj.11-0102ufm

Mielke, M.M., Fowler, N.R., 2024. Alzheimer disease blood biomarkers: considerations for population-level use. Nat. Rev. Neurol. 20, 495–504. https://doi.org/10.1038/s41582-024-00989-1

More, S.S., Beach, J.M., Vince, R., 2016. Early detection of amyloidopathy in Alzheimer's mice by hyperspectral endoscopy. Investig. Ophthalmol. Vis. Sci. https://doi.org/10.1167/iovs.15-17406

Mutlu, U., Colijn, J.M., Ikram, M.A., Bonnemaijer, P.W.M., Licher, S., Wolters, F.J., Tiemeier, H., Koudstaal, P.J., Klaver, C.C.W., Ikram, M.K., 2018. Association of Retinal Neurodegeneration on Optical Coherence Tomography With Dementia. JAMA Neurol. https://doi.org/10.1001/jamaneurol.2018.1563

O'Bryhim, B.E., Apte, R.S., Kung, N., Coble, D., Van Stavern, G.P., 2018. Association of Preclinical Alzheimer Disease with Optical Coherence Tomographic Angiography Findings. JAMA Ophthalmol. https://doi.org/10.1001/jamaophthalmol.2018.3556

Olatunji, I.E., Rauch, J., Katzensteiner, M., Khosla, M., 2022. A Review of Anonymization for Healthcare Data. Big Data. https://doi.org/10.1089/big.2021.0169

Palmqvist, S., Janelidze, S., Quiroz, Y.T., Zetterberg, H., Lopera, F., Stomrud, E., Su, Y.,

Chen, Y., Serrano, G.E., Leuzy, A., Mattsson-Carlgren, N., Strandberg, O., Smith, R., Villegas, A., Sepulveda-Falla, D., Chai, X., Proctor, N.K., Beach, T.G., Blennow, K., Dage, J.L., Reiman, E.M., Hansson, O., 2020. Discriminative Accuracy of Plasma Phospho-tau217 for Alzheimer Disease vs Other Neurodegenerative Disorders. JAMA - J. Am. Med. Assoc. https://doi.org/10.1001/jama.2020.12134

Patton, N., Aslam, T., MacGillivray, T., Pattie, A., Deary, I.J., Dhillon, B., 2005. Retinal vascular image analysis as a potential screening tool for cerebrovascular disease: A rationale based on homology between cerebral and retinal microvasculatures. J. Anat. https://doi.org/10.1111/j.1469-7580.2005.00395.x

Pead, E., Thompson, A.C., Grewal, D.S., McGrory, S., Robbins, C.B., Ma, J.P., Johnson, K.G., Liu, A.J., Hamid, C., Trucco, E., Ritchie, C.W., Muniz, G., Lengyel, I., Dhillon, B., Fekrat, S., Macgillivray, T., 2023. Retinal Vascular Changes in Alzheimer's Dementia and Mild Cognitive Impairment: A Pilot Study Using Ultra-Widefield Imaging. Transl. Vis. Sci. Technol. https://doi.org/10.1167/tvst.12.1.13

Qiu, Y., Jin, T., Mason, E., Campbell, M.C.W., 2020. Predicting thioflavin fluorescence of retinal amyloid deposits associated with alzheimer's disease from their polarimetric properties. Transl. Vis. Sci. Technol. https://doi.org/10.1167/tvst.9.2.47

Reid, C.M., Storey, E., Wong, T.Y., Woods, R., Tonkin, A., Wang, J.J., Kam, A., Janke, A., Essex, R., Abhayaratna, W.P., Budge, M.M., 2012. Aspirin for the prevention of cognitive decline in the elderly: Rationale and design of a neuro-vascular imaging study (ENVIS-ion). BMC Neurol. 12. https://doi.org/10.1186/1471-2377-12-3

Rieke, N., Hancox, J., Li, W., Milletarì, F., Roth, H.R., Albarqouni, S., Bakas, S., Galtier, M.N., Landman, B.A., Maier-Hein, K., Ourselin, S., Sheller, M., Summers, R.M., Trask, A., Xu, D., Baust, M., Cardoso, M.J., 2020. The future of digital health with federated learning. npj Digit. Med. https://doi.org/10.1038/s41746-020-00323-1

Roberts, K.L., Allen, H.A., 2016. Perception and cognition in the ageing brain: A brief review of the short- and long-term links between perceptual and cognitive decline. Front. Aging Neurosci. https://doi.org/10.3389/fnagi.2016.00039

Sabanayagam, C., Xu, D., Ting, D.S.W., Nusinovici, S., Banu, R., Hamzah, H., Lim, C., Tham, Y.C., Cheung, C.Y., Tai, E.S., Wang, Y.X., Jonas, J.B., Cheng, C.Y., Lee, M.L., Hsu, W., Wong, T.Y., 2020. A deep learning algorithm to detect chronic kidney disease from retinal photographs in community-based populations. Lancet Digit. Heal. https://doi.org/10.1016/S2589-7500(20)30063-7

Saeed, A., Hadoux, X., van Wijngaarden, P., 2024. Hyperspectral retinal imaging biomarkers

of ocular and systemic diseases. Eye. https://doi.org/10.1038/s41433-024-03135-9

Shang, X., Zhu, Z., Wang, W., Ha, J., He, M., 2021. The Association between Vision Impairment and Incidence of Dementia and Cognitive Impairment: A Systematic Review and Meta-analysis. Ophthalmology. https://doi.org/10.1016/j.ophtha.2020.12.029

Shi, H., Koronyo, Y., Rentsendorj, A., Regis, G.C., Sheyn, J., Fuchs, D.T., Kramerov, A.A., Ljubimov, A. V., Dumitrascu, O.M., Rodriguez, A.R., Barron, E., Hinton, D.R., Black, K.L., Miller, C.A., Mirzaei, N., Koronyo-Hamaoui, M., 2020. Identification of early pericyte loss and vascular amyloidosis in Alzheimer's disease retina. Acta Neuropathol. https://doi.org/10.1007/s00401-020-02134-w

Tampi, R.R., Forester, B.P., Agronin, M., 2021. Aducanumab: Evidence from clinical trial data and controversies. Drugs Context. https://doi.org/10.7573/dic.2021-7-3

Thieme, A., Nori, A., Ghassemi, M., Bommasani, R., Andersen, T.O., Luger, E., 2023. Foundation Models in Healthcare: Opportunities, Risks & Strategies Forward, in: Conference on Human Factors in Computing Systems - Proceedings. https://doi.org/10.1145/3544549.3583177

Tian, J., Smith, G., Guo, H., Liu, B., Pan, Z., Wang, Z., Xiong, S., Fang, R., 2021. Modular machine learning for Alzheimer's disease classification from retinal vasculature. Sci. Rep. https://doi.org/10.1038/s41598-020-80312-2

Ting, D.S.W., Wong, T.Y., Park, K.H., Cheung, C.Y., Tham, C.C., Lam, D.S.C., 2021. Ocular Imaging Standardization for Artificial Intelligence Applications in Ophthalmology: The Joint Position Statement and Recommendations from the Asia-Pacific Academy of Ophthalmology and the Asia-Pacific Ocular Imaging Society. Asia-Pacific J. Ophthalmol. https://doi.org/10.1097/APO.0000000000000421

Varadaraj, V., Munoz, B., Simonsick, E.M., Swenor, B.K., 2021. Vision Impairment and Participation in Cognitively Stimulating Activities: The Health ABC Study. Journals Gerontol. - Ser. A Biol. Sci. Med. Sci. https://doi.org/10.1093/gerona/glaa184

Wagner, S.K., Fu, D.J., Faes, L., Liu, X., Huemer, J., Khalid, H., Ferraz, D., Korot, E., Kelly, C., Balaskas, K., Denniston, A.K., Keane, P.A., 2020. Insights into systemic disease through retinal imaging-based oculomics. Transl. Vis. Sci. Technol. https://doi.org/10.1167/tvst.9.2.6

Walkiewicz, G., Ronisz, A., Van Ginderdeuren, R., Lemmens, S., Bouwman, F.H., Hoozemans, J.J.M., Morrema, T.H.J., Rozemuller, A.J., Hart de Ruyter, F.J., De Groef, L., Stalmans, I., Thal, D.R., 2024. Primary retinal tauopathy: A tauopathy with a distinct

molecular pattern. Alzheimer's Dement. https://doi.org/10.1002/alz.13424

Ward, M.E., Gelfand, J.M., Lui, L.Y., Ou, Y., Green, A.J., Stone, K., Pedula, K.L., Cummings, S.R., Yaffe, K., 2018. Reduced contrast sensitivity among older women is associated with increased risk of cognitive impairment. Ann. Neurol. https://doi.org/10.1002/ana.25196

Warnat-Herresthal, S., Schultze, H., Shastry, K.L., Manamohan, S., Mukherjee, Saikat, Garg, V., Sarveswara, R., Händler, K., Pickkers, P., Aziz, N.A., Ktena, S., Tran, F., Bitzer, M., Ossowski, S., Casadei, N., Herr, C., Petersheim, D., Behrends, U., Kern, F., Fehlmann, T., Schommers, P., Lehmann, C., Augustin, M., Rybniker, J., Altmüller, J., Mishra, N., Bernardes, J.P., Krämer, B., Bonaguro, L., Schulte-Schrepping, J., De Domenico, E., Siever, C., Kraut, M., Desai, M., Monnet, B., Saridaki, M., Siegel, C.M., Drews, A., Nuesch-Germano, M., Theis, H., Heyckendorf, J., Schreiber, S., Kim-Hellmuth, S., Balfanz, P., Eggermann, T., Boor, P., Hausmann, R., Kuhn, H., Isfort, S., Stingl, J.C., Schmalzing, G., Kuhl, C.K., Röhrig, R., Marx, G., Uhlig, S., Dahl, E., Müller-Wieland, D., Dreher, M., Marx, N., Nattermann, J., Skowasch, D., Kurth, I., Keller, A., Bals, R., Nürnberg, P., Rieß, O., Rosenstiel, P., Netea, M.G., Theis, F., Mukherjee, Sach, Backes, M., Aschenbrenner, A.C., Ulas, T., Angelov, A., Bartholomäus, A., Becker, A., Bezdan, D., Blumert, C., Bonifacio, E., Bork, P., Boyke, B., Blum, H., Clavel, T., Colome-Tatche, M., Cornberg, M., De La Rosa Velázquez, I.A., Diefenbach, A., Dilthey, A., Fischer, N., Förstner, K., Franzenburg, S., Frick, J.S., Gabernet, G., Gagneur, J., Ganzenmueller, T., Gauder, M., Geißert, J., Goesmann, A., Göpel, S., Grundhoff, A., Grundmann, H., Hain, T., Hanses, F., Hehr, U., Heimbach, A., Hoeper, M., Horn, F., Hübschmann, D., Hummel, M., Iftner, T., Iftner, A., Illig, T., Janssen, S., Kalinowski, J., Kallies, R., Kehr, B., Keppler, O.T., Klein, C., Knop, M., Kohlbacher, O., Köhrer, K., Korbel, J., Kremsner, P.G., Kühnert, D., Landthaler, M., Li, Y., Ludwig, K.U., Makarewicz, O., Marz, M., McHardy, A.C., Mertes, C., Münchhoff, M., Nahnsen, S., Nöthen, M., Ntoumi, F., Overmann, J., Peter, S., Pfeffer, K., Pink, I., Poetsch, A.R., Protzer, U., Pühler, A., Rajewsky, N., Ralser, M., Reiche, K., Ripke, S., da Rocha, U.N., Saliba, A.E., Sander, L.E., Sawitzki, B., Scheithauer, S., Schiffer, P., Schmid-Burgk, J., Schneider, W., Schulte, E.C., Sczyrba, A., Sharaf, M.L., Singh, Y., Sonnabend, M., Stegle, O., Stoye, J., Vehreschild, J., Velavan, T.P., Vogel, J., Volland, S., von Kleist, M., Walker, A., Walter, J., Wieczorek, D., Winkler, S., Ziebuhr, J., Breteler, M.M.B., Giamarellos-Bourboulis, E.J., Kox, M., Becker, M., Cheran, S., Woodacre, M.S., Goh, E.L., Schultze, J.L., 2021. Swarm Learning for decentralized and confidential clinical

machine learning. Nature. https://doi.org/10.1038/s41586-021-03583-3

Williams, E.A., McGuone, D., Frosch, M.P., Hyman, B.T., Laver, N., Stemmer-Rachamimov, A., 2017. Absence of Alzheimer disease neuropathologic changes in eyes of subjects with Alzheimer disease. J. Neuropathol. Exp. Neurol. https://doi.org/10.1093/jnen/nlx020

Wisely, C.E., Richardson, A., Henao, R., Robbins, C.B., Ma, J.P., Wang, D., Johnson, K.G., Liu, A.J., Grewal, D.S., Fekrat, S., 2023. A convolutional neural network using multimodal retinal imaging for differentiation of mild cognitive impairment from normal cognition. Ophthalmol. Sci. https://doi.org/10.1016/j.xops.2023.100355

Wisely, C.E., Wang, D., Henao, R., Grewal, D.S., Thompson, A.C., Robbins, C.B., Yoon, S.P., Soundararajan, S., Polascik, B.W., Burke, J.R., Liu, A., Carin, L., Fekrat, S., 2022. Convolutional neural network to identify symptomatic Alzheimer's disease using multimodal retinal imaging. Br. J. Ophthalmol. https://doi.org/10.1136/bjophthalmol-2020-317659

Xu, L., Ryu, J., Nguyen, J. V., Arena, J., Rha, E., Vranis, P., Hitt, D., Marsh-Armstrong, N., Koliatsos, V.E., 2015. Evidence for accelerated tauopathy in the retina of transgenic P301S tau mice exposed to repetitive mild traumatic brain injury. Exp. Neurol. https://doi.org/10.1016/j.expneurol.2015.08.014

Xu, Q.A., Boerkoel, P., Hirsch-Reinshagen, V., Mackenzie, I.R., Hsiung, G.Y.R., Charm, G., To, E.F., Liu, A.Q., Schwab, K., Jiang, K., Sarunic, M., Beg, M.F., Pham, W., Cui, J., To, E., Lee, S., Matsubara, J.A., 2022. Müller cell degeneration and microglial dysfunction in the Alzheimer's retina. Acta Neuropathol. Commun. https://doi.org/10.1186/s40478-022-01448-y

YouGovUK, 2018. Roughly how often, if at all, do you get your eyes tested? [WWW Document]. URL https://yougov.co.uk/topics/society/survey-results/daily/2018/07/23/eee7f/2 (accessed 1.4.24).

Youn, Y.C., Lee, B.S., Kim, G.J., Ryu, J.S., Lim, K., Lee, R., Suh, J., Park, Y.H., Pyun, J.-M., Ryu, N., Kang, M.J., Kim, H.R., Kang, S., An, S.S.A., Kim, S., 2020. Blood Amyloid-β Oligomerization as a Biomarker of Alzheimer's Disease: A Blinded Validation Study. J. Alzheimer's Dis. https://doi.org/10.3233/jad-200061

Zhang, K., Liu, X., Xu, J., Yuan, J., Cai, W., Chen, T., Wang, K., Gao, Y., Nie, S., Xu, X., Qin, X., Su, Y., Xu, W., Olvera, A., Xue, K., Li, Z., Zhang, M., Zeng, X., Zhang, C.L., Li, O., Zhang, E.E., Zhu, J., Xu, Y., Kermany, D., Zhou, K., Pan, Y., Li, S., Lai, I.F., Chi, Y., Wang, C., Pei, M., Zang, G., Zhang, Q., Lau, J., Lam, D., Zou, X., Wumaier,

A., Wang, J., Shen, Y., Hou, F.F., Zhang, P., Xu, T., Zhou, Y., Wang, G., 2021. Deep-learning models for the detection and incidence prediction of chronic kidney disease and type 2 diabetes from retinal fundus images. Nat. Biomed. Eng. https://doi.org/10.1038/s41551-021-00745-6

Zheng, D.D., Swenor, B.K., Christ, S.L., West, S.K., Lam, B.L., Lee, D.J., 2018. Longitudinal associations between visual impairment and cognitive functioning the salisbury eye evaluation study. JAMA Ophthalmol. https://doi.org/10.1001/jamaophthalmol.2018.2493

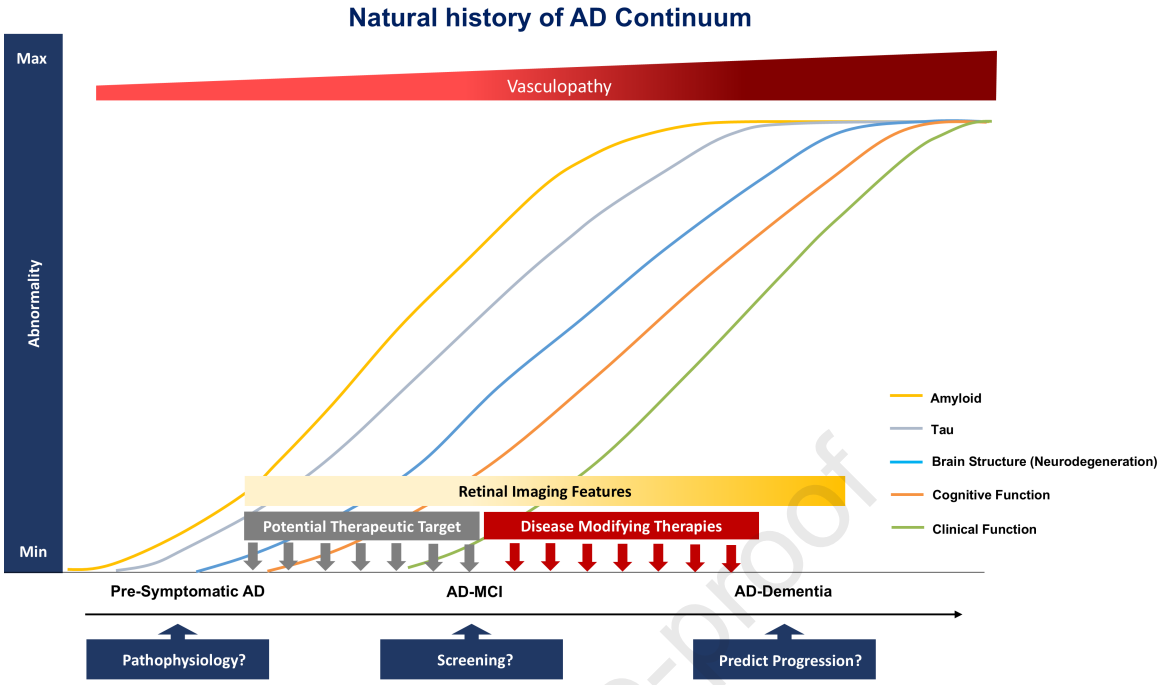
Zhou, Y., Chia, M.A., Wagner, S.K., Ayhan, M.S., Williamson, D.J., Struyven, R.R., Liu, T., Xu, M., Lozano, M.G., Woodward-Court, P., Kihara, Y., Allen, N., Gallacher, J.E.J., Littlejohns, T., Aslam, T., Bishop, P., Black, G., Sergouniotis, P., Atan, D., Dick, A.D., Williams, C., Barman, S., Barrett, J.H., Mackie, S., Braithwaite, T., Carare, R.O., Ennis, S., Gibson, J., Lotery, A.J., Self, J., Chakravarthy, U., Hogg, R.E., Paterson, E., Woodside, J., Peto, T., Mckay, G., Mcguinness, B., Foster, P.J., Balaskas, K., Khawaja, A.P., Pontikos, N., Rahi, J.S., Lascaratos, G., Patel, P.J., Chan, M., Chua, S.Y.L., Day, A., Desai, P., Egan, C., Fruttiger, M., Garway-Heath, D.F., Hardcastle, A., Khaw, S.P.T., Moore, T., Sivaprasad, S., Strouthidis, N., Thomas, D., Tufail, A., Viswanathan, A.C., Dhillon, B., Macgillivray, T., Sudlow, C., Vitart, V., Doney, A., Trucco, E., Guggeinheim, J.A., Morgan, J.E., Hammond, C.J., Williams, K., Hysi, P., Harding, S.P., Zheng, Y., Luben, R., Luthert, P., Sun, Z., McKibbin, M., O'Sullivan, E., Oram, R., Weedon, M., Owen, C.G., Rudnicka, A.R., Sattar, N., Steel, D., Stratton, I., Tapp, R., Yates, M.M., Petzold, A., Madhusudhan, S., Altmann, A., Lee, A.Y., Topol, E.J., Denniston, A.K., Alexander, D.C., Keane, P.A., 2023. A foundation model for generalizable disease detection from retinal images. Nature. https://doi.org/10.1038/s41586-023-06555-x

Table 1. Eight major trends shaping the role and potential value of retinal imaging in AD screening.

Evolving Landscape	Challenges	Potential Roles of Consortium
Trend 1: Emerging histopathological evidence for AD pathology in retina	• Insufficient understanding of the pathophysiology underlying the retinal changes in AD • Difficulty in obtaining post-mortem samples of brain and retina for AD and controls. • Discrepancies of histopathological methods between studies	• To study the underlying mechanism behind the retinal changes in AD • Harmonization of histopathological methods
Trend 2: Positioning of retinal imaging as a risk stratification tool (no risk or needs attention) for early AD.	• Difficulty in recruiting MCI subjects • Improper comparisons of retinal imaging with other biomarkers of AD	• To conduct prospective multi-centre studies recruiting MCI subjects to assess the discriminative ability of retinal changes in stratifying the risks of developing incident dementia. • To identify the role and value of retinal imaging as a risk stratification tool in AD screening
Trend 3: Application of AI in retinal imaging for AD screening	• Data hunger nature of developing a high-performance AI model	• To promote multi-centre collaboration and sharing of research data for development of AI model
Trend 4: Retinal imaging could leverage pre-existing eye care infrastructure for opportunistic screening of early AD.	• Regional differences in community eyecare services and infrastructure	• To address potential obstacles when applying retinal imaging in primary care setting of different countries

	• Lack of awareness of AD-associated ocular changes among regional eyecare professionals	• To promote the role of retinal imaging in AD screening among regional eyecare professionals
Trend 5: Increasing use of a multi-modal approach to AD screening	• Discrepancies in imaging protocols, machines, and qualities	• To harmonize multi-modal data across research institutes
Trend 6: Downstream modelling of retinal imaging may assist AD screening	• Paucity of health economic analyses • Lack of consensus on the screening workflow and referral pathway	• To assess health economic outcomes of retinal imaging in AD screening among developed and developing countries • To achieve consensus on potential screening workflow and referral pathway
Trend 7: The ATN framework can be expanded to include retinal vascular features.	• Insufficient recognition of retinal vascular changes in AD among dementia communities • Insufficient validation of retinal changes against other established biomarkers of AD (e.g. MRI and blood-based biomarkers)	• To promote the incorporation of retinal vascular imaging features in the ATNV framework
Trend 8: International collaboration can address current challenges in retinal imaging as a tool for AD screening.	• Developing harmonized protocols, accessible data sharing platforms	• To develop standard guidelines for imaging protocols, data standards,

Abbreviations: AD = Alzheimer's Disease; ATN framework = Amyloid/ Tau/ Neurodegeneration framework; ATNV framework = Amyloid/ Tau/ Neurodegeneration/ Vasculopathy framework; MCI = mild cognitive impairment



Potential Clinical Care Pathway

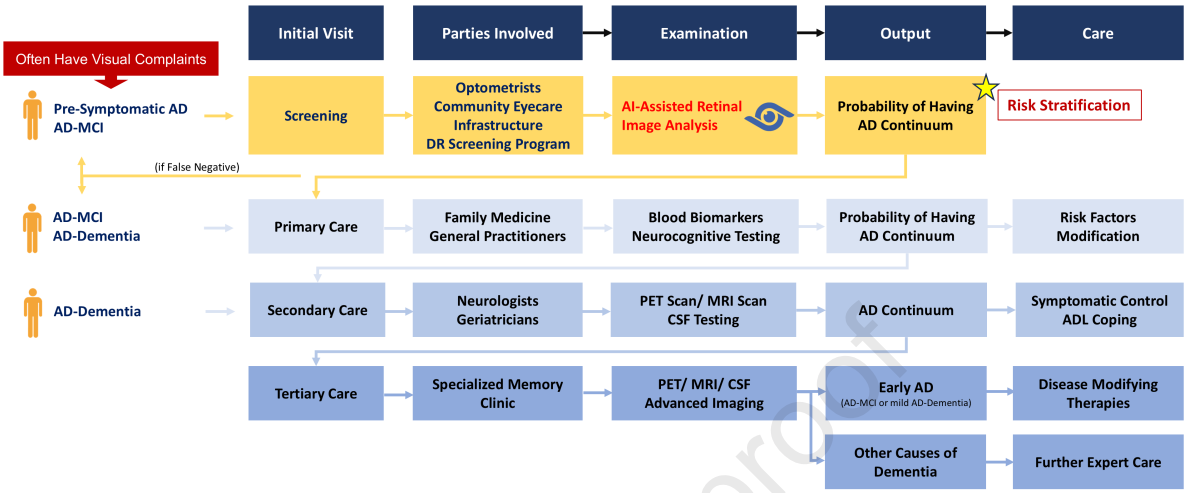


Table of Content