Artificial Intelligence in Predicting Systemic Parameters and Diseases From Ophthalmic Imaging

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Artificial Intelligence (AI) analytics has been used to predict, classify, and aid clinical management of multiple eye diseases. Its robust performances have prompted researchers to expand the use of AI into predicting systemic, non-ocular diseases and parameters based on ocular images. Herein, we discuss the reasons why the eye is well-suited for systemic applications, and review the applications of deep learning on ophthalmic images in the prediction of demographic parameters, body composition factors, and diseases of the cardiovascular, hematological, neurodegenerative, metabolic, renal, and hepatobiliary systems. Three main imaging modalities are included—retinal fundus photographs, optical coherence tomographs and external ophthalmic images. We examine the range of systemic factors studied from ophthalmic imaging in current literature and discuss areas of future research, while acknowledging current limitations of AI systems based on ophthalmic images.

Keywords: artificial intelligence, eye, retina, fundus photography, optical coherence tomography, imaging, machine learning, deep learning

INTRODUCTION

Artificial Intelligence (AI) has revolutionized clinical diagnosis and management of diseases in modern day healthcare. Most AI algorithms built for healthcare applications are supervised machine learning (ML) models—the desired solutions, or labels, are provided as inputs alongside the training examples. Iterative optimization and pattern recognition then allows trained models to predict labels in previously unseen test examples. Deep learning (DL) is a subset of ML comprising neural networks, which are adept at computerized visual perception and image recognition. DL algorithms have thrived in image-centric specialties such as ophthalmology (1–3), dermatology (4), radiology (5, 6), pathology (7, 8), and many other specialties. In ophthalmology, the applications of AI in detecting ophthalmic diseases based on images have been well-established. These include diabetic retinopathy (9–11), age-related macular degeneration (11–14), glaucoma (11), refractive error (15), and retinopathy of prematurity (16, 17). In recent years, application of AI-based analytics in ophthalmic images have not only shown its ability in detecting of ocular diseases, but also estimating systemic parameters and predicting non-ocular diseases (18–47).

The eye is a uniquely accessible window that allows direct visualization of neuro-vasculature using non-invasive imaging modalities. Because the retina and other end organs, such as the brain and kidneys, share similar anatomical and physiological properties, retinal vessels are
an indirect representation of the systemic microvasculature (48–50). Analysis of microvascular changes provides valuable information, as such changes often precede macrovascular diseases such as stroke and ischemic heart disease. Additionally, the retina is an extension of the central nervous system (CNS), and optic nerve fibers are effectively CNS axons. Many neurodegenerative conditions that involve the brain and spinal cord have ocular manifestations (51, 52). Retinal nerve fiber layer (RNFL) thickness (53) and visual acuity (54, 55) have been associated with early-stage cognitive impairment. Furthermore, the external eye (i.e., conjunctiva) is a primary area where clinical signs of jaundice, cholesterol deposits and anemia manifest. Finally, the technology-dependent and image-centric nature of ophthalmology greatly facilitates the accumulation of imaging datasets required for the development of AI algorithms. Hence, ophthalmic imaging coupled with AI analytics have great potential to predict systemic biomarkers and disease.

This review discusses the applications of AI analytics in predicting systemic parameters or disease from ophthalmic images. We provide an overview of the major ophthalmic imaging modalities currently used in AI and discuss how these images were used in the prediction of demographic parameters, body composition factors and diseases of the cardiovascular, hematological, neurodegenerative, metabolic, endocrine, renal, and hepatobiliary systems.

METHODS

For this narrative review, electronic bibliographic searches were conducted in PubMed, EMBASE and Web of Science up to 1 February 2022. MESH terms and all-field search terms were searched for “artificial intelligence,” “neural networks,” “machine learning,” “deep learning,” “imaging,” “eye.” Search results were screened for relevance. References cited within the identified articles were used to further augment the search. Abstracts, Reviews, Correspondence, Opinions, Editorials, and Letters were excluded. Studies were included if they used an ophthalmic imaging modality to predict or quantify a systemic, non-ocular condition or laboratory parameter. This review encompassed an international search, but only articles published in English were used. Information extracted for qualitative analysis includes study details, model architecture, dataset, population, imaging modality, body system/disease, internal/external validation methods, reference standard, raw data of diagnostic accuracy. This review is limited to articles published from 2012 onwards.

OPHTHALMIC IMAGES AS INPUT TO PREDICTIVE MODELS

Many imaging modalities are clinically available in ophthalmology—retinal fundus photography (RFP), optical coherence tomography (OCT), OCT-Angiography (OCT-A), fluorescein angiography, ultrasound biomicroscopy, anterior segment photographs; this list is non-exhaustive. Regarding input images, the development of robust AI models requires meaningful data at a sufficient scale, which can be difficult to acquire. Khan et al. (56) conducted a global review of publicly available datasets for ophthalmological images, and identified 94 open access datasets, of which the top imaging modalities were RFP (54/94, 57%), OCT or OCT-A (18/94, 19%) and external eye photographs (7/94, 7%). The three largest datasets were contributed by Kermay et al. for OCT images (3), the Eye Picture Archive Communication System (EyePACS) for RFP (36), and Media Research Lab Eye (MRL Eye) for external eye photographs (57). In the prediction of systemic biomarkers and diseases, a similar trend holds—the most widely used ophthalmic imaging modality is RFP, followed by OCT, then external eye images (such as anterior segment photographs or slit lamp photographs) (Table 1, Figure 1).

RETINAL FUNDUS PHOTOGRAPHY

RFP is a low-cost, simple imaging technique with widespread applications. Fundus cameras have evolved over time, from traditional table-top cameras to hand-held and smartphone-based cameras. In addition to portability, advancements in medical technology have allowed sharper images, non-mydriatic wide-field options and pupil tracking. Panwar et al. (64) reviewed the twenty-first century advancements in RFP technology and discussed the pros and cons of various types of fundus cameras. While the portability and reduced cost of newer devices are welcome for mass screening purposes, traditional office-based fundus cameras are a mainstay for research purpose because they generally provide the best image quality and have strong clinical validation in comprehensive clinical trials. The study by Poplin et al. (36), published in March 2018, was one of the earliest major studies that predicted systemic biomarkers from RFP. The study, conducted by a team of researchers from Google AI and Stanford School of Medicine, introduced the idea that robust RFP-based models can be trained to predict a wide range of non-ocular parameters. Supplementary Table 1 summarizes performances of RFP-based models in predicting non-ocular diseases and parameters. Anatomically, the fovea, macula, optic disc, and retinal vessels have all been described as essential structures used by AI models for prediction and classification (Figure 2).

Predicting Age and Gender From RFP

Nine studies predicted age or gender from RFPs (30, 31, 34, 36, 38, 45–47, 60). Age as a continuous parameter showed robust predictability in internal datasets ($R^2$: 0.74–0.92). Rim et al. (38) additionally investigated model performance in external datasets ($R^2$: 0.36–0.63), showing limited generalizability. In subgroup analysis of the Singapore Epidemiology of Eye Diseases (SEED) dataset, age was well-predicted across Chinese, Indian, and Malay ethnic groups. As a follow-up to Poplin et al. (36) which showed that RFP could be used to predict gender, Yamashita et al. (45) tried to understand what features are identified by algorithms as useful in predicting gender. They performed logistic regression on several features identified to be associated with sex, including papillomacular angle, tessellation...
| References | Imaging modality | Predicted parameter | Model | Test datasets | Recruitment | Test set size | Type of internal validation | External validation (Yes/No) | Reference standard |
|------------|------------------|---------------------|-------|--------------|-------------|--------------|-----------------------------|----------------------------|---------------------|
| Appaji et al. (58) | Fundus photographs | Schizophrenia | CNN | National Institute of Mental Health and Neurosciences, Bengaluru, India | Retrospective | 56 images | Random split | No | Clinical diagnosis |
| Aslam et al. (18) | OCT-A | Diabetic status | Random forest | Manchester Royal Eye Hospital, UK | Retrospective | 152 scans | Leave-one-out cross validation | No | Biochemical testing |
| Babenko et al. (59) | External eye images | HbA1c | Inception-v3 | EyePACS (CA cohort) | Retrospective | 41,928 images | Random split | No | Biochemical testing |
| Benson et al. (19) | Fundus photographs | Diabetic peripheral neuropathy | VGG-16 | University of New Mexico, Albuquerque, USA | Retrospective | 112 images | Random split | No | Monofilament and vibration testing |
| Betzler et al. (60) | Fundus photographs | Gender | VGG-16 | SEED | Prospective | 34,659 images | Random split | No | Demographics |
| Cavaliere et al. (20) | OCT | Multiple sclerosis | SVM | Miguel Servet University Hospital, Spain | Retrospective | 96 scans | Leave-one-out cross validation | No | Expert consensus (clinical diagnosis) |
| Cervera et al. (61) | Fundus photographs | Diabetic peripheral neuropathy | CNN | SNDREAMS | Retrospective | 23,784 images | Random Split | No | Vibration perception threshold testing |
| Chang et al. (21) | Fundus photographs | Carotid artery atherosclerosis | CNN | Health Promotion Center, Seoul National University Hospital, South Korea | Retrospective | 1,520 images | Random split | No | Expert consensus (ultrasonography) |
| Chen et al. (22) | Images of palpebral conjunctiva | Hemoglobin (anemia) | SVM | Saint Mary's Hospital, Luodong, Taiwan | Retrospective | 50 images | 10-fold cross validation | No | Biochemical testing |
| Chen et al. (23) | OCT | Hemoglobin (anemia) | Linear discriminant analysis classifier | Second Xiangya Hospital of Central South University, China | Retrospective | 571 scans | Leave-one-out cross validation | No | Biochemical testing |

(Continued)
| References          | Imaging modality | Predicted parameter | Model   | Test datasets | Recruitment | Test set size | Type of internal validation | External validation (Yes/No) | Reference standard                                      |
|---------------------|------------------|---------------------|---------|---------------|-------------|---------------|-----------------------------|-------------------------------|---------------------------------------------------------|
| Cheung et al. (24)  | Fundus photographs| Retinal vessel caliber | CNN     | SEED          | Prospective  | 1,060 images  | Random Split                | 10 external datasets—5,636 images | Expert graders                                                      |
| Dai et al. (25)     | Fundus photographs| Hypertension        | CNN     | He Eye Specialists Hospitals, Liaoning, China | Retrospective | 2,012 images  | 5-fold cross validation     | No                           | Clinical measurement                                    |
| Garcia-Martin et al. (26) | OCT     | Multiple sclerosis  | CNN     | Miguel Servet University Hospital, Spain | Prospective | 768 scans     | 10-fold cross validation    | No                           | Expert consensus (clinical diagnosis)                |
| Gerrits et al. (47)* | Fundus photographs| Age, Gender         | MobileNet-V2 | Qatar Biobank | Prospective | 2,400 images  | Random split                | No                           | Biochemical testing, Clinical measurement, Patient questionnaire |
| Jain et al. (27)    | Images of palpebral conjunctiva | Hemoglobin (anemia) | SVM CNN | Maulana Azad National Institute of Technology, Bhopal, India | Retrospective with artificial augmentation | 601 augmented images | Random split                | No                           | Not reported                                           |
| Kang et al. (28)    | Fundus photographs| eGFR                | VGG-19  | Chang Gung Memorial Hospital, Taoyuan, Taiwan | Retrospective | 2,730 images  | Random split                | No                           | Biochemical testing                                    |
| Khalifa et al. (29) | External eye images | Gender              | CNN     | Al-Azhar University, Cairo, Egypt | Retrospective with artificial augmentation | 3,000 augmented images | Random split                | No                           | Demographics                                            |
| Kim et al. (30)     | Fundus photographs| Age, Gender         | ResNet-152 | SBRIA         | Retrospective | 24,366 images | Random split                | No                           | Demographics                                            |
| Korot et al. (31)   | Fundus photographs| Gender              | CNN     | UK Biobank    | Prospective  | 1,287 images  | Random split                | Moorfields Eye Hospital—252 images | Demographics                                           |
| Mitani et al. (33)  | Fundus photographs| Hemoglobin (anemia) | Inception-v4 | UK Biobank | Prospective  | 22,742 images | Random split                | No                           | Biochemical testing                                    |
| Munk et al. (34)    | Fundus photographs| Age, Gender         | CNN     | University Clinic Bern, Switzerland | Retrospective | 13,566 images | Random split                | 8,554 OCT scans                | Demographics                                            |
| Nunes et al. (35)   | OCT             | Alzheimer’s Disease  | SVM     | University of Coimbra, Portugal | Retrospective | 75 scans      | 10-fold cross validation    | No                           | Expert consensus (clinical diagnosis)                 |

(Continued)
| References | Imaging modality | Predicted parameter | Model | Test datasets | Recruitment | Test set size | Type of internal validation | External validation (Yes/No) | Reference standard |
|------------|------------------|---------------------|-------|--------------|-------------|--------------|--------------------------|-----------------------------|--------------------|
| Pérez Del Palomar et al. (62) | OCT | Multiple sclerosis | Random Forest with Adaboost | Miguel Servet University Hospital, Spain | Retrospective | 260 scans | 10-fold cross validation | No | Expert consensus (clinical diagnosis) |
| Poplin et al. (36) | Fundus photographs | Age, Gender, Smoking status, Systolic BP, Diastolic BP, HbA1c, BMI, Major adverse cardiovascular events | Inception-v3 | UK Biobank EyePACS | Prospective | UK Biobank 24,008 images EyePACS 1,958 images | Random split | No | Biochemical testing, Clinical measurement, Patient questionnaire |
| Rim et al. (39) | Fundus photographs | Age, Gender, Body muscle mass, Height, Weight, Creatinine, Diastolic BP, Systolic BP, Hematocrit, Hemoglobin, RBC Count | VGG-16 | Severance Main Hospital, Seoul, South Korea | Retrospective and prospective datasets | 21,698 images | Random split | Severance Gangnam Hospital—9,324 images Beijing Eye Study—4,324 images SEED—63,275 images UK Biobank—50,732 images | Biochemical testing, Clinical measurement |
| Rim et al. (37) | Fundus photographs | Coronary artery calcification, RetiCAC | EfficientNet | Severance Main Hospital, Seoul, South Korea | Retrospective and prospective datasets | 8,930 images | Random split | Philip Medical Center, South Korea—18,920 images CMERC-HI, South Korea—1,054 images | Expert graders (cardiac CT) |
| Sabanayagam et al. (39) | Fundus photographs | Chronic kidney disease | cCondenseNet | SEED | Prospective | 2,594 images | Random split | SP2—7,470 images Beijing eye study—3,076 images | Biochemical testing |
| Samant and Agarwal (40) | Infrared iris images | Diabetes | Random forest | Thapar University Patiala, India | Retrospective | 338 images | 10-fold cross validation | No | Biochemical testing |
| Son et al. (41) | Fundus photographs | Coronary artery calcification | Inception-v3 | Seoul National University Bundang Hospital, South Korea | Retrospective | 44,184 images | 5-fold cross validation | No | Expert graders (cardiac CT) |
| Tian et al. (42) | Fundus photographs | Alzheimer's disease | SVM | UK Biobank | Prospective | 122 images | 5-fold cross validation | No | Expert consensus (clinical diagnosis) |
| Vaghefi et al. (43) | Fundus photographs | Smoking status | CNN | Auckland Diabetic Eye Screening Database, New Zealand | Prospective | 33,020 images | Random split | No | Patient questionnaire |

(Continued)
**TABLE 1 | Continued**

| References | Imaging modality | Predicted parameter | Model | Test datasets | Recruitment | Test set size | Type of internal validation | External validation (Yes/No) | Reference standard |
|------------|------------------|---------------------|-------|---------------|-------------|---------------|-----------------------------|-------------------------------|-------------------|
| Xiao et al. (44) | External eye (slit lamp) images fundus photographs | Hepatobiliary diseases Liver cancer Liver cirrhosis Chronic viral hepatitis NAFLD Cholelithiasis Hepatic cyst | ResNet-101 | Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China Huanishidong Medical Center of Akang Health Care, Guangzhou, China | Prospective | 1,069 slit lamp images 800 fundus images | Random split | No | Expert consensus Biochemical testing Hepatobiliary ultrasound/CT/MRI |
| Yamashita et al. (45) | Fundus photographs | Gender | Logistic regression | Kagoshima University Hospital, Japan | Prospective | 112 images | Leave-one-out cross validation | No | Demographics |
| Zhang et al. (46) | Fundus photographs | Hypertension FPG, TG Age, Gender Alcohol status Smoking status BMI, Waist-Hip ratio hematocrit Total bilirubin Direct bilirubin | Inception-v3 | Rural villages in Xinxiang County, Henan, China | Prospective | 122 images | Random Split | No | Biochemical testing Clinical measurement Patient questionnaire |
| Zhang et al. (63) | Fundus photographs | Chronic kidney disease Type 2 diabetes | ResNet-50 | CC-FII Tangshan City, Hebei Province, China | Prospective | 17,454 images | Random Split | Guangdong Province—16,118 images COACS—6,162 images | Biochemical testing |

BMI, body mass index; BP, blood pressure; BPPV, Benign Paroxysmal Positional Vertigo; CA, California; CAC, coronary artery calcium; CC-FII, China Consortium of Fundus Image Investigation; CMERC-Hi, Cardiovascular and Metabolic Disease Etiology Research Center-High Risk; CNN, convolutional neural network; COACS, China suboptimal health cohort study; CT, computed tomography; EyePACS, Eye Picture Archive Communication System; FPG, fasting plasma glucose; HbA1c, Hemoglobin A1C; HCT, hematocrit; MRI, magnetic resonance imaging; NAFLD, non-alcoholic fatty liver disease; OCT, optical coherence tomography; OCT-A, optical coherence tomography angiography; RBC, red blood cell; RetiCAC, deep-learning retinal coronary artery calcium; SBIRA, Seoul National University Bundang Hospital Retinal Image Archive; SEED, Singapore Epidemiology of Eye Diseases; SNDREAMS, Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetics Study; SP2, Singapore Prospective Study Program; SVM, support vector machine; TG, triglyceride; VGG, Visual Geometry Group.

1 Gerrits et al. (47) reported results on 17 cardiometabolic risk factors. Only 9 parameters deemed “predictable” are shown.
2 Mitani et al. (33) reported prediction results of 31 complete blood count components, detailed results can be found in their [Supplementary Material](#).
3 Rim et al. (38) reported results on 47 systemic biomarkers. Only 10 parameters deemed “predictable” are shown.
4 RetiCAC score defined as the probability of the presence of CAC based on retinal fundus photographs.
fundus index, retinal vessel angles and retinal artery trajectory. This was the only study utilizing logistic regression models for gender, and it achieved an area under the receiver operating curve (AUC) of 0.78. Other studies in this section used DL and neural network architectures. Some derived very robust predictive results for gender (AUC: 0.93–0.97) (30, 31, 36, 38, 47), while others had lower performances (AUC: 0.70–0.80) (34, 46). The reasons for this disparity could include the field of view of the RFP dataset, and whether they were derived from healthy or diseased patient populations. Gerrits et al. (47) performed similar analysis of age and gender in a Qatari dataset and suspected that their algorithm could be indirectly predicting age or gender during their performance on other intended biomarkers. For example, substantial differences in model performance were found between females and males for relative fat mass and testosterone. However, the performance of gender prediction in age-stratified subgroups, and vice-versa, were similar, suggesting that the features used during age and gender prediction are largely independent (47). In analysis of activation maps, Munk et al. (34) and Poplin et al. (36) reported that the optic disc, macula, peripapillary area, and larger blood vessels within the posterior pole seem crucial for gender and age prediction. Non-random sex prediction using RFP seems only possible if the fovea and optic disc were visible (34). Korot et al. (31) experimented with a code-free model to predict gender (AUC: 0.93). The Google Cloud automated machine learning (AutoML) platform was used to provide a graphical user interface (GUI), allowing physicians with no coding background to craft ML models for medical image analysis. This suggests that a code-free framework could be comparable to state-of-the-art algorithms designed for similar tasks by coders. Nevertheless, we note that using AI to predict age and gender inherently has poor clinical utility; however, these were two of the earliest parameters to be predicted from RFPs by neural networks as they are unambiguous, and easily available as data.

**Predicting Smoking and Alcohol Status From RFP**

Regarding smoking and alcohol status, current models describe notable prediction performance (36, 43, 46, 47). AUC of smoking status ranged from 0.71 to 0.86. Only one study by Zhang et al. (46) predicted alcohol status (AUC: 0.95). “Alcohol status” was defined as “current alcohol drinkers of >12 times in the past year” (46). One must note that the “ground-truths” for these parameters are self-reported from patients via questionnaires. Hence, model performance would be limited by information bias and patients’ truthfulness when stating their smoking frequency and alcohol intake.

**Predicting Body Composition Factors From RFP**

Body composition factors predicted from RFP include body mass index (BMI), body muscle mass, height, weight, relative fat mass, and waist-hip ratio (WHR) (36, 38, 46, 47). Performance of current algorithms in BMI prediction is generally poor with low $R^2$-values ($R^2$: 0.13–0.17). Model generalizability across ethnically distinct datasets was poor as well. Rim et al. (38) found that DL algorithms for prediction of height, body weight, BMI (and other non-body composition factors), trained on a South Korean dataset, showed limited generalizability in the UK Biobank dataset (majority White ethnicity) ($R^2 \leq 0.08$). Proportional bias was observed, where predicted values in the lower range were overestimated and those in the higher range were underestimated. While BMI is a parameter of interest due to its well-established associations with all-cause (65) and cause-specific mortality (66), prediction of other plausible parameters of body composition have been described. The prediction of body muscle mass is noteworthy, as it is a potentially more reliable biomarker than BMI for cardiometabolic risk and nutritional status (38). Rim et al. (38) reported that body muscle mass could be predicted with an $R^2$ of 0.52 (95% CI: 0.51–0.53) in
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FIGURE 2

Example heatmaps overlaid on retinal fundus photographs highlighting areas of interest. These examples were derived from the authors’ research database. (A) Original photograph with no overlay; (B) red blood cell count; (C) systolic blood pressure; (D) weight; (E) age; (F) body mass index; (G) creatinine; (H) diastolic blood pressure; (I) hemoglobin; (J) height.

the internal test set, and 0.33 (0.30–0.35) in one external test set with muscle mass measurement available (Severance Gangnam Hospital). If future DL algorithms exhibit improved prediction results and generalizability, this could have clinical utility in screening for sarcopenia. Zhang et al. achieved an AUC of 0.70 in predicting WHR, which has been described in association with diabetes and cardiovascular complications (67, 68). While the prediction results seem more promising than BMI, this needs more validation.

Predicting Cardiovascular Disease and Parameters From RFP

Cardiovascular parameters predicted from RFP include systolic and diastolic blood pressure (BP), hypertension, retinal vessel caliber, coronary artery calcium (CAC) and carotid artery atherosclerosis (21, 24, 36–38, 41, 46, 47, 69). RFP are thought to be robust input images for predicting cardiovascular disease, as they can directly capture many retinal features associated with increased cardiovascular risk, including vessel caliber, tortuosity, and bifurcations (70, 71). CAC is a pre-clinical marker of atherosclerosis, derived from cardiac CT measurements (72). Based on the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) consensus (73), compared to patients with CAC score of zero, a CAC score of 100–400 had a relative risk (RR) of 4.3 (95% CI 3.1–6.1) for major cardiovascular events. CAC scores of 401–999 had RR of 7.2 (95% CI 5.2–9.9), and CAC score of 1,000 had RR of 10.8 (95% CI 4.2–27.7) (73). Son et al. (41) predicted abnormal CAC scores at various thresholds, producing an AUC of 0.832 when the threshold was set at >100 units. Furthermore, Rim et al. (37) derived a deep learning-based CAC score predicted from RFP (RetiCAC) and used this new RetiCAC score for cardiovascular risk stratification. Based on RetiCAC, a new three-tier cardiovascular disease risk stratification system was proposed, which showed comparable performance to cardiac CT scans (the current clinical imaging method of choice) in predicting future CVD events (37). Therefore, this study suggests that RFP could be adopted as a more cost-effective method than cardiac CT, as a non-radiation-based imaging modality for cardiovascular risk stratification in low-resource settings. Cheung et al. (24) developed a DL to automatically measure retinal vessel calibers from RFP. They showed high agreement between human and DL measurements and quantified the correlations between specific retinal vessel features and CVD risk factors. Poplin et al. (36) constructed models to predict future onset of major adverse cardiovascular events within 5 years. The AUC of 0.70 using RFPs was comparable to the AUC of 0.72 using the composite European Systematic Coronary Risk Evaluation (74) (SCORE). It was acknowledged that hybrid models where fundus photography was augmented with clinical parameters were able to yield slightly better predictions (36). With regards to BP, predictions from fundus photographs have been suggested to be more reflective of accumulated damage over time (75), resembling how HbA1c levels are reflective of blood glucose levels over months. However, model performance for systolic and diastolic BP prediction in current literature was relatively poor, with R²-values ranging from 0.16 to 0.40.
Predicting Hematological Parameters From RFP
Hematological parameters predicted from RFP include anemia, hemoglobin concentration, red blood cell (RBC) count and hematocrit (33, 38, 46). Ophthalmic imaging-based DL algorithms have been used to predict cut-off points of hematological parameters (as a classification task). For instance, Mitani et al. (33) predicted anemia categories and Zhang et al. (46) predicted hematocrit ranges from fundus photographs with AUC > 0.75. There were also attempts to predict continuous parameters, such as RBC count (33), hemoglobin (38), and hematocrit (33, 38) from fundus photographs were poorer (RBC count: $R^2 0.14–0.35$; hemoglobin: $R^2 0.06–0.56$; hematocrit: $R^2 0.09–0.57$). Mitani et al. (33) further studied the importance of different anatomical features to anemia by blurring and cropping the RFPs during both training and validation. Notably, when the upper and lower hemispheres of the images were progressively masked, performance declined only after ~80% of the image was covered. Masking using a central horizontal stripe (covering the disc and macula) caused a drop in AUC when only 10% of the image was masked. The models performed better than chance even after high-resolution information was removed with substantial Gaussian blurs, and after image pixels were randomly scrambled, suggesting that the models could make use of the general pallor of the retina to predict anemia.

Predicting Neurodegenerative Disease From RFP
Most studies in current literature that predicted neurodegenerative disease used OCT-based models. These will be elaborated on in sections below. One study by Tian et al. (42) used RFP to predict Alzheimer’s Disease, producing promising results (Accuracy: 0.82, Sensitivity: 0.79, Specificity: 0.85). Saliency maps showed that small retinal vessel morphology was critical to the classification decision, more so than large vessels, which aligns with previous investigations on the constriction of small cerebral arterioles in the pathogenesis of neurovascular dysfunction in Alzheimer’s Disease (76). Tian et al. (42) further described their automated, multi-stage ML pipeline used to construct the RFP-based model, demonstrating the preliminary potential of retinal vasculature analysis using ML for Alzheimer’s Disease screening. It comprised of an image quality selector and excluder, U-net based vessel map generator, and a support vector machine (SVM) classifier (42).

Predicting Metabolic Disease and Parameters From RFP
Metabolic disease states/biomarkers predicted from RFP include diabetes, diabetic peripheral neuropathy, fasting plasma glucose (FPG), HbA1c, triglycerides and testosterone (19, 36, 46, 47, 61). Testosterone levels were predictable from RFP, but Gerrits et al. (47) learnt in further analysis that the model indirectly predicted gender. Model performance decreased when trained solely on male and female subgroups, implying that structural features on RFP that are important for gender prediction are used in estimating testosterone. Given the rise of teleophthalmology-based screening systems for diabetic retinopathy (DR) (77), and pre-existing associations of diabetic peripheral neuropathy with retinal vascular features (78, 79), Benson et al. (19) proposed leveraging RFP from annual DR screenings to assess for diabetic peripheral neuropathy as well. The workflow consisted of partitioning RFP images into 50 × 50 patches, using a neural network to extract features from individual patches, applying dimensionality reduction and combining them for use in an SVM classifier. By partitioning RFP images, the risk of diluting small, focal structural features throughout the retina was removed. This system produced promising results (Accuracy: 0.89, Sensitivity: 0.79, Specificity: 0.85) (19), although external validation and trials in clinical implementation are required. Additionally, Cervera et al. (61) trained a neural network to detect diabetic neuropathy from RFPs. AUC to predict DN on the whole cohort was 0.801 on the validation set and 0.710 on the external test set. The AUC increased to 0.8673 in the subgroup of patients with DR.

Prediction Renal Disease and Parameters From RFP
Renal parameters predicted by RFP include chronic kidney disease (CKD), estimated glomerular filtration rate (eGFR) and serum creatinine. In predicting CKD, the RFP-based model by Sabanayagam et al. (39) showed good performance in internal testing (AUC: 0.91), and external testing (AUC of 0.73–0.84). They additionally constructed models with CKD risk factors (age, sex, ethnicity, diabetes, hypertension status) as inputs, and a hybrid model with both RFP and risk factors, demonstrating that RFP images and risk factor information have similar predictive powers, when used as inputs for CKD risk assessment. In addition, performance of the RFP-only model in subgroups of patients with diabetes and hypertension was comparable to the entire cohort, supporting the clinical utility of RFP and DL as an alternative CKD screening tool. This study was followed by another paper by Zhang et al. (63), who constructed DL models to identify CKD and type 2 diabetes solely from fundus images or in combination with clinical metadata (age, sex, height, weight, BMI and blood pressure) with AUCs of 0.85–0.93. Using 6-year longitudinal data, individual images at baseline were stratified into low, medium, and high-risk groups on Kaplan–Meier curves for developing future CKD or T2DM. DL models were able to significantly distinguish between these groups ($p < 0.001$). Such time-to-critical-event modes based on longitudinal cohorts could provide great utility in managing patients during their early disease course. Prior to these two studies, only one DL algorithm based on kidney ultrasonography was described for CKD screening by Kuo et al. (80) (AUC: 0.90, Sensitivity: 0.61, Specificity: 0.92). This lacked external validation (80). Kang et al. (28) sought to predict early renal impairment from RFP, defined as eGFR < 90 ml/min/1.73 m$^2$, but observed poor specificity. They noted false positives arising from RFP with retinal scarring, subretinal fluid, or optic disc swelling. Hence, clinical utility might be limited as many concomitant ophthalmic pathologies can cause such retinal structural manifestations.
Features used to identify CKD or predict eGFR are unclear—saliency maps (28, 39) have highlighted changes in retinal vasculature (dilatation of venules, rarefaction of vessels) and abnormal lesions characteristic of retinopathy (hemorrhages and exudations). A model by Rim et al. (38) showed moderate performance in predicting creatinine levels ($R^2: 0.38$) when trained and tested on a South Korean dataset but was unable to generalize to a European dataset (UK Biobank, $R^2: 0.01$). Predictive performance of creatinine was similarly poor in White and non-White groups.

Predicting Hepatobiliary Disease and Parameters From RFP
Hepatobiliary disease and biomarkers predicted by existing studies include total and direct bilirubin levels, liver cancer, cirrhosis, chronic viral hepatitis, non-alcoholic fatty liver disease (NAFLD), cholelithiasis, and hepatic cysts (44, 46). Rim et al. (38) had earlier tried unsuccessfully to predict alanine aminotransferase (ALT) and aspartate aminotransferase (AST) from RFP as continuous variables ($R^2 \leq 0.10$). While Xiao et al. (44) achieved moderate to good predictive performance in various hepatobiliary pathologies (AUC ranging from 0.62 for chronic viral hepatitis to 0.84 for liver cancer), the retinal structural changes that result from hepatobiliary dysfunction remain undescribed in current literature. Xiao et al. (44) speculated that imperceptible retinal changes may be attributable to hyperammonemia, hypoalbuminemia, and decreased estrogen inactivation. Elevated portal venous pressure secondary to cirrhosis or splenomegaly can remodel retinal vascular beds (81), while anemia secondary to splenic sequestration can be detected on fundus photography. This would be a topic of interest in future research.

Implications and Clinical Utility
Prediction of systemic disease from RFPs is a hotly studied topic, and seems like the logical next step, given robust existing algorithms for predicting ocular diseases (for instance, diabetic retinopathy, age-related macular degeneration, and glaucoma) from RFPs (82). Prediction of certain outcomes, such as age, gender, weight, and BMI, may not be particularly meaningful, given the ease of determination or measurement of these outcomes without a complex computer algorithm. For more novel outcomes, such as Alzheimer’s Disease, CKD, atherosclerosis, and CAC, crafting algorithms to predict incidence of these conditions, rather than prevalence, might serve more clinical utility for early intervention. However, in reality, robust incidence data is more logistically difficult to acquire than prevalence data. Next, the introduction of smartphone-based fundus imaging in recent years presents a low-cost alternative to conventional RFP (83). There are several advantages of smartphone-based imaging, including portability, built-in connectivity and processing, and minimal need for training. This could make it suitable for telemedicine or primary screening purposes, particularly in lower income settings where tertiary care may not be easily accessible. However, smartphone fundus image quality varies considerably, and there is a need for inter-device comparison, leading researchers to consider a necessary reference standard for grading (83).

OPTICAL COHERENCE TOMOGRAPHY
OCT is a non-invasive diagnostic technique that provides high resolution in vivo cross-sectional images of retinal and choroidal structures. As OCT is a safe, fast, and non-invasive imaging modality with wide applicability in eye clinics, this technology has produced large volumes of clinical images (secondary only to RFP), making it a suitable candidate for training AI models. Kapoor et al. (84) has previously reviewed the applications of AI and OCT in ophthalmology, including the detection of macular edema (85), age-related macular degeneration (86), and glaucoma (87, 88). OCT-A is an advancement of OCT technology, based on the variable backscattering of light of moving red blood cells. This motion-contrast imaging accurately depicts retinal vessels through different segmented areas of the eye, eliminating the need for intravascular dyes (89).

Unlike RFP-based AI models, the systemic applications of AI and OCT or OCT-A are more limited in current literature (Table 2). Only one study by Aslam et al. (18) predicted diabetic status with OCT-A using various supervised ML architectures, reporting an AUC of 0.80 on the best performing, random forest model. However, the model was troubled by low specificity rates. OCT-A based outcome measures that were used to predict diabetes included ischemic areas around the fovea avascular zone (FAZ), FAZ circularity, mean capillary intensity and mean vessel intensity (18). Readers should be aware that using such OCT-A derived metrics as inputs, compared to the OCT-A image itself, is a fairly different task compared to using RFPs as inputs.

OCT models were largely used to predict neurodegenerative diseases, including multiple sclerosis (MS), Alzheimer’s Disease and Parkinson’s Disease (PD) (20, 35, 62). We observed that the models in this section were shallow learning algorithms—support vector machine (SVM) and random forest—as opposed to neural networks. Clinical studies have shown robust differences between the retinas of people with MS and healthy controls in the peripapillary RNFL, and macular ganglion cell layer—inner plexiform layer (90). Cavaliere et al. (20) and Pérez Del Palomar et al. (62) designed models around these thickness metrics (not the actual OCT images), predicting MS with an area under the receiver operating curve (AUC) of 0.97 and 0.99, respectively. They reported different methodologies of segmenting the retina to elucidate an optimal area of interest—Cavaliere et al. (20) divided the retina by TSNIT (temporal, superior, nasal, inferior, temporal) sectors and the Early Treatment of Diabetic Retinopathy Study (ETDRS) grid, while Pérez Del Palomar et al. (62) compared macular, peripapillary and wide protocols. Furthermore, using neural networks to analyze OCT scans, Garcia-Martín et al. (26) achieved an AUC of 0.95 in predicting MS. The diagnosis of MS is typically clinical, based on neurological symptoms and signs, alongside evidence of disseminated CNS lesions in space and time (91). The promising results of these studies suggest that OCT scans incorporated with AI analytics could have some utility as a screening adjunct.
| Imaging modality          | Predicted parameter | AUC 95% CI | Sensitivity 95% CI | Specificity 95% CI | Accuracy | Study | Dataset | Internal/External validation? |
|--------------------------|---------------------|------------|---------------------|--------------------|----------|-------|---------|-------------------------------|
| OCT                      | Alzheimer's disease | 0.80       | 0.84                | 0.93               | 0.82     | (35)  | University of Coimbra, Portugal | Internal                        |
| OCT                      | Parkinson's disease | 0.78       | 0.82                | 0.98               | 0.82     | (35)  | University of Coimbra, Portugal | Internal                        |
| OCT                      | Anemia*             | 0.82       | 0.82                | 0.82               | 0.84     | (23)  | Second Xiangya Hospital, China | Internal                        |
| OCT                      | Multiple sclerosis  | 0.97       | 0.90                | 0.97               | 0.91     | (20)  | Miguel Servet University Hospital, Spain | Internal                        |
| OCT                      | Multiple sclerosis  | 0.96       | 0.88–0.99           | 0.91               | 0.91     | (26)  | Miguel Servet University Hospital, Spain | Internal                        |
| OCT                      | Multiple sclerosis  | 0.99       | 0.91                | 0.91               | 0.91     | (62)  | Miguel Servet University Hospital, Spain | Internal                        |
| OCT B scans              | Gender              | 0.84       | 0.82                | 0.82               | 0.84     | (34)  | University Clinic Bern, Switzerland | Internal                        |
| OCT C scans              | Gender              | 0.90       | 0.90                | 0.90               | 0.90     | (34)  | University Clinic Bern, Switzerland | Internal                        |
| External eye images      | Diabetic status     | 0.80       | 0.73–0.87           | 0.49               | 0.84     | (34)  | University Clinic Bern, Switzerland | Internal                        |
| Palpebral conjunctiva    | Anemia < 11 g/dL    | 0.78       | 0.72                | 0.76               | 0.75     | (22)  | Saint Mary's Hospital Luodong, Taiwan | Internal                        |
| Palpebral conjunctiva    | Anemia < 11 g/dL    | 0.78       | 0.73                | 0.74               | 0.77     | (22)  | Saint Mary's Hospital Luodong, Taiwan | Internal                        |
| Slit lamp images         | Cholelithiasis      | 0.58       | 0.55–0.61           | 0.50               | 0.56     | (40)  | Thapar University Patiala, India | Internal                        |
| Slit lamp images         | Chronic viral hepatitis | 0.66   | 0.62–0.71           | 0.65               | 0.70     | (27)  | Bhopal, India | Internal                        |
| Slit lamp images         | Hepatic cyst        | 0.66       | 0.60–0.71           | 0.63               | 0.67     | (44)  | Third Affiliated Hospital of Sun Yat-Sen University | Internal                        |
| Slit lamp images         | Hepatobiliary diseases | 0.74   | 0.60–0.71           | 0.63               | 0.67     | (44)  | Third Affiliated Hospital of Sun Yat-Sen University | Internal                        |
| Slit lamp images         | Liver cancer        | 0.93       | 0.91–0.94           | 0.89               | 0.91     | (44)  | Third Affiliated Hospital of Sun Yat-Sen University | Internal                        |
| Slit lamp images         | Liver cirrhosis     | 0.90       | 0.88–0.91           | 0.89               | 0.92     | (44)  | Third Affiliated Hospital of Sun Yat-Sen University | Internal                        |
| Slit lamp images         | NAFLD               | 0.63       | 0.60–0.66           | 0.69               | 0.64     | (44)  | Third Affiliated Hospital of Sun Yat-Sen University | Internal                        |

AUC, area under the receiver operating curve; CI, confidence interval; HbA1c, Hemoglobin A1c; NAFLD, non-alcoholic fatty liver disease; OCT, optical coherence tomography; OCT-A, optical coherence tomography angiography.

*Chen et al. (23) and Jain et al. (27) did not describe how anemia was defined.
†Chen et al. (22) constructed a SVM model and CNN model. This row represents the SVM.
‡Chen et al. (22) constructed a SVM model and CNN model. This row represents the CNN.

None of the studies in this table reported $R^2$-values as a performance metric, or 95% CI for Accuracy.
Nevertheless, we note that MS is an idiopathic, heterogenous disease, making it difficult to generalize the predictive results of an OCT AI model from one population to another. Nunes et al. (35) achieved notable results in predicting and distinguishing between patients with Alzheimer’s Disease or Parkinson’s Disease from OCT images. However, extensive preprocessing required in their research workflow meant that the final OCT data used to train the model differed greatly from the raw data typically obtained in clinical settings. For instance, they used retinal layer thickness measurements to compute multivariable texture data. While this improved the discrimination power of the model, it reduces the likelihood that such models can be translated into clinical use.

Thanks to an abundance of OCT scans in modern tertiary eye centers, AI-based analysis of OCT images has expanded to improve patient screening and facilitate clinical decision-making. Given that OCT parameters have reported retinal and choroidal layers, a further step for future research could be exploring the utility of such parameters via machine learning techniques (for instance, choroidal thickness, choroidal vascularity index, retinal nerve fiber layer thickness) relative to deep learning techniques, where the algorithms are fed whole images. Regarding future trends, most current published studies in AI and OCT imaging focus on the posterior segment of the eye, but recent studies have started to explore its use in the anterior segment as well (84).

EXTERNAL EYE IMAGING

Photographs of the external eye, often either captured with cameras mounted on slit lamps, are often used to document anterior segment disease in ophthalmology. Systemically, AI studies in current literature have reported the use of such images to predict gender, HbA1c levels, diabetic status, anemia, and various liver pathological states (Table 2) (22, 27, 29, 40, 44, 59). As described in earlier sections, Xiao et al. (44) constructed two sets of models (slit lamp based and RFP based) to predict hepatobiliary disease states—model performances on slit lamp images was better than RFP in liver cancer, cirrhosis, and chronic viral hepatitis. Excessive bilirubin accumulation causing yellowing of the sclera and conjunctiva is a common presentation in compromised liver function. These robust manifestations, detectable on external eye images, could explain the difference in performance. Visualization techniques showed that in addition to the conjunctiva and sclera, iris morphology and color contained important predictive features (44), suggesting the presence of iris morphological changes secondary to liver damage that have yet to be elucidated.

Babenko et al. (59) predicted HbA1c at various cut-offs of 7, 8, and 9% using external eye images from EyePACS, a teleretinal screening service in the United States (92). Low resolution images of 75 x 75 pixels (0.1% of the resolution of an 8-megapixel smartphone camera) as inputs achieved moderate model performances of AUC 0.64–0.74. Ablation analysis and saliency maps indicated that information from the center of the image (pupil/lens, iris, cornea, limbus) was most related to HbA1c (59). Uses for such a screening system are manifold. Thresholds of HbA1c > 9% could highlight diabetic patients with difficulties controlling blood glucose levels, and in need closer follow-up or medication changes; thresholds of HbA1c > 7% could identify asymptomatic patients at risk for early or mild diabetes, allowing referral for a confirmatory blood test. Regarding anemia, while phlebotomy remains the gold standard of diagnosis, physical examination of the palpebral conjunctiva is a quick and arbitrary clinical assessment method. Chen et al. (22) managed to predict hemoglobin levels of < 11 g/dL from external eye images of the palpebral conjunctiva. However, dataset size was small (50 images). The model thus requires more input data, and validation on external datasets.

Looking beyond diabetes, liver diseases and anemia, the findings of the above studies raise the interesting possibility that external eye images could contain useful signals, both familiar and novel, related to other systemic conditions. For example, hyperlipidemia and atherosclerosis can manifest with xanthelasma (93). Thyroid eye disease can manifest with chemosis, conjunctival injection, lid retraction and lower scleral show (94). Obstructive sleep apnea is associated with floppy eyelid syndrome (95). Neurofibromatosis Type 1 manifests with melanocytic hamartomata of the iris (Lisch nodules) (96). Myasthenia Gravis can present with ptosis and ocular dysmotility (97). Dry eyes, conjunctival injection, and uveitis are all possible manifestations of systemic lupus erythematosus (98), while corneal deposits of uric acid have been reported in hyperuricemia and gout (99). Such manifestations could be readily captured on external eye photography for systemic disease prediction models. While these suggested diseases are relatively common, the practicality of such models would depend on the rarity of the associated eye signs, the fact that laboratory screening tests are much more commonplace, and whether such theoretical models can be built in the first place.

CURRENT LIMITATIONS, DIFFICULTIES, AND AREAS OF FUTURE RESEARCH

Areas of Potential Improvement

We have noted several limitations of existing work and areas with untapped potential. Firstly, many current studies lack external validation (Table 1), which is critical for establishing robust and generalized AI models. Sole internal validation cannot support firm conclusions regarding the algorithms’ value for disease screening in new populations. The ability of predictive models to generalize across various ethnic and geographical datasets is not a guarantee, or a simple task to achieve, but will add greatly to the clinical utility of the constructed AI system. Second, the field of ophthalmic imaging has unrealized potential in predicting additional systemic parameters. Several studies attempted predictions of other markers in addition to those reported, albeit with varying (and often poorer) results (38, 46, 47). For instance, Rim et al. (38) performed analysis on 47 biomarkers in total, although only 10 were eventually deemed “predictable.” The
fields of predicting hepatobiliary and neurodegenerative disease from ophthalmic imaging are particularly nascent. The models described by Xiao et al. (44) in 2021 was the first to establish qualitative associations between ocular features, liver cancer and cirrhosis, and future studies are needed to reaffirm their findings. Much of the ongoing work bridging neurodegenerative disease and retinal imaging involves OCT, although vascular features on RFP have shown meaningful associations with cognitive decline (75). Third, OCT-based algorithms to predict renal disease have not been explored in current literature. OCT, unlike RFP, allows imaging of the choroidal vasculature, and choroidal thinning has been associated with lower eGFR and higher microalbuminuria independent of age and other vascular risk factors (100, 101). Whether these OCT-based metrics reflect renal microvascular damage better than standard creatinine/eGFR/albumin-creatinine-ratio measurements could be tested in future studies, although we expect that this is unlikely, and it would be difficult to conduct such a comparative study. Fourth, given the widespread availability of OCT, slit-lamp imaging and RFP in ophthalmic clinical practice, AI systems built on two or more different ophthalmic imaging methods would provide alternatives and improve adaptability. Fifth, there is good potential for AI systems built on ophthalmic imaging in community screening programs or primary care settings. In principle, addition of various predicting models for systemic biomarkers to current teleophthalmology software could enable low-cost, non-invasive screening for multiple diseases in the general population. Aside from clinical validation, economic viability and cost-effectiveness would have to be evaluated as well. Sixth, most studies predicting systemic parameters from ophthalmic imaging are estimating current or prevalent disease. To predict incidence of these conditions, rather than prevalence, might serve more clinical utility; much potential utility of AI systems would be unlocked if they were able to detect disease where standard clinical examinations or laboratory tests fail to do so. Seventh, studies evaluating the ability of AI ophthalmic imaging algorithms to detect longitudinal changes in systemic disease, or to stage systemic disease severity, are currently lacking. This could be an area of future interest.

Challenges in Research

There are several challenges to be appreciated as AI becomes more integral to medical practice. Firstly, using ophthalmic imaging to predict systemic disease would require collaborative efforts across departments. This might pose difficulties as systemic parameters are not always required for management in ophthalmic clinics, and vice versa. Hence, input images and target variables may need to be collected separately and deliberately (102). Secondly, barriers of access to ophthalmic imaging datasets can be reduced—including issues of cost, time, usability, and quality (56). Third, labeling processes for publicly available datasets are often poorly defined; assurance of labeling accuracy is paramount because the standards used for labeling of ground truths have implications on any AI model trained on the dataset. Fourth, it may sometimes be necessary to acquire datasets from different local and international centers for training or external validation purposes. State privacy and data regulatory rules need to be respected, the process of which is time consuming and cost-incurring. Fifth, most of the datasets used for developing or testing DL models are based on retrospective datasets. Further validation using well-characterized prospective datasets would be needed to assess clinical utility.

Challenges in Real-World Applications

Regarding real-world applications, high-quality ophthalmic images may be difficult to acquire in patients with small pupils. Such patients may require pupil dilation with topical pharmaceuticals, increasing collection time per image. Databases to save and transfer high quality images are needed. Also, the potential for bias or error must be respected. Algorithmic outcomes reflect the data used to train them; they can only be as reliable (but also as neutral) as the data they are based on (103). Projection of biases inherent in the training sets by AI systems is a concern for medical ethics (104), and ensuring generalizability across different geographical and ethnic groups is essential to avoid inadvertent, subtle discrimination in healthcare delivery (105). Next, cost-effectiveness studies are required before real world implementation. Retinal images are currently used in diagnosis of ophthalmic pathologies. For systemic disease, however, the use of retinal images is not part of standard care. Cost effectiveness studies are needed to justify their use over or alongside current standard tests (for example, diagnosing anemia using retinal images vs. a full blood count), many of which are well-integrated into existing healthcare practice and infrastructure. Finally, DL algorithms suffer from the “black box” problem, because it is a program that discloses the input and output but gives no view of the intermediate processes. While it is common for many studies to provide overlay saliency maps for explanatory purposes, it remains unclear how the algorithms arrived at such predictions.

CONCLUSIONS

To date, RFP, OCT, and external eye imaging are the leading ocular imaging modalities for systemic AI applications. Ophthalmic AI models for predicting systemic disease is a novel field in its nascentcy, but there is great capacity for translation into wider practice in the future, if the technology is carefully designed, operated, and monitored under the supervision of clinicians. Further efforts are underway to explore other systemic risk factors and parameters that could be predicted from the ophthalmic images. If validated, these algorithms could be implemented as adjunctive screening in primary care settings. Prospective studies are needed to evaluate real-world reliability, efficacy, and cost-effectiveness, and to gain acceptance from various stakeholders. Collaborative efforts are needed to ensure the best medical technology available is incorporated into practice for the benefit of patients.

AUTHOR CONTRIBUTIONS

TR and C-YC conceived and planned the study. BB performed the literature search, organized the database, and wrote the first draft of the manuscript. BB, TR, CS, and C-YC wrote
sections of the manuscript, contributed to interpreting the results, and provided critical feedback to the manuscript. All authors contributed to the intellectual development of this paper. The final version of the paper has been seen and approved by all authors.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fdgth.2022.889445/full#supplementary-material
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**Conflict of Interest:** TR was a scientific adviser to Medi Whale Inc. TR received stocks as a part of the standard compensation package.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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