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REVIEW

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Accelerating precision ophthalmology: recent advances

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ABSTRACT

Introduction: The future of ophthalmology is precision medicine. With a growing incidence of lifestyle-associated ophthalmic disease such as diabetic retinopathy, the use of technology has the potential to overcome the burden on clinical specialists. Advances in precision medicine will help improve diagnosis and better triage those with higher clinical need to the appropriate experts, as well as providing a more tailored approach to treatment that could help transform patient management.

Areas covered: A detailed literature review was conducted using OVID Medline and PubMed databases to explore advances in precision medicine within the areas of retinal disease, glaucoma, cornea, cataracts and uveitis. Over the last three years [2019 – 2022] are explored, particularly discussing technological and genomic advances in screening, diagnosis, and management within these fields.

Expert opinion: Artificial intelligence and its subspecialty deep learning provide the most substantial ways in which diagnosis and management of ocular diseases can be further developed within the advancing field of precision medicine. Future challenges include optimal training sets for algorithms and further developing pharmacogenetics in more specialized areas.

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Precision medicine; artificial intelligence; glaucoma

1. Introduction – precision medicine, deep learning and artificial intelligence

Precision medicine involves techniques that facilitate the tailored medical treatment for patients based on their individual characteristics. Individuals can be grouped into classes based on their susceptibility to a particular disease based and response to treatment; this allows analysis of characteristics of disease [1]. It is a term that has now superseded 'personalized medicine' as it encompasses biomedical data beyond the traditional observable parameters such as symptomatology. The novel concept incorporates clinical, lifestyle, genetic data, and biomarkers under its umbrella as factors with the goal to improve patient management [2].

Precision medicine is now converging to include both digital health and data science within its ecosystem. Large datasets of bioinformatics are being formed and used in standardized methods of data analysis and aggregation involving innovative computational techniques such as machine learning (ML), natural language processing (NLP), and a subset of ML, deep learning. Application of these novel technologies are enabling physicians to analyze and observe dynamic patterns in disease facilitating cost-efficient and sustainable models of care [2]. Ophthalmology, an image-intensive specialty, provides an excellent platform for the use of a subset of precision medicine; data science and artificial intelligence (AI). Moroi et al. defined the applications of precision medicine presented as four categories [3]:

(1) Understanding disease susceptibility amongst the population that involves screening and searching for the disease.
(2) Prognosis which involves recognition of biomarkers and risk factors to predict progression.
(3) Investigation into the efficacy and response of treatment.
(4) Monitoring to enhance decision making into continuation or modification of treatment.

Whilst these parameters were defined in relation to glaucoma, they are easily applicable to a myriad of other ocular pathologies.

Within the myriad of developments in precision medicine, at the forefront and still expanding is the field of artificial intelligence. AI is a branch of computing that involves simulating intelligent behavior in computers with the ability to reduce labor-intensive processes. Machine Learning is a category within AI harnessing algorithms to recognize patterns in data without human programmer involvement. Initially, human-designed code is required to transform raw data, examples of algorithms include k-Nearest neighbor, decision trees, and Support Vector machines (SVMs). Deep learning (DL) employs representation learning whereby the algorithms learn features from data automatically, providing enough data that have been inputted. This means that the algorithms may notice more subtle and comprehensive features that may have not been curated by the human eye. Artificial neural networks involve

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Article highlights

- The future of ophthalmology is precision medicine.
- Technology has the potential to overcome the burden of disease on clinical specialists by improving diagnosis and triage of those with higher clinical need to the appropriate experts.
- Artificial intelligence and its subspecialty deep learning provide the most potential within the field of precision ophthalmology.
- Future challenges in precision ophthalmology include optimal training sets for algorithms and further developing pharmacogenetics in more specialized areas such as uveitis.

multiple layers of 'neurons'- simple algorithms that receive input, perform computations and result in an output. Convolutional neural network (CNN) is a type of deep-learning network that is applied to analyzing visual imagery. It that has been at the forefront of application providing output that sometimes surpasses that of humans for a variety of tasks. There are multiple steps involved in training a deep learning algorithm of which an initial step is to obtain a substantial training set [4,5]. Different methods of training result in modified output based on what the algorithm has learnt; applications of these within glaucoma have been observed due to its image heavy focus in both diagnosis and prognostication.

This article aims to review the latest advances in precision medicine within the fields of glaucoma, retinal disease such as diabetic eye disease and AMD (age-related macular degeneration), cornea, cataracts, and uveitis within the last three years and provide an insight into the future of precision in ophthalmology.

2. Methods

2.1. Methods of literature search

A detailed literature review was conducted to identify all potential relevant studies using OVID Medline and PubMed databases for reporting artificial intelligence in ophthalmology. The articles were searched with the search terms: 'ophthalmology' and 'precision medicine,' 'precision medicine' and 'glaucoma,' 'precision medicine,' and 'retinal diseases,' 'precision medicine' and cornea," 'precision medicine' and cataract.'

2.2. Inclusion and exclusion criteria

The primary goal of this review was to include all published articles which explored the use of precision medicine in different specialties of ophthalmology. Inclusion and exclusion criteria of the articles are as follows: a) Exposure of interest: only studies relating to use of precision medicine within different fields of ophthalmology were included. b) Language: Only studies written in English were included. c) Period of studies: only studies published within the last three years (2019–2022) were included. d) Type of publication: Review articles were excluded.

2.3. Data extraction

The titles and abstracts of all identified studies were screened. Irrelevant and duplicate papers were included. The remaining articles underwent a full-text review for compliance with requirements for inclusion and exclusion.

3. Application in glaucoma

Glaucoma is the leading worldwide cause of irreversible vision loss affecting more than 70 million people with 10% being bilaterally blind [6]. Until it is quite advanced, glaucoma is asymptomatic; thus its true prevalence may be higher than recorded. The number of affected glaucoma patients is expected to reach 111.8 million by 2040 [7]. Due to the potential impending disease burden, more aspects of disease management including diagnosis, therapy, and long-term follow-up requires modernizing as well as increased efficiency. Early and accurate diagnoses are of utmost importance; novel technologies allow earlier diagnosis as well as an increased armamentarium to manage diseases medically and surgically.

Glaucoma has been defined as a group of diseases [primary and secondary causes] characterized by a distinctive visual field (VF) defect in association with changes at the optic disc [8]. They are characterized by the retinal ganglia progressively degenerating due to multiple factors. Both primary open angle and angle closure glaucoma result in gradual retinal ganglion cell death [8]. Retinal imaging of glaucoma patients demonstrates erosion of the neuroretinal rim which clinically manifests as optic nerve head (ONH) cupping [9] and as retinal fiber layer loss.

Current management of glaucoma depends on an evaluation of the patient clinically; the degree of structural changes alongside risk factors determines the rate of progression [5]. The only modifiable risk factor that can be controlled is IOP, thus most therapies focus on lowering the IOP to limit disease progression [10]. Defining the value of each treatment modality and its effect on the IOP will provide clinicians with the means to best tailor management for the individual patient and reduce disease progression. There seems to be a clear indication for early recognition of glaucoma thus enabling prevention; parameters to measure treatment efficacy involve a target IOP which has become accepted in clinical practice, albeit not without criticism. Recent literature relates to screening, diagnosis, and monitoring of glaucoma, concentrating on the utilization of data science and artificial intelligence, and will be the focus of this section.

Identifying and monitoring structural changes in optic nerve plays an important role in glaucoma management. Raghavendra et al., developed a CNN system that was accurately able to measure the glaucomatous changes in retinal images. His system was trained on over 1400 retinal images and reached over 98% in both accuracy and positive predictive value (PPV) [11]. Another study conducted by Hemelings et al. used retinal nerve fiber layer (RNFL) analysis to detect glaucoma beyond the ONH [12]. Deep-learning models were trained to analyze regions beyond the ONH and provide explainability (decision-making transparency of a CNN) in detection of glaucoma; previously used models had provided low insight into the process of decision. Several CNNs were trained with varied amounts of image cropping analyzed to compare performance. Results demonstrated that, compared to original images, models analyzing images with an absence of the ONH were able to maintain significant performance levels with an area under the curve (AUC) of 0.88 (95% CI 0.77–0.79) compared to 0.94 (95% CI −0.92-0.96) with the ONH centered. This demonstrated that CNNs are able to detect glaucoma from fundus image regions outside of the ONH [12]. This would provide scalability to conditions that focus on areas outside of the retinal rim such as pathological myopia.

Cupping of the ONH can be assessed using VCDR as well as the vertical disc diameter (VDD). Normally, images are manually assessed, however deployment of a deep-learning models allows larger scale image analysis that may be used for epidemiological studies. In a study from 2021, a CNN trained by 70,000 photographs identified 200 loci associated with VCDR and VDD; it also recognized that within patients of Asian and African descent, the aforementioned parameters were higher versus the rest of the population [13]. Machine learning has two different approaches: Supervised vs Unsupervised. Supervised learning uses 'labeled' data set and it is used to 'train' the algorithms to learn and predict the outcome. Whereas unsupervised concept uses pure machine learning to analyze and cluster the data set [14]. An unsupervised learning model by Liu et al. verified the effectiveness of three public datasets. An adversarial learning-based model was deployed with the aim to segment the optic disc (OD) and optic cup (OC) to then predict a diagnosis. Better segmentation and classification were seen in the learning models, but there were limitations such as introduction of new unlabeled image sets requires retraining of the model [15].

Optical Coherence Tomography (OCT) is a commonly used form of imaging to evaluate the structural damage caused by glaucoma. Spectral domain OCT (SD-OCT) is a newer iteration which has a faster scanning speed and is less susceptible to eye movement artifacts [16]. Thakoor et al. utilized CNN to analyze OCT images and detect glaucoma; end-to-end deep-learning architectures utilizing pre-trained CNNs such as ResNet, Inception V3, and VGG-16 were fine-tuned to enhance robustness. They highlighted the value of combining data sets to improve interpretability of deep-learning models [17].

SD-OCT assesses the structural loss of RNFL and the macular ganglion cell-inner plexiform layer (mGCIPL) used for not only diagnosis but also for monitoring even before obvious VF change. A hybrid deep-learning model (HDLM) was developed to quantify mGCIPL thickness from retinal nerve fiber layer photographs (RNFLPs). Strong correlation and good agreement were demonstrated even with optic nerve masking when deploying the novel model. The trained algorithm showed great capability for mGCIPL thickness prediction with a correlation coefficient $r = 0.739$; $p < 0.001$ and an AUC of 0.918 95% CI (0.898–0.939) [18]. Wang et al. deployed an unsupervised AI model to determine RNFLT patterns and zones within the visual field. The patterns significantly improved the prediction of sensitivities within the visual field mapping. The study provided an alternative way to quantify regional RNLFTs compared to the traditional circular sector method to improve assessment of structural progression [19].

Management of patients at risk of AACG involves using gonioscopy to evaluate the angle and detect angle closure; it is the current clinical standard. Chiang et al. conducted a study using CNN to find alternatives to a skill dependent and manually intensive procedure. A classifier was developed to sort Eyecam goniophotographs. It achieved an AUC of 0.969 (95% CI 0.961–0.976) in detecting angle closure. Human graders demonstrated a range of performance in the same task with most true positive rates (range = 0.701–0.973; $P = 0.01$) versus false positive rates (range = 0.042–0.219; $P = 0.31$) with higher levels of clinical experience [20].

Visual Field Test directly assesses the visual function and is another way of monitoring disease progression in glaucoma, neuro-ophthalmology and in thyroid diseases for instance. However, analysis of VFT is dependent on the observer's experience and there could be significant difference in interpretations as a result. Many studies have advocated the application of deep learning in automated visual field testing. A review article by Wu, Yue, et al. summarizes that AI has shown a great potential in analyzing complex visual fields and can be used to differentiate glaucomatous fields from that of normal field tests [21].

Another study by Yousefi, Siamak, et al. looking into the visual fields tests of over 2000 eyes concluded that machine learning can consistently and accurately pick up even the slow progressing field defects [22]. Furthermore, Kim et al., successfully managed to combine the data of RNFL thickness and visual fields to create many AI models [23]. Models such as these with combined functional and structural models perform impressively well in glaucoma detection. Table 1.

4. Application in retinal diseases

Anatomical visualization of the eye has rapidly developed since the advent of ocular coherence tomography (OCT) [24]. The increasing use of OCT imaging and growing datasets has allowed for the potential development of models to facilitate automated detection of retinal pathologies [25].

4.1. Application in diabetic retinopathy

Diabetic retinopathy (DR) is the leading cause of blindness in the developed world, leading to vision loss in over 4 million people worldwide [26]. Traditionally, it is divided into two stages: nonproliferative DR (NPDR) and proliferative DR [PDR] based on the early ETDRS system. Harding, S. et al. explains the new and more inclusive grading system in their review [27]. The modern DR grading incorporates diabetic macular edema (DMO) and photocoagulation as categories. In summary, DR is now graded into four stages; no DR (R0), background DR (R1), preproliferative (R2) and proliferative (R3). M1 denotes the presence of DMO and M0 the absence of it. Finally, a prior photocoagulation warrants P1 and P0 if no retinal lasers were previously applied.

Multiple automated retinal image analysis systems (ARIAS), based on AI and DL methods, have emerged in recent years to support the identification of retinal pathology. In diabetic retinopathy screening, ARIAS has the potential to overcome the increasing demands set by the growing prevalence of diabetes mellitus on specialists worldwide [28]. There is a clear need for more efficient and accurate ARIAS and it may be the vital cog in keeping up with the rising demand. Various ARIASs have emerged in recent years with the purpose of helping to manage the increased demand on DR screening [28]. Liu et al. created an AI-assisted nonmydriatic point-of-care screening that can be administered during primary-care visits [29]. In this study, adults with a clinical

Table 1. A summary of some recent AI studies in glaucoma over the last three years.

Studies	Year of publication	AI model	Function	Results	Conclusions
Hemelings R.et al [12].	2021	ResNet	Detection of vertical cup-disc ratio (VCDR) in glaucoma using fundus image	AUC 0.88 [95% CI 0.85–0.9]	First irrefutable evidence that deep learning can detect glaucoma from fundus image regions outside the optic nerve head.
Han X.et al [13].	2021	Convolutional neural network (CNN)	Assessments of the optic nerve head using photographs	200 loci associated with both VCDR and VDD were identified	The potential for CNN in identifying potential genes in glaucoma.
Chiang M. et al [20].	2021	CNN based on ResNet-50	Detection of angle closure in EyeCam goniophotographs	AUC of 0.969 (95% CI 0.961–0.976) in detecting angle closure WITH CNN MODEL Human graders demonstrated a range of performance in the same task with most true positive rates (range = 0.701–0.973; $P = 0.01$) versus false positive rates (range = 0.042–0.219; $P = 0.31$) with higher levels of clinical experience	CNN classifier can effectively detect angle closure in goniophotographs, and is comparable to the performance of an experienced glaucoma specialist.
Liu B.et al [15].	2022	ECSD-Net (unsupervised model)	Segmentation of the optic disc and cup	Combined segmentation result and classification result for the final glaucoma classification is better than the single-use of the segmentation network or the classification network.	This method can assist clinicans in screening and diagnosis of glaucoma that has the potential for real world applications
Thakoor KA.et al [17].	2021	CNN	Detection of glaucoma in OCT	160 random concept experiments conducted to assess test conduct activation vectors (TCAV) High TCAV scores achieved comparing human vs CNN	Pre-trained CNNs followed by fine-tuned layers enhanced robustness when tested on new dataset. Critical parameters to detect glaucoma demonstrated by TCAVs show RNFL/RCGP probability maps as well as RGCP thickness maps are most important
Lee J.et al [18].	2020	Hybrid deep learning model (HDLM)	Detection of macular ganglion cell-inner plexiform layer (mGCIPL) thickness from red-free retinal nerve fiber layer photographs (RNFLPs) in SD-OCT	Trained algorithm had a correlation coefficient r=0.739; p <0.001 and an AUC of 0.918 95% CI (0.898–0.939) for mGCIPL thickness prediction.	The trained HDLM algorithm showed greater capability for mGCIPL thickness prediction for RNFLPs.
Wang M. et al [19].	2020	NMF (unsupervised model)	Assessment of the spatial patterns of retinal nerve fiber layer thickness (RNFLT) in visual field (VF) and OCT	16 distinct RNFLT patterns were determined by NMF and improved VF prediction when compared to sectoral RNFLTS (P<0.001)	The patterns significantly improved the prediction of sensitivities within the visual field mapping

diagnosis of diabetes underwent nonmydriatic fundus photography followed by automated image analysis using EyeArt v2.0 automated DR screening software with human supervision. Patients were referred for a comprehensive ophthalmic assessment if there were positive or inconclusive findings. The results showed that the automated platform had a sensitivity of 100% (95% confidence interval 92.3–100) in detecting abnormal screening results but specificity of only 65.7% (57.0–73.7). Most significantly, adherence to referral recommendations was significantly higher than historical rates (55.4% v 18.7%) using this method.

A different automated AI algorithm run on EyeArt v2.1.0 from British study was tested on fundus images from 30,405 patients from three diabetic eye screening programmes around the UK [30]. Patients were deemed referable to secondary care if there was evidence of referable maculopathy (R1M1), moderate-to-severe non-proliferative retinopathy (R2), proliferative retinopathy (R3), or ungradable images. The AI algorithm was found to have a high sensitivity for detection of referable retinopathy (RDR) 95.7% (94.7–96.5%), comprising of 98.3% (97.3–98.9%) for R1M1, 100% (98.7–100%) for R2 and 100% (97.9–100%) for R3 stages.

Pegasus, another AI system for DR detection, was tested on images captured using a handheld portable fundus camera with the performance in assessing RDR and PDR being compared to the publicly available desktop camera benchmark dataset [31,32]. Performance of Pegasus was inferior in detecting RDR (AUC 89.4% v 98.5%), but very similar in detecting PDR (94.3% v 92.2%) when compared to the benchmark dataset. There is a great potential for the use of Pegasus fundus images taken handheld devices which may increase access to retinal screening, but there are still limitations, mostly due to issues with image quality, for more widespread use.

Xie et al. developed two different DL approaches for detecting DR; a semi-automated model that serves as a triage filter prior to human assessment, and a fully automated approach that does not require human assessment [33]. These models were an ensemble consisting of three deep neural networks (VGGNet, ResNet and DenseNet) designed to detect RDR, developed using images from the Singapore Integrated Diabetic Retinopathy Programme. A decision tree model developed using TreeAge Pro 2019 R1.0 was used to compare the costs of screening with the different models compared to a solely human grading. The semi-automated model came out on top, showing the best economic return, with the potential of saving $15 per patients compared to manual grading.

Table 2. Some recent AI studies in AMD over the last three years.

Studies	Year of publication	AI model	Function	Results	Conclusions
Ji Z.et al [41].	2018	A deep network	Segmentation of geographic atrophy (GA) in OCT	• 2 image data sets used • Mean overlap ratio 86.94% ± 8.75% and 81.66% ± 10.93% respectively • Absolute area difference (AAD) 11.49% ± 11.5% and 8.30% ± 9.09%, respectively • Correlation coefficients 0.9857 (1st dataset) 0.9952 (2nd dataset)	Proposed algorithm can improve >5%-10% segmentation accuracy compared to other algorithms
Saha S. et al [42].	2019	Deep convolution neural networks (CNN)	Automated analysis of AMD biomarkers in OCT	• 3 convolutional neural networks (CNN) compared. • Inception- V3 accuracy (IHRF vs hRF vs SDD) 89%, 88% and 84% • ResNet50 accuracy 88% vs 87% vs 81% • InceptionResNet50 89%, 87% and 85%, respectively	87% accuracy in identifying early AMD biomarkers
Zhang, G. et al [43].	2021	A modified U-Net	Segmentation of macular atrophy in OCT	• Similarity between deep learning model and human specialist grading: median Dice similarity coefficient (DSC) 0·96 [IQR 0·10]; intraclass correlation coefficient [ICC] 0·93] vs human graders (DSC 0·80 [0·28]; ICC 0·79) • Accuracy of segmentation for three features of GA: retinal pigment epithelium loss (median DSC 0·95 [IQR 0·15]), overlying photoreceptor degeneration (0·96 [0·12]), and hypertransmission (0·97 [0·07])	Deep learning composite model for segmentation of GA acheives performance at a similar level to manual specialist assessment
Liefers, B. et al [44].	2021	CNN	Segmentation of 13 features in AMD	• Model vs human observes DSC: 0.63 ± 0.15, vs 0.61 ± 0.17 • Mean ICC 0.66 ± 0.22, compared with 0.62 ± 0.2	Automatic segmentation quality acheives results that match experienced graders and exceeding human performance for some features

Improving the process of retinal image analysis will allow for more timely diagnosis of referable diabetic retinopathy and improved adherence to referral recommendations, allowing for the potential of earlier intervention and reducing vision loss from diabetes. It can also help overcome economic boundaries to help further expand the retinal screening programmes worldwide.

4.2. Application in macular degeneration

Machine Learning (ML) and Deep Learning (DL) are becoming popular image analyzing aids in medical retina, particularly in Age-related Macular Degeneration (AMD). Deep-Learning-based algorithms are currently used in classification and prediction of AMD, particularly in wet AMD. The AI-based systems are capable of analyzing medical data and automatically identifying AMD, which could provide crucial clinical decision-making support [34].

Several novel OCT-based features have been identified by numerous studies to help monitor the risk of AMD progression [35]. Drusen volume, pigment epithelium detachment, subretinal hyperreflective material, subretinal drusenoid deposits, and subretinal/intraretinal fluid can all be used to monitor disease progression. DS Kermany et al., for instance, applied imageNet to detect the presence of AMD indicators, such as CNV and drusens, and this method is now widely used in clinical practice [36]. OCT-based biomarkers have been proposed to automatically detect and classify AMD using deep-learning method. With the help of OCT technology advancement, deep-learning provides a strong correlation between OCT-based features and AMD, and presents detailed structural changes during the progression.

Many ML-based algorithms have been validated for OCT image analysis, including algorithms that can review retinal layers segmentations and that can identify specific biomarkers in OCT. Retinal layer segmentation analysis is a particularly interesting concept. Ronneberger, Olaf et al. concludes that layer segmentation analysis not only requires less computational power than many other DL methods and it also demands less data set to train the system. The utilized U-Net concept was able to accurately detect various retinal lesions as well as pinpoint their exact locations in the retinal layers [37]. Deep learning with artificial multi-layer neural networks, particularly convolutional neural networks, have been very successful in OCT image analysis. It can be applied for OCT image segmentation, where structures are delineated using DL models to allow detection of conditions such as macular edema [38]. A CNN, trained on OCT-B scan images anatomically segmented and annotated by a retinal specialist, was applied to spectral domain (SD) and swept-source (SS) OCT images and compared to a benchmark set graded manually by specialists and found to have a high level of agreement with all graders [39]. Another CNN trained in OCT image segmentation, enhanced with a Traceable Relevance Explainability (T-REX) technique, also showed similar performance to human graders, with an overall average variability of 1.75% between automated and manual grading [40]. These recent advancements in DL highlight the comparable accuracy of automated OCT image segmentation with manual grading, a resource-intensive, time-consuming task, showing its potential in anatomical delineation and retinal disease detection (Table 2).

Diagnosis of myopic macular degeneration (MMD), a sight threatening complication of patients with high myopia, typically requires specialist assessment and equipment [45]. AI approaches have the potential to better risk stratify those at risk and need specialist assessment. Tan et al. developed and tested retinal photograph-based deep-learning (DL) algorithms developed using ResNet-101 to detect high myopia and MMD [46]. The DL was tested against internally and externally validated datasets and had robust performance with an AUC of >0.969 (95 CI 0.959–0.977) for MDD detection and >0.913 (0.906–0.920) for high myopia detection. It was also tested against a randomly selected dataset of 400 images and had outperformed six expert graders for MMD (AUC 0.978 [0.957–0.994]) and high myopia detection (AUC 0.973 [0.941-0/995), thus showing the clear benefits of DL algorithms in risk stratification and screening in these conditions.

4.3. Other applications of ARIAS

The Comprehensive AI Retinal Expert (CARE) system, a DL system trained on 207,228 color fundus photographs from China, was internally validated using 21,867 photographs and externally tested using 18,136 images across China [47]. It was trained to identify the 14 most common retinal abnormalities including RDR, referable hypertensive retinopathy, retinal detachment, macular edema, the epiretinal membrane (ERM), and retinal vein occlusion and compared to the manual analysis by ophthalmologists. There was similar performance seen between CARE and the human grader, with an AUC of 0.955 for internal validation set, and an average AUC of 0.967 in the external validation set and continued to strong performance in identification of RDR (AUC 0.960).

RetiSort is multi-step DL algorithm with the potential for automated sorting of retinal photographs [48]. It was developed from retinal photographs sourced from the Singapore Epidemiology of Eye Diseases (SEED) and composed of three steps (two DL algorithms and one rule-based classifier) in order to accurately label the type and laterality of retinal photographs (in relation to the optic disc). It was applied to 5000 randomly selected images from SEED and to three publicly available databases and found to have an accuracy of 99.0% for the SEED datasets, and an average of 99.1% accuracy in the external sets, and this degree of accuracy visibly shows the benefits of this multi-step DL algorithm.

4.4. Epiretinal membrane detection

The ERM is a pathological fibrocellular tissue that can form on the inner surface of the retina. It may be idiopathic or secondary to conditions such as inflammatory eye disease, retinal vascular disease or retinal detachment [49]. Patients may be asymptomatic; however, in some cases, there is risk of visual disturbance and even vision loss if left untreated [50]. Diagnosis is typically through clinical examination which can be challenging and limited by expertise, therefore technological support for ophthalmologists may help mitigate this. Current DL models in ERM detection have been non-inferior to expert grading, however Lo et al. created a DL model to try and further improve the accuracy [51]. The DL model created was applied to OCT image dataset to detect ERM and compared to those diagnosed by non-retinal specialized ophthalmologists, the gold standard for this study. It was found to have a diagnostic accuracy of 98.1% (95% CI 96.5–99.1%), sensitivity of 98.7% and specificity of 98%, concluding that an ophthalmologist-level DL model can be built to help assist clinicians in diagnosing ERM, which would ultimately promote efficiency and safety of healthcare in the future.

5. Application in Corneal disease

Corneal confocal microscopy (CCM) is a noninvasive ophthalmic imaging technique that enables imaging of the cornea without tissue damage. The use of CCM has significantly advanced the understanding of corneal pathologies such as infective keratitis, immune, and autoimmune corneal diseases, and this has allowed for the possibility of providing better, more tailored treatment to patients everywhere [52].

Corneal inflammatory diseases such as infective keratitis, immune, and autoimmune corneal diseases can cause persistent corneal inflammation, leading to opacification and sometimes even visual impairment [53,54]. Anti-inflammatories remain the mainstay for treatment and regimes are typically adjusted based on the degree of inflammatory response within the cornea. Corneal inflammatory activity can be monitored through repeated clinical examination, but this can be time-consuming and resource-intensive. CCM is a noninvasive novel technique used to overcome this, where degree of corneal inflammatory activity can be quantified through analysis of inflammatory cell activation [55,56].

Analysis of CCM images usually requires human grading by trained ophthalmologists, which limits its accessibility. A network-based deep-transfer learning (DTL) model, which refers to the reuse of partial network structures and parameters that are pretrained in the source task, was constructed in a study by Xu et al. consisting of a pre-trained network and an adaption layer to analyze the CCM images [57]. In the study, five different pre-trained models were trialed. All models were found to perform well, with the Inception-ResNet V2 transfer model coming out on top with an AUC of 0.9646 ($P < 0.001$) in identifying activated dendritic cells (accuracy, 0.9319, sensitivity, 0.8171, and specificity, 0.9517). DTL models have shown a high level of accuracy for automated analysis of corneal inflammation which may provide huge advancements for the scope of precision medicine in corneal disease management and help overcome barriers such as limitations in accessing expertise within health care.

Screening for diabetic peripheral neuropathy (DPN), a highly prevalent disease that affect up to 50% of the general population, is historically performed using the 10 g monofilament test. Although this can help identify patients at risk of foot ulceration, it does not assess and quantify small fiber neuropathy (SFN), an early stage of diabetic peripheral neuropathy [58]. Currently, skin biopsies are performed to quantify SFN; however, the invasive nature of this procedure is one of its major drawbacks. The cornea, the most densely innervated tissue in the human body, has a network of unmyelinated axons called the sub-basal nerve plexus (SBP). CCM can be used to image the SBP and reliably quantify the SFN within it in a noninvasive manner. However, screening of DPN though CCM analysis in its current form would be limited by its labor-intensive nature, thus accurate, automated methods of SFN quantification are required. Williams et al. developed a DL algorithm employing a convolution neural network (CNN) with data augmentation [59]. The algorithm was tested against ACCMetrics, a validated automated analysis programme used in diagnosis of DPN [60], and was found to be superior in analysis of DBP in all metrics including total corneal nerve fiber length (AUC 0.933 v 0.825), mean length per segment (0.656 v 0.325, number of branch points (0.891 v 0.570) and number of nerve segments (0.878 v 0.504). The proposed algorithm has the potential for super quantification of corneal nerve fibers than existing systems, showing its potential for use in screening programmes and earlier detection of DPN.

The corneoscleral limbus is a key structure within the eye, containing limbal stem cells which play an essential role in the regeneration of the corneal epithelium [61]. Identifying the position of the corneoscleral limbus is important for clinical tasks such as contact lens fitting, where proper fitting is determined by the distance between the contact lens edge and the corneoscleral limbus [62], and in the estimation of the iridocorneal angle that can play role in diagnosis of angle-closure glaucoma [63]. Corneoscleral limbal points (external and internal) can be identified using anterior segment OCT images. A fully automated method for this has been designed which locates the external limbal point at the anterior ocular surface by estimating the local radii of curvature along the whole anterior ocular surface, and the internal limbal point using the estimation of the actual thickness profile of the cornea [64]. This method was compared to manual delineation by an ophthalmologist and optometrist that is typically a time-consuming process. The automated method found to overestimate the external limbus diameter by 0.24 mm and 0.21 mm when compared to the ophthalmologist and optometrist, respectively, and underestimate internal limbus diameter by 0.04 mm and 0.13 mm when compared to the ophthalmologist and optometrist, respectively. Consequently, despite the small discrepancies shown, the automated methods provided more precise results with excellent repeatability, suggesting the possibility of its use in larger scale image processing.

Keratoconus is a common, non-inflammatory eye disease, affecting one in every 375 people in the general population [65]. It is typically characterized by asymmetrical conical protrusion secondary to focal thinning of the cornea and can cause severe visual problems. In the developed world, it is a major indication for corneal transplantation [66]. Artificial intelligence models have the potential to monitor progression of keratoconus which is assessed by identifying increases in maximum anterior curvature (Kmax) of the cornea. Shetty et al. trained three AI models to detect these increases in Kmax [67]. All three models performed excellently with a classification accuracy, sensitivity and specificity of 85%, 82%, and 83%, respectively, for Model A, respectively, 86%, 82%, and 88% respectively, for Model B and 89%, 81%, and 91%, respectively, for Model C, highlighting the benefits of AI in monitoring progression in keratoconus.

Genome-wide association studies (GWASs) in the past have not found a genetic region for keratoconus with significant genomewide association [66,68]. Large meta-GWAS have previously identified keratoconus-susceptibility genes relating to those that determine central corneal thickness (CCT). A Japanese study in 2020 has found that a CCT-increasing allele called *STON2* rs237159, identified using a traditional two stage GWAS, to be strongly associated with keratoconus development (P = 0.041) [69]. Additionally, predictive analysis using AI technology (IBM's Watson for Drug Discovery) identified *SMAD3* rs12913547, a CCT-reducing allele, as a keratoconus susceptibility gene. The continued discovery of these genes associated shows the potential for GWAS in predicting the development of keratoconus that may play a role in the future diagnosis and management of the condition.

6. Application in Cataract

Cataracts is the leading cause of visual impairment worldwide, representing the cause of more than half of blindness cases worldwide, and is most commonly secondary to age [70]. Cataract-induced blindness disproportionally affects low-income countries and numbers in regions such as Africa continue to rise [69]. Therefore, advancements in diagnosis and management in a cost-effective manner are essential in increasing availability of healthcare and reducing cataract rates in these countries.

The biggest effort in reducing rates of cataract-induced blindness is through high volume cataract surgery campaigns. These campaigns need to be cost effective and efficient to provision of care. An intra-ocular lens (IOL) supply consisting of various different IOL powers and bought prior to each campaign, to try and ensure that all patients receive an IOL that is as close to their target power as possible in order to minimize the refractive error post-operatively. Current campaigns have a surplus of IOLs to try ensure this, but even this may have not always been able to optimize to patient needs. Thus, a machine learning (ML) algorithm, a variant of Gradient descent, trained using data from previous outreach campaigns, was used to determine the optimal stock of IOL supply for an Ethiopian outreach campaign, in order to minimize the difference between actual implanted IOL power and targeted IOL power [71]. The ML algorithm-generated IOL supply ensured that 99.5% of patients received their target IOL whilst only requiring a 39% IOL surplus. This was significantly superior to current inventory supplies (from campaigns between 2017 and 2018) where only 45.6% of patients received their target IOL power whilst also requiring a surplus of 50%. The ML algorithm has shown that it can help optimize the IOL inventory, and can be a key component in reducing costs that will help maximize the efficiency of high-volume cataract surgery campaigns.

Another area where ML has been explored is in surgical teaching. Studies have shown the correlation between surgical experience and postoperative outcomes. In cataract surgery, there is a 1.6 times higher reported risk of patients developing reactive corneal edema after having cataract surgery by a novice surgeon when compared to an experienced surgeon [72]. A study in Japan tested the ability of a neural network model, Inception V3, in performing real-time extraction of two important surgical phases, continuous curvilinear capsulorrhexis (CCC) and nuclear extraction, from cataract surgery videos [73]. The extraction for each phase was compared to results identified by an ophthalmologist (the gold-standard). The neural network was found to recognize important surgical phases at an average accuracy of 96.5% (90.7% for CCC and 94.5% for nuclear extraction, respectively), and determined start and end time of these phases with a 5 second error on average. The model's ability to perform real-time classification more quickly but on a similar level to an expert show that it has the potential to revolutionize surgical training in an era where exposure is becoming more limited.

Cataracts are diagnosed and graded into four grades based on degree of lens opacification (normal, mild, moderate, and severe) [74]. Computer-associated cataract diagnosis (CACD) can play a key role in early cataract detection and classification. Unfortunately, due to the high level of noise in fundus retinal images, current convolutional neural network (CNN)-based CACD models have been limited [75–77]. Pratap et al. have proposed the use of a robust CACD under additive white Gaussian noise (AWGN) which helps extract features at various noise level [78]. The proposed model performed better than existing models at all noise levels, especially at higher noise levels where the proposed model testing accuracy is three times when compared to the existing models. CACD has the potential for more timely cataract diagnosis, and the potential for this model to enhance this method can have positive implications for the future of cataracts.

7. Application in Uveal disease

Uveitis is a broad term relating to intraocular inflammation that may be secondary to infectious agents (infectious uveitis) or autoimmune conditions (non-infective uveitis) [79]. Early treatment is essential due to the risk of visual impairment and blindness, however management of noninfectious uveitis remains a challenge due to limitations in knowledge of disease pathogenesis [80]. Identifying potential markers and thus therapeutic targets has the potential to better tailor treatment in a field of ophthalmology which has been late to the application of precision medicine. Bonacini et al. attempted to identify potential markers in noninfectious uveitis associated with Behçet's disease (BD) and Vogt Koyanagi Harada (VKH) disease, by investigating the concentrations of 27 cytokines from aqueous humor (AH) samples from patients with active uveitis (secondary to BD and VKH) compared to healthy controls [81]. The results showed that interferon gamma (IFNγ), interleukin-1ra (IL-1ra) and IL-6 concentrations were higher in AH samples from patients with active uveitis secondary to both BD and VKH than in healthy controls. The concentrations of cytokines including IL-6, IL-8, IFNγ and IL-1ra positively correlated with leukocyte concentrations in AH, thus implying the link between cytokine concentration and degree of inflammation. Consequently, the evidence from AH sampling highlights the associations between specific cytokines and anterior uveitis which have the potential to be therapeutic targets that can help accelerate precision ophthalmology within uveitis.

Anterior Segment OCT can be used in grading anterior chamber (AC) cell activity, particularly in children. The currently and widely used method of slit lamp examination to grade AC activity depends on the mercy of a cooperative patient and is open to significant inter-observer variation. A study by Bhatti U, Akbarali S, Solebo AL, *et al*. utilized two deep-learning algorithms, Multi-layer perceptron (MLP) and Convolutional neural network (CNN). Whilst MLP outperformed the latter, both binaries showed great potential in automated cell counting [82].

Uveitis is a field of ophthalmology with limited specialists and has proven to be a diagnostic challenge to junior doctors and senior ophthalmologists. Expert systems (ES) are artificial intelligence based technologies that can attempt to simulate the judgment of a specialist [83]. In uveal tract disease, it can help overcome the barriers to treatment secondary to limited availability of specialists, especially within the developing world. A multi-layered rule-based ES was designed by Mutawa et al. and applied in the diagnosis of uveitis [84]. It was tested on 62 patients and found to have an accuracy of 75% and was found to effectively address the inconsistency and variability in the clinical presentation of uveitis. Although there is still some way to go in improving the accuracy rate of this method, it highlights that there may be benefits in use of ES systems to help overcome the diagnostic challenge faced by doctors within this field.

8. Conclusion

A similar systemic review article by Shetty DK *et al*. explored the artificial intelligence application in Ophthalmology. They pointed out the additional role of AI outside of a clinic. For instance where an Ophthalmologist is not available in a rural setting, AI can improve the access to eye care, thus reducing social inequalities in certain countries [85].

In the UK, many hospitals already run diagnostic and virtual clinics for conditions such as diabetic retinopathy and glaucoma. Many healthcare trusts have adapted electronic patients records and coupled with advancement in telecommunication and video conferencing, telemedicine is picking up real momentum in certain disease management. Ting DS *et al*. mentioned the emerging role of "teleOphthalmogy" and the platform was able to increase the service capacity by nearly 10 fold [86].

There is huge scope for precision medicine in a field such as ophthalmology, where diagnoses are heavily reliant on imaging techniques. ARIAS has changed the scope for retinal image screening of conditions such as diabetic retinopathy, and new programmes such as CARE and RetiSort have the potential for future application in diagnosing other retinal diseases.

Glaucoma- and cataract-related conditions are increasing in prevalence with a substantial disease burden predicted. Use of AI enables screening and diagnosis without requiring human input thus largely reducing the onus on clinicians. Furthermore, monitoring of disease progression using CNN has extensive breadth; the technology at its full potential will massively impact efficiency and continuity of care. Current available studies have demonstrated incredibly accurate and reproducible results, however implementation and translation into clinical care are yet to be optimized. Enhancing IOL inventories for cataract surgery campaigns in low-income countries provides a platform for AI use. Niche applications include processing surgical videos to improve surgical teaching as well as computer-aided cataract diagnoses from fundus retinal images. CCM analysis exhibits large potential with the implementation of AI; monitoring and progression of diseases such as keratoconus and corneal inflammatory disease will become less labor-intensive. Moreover, management will be precise and targeted toward the individual. Expert systems have been developed to support clinicians in the challenging diagnosis of uveitis; identification of disease markers have the potential to be therapeutic targets thus improving the quality of treatment received.

Major advances in precision ophthalmology have been made within the last three years. Although certain technologies still require optimization to be smoothly implemented into clinical practice, it is hopeful that these developments will reduce the strain of the increasing burden of ophthalmic diseases worldwide as well as further hone screening, diagnosis and management.

AI has a great potential in becoming a mainstay in ophthalmological assessments. Several studies have proven the ability of AI to consistently and accurately identify the pathologies. However, the end results invariably depend on the quality of the imaging modalities, the operator skills and the volume of the data applied into the algorithm.

9. Expert opinion

Precision medicine plays a significant role in managing ocular diseases. Diagnosis, screening, progression and management are all becoming increasingly advanced and labor-intensive.

Since the COVID-19 pandemic, there is a marked backlog of patients and an increasing number of undiagnosed and untreated ophthalmic pathology. There has been a growth of lifestyle associated conditions such as diabetes and hypertension and their ocular manifestations. Obvious benefits of artificial intelligence-based retinal screening programmes facilitate reduction of the burden on clinicians as well as aiding precise specialist input where required. Earlier diagnosis and screening of retinal pathology, normally noted to be labor-intensive and skill-dependent, will be enabled through honing of this developing technology. In tandem with genomics, this provides an opportunity to predict inheritance patterns, develop screening programmes and long-term management.

An area that has arguably been one of the most impacted by the COVID-19 pandemic has been surgical training; a truly novel area with a wide breadth of application across the entirety of training – both medical and surgical. The lack of surgical experience in all subspecialties of ophthalmology will likely have future implications on confidence and competence of trainees. There is certainly more scope for the implementation of artificial intelligence to support surgical training allowing for increased real-time feedback intra-operatively thus encouraging trainees to thrive with every learning experience.

Corneal confocal microscopy (CCM) is another notable research area which has shown potential in the diagnosis of systemic diseases and guiding management. Analysis of the images is a notoriously specialist skill, but ML methods have shown potential to overcome this. The future of analysis of CCM images will be a fast, fully automated process to allow for targeted management of corneal inflammatory disease; additionally monitoring of disease progression may be managed in the community due to the reduced need of specialist input.

Monitoring of glaucoma using CNNs has been well-researched, and studies are slowly refining techniques. Application of these in a clinical setting will require further training datasets which may prove to be a hindrance to the speed of which these are implemented. Deep learning is very suited to glaucoma due to the use of multiple imaging techniques and pattern recognition. Uveitis is the least developed subspecialty in relation to precision medicine; the disease is poorly understood and difficult to diagnose thus perhaps is the sector that requires the greatest push for more research. Understanding the genomics of the disease would assist targeted therapy and improvement in diagnosis; there is still potential to establish more pharmacogenetics by understanding pathophysiology behind the disease. Uveitis has the largest scope for development which is particularly essential in a field which is complex with such few specialists – even more so given the worldwide backlog of patients due to the pandemic.

> Precision medicine concept raises two fundamental questions. In the traditional healthcare setting, at which point can the concept be started? Where is the end point? Depending on the point of start and the point of end, there may be different sets of data and therefore the derived outcome may differ. Secondly, can the concept be really used in global clinical settings to better the care provided? There is also the hurdle against collecting a huge amount of sensitive patient information. There may not be sufficient patient cooperation or participation as a result. These are some of the challenges that need to be overcome for mass adaptation of the concept.

Precision medicine should be viewed as an ever evolving and dynamically changing entity. It is not an end-point measurement. Precision medicine and the outcome should be constantly reintroduced into the algorithms to grow and nurture the data set. The more information a system is fed, the more accurate the learning and therefore the outcome become. However, this exact mechanism is the major hurdle in the adaptation of the technology. The main purpose of precision medicine and its derivative, machine learning is to reduce the burden on clinicians and expenditure. The set up and running of machine learning, such as data gathering, developing the algorithms and monitoring outcomes are both time consuming and laborsome initially. However, once set up, precision medicine with the aid of machine learning will undoubtably not only improve the diagnostic accuracies and also will discover new correlation and patterns within and between various pathologies.

A huge potential for further growth and applications within both ophthalmology and the wider scope of medicine remain with precision medicine. Further research into deep learning methods and their application is warranted to truly reach the full scope of precision medicine.

Precision medicine and machine learning are the future of healthcare.

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