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REVIEW ARTICLE

Artificial intelligence applications in inherited retinal dystrophies

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Abstract

Purpose Inherited retinal dystrophies (IRDs) are a heterogeneous group of diseases characterized by genotypic and phenotypic variability and are among the leading causes of blindness in the working-age population in developed countries. Despite advancements in genetic testing, obtaining a molecular diagnosis remains a lengthy and challenging process due to limited resources and high costs. Artificial intelligence (AI) offers promising solutions to streamline diagnostic pathways and improve clinical outcomes.

Methods We reviewed current literature on AI-driven approaches in IRDs.

Results AI models have demonstrated potential in predicting disease-causing variants, distinguishing phenotypically similar IRDs, and segmenting retinal layers. However, their routine clinical adoption remains limited. Efforts are ongoing to lower genetic testing costs, reduce diagnostic delays, and enhance molecular diagnostic yield. Future applications may include genetic counselling, prediction of IRD progression, evaluation of novel mutation pathogenicity, identification of gene therapy candidates, and prediction of personalized outcomes post-treatment. Barriers to widespread AI adoption include a lack of standardized nomenclature, ethnic and regional variations, inconsistent multimodal imaging quality, data ownership concerns, clinical safety, cybersecurity, and the opaque nature of AI decision-making, known as the "black-box" problem.

Conclusions AI models have shown promise in diagnosing IRDs, predicting causative genes, and segmenting retinal layers. While AI has the potential to revolutionize IRD diagnosis and management, significant challenges must be addressed. Continued research and collaboration are crucial to overcoming these barriers and unlocking AI's full potential in IRDs.

Key messages

What is known

- Inherited retinal dystrophies (IRDs) are a genetically and phenotypically heterogeneous group of diseases, often leading to early visual impairment and high societal costs.
- Artificial intelligence (AI) algorithms, especially deep learning, have shown promise in differentiating IRD subtypes and segmenting retinal layers using multimodal imaging.

What is new

- Recent developments highlight AI's potential to facilitate causative gene prediction, lower genetic testing costs, reduce diagnostic delays, and improve molecular diagnostic yield in genetic testing.
- Novel AI-based methods might help identify candidates for approved gene therapy and ongoing or future gene therapy trials, as well as predict personalized treatment outcomes to demonstrate gene therapy efficacy.

Keywords Inherited retinal dystrophies · IRD · Artificial intelligence · Deep learning · Multimodal imaging · Gene therapy

Introduction

Inherited retinal dystrophies (IRDs) are a heterogeneous group of rare ocular diseases characterized by genetic and phenotypic variability. They primarily affect the photoreceptors (rods and cones), the retinal pigment epithelium (RPE), and the choroid, often leading to significant visual impairment and blindness [1, 2]. With a global prevalence estimated between 0.06% and 0.2%, IRDs impact 5–10 million people and are the leading cause of blindness among the working-age population in the UK and worldwide [3–5]. Because IRDs cause early visual impairment

Extended author information available on the last page of the article

in the working-age population, they are associated with high societal cost [6]. To date, mutations in more than 300 genes have been described with IRDs [6, 7]. Approximately 70% of IRDs are inherited through autosomal recessive patterns, 25% follow autosomal dominant inheritance, and the rest follow X-linked or mitochondrial inheritance patterns [8]. The four main subtypes of IRD phenotypes include rod-cone dystrophies, cone-rod dystrophies, chorioretinal dystrophies, and macular dystrophies. Morphological and functional parameters of each subtype correspond to the affected retinal cells. Rod-cone dystrophies, the most prevalent IRDs, begin with night blindness and peripheral visual field loss due to early rod degeneration, progressing to central and colour vision worsening as cones become affected as well. In contrast, cone-rod dystrophies primarily start with a decline in light sensitivity, visual acuity, and colour vision. Chorioretinal dystrophies can present with various symptoms, typically starting with night blindness and peripheral vision loss, and progressing to cone-mediated central vision loss. Macular dystrophies most commonly present with metamorphopsia, decreased visual acuity, and central scotoma, while generally preserving peripheral vision [9].

Interest in IRDs has significantly increased after the approval of voretigene neparvovec (VN) for RPE65-mediated IRDs in 2017 [10, 11]. For pioneering gene therapy efforts, the eye is an optimal target due to its immune-privileged environment, which exhibits high tolerance to viral vectors, minimal inflammatory responses, and low risk of systemic dissemination. Moreover, only small doses are needed to achieve therapeutic effects with highly accessible surgical methods for delivering vectors via intravitreal, subretinal, or suprachoroidal approaches [12–14]. Additionally, treatment efficacy, side effects, and disease progression can be easily evaluated with multimodal imaging techniques and quantified with visual function tests [5]. Currently, there are around 45 ongoing gene therapy trials (www.clinicaltrials.gov) sponsored by research groups and pharmaceutical companies.

Artificial intelligence (AI) applications have started to develop predominantly in medical specialties that heavily rely on imaging modalities, such as radiology, dermatology, and pathology [15]. In ophthalmology, AI applications have primarily been utilized for diabetic retinopathy, glaucoma, retinopathy of prematurity, and age-related macular degeneration (AMD) due to the exponential increase of multimodal imaging data. AI is a branch of computer science focused on developing systems that can perform tasks typically attributed to human intelligence, such as problem-solving, learning, reasoning, and perception [16]. Machine Learning (ML) is a subset of AI that focuses on developing algorithms capable of learning from data and making data-driven decisions. In practice, labelled images are provided to the machine, which learns from the data, develops an algorithm, and produces an output such as a diagnosis [17]. Deep Learning (DL) is a subset of ML that utilizes artificial neural networks, which can be expanded to include several hidden layers between the input and output. This architecture is known as a Convolutional Neural Network (CNN). Learning can be unsupervised, semi-supervised, or supervised, allowing deep learning systems to identify previously unknown disease features on multimodal imaging for retinal specialists [16]. A significant advantage of DL over ML is that as the amount of data increases, the performance of DL models continues to improve, whereas the performance of traditional ML models tends to plateau [16]. In retinal conditions, AI has primarily been utilized for diagnosis and classification, segmentation, and prediction. For classification, AI has been employed to screen patients for diseases, determine disease stages, and identify disease types. It has been used to segment morphological parameters such as retinal layer thickness, fluid volume, subretinal hyperreflective material, number of hyperreflective foci, pigment epithelium detachment size, drusen size, ellipsoid zone (EZ) disruption, and geographic atrophy lesion size. In terms of prediction, AI has been used to predict natural disease progression and treatment outcomes [16].

In IRDs, obtaining an accurate molecular diagnosis is important to understand the likely progression of the condition, offer genetic counselling to patients and their families, and potentially enrol patients in gene therapy trials [18]. However, there are major roadblocks for patients in obtaining a molecular diagnosis. Firstly, clinical expertise in IRDs is most developed in the Western world, with other regions lagging behind. Secondly, molecular diagnostic yields in IRDs are only around 55–65% [19, 20]. Thirdly, the cost of establishing a genetic diagnosis can reach up to £10,000, which is unaffordable for many countries around the world. Fourthly, even when knowledge And funding are available, the majority of individuals in the UK have to wait more than 5 years to obtain a genetic diagnosis [21].

To facilitate the identification of the causative pathogenic genetic mutation, a patient's medical history, clinical examination, and multimodal imaging are considered to test only specific genes [22]. Stone et al. reported a high identification rate of 76% using a phenotype-driven genetic testing strategy. With this approach, around 57% of families were identified without the need for next-generation sequencing (NGS) [23]. This clinically tiered strategy resulted in improved sensitivity, lower costs, and a lower false genotype rate (FGR) compared to whole-genome sequencing. However, such resources and expertise are often not available worldwide [23]. Therefore, a globally accessible AI algorithm could narrow down the potential list of causative genes and provide a low-cost option for a

phenotype-driven genetic testing strategy. A similar algorithm is currently being developed through the Eye2Gene project, which aims to assist in IRD diagnosis by narrowing down the possibilities of genetic mutations based on phenotype. This could lead to increased diagnostic rates of IRDs and reduced costs [21].

In this review, we will describe manuscripts involving AI in IRDs, discuss possible future applications and shortcomings, and evaluate the potential impact of AI algorithms on IRD clinical practice.

Literature review

The literature review included scholarly databases such as PubMed with manuscripts published up to November 2024. The search keywords included terms related to inherited retinal diseases ("retinal dystrophy," "inherited retinal dystrophy," "IRD," "retinitis pigmentosa," "Stargardt," "Best disease," "choroideremia"), artificial intelligence methods ("artificial intelligence," "machine learning," "deep learning," "convolutional neural network," "CNN"), and imaging modalities ("optical coherence tomography," "OCT," "fundus autofluorescence," "FAF," "fundus photography"). The results of this search And screening process are summarized in the PRISMA 2020 flow diagram (Fig. 1).

Artificial intelligence in diagnosing and predicting causative gene

Fujinami-Yokokawa and colleagues investigated the use of a deep neural network for predicting the genes involved in IRDs by utilizing foveal OCT scans. They compared the algorithm's accuracy in identifying macular dystrophy

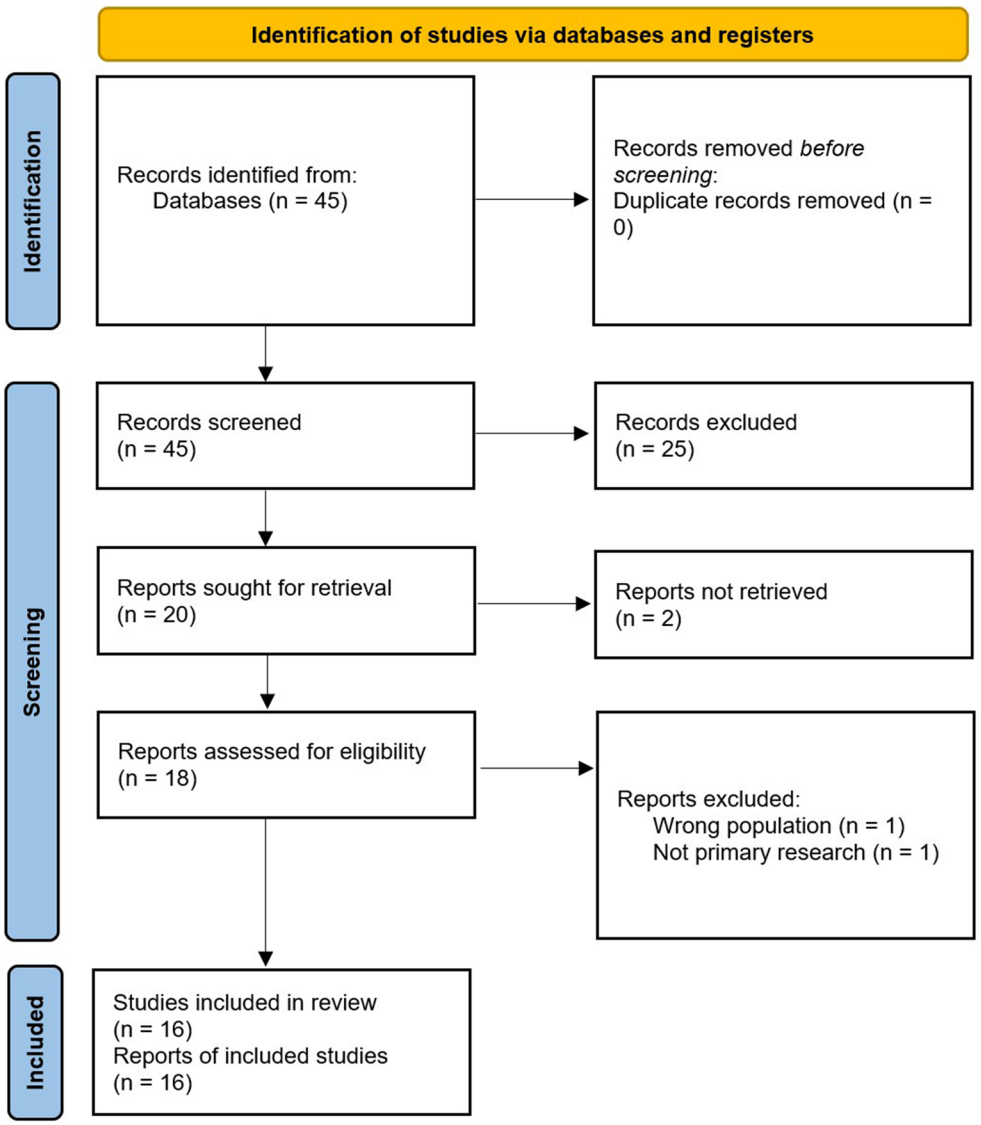

Fig. 1 PRISMA 2020 flow diagram showing study selection for the review of artificial intelligence applications in inherited retinal dystrophies

associated with ABCA4 (10 patients) and RP1L1 (20 patients) pathogenic mutations, retinitis pigmentosa linked to the EYS gene mutation (28 patients), and healthy individuals (17 individuals). The mean training accuracy ranged from 90.6 to 100.0%. Accuracy per gene category was highest for ABCA4 (100%), followed by healthy individuals (93.4%), EYS (89.8%), and RP1L1 (78.0%). While the algorithm showed high training accuracy, overfitting was evident, particularly for RP1L1 and EYS-associated IRDs. This study was the first to show the potential of AI applications in determining pathogenic genes; however, it was limited to just three genes [24]. Miere And colleagues utilized deep learning techniques with multilayer CNN to distinguish between individuals with IRDs using FAF images. They included 73 images from healthy individuals, 125 images from Stargardt patients, 160 images from patients with retinitis pigmentosa, And 125 images from patients with Best's disease. The precision-recall area under the curve (PRC-AUC) averaged at least 0.988 in various IRD groups and healthy controls. However, patients with these IRDs have very distinct and different phenotypes when compared to each other, so high AUC values should be expected [25]. Shah et al. published a study investigating if deep learning algorithms can be used to differentiate between OCT scans from Stargardt patients And healthy individuals. They used two models, the first was a pretrained CNN, while the second used a new CNN architecture. They included 102 OCT scans from healthy individuals, And 647 OCT scans from patients with Stargardt disease. The first model achieved An accuracy of 99.6%, specificity of 98.0%, sensitivity of 99.8%, and a Jaccard similarity score (JSS) of 0.990, while the second model achieved An accuracy of 97.9%, specificity of 98.0%, sensitivity of 97.9%, And a JSS of 0.976. They concluded that CNN algorithms can be used with high accuracy to differentiate Stargardt patients from healthy individuals, even with smaller datasets [26]. Chen et al. developed three pre-trained CNN models to identify patients with retinitis pigmentosa based on colour fundus photos compared to photos of healthy individuals. For training, 935 fundus photos of retinitis pigmentosa patients And 324 fundus photos of healthy individuals were used. Of the three models tested, the Xception model achieved the best performance with An AUROC of 96%. The CNN model performed comparably or slightly better than four general ophthalmologists (81%) and similarly to an IRD specialist (96%). The authors concluded that their study validated the utility of CNN in automatically identifying retinitis pigmentosa patients from fundus photos [27]. In 2021, Miere et al. developed a CNN algorithm to automatically classify if geographical atrophy (GA) has developed secondary to AMD or late atrophic stages of IRD (Stargardt disease and Pseudo-Stargardt Pattern Dystrophy). Their dataset included 204 FAF images from (pseudo) Stargardt patients And 104 FAF from AMD patients. They used 70% of the dataset for training, 10% for validation, And 20% for testing. The model's performance showed An accuracy of 0.92 And An AUCROC of 0.981 in testing, with a mean accuracy of 0.79 in cross-validation. The authors concluded that AI can be helpful in differential diagnosis of late dry AMD with GA and late-onset IRDs masquerading as GA [28]. Miere et al. conducted a study to evaluate whether a CNN could distinguish between ABCA4-associated Stargardt disease (STGD1) and PRPH2-associated pseudo-Stargardt pattern dystrophy, which are clinically challenging to differentiate due to phenotypic similarities. Using 729 FAF images, the CNN achieved a precision of 0.883, sensitivity of 0.883, And An AUROC of 0.890. In comparison, the accuracy was 0.816 for retinal specialists And 0.724 for retinal fellows. The study concluded that a pretrained CNN can effectively distinguish between STGD1 and PRPH2-associated pseudo-Stargardt with high accuracy [29]. Adult vitelliform macular dystrophy (AVMD) and Best vitelliform macular dystrophy (BVMD) exhibit similar phenotypic changes on FAF and OCT. Crincoli et al. developed a deep learning algorithm with 90% accuracy to differentiate AVMD from BVMD, outperforming human graders [30]. Liu et al. evaluated whether a deep learning algorithm could predict visual acuity (VA) of at least 20/40 in retinitis pigmentosa patients using infrared (IR), optical coherence tomography (OCT), and combined images (CI). In internal testing, the AUCs were 0.83, 0.87, And 0.85 for IR, OCT, And CI, respectively, while in external testing, the AUCs were 0.78, 0.87, And 0.85. The authors concluded that visual impairment in retinitis pigmentosa patients can be predicted using confocal scanning laser ophthalmoscopy imaging [31]. Developing AI models for IRDs is challenging due to the low number of patients with specific IRDs or mutations and limited multimodal imaging, leading to class imbalances in datasets and biased prediction models. Veturi et al. generated synthetic IRD FAF images using a StyleGAN2 model trained on IRD data at a resolution of 512×512 pixels. In a Visual Turing Test, the mean true recognition rate was 63%, And the fake recognition rate was 47%. However, BRISQUE score analysis indicated significantly lower quality in synthetic images. Additionally, CNN diagnostic performance did not improve with synthetic data input. Nevertheless, the authors concluded that synthetic data can achieve similar performance to real data and could serve as a proxy when real data is limited [32]. Table 1 presents a summary of AI studies investigating IRD classification, causative gene prediction, and clinical subgroup assignment.

Table 1 Artificial intelligence studies that classify IRDs/predict the causative gene or clinical subgroup

Study (year)	Gene(s)/clinical condition(s) distinguished	Imaging modality	AI/ML model	Patients/images	Controls/images	Key performance
Fujinami-Yokokawa et al. (2020)	ABCA4, RP1L1, EYS macular dystrophies; healthy	OCT (foveal scan)	CNN	58 patients (10 ABCA4, 20 RP1L1, 28 EYS)	17 healthy patients	Training accuracy: 90.6–100%; test class accuracy: ABCA4 100%, healthy 93.4%, EYS 89.8%, RP1L1 78.0%
Miere et al. (2019)	Stargardt (ABCA4), RP, Best disease vs. healthy	FAF	CNN	410 patients (125 Stargardt, 160 RP, 125 Best)	73 healthy patients	AUPRC ≥ 0.988 across all groups
Shah et al. (2020)	Stargardt (ABCA4) vs. healthy	OCT	(i) Pretrained CNN, (ii) custom CNN	647 images (Stargardt)	102 images (healthy)	Accuracy: 99.6%/97.9%; sensitivity: 99.8%/97.9%; specificity: 98.0%/98.0%; JSS 0.990/0.976
Chen et al. (2020)	RP (various genes) vs. healthy	Colour fundus	CNN	935 images (RP)	324 images (healthy)	AUROC 0.96; better than 4 general ophthalmologists (0.81) and similar as IRD specialist (0.96)
Miere et al. (2021)	Late GA AMD vs. late stage (Pseudo) Stargardt	FAF	CNN	204 images (IRD)	104 images (GA AMD)	Test accuracy 0.92; AUROC 0.981
Miere et al. (2022)	ABCA4 STGD1 vs. PRPH2-pseudo Stargardt PD	FAF	CNN	729 images (IRD)	—	Precision 0.883; sensitivity 0.883; AUROC 0.890 (vs. retina specialists 0.816)
Crincoli et al. (2023)	AVMD vs. BVDM	FAF & OCT	CNN	96 AVMD eyes (287 OCT & 208 FAF); 118 BVMD eyes (355 OCT & 325 BAF)	—	Accuracy 0.90, outperformed human graders
Liu et al. (2024)	Predict VA ≥ 20/40 in RP	IR SLO, OCT, combined	DL	314 patients (RP)	—	AUROC 0.83 (IR), 0.87 (OCT), 0.85 (combined); external testing: 0.78 (IR), 0.87 (OCT), 0.85 (combined)
Veturi et al. (2024)	Synthetic IRD FAF generation (StyleGAN2)	FAF	StyleGAN2 + CNN	15,692 images (IRD)	—	Visual Turing Test image recognition: true 63%; fake 47%; CNN performance unchanged with synthetic data

AI: artificial intelligence; *ML*: machine learning; *DL*: deep learning; *OCT*: optical coherence tomography; *FAF*: fundus autofluorescence; *IR SLO*: infrared scanning laser ophthalmoscopy; *CNN*: convolutional neural network; *AUROC*: area under the receiver operating characteristic curve; *AUPRC*: area under the precision–recall curve; *JSS*: Jaccard similarity score; *VA*: visual acuity; *GA AMD*: geographic atrophy secondary to age-related macular degeneration; *STGD1*: Stargardt disease type 1; *PD*: pattern dystrophy; *AVMD*: adult-onset vitelliform macular dystrophy; *BVMD*: Best vitelliform macular dystrophy

Artificial intelligence in segmenting retinal layers

In 2018, Camino et al. developed an algorithm based on a CNN to determine regions of preserved photoreceptors on *en face* OCT in 20 choroideremia And 22 retinitis pigmentosa patients. The performance of the algorithm was evaluated using the JSS. For retinitis pigmentosa, the algorithm achieved a JSS of 0.894 ± 0.102, which is slightly lower than the 0.912 ± 0.055 obtained for choroideremia. The authors concluded that an automated algorithm can effectively segment and classify preserved and disrupted EZ areas in choroideremia, retinitis pigmentosa, and possibly other IRDs from OCT images [33]. Davidson et al. developed a deep learning algorithm to automatically localise cone photoreceptors within adaptive optics scanning light ophthalmoscopy (AOSLO) split-detection images. Monitoring cones with AOSLO provides insights into retinal structure and health, allowing evaluation of natural progression or treatment effectiveness. Generally, AOSLO split-detection images are manually analysed to identify the locations of cone photoreceptor cells. For the segmentation and classification task, the authors used a combination of convolutional layers, multi-dimensional long short-term memory (MDLSTM) layers, And fully connected layers to develop the optimal model, achieving a Dice score of 0.9577 on the validation set. They validated their method using images from healthy subjects and those with Stargardt disease, demonstrating that it was more accurate and faster in localizing cones compared to manual segmentation [34]. Wang et al. developed a random forest-based ML method to automatically determine the integrity of the EZ in 16 patients with choroideremia. After post-processing, they achieved a JSS value of 0.876 ± 0.066. According to the authors,

major challenges for the study included shadows caused by retinal vessels and/or vitreous floaters. The algorithm was applied to *en face* images, requiring only the delineation of Bruch's membrane, which avoided the difficulties of segmenting the EZ in severely degenerated retinas in IRDs [35]. Charng et al. developed a deep learning algorithm to segment hyperautofluorescent flecks on FAF imaging in Stargardt patients. The number And size of hyper-autofluorescent flecks increase with disease progression; however, manual segmentation is time-consuming. A total of 47 FAF images from 24 patients with Stargardt disease were used. Dice scores between deep learning And manual segmentation were calculated for 10 left eye images, ranging from 0.33 to 0.80. The authors suggested that the lower Dice scores were observed due to the training set's inclusion of images with only a few flecks and speckled signals on autofluorescence. They recommended that future studies include images with well-defined and more numerous fleck lesions [36]. A study from Sumaroka et al. investigated a supervised ML approach to predict foveal sensitivity and visual acuity from foveal OCT scans in patients with blue cone monochromacy (BCM). They employed two random forest models trained on BCM foveal scans to predict foveal sensitivity and visual acuity. The models accurately anticipated foveal sensitivity using the OCT data while also showing different predicted and measured sensitivities, which could indicate treatment potential in gene therapy trials. The authors concluded that foveal sensitivity and potential vision improvement with gene therapy in BCM patients could be predicted based on foveal morphological parameters using ML and curve fitting approaches [37]. Loo et al. validated a deep learning-based algorithm, originally developed for macular telangiectasia type 2, to automatically segment the EZ on OCT images of USH2A retinitis pigmentosa patients. The algorithm achieved An average Dice similarity coefficient of 0.79 ± 0.27, which the authors evaluated as a good performance. They concluded that this algorithm could be applied to other retinal diseases involving EZ disruption [38]. Eckardt et al. developed a U-Net-based model trained on healthy individuals to detect outer nuclear layer (ONL) segmentation in OCT scans of IRD patients, achieving a Dice score of 98.7% [39]. Table 2 presents a summary of AI studies investigating segmentation of retinal layers/structures or visual function prediction.

Future applications of artificial intelligence in IRD

As discussed previously, the ongoing Eye2Gene project will include 10,000 participants from three UK And one Japanese eye hospital with the aim of predicting a causative IRD gene based on multimodal imaging. For training And validation purposes, patients with the 36 most common IRD genes will be included, and multiple deep CNNs will be applied [21]. The aim is to reduce the diagnostic "odyssey" and

Table 2 Artificial intelligence studies that segment retinal layers/structures or predict visual function

Study (year)	Investigated disease/gene	Imaging modality & layer segmented/parameter predicted	Model architecture	Dataset (eyes/images)	Performance metric
Camino et al. (2018)	CHM, RP	En-face OCT, EZ integrity	CNN	42 eyes (20 CHM, 22 RP)	JSS (EZ): RP 0.894 ± 0.102; CHM 0.912 ± 0.055
Davidson et al. (2019)	Stargardt (ABCA4) & healthy patients	AOSLO, cone localisation	CNN + MD LSTM	142 healthy, 148 Stargardt images	Dice score: 0.958 (validation)
Wang et al. (2020)	CHM	En-face OCT, EZ integrity	Random Forest ML	16 patients	JSS (EZ): 0.876 ± 0.066
Charng et al. (2020)	Stargardt (ABCA4)	FAF, hyperautofluorescent flecks	U-net CNN	47 images (24 pts)	Dice score: 0.33–0.80
Sumaroka et al. (2021)	BCM	OCT foveal scan → predict foveal sensitivity/VA	Random Forest regression	18 BCM eyes	Accurate foveal sensitivity and VA prediction
Loo et al. (2022)	RP (USH2A)	OCT, EZ segmentation	Pretrained DL (Mac Tel-2 model)	127 OCT volume scans	Dice 0.79 ± 0.27
Eckardt et al. (2023)	IRDs, healthy	OCT, ONL segmentation	U-net (healthy individuals)	12 healthy, 25 IRD OCT volume scans	Dice 0.987

AOSLO: adaptive optics scanning laser ophthalmoscopy; *BCM*: blue cone monochromacy; *CHM*: choroideremia; *CNN*: convolutional neural network; *DL*: deep learning; *EZ*: ellipsoid zone; *FAF*: fundus autofluorescence; *IRDs*: inherited retinal diseases; *MD LSTM*: multidimensional long short-term memory; *ML*: machine learning; *Mac Tel 2*: macular telangiectasia type 2; *OCT*: optical coherence tomography; *ONL*: outer nuclear layer; *RP*: retinitis pigmentosa; *USH2A*: Usher syndrome type IIA; *VA*: visual acuity; *JSS*: Jaccard similarity score.

lower costs by suggesting the causative gene from imaging. By suggesting the causative gene through AI, reduced costs, shorter waiting times, and improved diagnostic rates could be achieved through a tiered AI-driven genetic testing strategy, not only in the UK but also worldwide [21].

In IRDs, medical history, including family history data, age of onset, type of visual symptoms, and other medical history to identify syndromic IRDs, is very important for establishing the diagnosis and determining the causative gene. Therefore, a user-friendly ChatGPT-like language model could first acquire medical history data before requesting input from the patient on specific multimodal imaging modalities and then suggest the diagnosis, causative gene, and progression. Moreover, after obtaining inputs on medical history, multimodal imaging, and molecular testing results, a ChatGPT-like language model could also provide genetic counselling to patients.

With longitudinal multimodal imaging data and accurate molecular diagnoses, AI algorithms could be developed to model morphological and functional progression in specific IRDs. Moreover, by inputting morphological and functional data, AI algorithms could predict visual function changes based solely on multimodal imaging data. Additionally, through pattern recognition, they could identify previously undetected morphological parameters that correlate with visual function impairment. AI algorithms could also predict pathogenicity in novel mutations currently classified as variants of uncertain significance (VUS).

Lastly, AI applications could significantly benefit the identification of patients eligible for gene therapy interventions and assist in determining realistic and personalized outcomes in gene therapy trials. Mutations in *RPE65* account for approximately 2–16% of cases of Leber congenital amaurosis (LCA) And 1–2.7% of cases in patients with autosomal recessive retinitis pigmentosa [40]. Genetic testing for all patients with LCA and retinitis pigmentosa is unattainable in many countries due to high costs and lack of infrastructure. Consequently, many patients with *RPE65*-associated IRDs who could benefit from VN gene therapy remain unrecognized. An AI classification algorithm could be developed to differentiate RPE65-associated IRDs from retinitis pigmentosa caused by other pathogenic mutations using clinical imaging. Such a tool could serve as a clinically useful, low-cost, and rapid screening method to identify patients for confirmatory genetic testing for RPE65-associated IRDs. Similar AI models could be used to facilitate the identification of patients with specific causative gene mutations for inclusion in several ongoing or future gene therapy trials. Several ocular gene therapies for IRDs have failed, partly due to the use of functional endpoints more suitable for prevalent And homogeneous disease entities, where a visual acuity improvement of 3 lines is considered significant. In many IRDs, achieving such a treatment effect is unrealistic; some patients maintain very good visual acuity until the late stages of the disease (e.g., choroideremia, retinitis pigmentosa), And a ceiling effect makes such improvements difficult or impossible to achieve. In other IRD patients, visual acuity gains are limited by irreversible structural changes, allowing for a maximum VA improvement of less than 3 lines, even in the best-case scenario. A robust AI algorithm capable of predicting an individual's potential for VA gain could help identify treatment responses in low-prevalence diseases such as IRDs. For some patients, An AI algorithm might predict that a vision improvement of 2 lines is sufficient to demonstrate efficacy in one patient, while in another, stabilization of vision could be considered a successful outcome.

However, several limitations remain before AI applications can be widely adopted in everyday clinical practice globally. Nomenclature and classification systems are not standardized, and ethnic and regional variations within the same disease-causing gene worldwide may restrict the applicability of AI algorithms to regions with patient populations similar to those in the training dataset. Additionally, obtaining standardized, high-quality multimodal imaging is essential for the effective application of AI algorithms. Other challenges include concerns about clinical safety and medical liability, ownership of health data and AI algorithms, cybersecurity issues, and the "black-box" problem, which refers to the lack of transparency in how AI algorithms make decisions [41].

Conclusion

We have conducted a comprehensive review of AI applications in IRDs. Currently, AI is primarily used for diagnosis, prediction of causative genes, and segmentation of retinal layers. Although significant advances have been made, AI models are not yet widely implemented in everyday clinical practice. Ongoing efforts are focused on developing AI algorithms to reduce costs, shorten time to diagnosis, and improve diagnostic rates. In the future, AI applications in IRDs could expand to include genetic counselling, predicting the natural course of IRDs, assessing the pathogenicity of novel mutations, identifying patients eligible for gene therapy interventions, and predicting personalized outcomes after gene therapy.

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Declarations

Ethical approval This review solely involves analysis of existing literature without any new experiments on humans or animals.

Competing interests The authors declare no competing interests.

Consent for publication Not applicable.

Consent to participate Not applicable.

References

1. Heath Jeffery RC, Mukhtar SA, McAllister IL, Morgan WH, Mackey DA, Chen FK (2021) Inherited retinal diseases are the most common cause of blindness in the working-age population in Australia. Ophthalmic Genet 42(4):431–439
2. Amato A, Arrigo A, Aragona E, Manitto MP, Saladino A, Bandello F et al (2021) Gene therapy in inherited retinal diseases: an update on current state of the art. Front Med (Lausanne) 8:750586
3. Galvin O, Chi G, Brady L, Hippert C, Del Valle Rubido M, Daly A et al (2020) The impact of inherited retinal diseases in the Republic of Ireland (ROI) and the united Kingdom (UK) from a Cost-of-Illness perspective. Clin Ophthalmol 14:707–719
4. Hanany M, Rivolta C, Sharon D (2020) Worldwide carrier frequency and genetic prevalence of autosomal recessive inherited retinal diseases. Proc Natl Acad Sci U S A 117(5):2710–2716
5. Fenner BJ, Tan TE, Barathi AV, Tun SBB, Yeo SW, Tsai ASH et al (2021) Gene-Based therapeutics for inherited retinal diseases. Front Genet 12:794805
6. Gong J, Cheung S, Fasso-Opie A, Galvin O, Moniz LS, Earle D et al (2021) The impact of inherited retinal diseases in the united States of America (US) and Canada from a Cost-of-Illness perspective. Clin Ophthalmol 15:2855–2866
7. Duncan JL, Pierce EA, Laster AM, Daiger SP, Birch DG, Ash JD et al (2018) Inherited retinal degenerations: current landscape and knowledge gaps. Transl Vis Sci Technol 7(4):6
8. Karali M, Testa F, Di Iorio V, Torella A, Zeuli R, Scarpato M et al (2022) Genetic epidemiology of inherited retinal diseases in a large patient cohort followed at a single center in Italy. Sci Rep 12(1):20815
9. Sahel JA, Marazova K, Audo I (2014) Clinical characteristics and current therapies for inherited retinal degenerations. Cold Spring Harb Perspect Med 5(2):a017111
10. Maguire AM, Russell S, Wellman JA, Chung DC, Yu ZF, Tillman A et al (2019) Efficacy, safety, and durability of voretigene Neparvovec-rzyl in RPE65 Mutation-Associated inherited retinal dystrophy: results of phase 1 and 3 trials. Ophthalmology 126(9):1273–1285
11. Russell S, Bennett J, Wellman JA, Chung DC, Yu ZF, Tillman A et al (2017) Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. Lancet 390(10097):849–860
12. Kaur C, Foulds WS, Ling EA (2008) Blood-retinal barrier in hypoxic ischaemic conditions: basic concepts, clinical features and management. Prog Retin Eye Res 27(6):622–647
13. Anand V, Duffy B, Yang Z, Dejneka NS, Maguire AM, Bennett J (2002) A deviant immune response to viral proteins and transgene product is generated on subretinal administration of adenovirus and adeno-associated virus. Mol Ther 5(2):125–132
14. Liang FQ, Anand V, Maguire AM, Bennett J (2001) Intraocular delivery of recombinant virus. Methods Mol Med 47:125–139
15. Jiang F, Jiang Y, Zhi H, Dong Y, Li H, Ma S et al (2017) Artificial intelligence in healthcare: past, present and future. Stroke Vasc Neurol 2(4):230–243
16. Schmidt-Erfurth U, Sadeghipour A, Gerendas BS, Waldstein SM, Bogunović H (2018) Artificial intelligence in retina. Prog Retin Eye Res 67:1–29
17. Jordan MI, Mitchell TM (2015) Machine learning: trends, perspectives, and prospects. Science 349(6245):255–260
18. Britten-Jones AC, Schultz J, Mack HG, Kearns LS, Huq AJ, Ruddle JB et al (2024) Patient experiences and perceived value of genetic testing in inherited retinal diseases: a cross-sectional survey. Sci Rep 14(1):5403
19. Weisschuh N, Mazzola P, Zuleger T, Schaeferhoff K, Kühlewein L, Kortüm F et al (2024) Diagnostic genome sequencing improves diagnostic yield: a prospective single-centre study in 1000 patients with inherited eye diseases. J Med Genet 61(2):186–195
20. Kiraly P, Downes SM, Fischer MD (2023) Retinal angiomatous proliferation in a patient with retinitis pigmentosa. Genes(Basel). 2023;14(7). https://doi.org/10.3390/genes14071438
21. Nguyen Q, Woof W, Kabiri N, Sen S, Daich Varela M, De Cabral TA et al (2023) Can artificial intelligence accelerate the diagnosis of inherited retinal diseases? Protocol for a data-only retrospective cohort study (Eye2Gene). BMJ Open 13(3):e071043
22. Tan TE, Chan HW, Singh M, Wong TY, Pulido JS, Michaelides M et al (2021) Artificial intelligence for diagnosis of inherited retinal disease: an exciting opportunity and one step forward. Br J Ophthalmol 105(9):1187–1189
23. Stone EM, Andorf JL, Whitmore SS, DeLuca AP, Giacalone JC, Streb LM et al (2017) Clinically focused molecular investigation of 1000 consecutive families with inherited retinal disease. Ophthalmology 124(9):1314–1331
24. Fujinami-Yokokawa Y, Pontikos N, Yang L, Tsunoda K, Yoshitake K, Iwata T et al (2019) Prediction of causative genes in inherited retinal disorders from Spectral-Domain optical coherence tomography utilizing deep learning techniques. J Ophthalmol 2019:1691064
25. Miere A, Le Meur T, Bitton K, Pallone C, Semoun O, Capuano V et al (2020) Deep learning-based classification of inherited retinal diseases using fundus autofluorescence. J Clin Med. 2020;9(10). https://doi.org/10.3390/jcm9103303
26. Shah M, Roomans Ledo A, Rittscher J (2020) Automated classification of normal and Stargardt disease optical coherence tomography images using deep learning. Acta Ophthalmol 98(6):e715–e21
27. Chen TC, Lim WS, Wang VY, Ko ML, Chiu SI, Huang YS et al (2021) Artificial intelligence-assisted early detection of retinitis pigmentosa - the most common inherited retinal degeneration. J Digit Imaging 34(4):948–958
28. Miere A, Capuano V, Kessler A, Zambrowski O, Jung C, Colantuono D et al (2021) Deep learning-based classification of retinal atrophy using fundus autofluorescence imaging. Comput Biol Med 130:104198

29. Miere A, Zambrowski O, Kessler A, Mehanna CJ, Pallone C, Seknazi D et al (2021) Deep learning to distinguish *ABCA4*-related Stargardt disease from *PRPH2*-related pseudo-Stargardt pattern dystrophy. J Clin Med. https://doi.org/10.3390/jcm10245742
30. Crincoli E, Zhao Z, Querques G, Sacconi R, Carlà MM, Giannuzzi F et al (2022) Deep learning to distinguish best vitelliform macular dystrophy (BVMD) from adult-onset vitelliform macular degeneration (AVMD). Sci Rep 12(1):12745
31. Liu TYA, Ling C, Hahn L, Jones CK, Boon CJ, Singh MS (2023) Prediction of visual impairment in retinitis pigmentosa using deep learning and multimodal fundus images. Br J Ophthalmol 107(10):1484–1489
32. Veturi YA, Woof W, Lazebnik T, Moghul I, Woodward-Court P, Wagner SK et al (2023) Syntheye: investigating the impact of synthetic data on artificial intelligence-assisted gene diagnosis of inherited retinal disease. Ophthalmol Sci 3(2):100258
33. Camino A, Wang Z, Wang J, Pennesi ME, Yang P, Huang D et al (2018) Deep learning for the segmentation of preserved photoreceptors on en face optical coherence tomography in two inherited retinal diseases. Biomed Opt Express 9(7):3092–3105
34. Davidson B, Kalitzeos A, Carroll J, Dubra A, Ourselin S, Michaelides M et al (2018) Automatic cone photoreceptor localisation in healthy and Stargardt afflicted retinas using deep learning. Sci Rep 8(1):7911
35. Wang Z, Camino A, Hagag AM, Wang J, Weleber RG, Yang P et al (2018) Automated detection of preserved photoreceptor on optical coherence tomography in choroideremia based on machine learning. J Biophotonics 11(5):e201700313
36. Charng J, Xiao D, Mehdizadeh M, Attia MS, Arunachalam S, Lamey TM et al (2020) Deep learning segmentation of hyperautofluorescent fleck lesions in Stargardt disease. Sci Rep. https://doi.org/10.1038/s41598-020-73339-y
37. Sumaroka A, Cideciyan AV, Sheplock R, Wu V, Kohl S, Wissinger B et al (2020) Foveal therapy in blue cone monochromacy: predictions of visual potential from artificial intelligence. Front Neurosci 14:800
38. Loo J, Jaffe GJ, Duncan JL, Birch DG, Farsiu S, Validation of a deep learning-based algorithm, for segmentation of the ellipsoid zone on optical coherence tomography images of an ush2a-related retinal degeneration clinical trial (2022) Retina 42(7):1347–1355
39. Eckardt F, Mittas R, Horlava N, Schiefelbein J, Asani B, Michalakis S et al (2024) Deep Learning-Based retinal layer segmentation in optical coherence tomography scans of patients with inherited retinal diseases. Klin Monbl Augenheilkd
40. Kiraly P, Cottriall CL, Taylor LJ, Jolly JK, Cehajic-Kapetanovic J, Yusuf IH et al (2023) Outcomes and adverse effects of voretigene neparvovec treatment for biallelic *RPE65*-mediated inherited retinal dystrophies in a cohort of patients from a single center. Biomolecules.2023;13(10). https://doi.org/10.3390/biom13101484
41. Veritti D, Rubinato L, Sarao V, De Nardin A, Foresti GL, Lanzetta P (2024) Behind the mask: a critical perspective on the ethical, moral, and legal implications of AI in ophthalmology. Graefes Arch Clin Exp Ophthalmol 262(3):975–982

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