Adaptive optics imaging of inherited retinal diseases

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ABSTRACT
Adaptive optics (AO) ophthalmoscopy allows for non-invasive retinal phenotyping on a microscopic scale, thereby helping to improve our understanding of retinal diseases. An increasing number of natural history studies and ongoing/planned interventional clinical trials exploit AO ophthalmoscopy both for participant selection, stratification and monitoring treatment safety and efficacy. In this review, we briefly discuss the evolution of AO ophthalmoscopy, recent developments and its application to a broad range of inherited retinal diseases, including Stargardt disease, retinitis pigmentosa and achromatopsia. Finally, we describe the impact of this in vivo microscopic imaging on our understanding of disease pathogenesis, clinical trial design and outcome metrics, while recognising the limitation of the small cohorts reported to date.

INTRODUCTION
Inherited retinal disease (IRD) is the leading cause of legal blindness in England and Wales among the working age population and the second most common in childhood.1 IRD is a group of clinically heterogeneous conditions, which can result in diagnostic challenges, often thereby necessitating detailed multimodal retinal imaging, as well as electrophysiological and psychophysical evaluation. They are subject to a broad range of research avenues and interventions which have been recently reviewed.9 Here, we categorise IRDs on the basis of natural history (stationary or progressive) and the primarily affected retinal cell type.

In vivo retinal imaging has been rapidly evolving over the last decades primarily due to advances in optics, electronics and computer technology. The introduction of optical coherence tomography (OCT) has revolutionised the clinical investigation of retinal diseases.34 One of the main limiting factors for in vivo retinal imaging is ocular aberrations, due to the optical imperfections of the eye.5 Adaptive optics (AO) can be employed in ophthalmology to overcome the aforementioned limitation.6

BRIEF OVERVIEW OF AO RETINAL IMAGING
The incorporation of AO to any ophthalmoscopic technique, including fundus photography, OCT and scanning laser ophthalmoscopy (SLO), provides in vivo microscopic imaging.6–9 AO ophthalmoscopes typically use a wavefront sensor to measure the ocular monochromatic aberrations and a deformable mirror to correct for the detected aberrations.6 9 10 Herein we will be focusing on AOSLO photoreceptor imaging as this is the modality that has been most extensively used in patients with IRD. By focusing a scanning light source on the photoreceptor layer and rejecting out-of-focus light through the use of a confocal aperture, axial sectioning is achieved, thereby increasing image contrast.8 11 Photoreceptors with relatively intact outer segments waveguide some incident light, and backscatter a very small fraction (less than 0.1%), which is used for imaging.12 When collecting that light in a confocal detector, the cone,8 13 14 and perifoveal rod8 15 16 mosaics can be resolved. Several systems have been developed including both custom-built and commercially available devices.

The non-confocal backscattered light can also be exploited to reveal the photoreceptor inner segment mosaic. For example, the split detection (SD) technique (SD-AOSLO) does so by subtracting images created by capturing the light to the left of the confocal aperture with one detector and the light to the right of it with a different one.17 This recent development was transformational because cones with compromised outer segments (as would be anticipated in the majority of IRDs) can now be reliably identified for the first time. This has major implications for patient stratification and targeting of intervention.18–25

Due to light safety restrictions, each individual AOSLO raw frame is captured using very low illumination power (≈100 µW at the pupil) and thus the resulting images are inherently noisy. Therefore, AOSLO image sequences are captured at each retinal location of interest, and used to create a higher signal-to-noise ratio (SNR) image by averaging a few of these frames after correcting for eye motion and scanning distortions.26 These high SNR images are then stitched together to create a larger montage (figure 1). A range of photoreceptor metrics have been employed to date, with cone density for a given eccentricity being the most widely used, and usually compared with normative data from histology27 or imaging studies.13 28 29 Other metrics include (1) cone spacing—average distance between cells in a given location, (2) Voronoi analysis (figure 1) which involves counting the number of neighbouring cells based on the distance between them, thereby assessing mosaic geometry,28 (3) reflectivity,18 and (4) metrics for the preferred orientation of cones and local spatial anisotropy.30

The combination of OCT and AO (AO-OCT) is an evolving field, aiming for 3D reconstruction and offers greater axial resolution compared with AOSLO.31
IRDS and AO retinal ophthalmoscopy

The selected conditions below have been prioritised based on the ability of published AO ophthalmoscopy studies to demonstrate clinical, research or trial utility. There are inherent limitations due to the often small cohorts reported to date. These are usually small due to the vast genetic and phenotypic heterogeneity of IRDs, the low prevalence of each genotype and due to the difficulty of establishing multicentre studies given the limited availability of AOSLO. However, similar limitations are often faced by other studies using other modes of high-resolution imaging. For clarity, we have included the number of subjects in each study we describe and whether the patients were molecularly confirmed (online supplementary table 1).

Macular dystrophies

Stargardt disease

Stargardt disease (STGD1) is the most common form of hereditary macular dystrophy.12 Confocal AOSLO (cAOSLO) has demonstrated abnormal and decreased cone spacing in regions corresponding to areas of reduced and irregular fundus autofluorescence (FAF), in predominantly late-onset/foveal sparing molecularly proven patients (11 of 12 patients).33 Moreover, foveal retinal pigment epithelium (RPE) cells were imaged in areas where the photoreceptor mosaic appeared disrupted in confocal reflectance imaging, suggesting photoreceptor loss preceding RPE cell loss—although the application of SD-AOSLO would address whether there are in fact cone inner segments present.33 Song et al also reported increased photoreceptor spacing, in genetically proven STGD1 (n=2), in otherwise normal appearing areas on OCT and FAF imaging; also consistent with photoreceptor loss preceding clinically detectable RPE disease.34 Interestingly, SD-AOSLO derived cone density has been shown to correlate well with OCT measurements of outer nuclear layer thickness and retinal sensitivity (n=14; all molecularly confirmed), demonstrating a valuable structure-function association, even though the extent of atrophic changes was not corresponding to visual acuity.19 Using cAOSLO and SD-AOSLO, Tanna et al investigated the reliability and repeatability of cone counting in patients with STGD1 (n=12), suggesting superior reliability and repeatability with SD-AOSLO.35

Longitudinal imaging studies of the photoreceptor and RPE mosaic in large molecularly proven specific STGD1 cohorts (ie, childhood-onset, adult-onset and late-onset/foveal sparing) are needed to evaluate cellular disease progression and potentially identify the most suitable participants for ongoing and multiple planned gene therapy and pharmacological interventions.39 33 34 36 AO ophthalmoscopy may be a useful method of monitoring in trials, since ‘classic’ parameters of ophthalmological examination including best corrected visual acuity (BCVA) are not sufficiently sensitive outcome measures for conditions such as STGD1.37

Best disease

Normal photoreceptor structure and cone densities in areas adjacent to clinically visible lesions have been reported, with persistent photoreceptor structure overlying stage 1 and 2 vitelliform Best disease lesions, in keeping with relatively intact visual acuity (VA).38 Using AOSLO and SD-AOSLO, variable photoreceptor architecture has been observed to be associated with different stages of the disease and the location within the lesions, including reduced cone density, due to major discontinuities/gaps in the mosaic, and cone inner segment enlargement.21

X-linked retinoschisis

Duncan et al19 have reported increased and irregular cone spacing within the foveal schisis characterising X-linked retinoschisis. Interestingly, cone spacing was normal and regular elsewhere. The preserved waveguiding cones at the fovea and eccentric macular regions may indicate increased likelihood of successful rescue with intervention—and could also be helpful in patient selection.

Stationary dysfunction syndromes

Cone dysfunction syndromes

This group of disorders has been reviewed in detail previously40 (figure 2).

Achromatopsia

Early investigations with cAOSLO identified ‘dark spaces’ in the cone mosaic, increased cone spacing and/or decreased cone density in patients with achromatopsia (ACHM)16 18 41 42 (figure 2: 1C and 2C). Marked variability in the cone mosaic has been observed across patients; with no significant difference between the two most common genotypes, CNGA3 and CNGB352 43; and the rarer GNAT2 genotype associated with

![Figure 1](image-url) Adaptive optics scanning laser ophthalmoscopy (AOSLO) imaging of a healthy subject and cone quantification. (A) Colour fundus photograph (30°) of a healthy subject (MM_0136), with AOSLO montage superimposed. The white square encompasses the foveal avascular zone (region of interest, ROI), which is magnified in (B). (B) Confocal AOSLO of the ROI, the estimated foveal centre is marked with a white cross and the 55 μm×55 μm area of sampling for cone counting with a white box at 0.35° from the foveal centre. Scale bar=100 μm. (C) Magnified view of the sampled area. (D) The sampled area with cones marked. (E) The sampled area with Voronoi domains. (F) The Voronoi representation coloured according to the number of neighbouring cells. Green represents six-sided bound cones. Scale bar for (C–F)=20 μm.
the relatively least disrupted photoreceptor mosaic. Until the advent of SD-AOSLO, it was unknown if these “dark spaces” harboured non-waveguiding cones or indicated loss of cones— with the presence or absence of cones being directly related to potential rescue with intervention. Simultaneous cAOSLO and SD-AOSLO have allowed the identification of cone inner segment structure in these spaces, with transformational implications on our understanding of ACHM and participant selection for ongoing CNGA3-ACHM and CNGB3-ACHM gene therapy trials (figure 2: 1D and 2D).

Given the potential disconnect between OCT and AO measures of cone integrity and the ability of AO to directly visualise the target cones for gene replacement, non-confocal SD-AOSLO imaging would be the modality of choice to identify patients most likely to benefit from cone-directed rescue.

In the largest AO ophthalmoscopy ACHM study to date (n=52), significantly decreased peak foveal cone densities and increased spacing, using SD-AOSLO in CNGB3-ACHM has been reported. Interestingly, the peak foveal density ranges were shown to overlap between the previously described OCT grades, in keeping with the aforementioned disconnect.

Reduced reflectivity in the majority of residual cones in CNGA3 and CNGB3 has also been noted, with relative preservation in GNAT2. Changes in cone reflectivity could potentially provide a clinical trial outcome metric.

Directly relevant to the ongoing debate on whether ACHM is significantly progressive, based on serial OCT and AOSLO, a longitudinal study of CNGB3-ACHM, with follow-up of 6–26 months, showed little or no detectable change in foveal cone structure over time.

**Blue cone monochromacy**

Blue cone monochromacy (BCM) is associated with a range of opsins array genotypes, affecting both L and M cones. The condition is X-linked, and despite female carriers being asymptomatic, cAOSLO has demonstrated variably reduced cone density, increased spacing and disrupted organisation, with phenotypic variability likely relating to random X-chromosome inactivation. Affected men have a more severe phenotype, although the degree of cone mosaic disruption is also highly variable and may be partly related to specific genotype group.

**Figure 2** Adaptive optics scanning laser ophthalmoscopy (AOSLO) imaging of the cone dysfunction syndromes. Column (A) shows the infrared reflectance (IR) fundus photographs for each subject (1, 2, 3, 4). The green arrow represents the section in which the optical coherence tomography (OCT) (Spectrals HRA+OCT, Heidelberg Engineering, Heidelberg, Germany) presented in column (B) is taken; the black square represents the 450 μm×300 μm region of interest imaged with AOSLO which is presented in columns (C) and (D). Column (B) shows OCT horizontal scans through the fovea and the white arrows mark the corresponding AOSLO area (450 μm wide). Column (C) depicts confocal AOSLO (cAOSLO) and column (D) split detection (SD) AOSLO. Subjects (1) and (2) have achromatopsia associated with CNGB3 and CNGA3 gene mutations, respectively. (1C/2C) Dark spaces are observed, due to loss of cone waveguiding properties, which correspond to visible foveal cone inner segments in (1D/2D), respectively, with a substantial difference in cone numerosity between the two subjects. (3) A molecularly confirmed subject with blue cone monochromacy. (3C) Dark foveal centre, with a sparse array of large bright spots, which are believed to be S cones, immediately surrounding it. (3D) Remnant inner segment structure. (4) A molecularly confirmed subject with Bornholm eye disease (LIAVA haplotype). (4C) All cones are resolved in cAOSLO, with a few apparent non-waveguiding cones (dark spaces). (4D) SD-AOSLO does not resolve foveal inner segments due to the better preserved mosaic (smaller cone diameters and tighter packing geometry) compared with the other cone dysfunction syndromes. All AOSLO images were acquired using a custom-built AOSLO housed at University College London/Moorfields Eye Hospital, London. Scale bar=50 μm.
L/M interchange haplotypes have been associated with significantly greater residual parafoveal cone structure, with localised loss of waveguiding cones at the fovea. In contrast, the inactivating Cys203Arg missense mutation genotype group is associated with greater loss of waveguiding L/M cones. cAOSLO images of the cone mosaic typically show a dark foveal centre, with a sparse array of large bright spots, which are believed to be S cones, immediately surrounding it (figure 2C). It is possible to estimate with reasonable confidence the number of L and M cones in the parafovea, as they appear as dark gaps within the rod mosaic. cAOSLO has demonstrated a reduced number of cones in the parafovea (both reflective S cones and non-reflective L cones and M cones) to that of about 25% of normal, with evidence of even greater loss of cone cells in the locus control region deletion genotype group of BCM. Moreover, SD-AOSLO images have revealed remnant inner segment structure (figure 2B) both at the fovea and the parafovea. Importantly, however, despite low cone density in BCM, the number is higher than that expected for the S cone submosaic, in keeping with remnant L/M cones.

Overall, these AOSLO imaging studies have identified significant intersubject variability in cone mosaic integrity and illustrate the importance of cellular imaging in the identification of remnant cones that have the potential to be rescued in planned interventions.

Oligocone trichromacy and RGS9/R9AP-associated retinopathy (‘Bradyopia’)
The cone photoreceptor mosaic in three patients with typical oligocone trichromacy has been investigated, and in keeping with the original disease mechanism hypothesis, a decreased number (‘oligocone’) of otherwise normal appearing foveal cones (thereby permitting ‘trichromacy’) were observed, with absence of visible structure beyond the central fovea. RGS9/R9AP-associated retinopathy is clinically indistinguishable from oligocone trichromacy, but can be discerned using non-standard extended electrophysiological assessment or molecular genetic testing. However, unlike in oligocone trichromacy, cAOSLO has revealed a normal cone photoreceptor mosaic in subjects with RGS9/R9AP retinopathy, which is in agreement with the electroretinography (ERG) findings of normal initial response in dark-adapted flicker ERGs performed with a dim stimulus. Cellular phenotyping is therefore able to readily differentiate between these two conditions with common clinical features—with an intact photoreceptor mosaic in bradyopia and disruption in oligocone trichromacy.

Bornholm eye disease
Similar to BCM, Bornholm eye disease (BED) is an X-linked cone dysfunction syndrome that is associated with mutations in the L/M gene array. Predominantly due to the heterogeneity in the underlying genotype (predominantly L/M interchange haplotypes), the degree of photoreceptor mosaic disruption in affected men is highly variable, with cone density ranging from near normal to more than 75% reduction (figure 2: 4C and 4D). However, there is also high variability in the appearance of the cone mosaic within brothers who share the same genotype, likely owing to variations in L/M cone ratio. Cone density has been found to correlate with both axial length and the degree of myopia; however, systematic analysis of the relationship between these factors and the specific underlying L/M opsin variant is lacking, due to small numbers of subjects within each genotype group to date. Additionally, previous investigations employing AOSLO imaging have been cross-sectional, so there is a need for longitudinal studies to track larger genetically confirmed cohorts, both for BED and BCM, to determine natural history and thereby establish the potential for intervention.

Rod dysfunction syndromes

Congenital stationary night blindness
Godara et al reported Retinal structure in three patients with GRM6-associated congenital stationary night blindness. They identified a contiguous cone mosaic and normal cone densities with cAOSLO, in keeping with previous histopathology. They identified photoreceptor mosaic integrity and reported thinning of inner retinal layers on OCT, suggesting a functional defect in retinal neurotransmission, rather than a structural photoreceptor defect.

Oguchi disease
Oguchi disease is a very rare form of night blindness having the unusual distinguishing features of the Mizuo-Nakamura phenomenon: diffuse fundus discoloration and return to normal colour after prolonged dark adaption. To probe the underlying basis of this intriguing phenomenon, the photoreceptor mosaic has been investigated, both in light and dark-adapted conditions, in two molecularly confirmed siblings. Normal photoreceptor densities were identified; however, rod reflectivity (unlike cone) was shown to increase over time, changing from scotopic to photopic conditions, suggesting that rods are responsible for the unique fundus findings in Oguchi disease.

Fundus albipunctatus
Using fluorescence AOSLO and cAOSLO, Song et al have reported decreased foveal cone density and increased cone spacing at 10° of eccentricity, despite this predominantly being a rod disorder. No photoreceptors or RPE cells were visualised within the albipunctate spots. Another study also identified decreased perifoveal cone density and mosaic disruption using cAOSLO in RDH5-associated fundus albipunctatus.

Progressive retinal dystrophies

Rod-cone dystrophies
Non-syndromic retinitis pigmentosa
In X-linked RPGR-associated retinopathy, there is a phenotypic heterogeneity (both intrafamilial and interfamilial) among affected men. Female carriers’ phenotypes can vary widely, ranging from asymptomatic to severely affected (although not to the extent of affected men) and almost always present with a radial pattern of increased retinal reflectivity, the so-called tapetal-like reflex. The patchy appearance of rods and cones observed both ex vivo and in vivo (mosaicism) is believed to be due to random X-chromosome inactivation.

Several studies have reported a decrease in cone density and/or increased cone spacing using cAOSLO in patients with retinitis pigmentosa (RP), with approximately half of the subjects having an established genetic diagnosis (figure 3). Sun et al examined both patients with RP and Usher syndrome (USH) (see below) using cAOSLO and SD-AOSLO, and found that foveal cone density was reduced by up to 38% before VA was affected, without any visible findings on OCT (however, increased cone spacing was not identified in isolated RP cases). This was in keeping with a previous study reporting normal VA and retinal sensitivity in patients with up to 62% reduction in peak cone density. These studies illustrate the remarkable redundancy in
cone populations, the importance of multimodal imaging and the disconnect between retinal structure and function, with major implications for gene therapy, and also stem cell replacement strategies—including the potential need to successfully integrate smaller numbers of cones than previously believed.

A phase II/III trial has been undertaken with intravitreal implants of encapsulated human RPE cells engineered to continuously secrete ciliary neurotrophic factor (CNTF) protein in patients with early-stage and late-stage RP. Patients were randomly assigned to receive a high-dose or low-dose implant in one eye and sham surgery in the fellow eye. Primary endpoints were change in BCVA at 12 months for late-stage RP and change in visual field sensitivity at 12 months for early RP. Neither study showed a therapeutic benefit. However, a pilot study using AOSLO in three patients with CNTF implants over a 24-month period found that cone density remained stable in eyes with a CNTF implant, whereas there was continued cone loss in untreated fellow eyes, suggesting that more sensitive metrics are needed as primary outcome measures in progressive diseases such as RP.

AOSLO has been previously undertaken in one patient with USH type II, and three patients with USH type III. In USH-III, a relative preservation of foveal cone density was observed, with loss of cone structure in areas of absent retinal sensitivity. Using cAOSLO and SD-AOSLO as complementary modalities, Sun et al identified lower foveal and parafoveal cone densities in USH-II (n=4, USH2A) compared with non-syndromic RP (n=9 (2 X-linked RP RPGR; 3 autosomal recessive RP=2 USH2A and 1 EYS; 4 autosomal dominant RP=3 RHO and 1 RP1)) despite the normal appearance of interdigitation (IZ) and ellipsoid zones (EZ) on OCT, which was attributed by the authors to the decreased number of normal waveguiding cones (outer segment defects), possibly a result of the different molecular pathways affected in each condition and the localisation of the affected protein either in the connecting cilium or outer segment.

**Figure 3** Multimodal imaging of retinitis pigmentosa. (A) Infrared reflectance (IR) fundus photograph of a subject (MM_0205) with X-linked retinitis pigmentosa associated with RPGR gene. The white arrow represents the section of the optical coherence tomography (OCT) presented in (B). (B) Horizontal transfoveal OCT line scan, with the white arrows indicating the width of the corresponding AOSLO imaged area in (D). (C) Fundus autofluorescence imaging, with the confocal AOSLO (cAOSLO) imaged area (D) superimposed over the foveal avascular zone and the white arrow represents the section presented in the OCT scan (B). (D) cAOSLO imaging revealing a disrupted waveguiding mosaic, not as uniform in appearance as in a healthy subject (figure 1). (E) Magnification of cAOSLO over the estimated foveal centre (marked with a white dashed square in (D)) shows irregularly waveguiding cones, which appear dim (some are indicated with white arrows); and (F) the corresponding split detection AOSLO in exact spatial registration showing relatively healthy-appearing cone inner segments, the white arrows indicate the corresponding inner segments for the irregularly waveguiding cones identified with white arrows in (E).
Cone and cone-rod dystrophies

Cone-rod dystrophy

Using an AO flood-illuminated ophthalmoscope, one subject has been imaged showing a lack of waveguiding cones within clinically apparent atrophic regions and a contiguous cone mosaic elsewhere with enlarged cones and reduced peak cone densities. A correlation was observed between cone densities and multifocal ERG (mfERG) peak amplitudes. Similar observations, including structure-function correlation with mfERG, have been observed in three further studies of nine subjects in total. AOSLO cone spacing measurements also correlated significantly with mfERG amplitude, retinal sensitivity and VA. 

Cone dystrophy with supernormal rod responses

Vincent et al assessed macular morphology in cone dystrophy with supernormal rod responses with cAOSLO and reported decreased cone densities and a disrupted mosaic, with cones in groups, surrounded by patches of absent or non-waveguiding cones. It will be of interest to further investigate subjects with SD-AOSLO to probe whether the non-waveguiding cones are indeed absent or whether inner segments are present.

Chorioretinal dystrophies

Chorioideremia

Patchy cone loss in symptomatic carriers and a normal photoreceptor mosaic in asymptomatic carriers have been observed. Disrupted parfoveal mosaics, with increased cone spacing, were seen in affected men, with more regular spacing near the borders of atrophy. In combination with OCT findings, likely simultaneous degeneration of the RPE and photoreceptors was identified by Sun et al. No RPE cells were visible in areas of cone loss, with IZ dropout preceding EZ disruption. Investigators thereby proposed that chorioideremia (CHM) is primarily an RPE disorder followed by photoreceptor degeneration, with implications for intervention and the ongoing debate on cellular pathogenesis of CHM.

Only by using non-confocal SD-AOSLO has reliable visualisation of cones been possible in the bordering areas of atrophy, with abnormal and heterogeneous morphology, density and diameter. The cone mosaic terminates sharply before those areas, in direct contrast to previously reported RP transition zone imaging, which may relate to the likely primary RPE pathology in CHM. This study also concluded that RPE degeneration precedes photoreceptor loss. These studies have resulted in AOSLO being incorporated in many ongoing CHM gene therapy trials and natural history studies.

AO ophthalmoscopy offers invaluable identification of structural detail on a cellular level, with several studies described herein exploring correlation between structure and function. Evolving AO-guided retinal sensitivity assessments (‘nanopermetry’) will better allow correlation between cellular imaging and functional testing with exquisite retinotopic precision.

One major common limitation is the challenge in imaging patients with nystagmus (eg, ACHM) and/or poor fixation (eg, STGD). Eye tracking systems incorporated into AO systems can allow imaging of more subjects and improve data acquisition. Moreover, image processing and analysis are substantial bottlenecks that developments in, for example, machine learning, will hopefully solve in the near future, thereby allowing a broader application of AO technology.

While our review concentrates on IRDs, AO has been applied to many other conditions including albinism, age-related macular degeneration, diabetic retinopathy and autoimmune retinopathy, and also in basic and applied research, including facilitating insights in visual system neurophysiology.

CONCLUSIONS

AO is a rapidly evolving field, which has a place in diagnosis, advice on prognosis, monitoring and management of IRDs. It can also probe underlying pathophysiology and facilitate improved understanding of cellular retinal anatomy and biology. We anticipate an increasing use of AO systems in the future due to the complementary information they provide compared with other imaging modalities and the ability to target functional measurements on individual cells, with particular application in longitudinal natural history studies and ongoing/planned interventional trials both for participant selection and monitoring treatment safety and efficacy.

METHODS OF LITERATURE SEARCH

PubMed was searched for articles related to AO and IRDs up to June 2017 with key words: Adaptive Optics, AO, AOSLO, Retinal Imaging individually and in combination with the conditions’ name (eg, Achromatopsia) as well as their abbreviations (eg, ACHM).

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DISCUSSION AND FUTURE POSSIBILITIES

IRDs are the most genetically and phenotypically heterogeneous conditions in medicine, with certain genotypes being extremely rare making it challenging to establish large informative cohorts, suggesting the need for multicentre studies. Many of the studies incorporated in our review highlight the need for longitudinal monitoring. Insights into disease progression are of great value including identification of the optimal therapeutic window and participant stratification.
Review


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