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INVITED REVIEW

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Inherited retinal diseases: Therapeutics, clinical trials and end points—A review

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Abstract

Inherited retinal diseases (IRDs) are a clinically and genetically heterogeneous group of disorders characterised by photoreceptor degeneration or dysfunction. These disorders typically present with severe vision loss that can be progressive, with disease onset ranging from congenital to late adulthood. The advances in genetics, retinal imaging and molecular biology, have conspired to create the ideal environment for establishing treatments for IRDs, with the first approved gene therapy and the commencement of multiple clinical trials. The scope of this review is to familiarise clinicians and scientists with the current management and the prospects for novel therapies for: (1) macular dystrophies, (2) cone and cone-rod dystrophies, (3) cone dysfunction syndromes, (4) Leber congenital amaurosis, (5) rod-cone dystrophies, (6) rod dysfunction syndromes and (7) chorioretinal dystrophies. We also briefly summarise the investigated end points for the ongoing trials.

KEYWORDS

inherited retinal disease, retina, gene therapy, pharmacological therapy, stem cell

1 | INTRODUCTION

The inherited retinal diseases (IRDs) are a large group of clinically and genetically heterogeneous conditions which constitute the leading cause of legal blindness in England and Wales amongst working-age adults, and the second commonest in childhood.[1] Inherited disorders are classically divided into two sub-types: stationary[2] and progressive.[3] The stationary disorders (cone and rod dysfunction syndromes) are congenital or early-infantile onset, and give rise to predominantly cone or rod dysfunction, whereas progressive cone dystrophy (COD), cone-rod dystrophy (CORD), and rod-cone dystrophy (RCD) are usually of later-onset. The exception being Leber congenital amaurosis/early onset severe retinal dystrophy (LCA/EOSRD), with the vast majority of

affected individuals being legally blind from birth or early infancy. Recent advances in molecular genetics, particularly next generation sequencing (NGS), have greatly improved molecular diagnosis, as the underlying causative genes and pathogenic variants can be identified in a large proportion of patients.[4] Molecular genetic testing is crucial for accurate diagnosis, prognostication, and for the treatment prospects of targeted therapeutics.

Management of most forms of IRDs is symptomatic. Correction of refractive error and clear media (eg, cataract surgery), optimise visual potential and prevent amblyopia. The age of disease onset influences management. Infants with severe visual impairment may also have delays or difficulties with speech, social skills, and behaviour, highlighting the importance of a multispecialist approach. Access to low vision aids and assistive technologies, educational and work-related support and counselling, are all of paramount importance. The molecular characterization of patients is the cornerstone, in order to facilitate access to, and potential benefit from, the ongoing advances in the field. The first FDA- (Food and Drug Administration), EMA- (European Medicine Agency) and TGA- (Therapeutics Goods Administration) approved IRD gene therapy is available for *RPE65*-associated retinopathy,[5,6] and there are multiple other trials exploring multiple avenues underway for other IRDs. We have recently reviewed the retinal imaging findings of IRDs,[7] and the clinical phenotypes of: (1) macular dystrophies,[8] (2) COD and CORD,[9] (3) cone dysfunction syndromes[2] and (4) LCA/EOSRD.[10]

Herein we present the current management and the prospects for novel therapies for: (1) macular dystrophies, (2) COD and CORD, (3) cone dysfunction syndromes, (4) LCA/EOSRD, (5) RCDs, (6) rod dysfunction syndromes and (7) chorioretinal dystrophies. We also briefly summarise the investigated end points for the ongoing therapeutic trials, to help and guide clinicians through patient stratification and clinical trial results.

2 | MACULAR DYSTROPHIES

Macular dystrophies (MD) are a group of IRDs that cause significant visual loss, most often as a result of progressive macular atrophy. They are characterised by bilateral, relatively symmetrical macular abnormalities that significantly impair central visual function.[11] While the fundus findings may be predominantly located at the central retina, in the majority of MD there is psychophysical, electrophysiological, or histopathological evidence of more widespread generalised retinal involvement.[8]

2.1 | General management of MD

No specific curative treatment is available for MD. Current management includes refractive correction, low visual aids and educational support.[2] Tinted lenses (spectacles or contact lenses) can help with disabling photophobia, improving the quality of vision and ocular comfort.[12] Over the last decade, there have been multiple advances that now provide us a better understanding of the molecular mechanism(s) and associated pathophysiology underlying each subtype of macular dystrophy. This has thereby facilitated the development of therapeutic strategies to slow/halt progressive visual loss, or potentially restore a degree of visual function.[13]

2.2 | Stargardt disease (STGD)

ABCA4-associated STGD (STGD1, *ABCA4*, OMIM 601691) is the most common macular dystrophy. In addition to general recommendations, patients are advised not to take vitamin A supplements, due to toxic by-products of vitamin A having a crucial role in retinal toxicity secondary to ABCA4-deficiency, and to limit UV exposure to potentially slow disease progression, given the evidence of phototoxicity in animal models and patients with STGD1.[14,15]

Pharmacotherapy directly or indirectly targeting the visual cycle has been developed, including the complement-mediated response to accumulated by-products of the visual cycle.[16] Drugs such as soraprazan, emixustat, ALK-001, LBS-008, STG-001, fenretinide and A1120 are visual cycle modulators that impede formation (or enhance removal [soraprazan]) of A2E and lipofuscin, by either slowing the rate of vitamin A dimerization (ALK-001), or by competitive inhibitory mechanisms on the retinal binding protein-4 (LBS-008, STG-001, fenretinide and A1120), or by modulating the activity of RPE65 (emixustat). Many of these drugs are in Phase 1/2 or 3 trials (LBS-008: NCT03735810, emixustat: NCT03772665 and NCT03033108, ALK-001: NCT02402660). Avacincaptad pegol, a complement C5 inhibitor, is also being investigated in a Phase 2 trial (NCT03364153), as it is an antioxidant supplementation (saffron) (NCT01278277).

Pre-clinical studies in gene replacement that showed phenotypic improvement in *abca4*$^{-/-}$ mice have encouraged the development of human gene therapy trials[17,18]; currently employing a lentiviral vector (NCT01736592, NCT01367444).[19] Adeno-associated virus (AAV) has many advantages over lentiviral vectors but has limited cargo capacity; several strategies are being explored to try and accommodate the large *ABCA4* gene and thereby commence AAV-based gene therapy trials.[17,19]

In advanced disease, cell replacement strategies offer potential benefit. The only Phase 1/2 clinical trial (NCT01469832) of human embryonic stem cell (hESC)–

derived retinal pigment epithelium (RPE) cells in STGD has been completed.[20,21] Findings from the U.K. site of this trial identified subretinal hyperpigmentation consistent with the survival of viable transplanted hESC-derived RPE cells. Borderline improvements in visual acuity (VA) were noted in 4 of 12 patients; however, microperimetry did not demonstrate evidence of functional benefit at 12 months. Further trials are anticipated, including evaluation of combined RPE and photoreceptor transplants, which are either derived from hESCs or induced pluripotent stem cells (iPSC).

2.3 | Best disease (BD)

Best disease (*BEST1*, OMIM 607854) is the second commonest MD, and caused by dominant disease-causing variants in *BEST1*. Recessive alleles in *BEST1* cause autosomal recessive bestrophinopathy (ARB). Prognosis can often be relatively good in BD. However, progressive resorption of subretinal material can be associated with slow central visual deterioration, unless BD is complicated by choroidal neovascularization (CNV), which can result in acute marked visual loss. Acute visual loss and metamorphopsia, retinal haemorrhage and *intraretinal* fluid should raise suspicion of CNV and investigation; subretinal fluid (SRF) is unhelpful, given it is often observed in BD not complicated by CNV (thereby SRF is also not a useful indicator of CNV treatment response). Treatment with *anti*-vascular endothelial growth factor (VEGF) agents such as intravitreal bevacizumab has been found to be very effective, with improvement in structural and functional measurements, in direct contrast to observation alone.[22] Unlike other causes of CNV, those associated with IRD, often require limited injections, usually one or two are sufficient. Canine models of ARB have been successfully rescued with AAV-mediated gene replacement,[23,24] and investigation of disease natural history in humans has identified a wide window for intervention.[25] Research avenues for *BEST1*-dominant disease are at present limited. Human inducible pluripotent stem cell (hiPSC)–derived RPE models from patients harbouring autosomal dominant (AD) *BEST1* variants can potentially determine whether the gene augmentation approach would also be beneficial for dominant disease.[26]

2.4 | X-linked retinoschisis (XLRS)

XLRS (*RS1*, OMIM 300839) is the most common form of juvenile-onset retinal degeneration in males. It is traditionally classified under MD, given it primarily affects the macula, with peripheral retinal involvement being common. Prognosis is variable but can be relatively good in childhood if not complicated by retinal detachment (RD), or vitreous haemorrhage (VH)—which are both associated with a poor prognosis in childhood or adulthood.[27,28] Carbonic anhydrase inhibitors (CAIs) have been shown to be useful in managing schisis in XLRS.[29,30] There has also been a disconnect reported between VA improvement and lack of structural change.[31]

Intravitreal *RS1* gene replacement in knockout mice has resulted in functional ERG improvement.[32,33] This has led to two Phase 1/2 XLRS gene therapy trials (NCT02416622 and NCT02317887) delivering gene replacement intravitreally. The former trial has ceased due to ocular inflammation associated with intravitreal delivery and lack of robust efficacy signals, while the latter has added additional agents to the standard oral steroids used in subretinal gene supplementation trials to address the uveitis adverse events.

2.5 | Pattern dystrophy (PD)

PD is an AD condition most often due to variants in *PRPH2* (*PRPH2*, OMIM 179605) with variable distribution of pigment deposition at the level of the RPE. Successful integration and material transfer of donor- or stem cell-derived cone photoreceptors in $Prph2^{rd2/rd2}$ murine models of the disease is promising.[34]

2.6 | Sorsby fundus dystrophy (SFD)

Sorsby fundus dystrophy (*TIMP3*, OMIM 188826) is a rare AD drusen-associated MD often leading to bilateral central visual loss in the fifth decade of life due to development of atrophy with or without CNV. Prompt use of anti-VEGF injections may improve outcome for SFD complicated by CNV. Early attempts at treating SFD involved oral vitamin A at 50000 IU/day, with a short-term reversal of night blindness in patients at early stages of disease.[35] Due to the potential toxicity of long term high dose Vitamin A and reports of lack of efficacy at lower doses (15 000 IU/day) in advanced disease, vitamin A is not a widely used treatment.[36] Currently, no animal or cell culture model capable of recapitulating human SFD is available. Patient-derived iPSC-RPE models may provide a suitable platform for investigating SFD.[37]

3 | CONE DYSFUNCTION SYNDROMES

The cone dysfunction syndromes (CDS) are stationary cone disorders with congenital/early-infantile onset, variably

characterised by reduced central vision, colour vision abnormalities, nystagmus, and photophobia. Several genes have been implicated to date, associated with five distinct phenotypes: achromatopsia (complete and incomplete), blue-cone monochromatism, oligocone trichromacy, *RGS9/R9AP*-associated retinopathy ("Bradyopsia") and Bornholm eye disease. Those with therapeutic avenues being explored are discussed below.

3.1 | General management of CDS

No specific curative treatment is available for any CDS. Optimal refractive correction, low visual aids, educational support, tinted lenses (spectacles or contact lenses) can help symptomatic management, improving the quality of vision and ocular comfort.[12] Ongoing and upcoming gene therapy trials in CDS underline the importance of an accurate genetically confirmed diagnosis.

3.2 | Achromatopsia

Achromatopsia (ACHM) is the most common CDS (1:30 000). It presents either at birth or early infancy, with poor VA (20/120-20/200), pendular nystagmus, marked photophobia, and colour vision loss along all three axes of the colour space.[2,38] Disease-causing variants in *CNGB3* (OMIM 605080) and *CNGA3* (OMIM 600053) together account for the majority of ACHM,[39] with *CNGB3* accounting for 40-50% of cases in Europe.[40,41] The prevalence of each *GNAT2* (OMIM 139340)-, *ATF6* (OMIM 605537)-, *PDE6H* (OMIM 601190)-, and *PDE6C* (OMIM 600827)-associated ACHM is approximately 2% of patients.[39,42-46] It is a functionally stationary disorder, and is believed to be associated with a slow degeneration of the non-functional cones in a minority of patients.[47,48] Deep red tinted lenses can help with disabling photophobia, by reducing rod saturation.[12]

In *CNGB3*-ACHM, gene supplementation in a canine model showed improved cone function and daylight vision.[49] Currently there are two ongoing Phase 1/2 gene therapy trials (NCT03001310 and NCT02599922). A canine study that explored ciliary neurotrophic factor (CNTF) effects on cone photoreceptors had promising efficacy.[50] However, in humans, no measurably enhanced cone function was observed, which may partly be due to a species difference between human and canine CNGB3, cone response to CNTF (NCT01648452).[51]

In *CNGA3*-ACHM, gene supplementation in a knockout *CNGA3* mouse model has shown restoration of cone-specific visual processing in the central nervous system.[52] Further investigation showed greater therapeutic benefit (improvement of electroretinogram (ERG) amplitude) in younger mice, suggesting that age of treatment and the extent of photoreceptor degeneration may affect outcome.[53] In a naturally occurring *CNGA3* mouse model, gene replacement resulted in restoration of cone ERG responses, improvement of VA and contrast sensitivity (CS), and halted cone degeneration.[54] In a sheep model, similar intervention lead to an improved cone ERG, with a sustained effect.[55] Currently there are three ongoing Phase 1/2 gene therapy trials (NCT03758404, NCT02935517 and NCT02610582).

In a *Gnat2* (cpfl3) mouse model, gene supplementation was observed to improve cone-mediated ERGs and optomotor behaviour; with a lasting effect for at least 7 months.[56] A naturally occurring nonhuman primate with a homozygous R565Q missense variant in *PDE6C* may serve as a model for gene replacement in this form of ACHM, but may also be helpful for cone cell transplantation approaches.[57]

3.3 | Blue cone monochromatism (BCM)

BCM is an X-linked condition characterised by an absence of L and M wavelength-sensitive cone function, with fundus examination revealing a myopic but otherwise normal retina.[2,58] The presenting symptoms can be similar to ACHM, including photophobia, nystagmus, and decreased VA.[2] Female carriers are asymptomatic. No proven treatment is available. Current management includes optimal correction of the often-observed refractive error (high myopia) and tinted glasses/spectacles for the photoaversion (often with a magenta tint). BCM is caused by variants in the red and green opsin gene array *OPN1LW* (OMIM 300822) and *OPN1MW (OMIM 300821)*, thereby affecting the corresponding cones. The genetic mechanisms can be broadly divided into three groups: (1) deletions confined to the Locus Control Region (LCR), (2) *OPN1LW* (encodes L-cone opsin) and *OPN1MW* (encodes M-cone opsin)-related variants, where in a 2-step process, often a single L-/M-hybrid opsin gene is inactivated by a missense variant (p.[C203R] being the commonest) and (3) specific combinations of single nucleotide polymorphisms in exon 3 of L-/M- opsins ("L/M interchange haplotypes"), which cause aberrant splicing (LIAVA being one of the most common).

Exogenously expressed human opsins can regenerate cone outer segments and rescue M-cone function in *Opn1mw*$^{-/-}$mice, thus providing a proof-of-concept gene therapy in an animal model of BCM.[59,60]

3.4 | Bornholm eye disease (BED)

BED is an X-linked cone dysfunction syndrome associated with dichromacy and myopia, decreased VA, RPE thinning,

and visible choroidal vessels in the posterior pole.[2,61] Affected males have myopia, astigmatism and impaired VA (often 20/40 to 20/80) from birth/early infancy, myopic fundi, deuteranopia or protanopia, and reduced cone responses on ERG.[61-64] Current management includes correct diagnosis, increasingly aided by molecular genetic testing, and optimal correction of the refractive error. L/M interchange haplotypes at polymorphic positions in exon 3 of the opsin genes (resulting from intermixing between L- and M-opsin genes, *OPN1LW* (OMIM 300822) and *OPN1MW (OMIM 300821)*, respectively) are the principal underlying genetic basis of BED. Antisense oligonucleotide-mediated exon skipping to abrogate some of these disease-causing variants is being therapeutically explored for BED and BCM; and are currently in clinical trial for other IRDs including LCA-*CEP290* and *USH2A*-associated retinopathy.

4 | CONE AND CONE-ROD DYSTROPHIES

Progressive COD/CORD are characterised by cone photoreceptor degeneration, which is often followed by subsequent rod photoreceptor loss.[9] These disorders typically present with progressive loss of central vision, photophobia and colour vision disturbance.[65] Considerable progress has been made in elucidating the molecular genetics and genotype-phenotype correlations associated with these dystrophies, with disease-causing variants in at least 30 genes implicated in this group of disorders.[9,66]

4.1 | General management of COD and RCD

At present, there are no proven treatments for CODs and CORDs that halt progression or restore lost vision. Molecular diagnosis is an important step to facilitate genetic counselling, advice on prognosis and participation in anticipated clinical trials.[67] Animal models of disease (murine and canine) in *GUCA1A*,[68] *PRPH2*,[69] *ABCA4*[18] and *RPGR*[70] have shown significant increase in photoreceptor survival following gene-based therapies. Patients with specific forms of COD/CORD can be advised to adopt strategies, based on a knowledge of gene function or investigation of animal models, to try to slow degeneration, as presented below.

4.2 | AD *GUCA1A*-associated COD/CORD

GUCA1A (*GUCA1A*, OMIM 600364) encodes guanylate cyclase-activating protein-1 (GCAP1), which is required for retinal guanylate cyclase (RetGC) activation and cGMP regeneration.[71] GCAP1 contains three Ca^{2+}-binding motifs, structural alterations to which occur in most disease-causing *GUCA1A* sequence variants.[72] These result in persistent stimulation of RetGC, excess cGMP levels in the dark and photoreceptor apoptosis secondary to Ca^{2+} dysregulation.[73,74] These include the gain-of-function variants p.(Tyr99Cys), p.(Glu155Gly) and p.(Asp100Gly).[8] Sleeping with the lights on is advocated by some clinicians for preventing accumulation of cGMP, which otherwise occurs at night and causes photoreceptor damage.[9] Knock out of the gain-of-function variant may be a potential therapeutic approach.

4.3 | AD *GUCY2D*-associated COD/CORD

GUCY2D variants (*GUCY2D*, OMIM 600179) are a common causes of AD COD and CORD.[9] Recessive *GUCY2D* variants can cause LCA/EOSRD.[75] *GUCY2D* encodes the photoreceptor enzyme guanylate cyclase 2D (GC-E; RetGC), a component of the phototransduction cascade, that is regulated by intracellular Ca^{2+}-sensor proteins such as GCAP1. Somatic gene editing using AAV-delivered CRISPR/Cas9 has been used to edit the *GUCY2D* early coding sequence in mouse and macaque photoreceptors in vivo, thereby knocking out retGC1 expression, and demonstrating promising results, altering both retinal function and structure.[76]

4.4 | Autosomal dominant *PRPH2*-associated CORD

PRPH2 (*PRPH2*, OMIM 179605) is a three-exon gene encoding peripherin-2, a cell surface glycoprotein in the outer segment with an essential role in disc morphogenesis.[77] CORD-associated variants in *PRPH2* can be attributed to the region encoding the second intradiscal loop between its four transmembrane components. No disease-specific treatment is available for *PRPH2*-CORD, although interventions are being explored (Section 2.5).[78]

4.5 | Autosomal recessive *ABCA4*-associated COD/CORD

ABCA4-associated COD/CORD (*ABCA4*, OMIM 601691) is the commonest cause of autosomal recessive (AR) COD/CORD. Symptomatic onset of COD/CORD usually occurs in childhood with a central scotoma and

rapidly progressing macular atrophy.[79] The majority of patients have rod involvement at presentation (CORD), which is associated with a worse prognosis.[80] Light avoidance using tinted spectacles may confer benefit in *ABCA4*-associated retinopathy by inhibiting A2E production,[81] which produces DNA-damaging epoxides.[82] Vitamin A should also be avoided in *ABCA4*-associated retinopathy as it may enhance A2E production and, therefore, disease progression.[83] Human treatment trials of gene replacement therapy are underway (NCT01367444). For more details on therapeutic approaches for *ABCA4* disease, see the *ABCA4* MD paragraph (Section 2.2).

4.6 | X-linked *RPGR*-associated COD/CORD

Most disease-causing variants in *RPGR* (*RPGR*, OMIM 312610) result in RP,[84] but those leading to COD/-CORD are preferentially sequestered at the 3′ end of the open reading frame 15 (ORF15) region.[85] *RPGR*-associated CORD is characterised by central visual loss, mild photophobia and myopia, and presents in the second to fourth decade in affected males.[86] *RPGR* RP is discussed in Section 6.9; with three ongoing gene therapy trials (NCT03252847, NCT03116113 and NCT03316560).

5 | ROD DYSFUNCTION SYNDROMES

Rod dysfunction syndromes are a genetically diverse group of non-progressive primary dysfunctions of the rod system, most commonly causing congenital stationary night blindness (CSNB) – with abnormal fundi (Fundus Albipunctatus (FA) and Oguchi Disease) or normal fundi (complete and incomplete CSNB).[87]

5.1 | General management of rod dysfunction syndromes

Management of rod dysfunction syndromes is symptomatic, and as in other IRDs includes optimal refractive correction, use of low vision aids as necessary, and optimal access to educational and work-related opportunities. Low lighting exacerbates the severity of symptoms experienced in this group of patients. Electrical lighting and the use of bright screens, significantly improves quality of life (QoL) and makes the disease less debilitating.

5.2 | Complete and incomplete congenital stationary night blindness (cCSNB/iCSNB)

In contrast to FA and Oguchi disease, cCSNB/iCSNB has no distinctive fundus appearance with normal or myopic fundi.[88] cCSNB/iCSNB has a heterogeneous genetic background including AD, AR and X-linked, with variable VA and night blindness.[87] No specific treatment is available.

5.3 | Fundus Albipunctatus (FA)

FA is an AR disease characterised by multiple white subretinal spots,[89] throughout the retina. FA has been attributed to variants in *RDH5* (OMIM 601617), *RLBP1* (OMIM 180090) and *RPE65* (OMIM 180069).[90] Development of macular atrophy/cone dysfunction can be observed in later stage disease.[91-93] No specific treatment is available. Gene therapy is available for *RPE65*-retinal dystrophy but has not been explored in FA.

6 | ROD-CONE DYSTROPHIES

Rod-cone dystrophies (RCDs) are a variable group of inherited retinal conditions, both in terms of phenotype and genotype, with a prevalence of 1/3000-1/4000 in the general population.[94] It is the most common IRD phenotype.

6.1 | General management of RCD

Management of most forms of RCD is symptomatic. The two most common vision limiting complications are: (1) cataract, (2) cystoid macular oedema (CMO). CMO is most prevalent in patients with AD inheritance (71.4% with CMO in at least one eye), followed by AR/sporadic inheritance (58.9%) and least common in XL inheritance (12.5%).[95] Treatment approaches include: topical CAIs, oral CAIs, periocular and intravitreal steroids, and intravitreal anti-VEGF agents.[96] There is no level 1 evidence supporting topical/oral CAIs use and reports have demonstrated highly variable efficacy. In a 12-month retrospective study, with primary end point the reduction of central macular thickness (CMT) on ocular coherence tomography (OCT) of at least 11% between visits: 53.1% of patients following treatment with topical dorzolamide and 41.2% of patients following treatment with oral acetazolamide demonstrated response.[97] A prospective exploratory study demonstrated both the safety and acceptability of serial intravitreal aflibercept (ivA) in patients with RCD-CMO, with 37.9% of patients responding to treatments via

12 months. All patients demonstrating anatomical response did so after their first injection.[98] Beyond cataract and CMO, orientation and mobility training combined with low-vision aids such as night-vision goggles, flashlights and/or reverse telescopes can optimise residual visual function in advance RP and increase patients' independance.[99]

6.2 | RCD (retinitis pigmentosa)

RCDs are characterised by nyctalopia and gradual constriction of the visual field, with eventual loss of central vision, progressing to legal blindness.[100,101] RCD can be inherited as an AD, AR or X linked trait. Due to the large number of genes involved (>100 genes) the development of genotype specific treatments is challenging.

Two neurotrophic, pharmacological approaches have been explored that would potentially be relevant for all genetic forms of RCD. CNTF-releasing encapsulated RPE cell implant (NCT01530659) has been investigated in a Phase 2/3 trial, with high-dose or low-dose implant. Neither study showed therapeutic benefit—with some patients experiencing loss of retinal sensitivity that was reversible on removal of the implant.[102] However, a pilot study using adaptive optics imaging to investigate in vivo cone structure 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.[103] A phase 1 trial (NCT03063021) assessed the safety and tolerability of N-acetylcysteine (NAC) in patients with RP. NAC was well tolerated and mean best-corrected VA (BCVA) significantly improved at 0.4, 0.5 and 0.2 letters/month in 600 mg (cohort 1), 1200 mg (cohort 2) and 1800 mg (cohort 3) cohorts, respectively. There was no significant improvement in mean sensitivity over time in cohorts 1 and 2, but there was in cohort 3 (0.15 dB/month). There was no significant change in mean ellipsoid zone (EZ) width in any cohort.[104] A randomised, placebo-controlled trial is needed to determine if oral NAC can provide long-term stabilization and/or improvement in visual function; plans are ongoing.

There is currently no proven specific gene-guided treatment for RCD, but there are many ongoing trials; prioritised studies are discussed below.

6.3 | *MERTK*-RCD

MERTK-RCD is a primary RPE disease, due to variants in MER proto-oncogene, tyrosine kinase (*MERTK*) gene. Proof-of-concept in a rodent disease model with various viral vectors, suggested halting of degeneration and preservation of ERG responses.[105,106] A subretinal AAV phase 1 gene therapy trial (NCT01482195) in six patients had limited efficacy after 2 years.[107] RPE transplantation (hESC or iPSC-derived) is also under consideration for trial. Investigation of disease natural history may help to better stratify patients for future trials and optimal outcomes.

6.4 | *MYO7A*-RCD

MYO7A variants (*MYO7A*, OMIM 276903) cause combined RCD and neurosensory hearing loss (Usher Syndrome 1B). The *MYO7A* gene is too large for the AAV carrying capacity. Delivery with an equine infectious anaemia virus–based lentiviral vector was successful in the *shaker1* mouse model,[108] and further investigated in a phase 1/2 trial (NCT01505062), which was terminated prematurely, due to review of clinical development plans and priorities by the sponsor. Dual adeno-associated virus vectors were efficient for the in vitro and in vivo expression of the oversized *MYO7A* gene,[109] and is currently being investigated for human trials (UshTher, https://www.ushther.eu/).

6.5 | *USH2A*-RCD

USH2A variants (*USH2A*, OMIM 608400) cause either combined RCD and neurosensory hearing loss (Usher Syndrome 2A) or isolated RCD – being the commonest cause of autosomal recessive RCD. Antisense oligonucleotide-mediated exon skipping to abrogate exon 13 disease-causing variants is currently in phase 1/2 trial (STELLAR, NCT03780257), and is administrated by intravitreal injection. Three-month interim analysis has been shared that the treatment was well tolerated, with no serious adverse events, and 2 out of 8 participants demonstrated a degree of improvement. An ongoing international multi-centre study is exploring disease natural history study, which will aid ongoing therapeutic efforts (RUSH2A, NCT03146078).[110]

6.6 | *PDE6B*-RCD

PDE6B causes forms of AR RCD in mice, humans and dogs, and rarely is associated with AD RCD and AD CSNB. *PDE6B* (*PDE6B*, OMIM 180072) encodes the beta-subunit of rod cGMP-phosphodiesterase, which is a key enzyme specific for phototransduction activation in rod photoreceptors. Animal models demonstrate a fast degeneration of the rods and early studies with subretinal AAV in a murine model had limited efficacy.[111] In slower degenerating mouse line and in dogs, with early

treatment, a greater efficacy was observed.[112,113] In humans there is preservation of foveal structure and loss of the surrounding (rod dominated) retina, with significant constriction of the visual field.[114] A phase 1/2 trial (NCT03328130) is ongoing, employing AAV2/5-hPDE6B to explore rod-directed gene augmentation. The primary outcome of the trial is safety, with secondary outcome being improvement in visual function, assessed by (1) mobility test, (2) visual fields, (3) reading speed, and QoL measured by QoL questionnaire National Eye Institute Visual Function Questionnaire (NEI VFQ-25).

6.7 | *RLBP1*-RCD

RLBP1 variants (*RLBP1*, OMIM 180090) cause a spectrum of AR phenotypes. Nonclinical safety evaluation of scAAV8-*RLBP1* (CPK850) in *Rlbp1*$^{-/-}$ mice, targeting RPE and Müller cells, proved detectable mRNA expression, dose-dependent intraocular inflammation and retinal thinning.[115] An ongoing phase 1/2 gene therapy trial (NCT03374657) is exploring safety, tolerability and efficacy of subretinal administration of CPK850 in patients with *RLBP1*-RCD. Primary outcome is safety with secondary outcomes including: recovery of cone or rod function during dark adaptation, automated static perimetry, CS, light-adapted microperimetry, multifocal and full-field ERG, reading speed, eye dominance, mobility testing (navigation through a maze under varying light conditions), NEI-VFQ 25 and low luminance questionnaire (LLQ) scores.

6.8 | *RHO*-RCD

Rhodopsin (*RHO*, OMIM 180380) can cause a range of (RCD) phenotypes, including typical RCD, sector RP, pericentral RP and CSNB.[116] The severity of *RHO*-associated phenotypes varies significantly, from asymptomatic to severe disease. A phase 1/2 trial evaluating the safety and tolerability of antisense oligonucleotide therapy in subjects with RCD secondary to the P23H variant in *RHO* is ongoing (NCT04123626). Another phase 1/2 trial is also targeting P23H *RHO* RCD with 12 months of treatment with oral hydroxychloroquine (HCQ) (NCT04120883). The hypothesis is that treatment with HCQ is safe and tolerable, and may arrest progression of retinal degeneration by altering the autophagy pathway in photoreceptors.

6.9 | *RPGR*-RCD

X-linked RCD is one of the most severe forms of RCD.[100] The most common cause is *RPGR* gene variants (*RPGR*, OMIM 312610), and several preclinical and clinical gene augmentation trials focus on the disease. Successful AAV gene augmentation has been performed in murine and canine models, with preservation of photoreceptor nuclei and inner/outer segments limited to treated areas.[117,118] The arrest of disease progression was also achieved in late stages of retinal degeneration in a canine model, suggesting a wide therapeutic window.[119] The ORF15 sequence contained within this AAV vector in the canine trials had ORF15 DNA sequence variations, that are likely due to the repetitive purine nucleotides.[120] This mutability has been overcome with codon optimised sequence,[121] and abbreviation of the repetitive sequence.[117]

Three Phase 1/2 clinical trials (NCT03316560, NCT03252847 and NCT03116113) are using a submacular injection of AAV-gene delivery. Early results of NCT03116113 have been published. Eighteen patients were treated during a dose escalation phase and followed for 6 months, with no notable safety concerns after subretinal delivery of an AAV8 encoding codon-optimised human RPGR (AAV8-coRPGR), apart from steroid-responsive subretinal inflammation in patients at the higher doses, thereby meeting the pre-specified primary safety end point. In six patients, visual field improvements were noted at 1 month and maintained to the last point of follow-up.[122] NCT03252847 explores the safety and efficacy of AAV5-RPGR with primary end-point the absence of safety events, and secondary outcome measures being the improvement in visual function, retinal sensitivity, functional vision (mobility maze), and QoL improvement as measured by QoL questionnaires. The nine-month data from the clinical trial, demonstrated that the AAV5-RPGR was generally well tolerated and produced significant improvement in vision. NCT03316560 investigates AGTC-501 (rAAV2tYF-GRK1-*RPGR*) with primary outcome the number of participants experiencing adverse events and clinically relevant haematology/clinical chemistry parameters. Secondary outcomes are changes from baseline in visual function by perimetry, VA by ETDRS, retinal structure by imaging and QoL questionnaire. NCT04517149, a phase 1/2 trial, in contrast to the previous studies, is designed to investigate the safety and efficacy of a single intravitreal administration of AAV-RPGR (4D-125) at two dose levels.

6.10 | *RP2*-RCD

RP2 (*RP2*, OMIM 300757) functions as GTPase-activating protein (GAP) for a small GTPase (arl3) and has a significant role in prenylated protein trafficking.[123,124] The *RP2* coding sequence is 1050 base pairs in size rendering it suitable for packaging in AAV. AAV8-*RP2* was delivered to an *Rp2* knockout mouse, which in contrast to humans have

predominantly cone degeneration, via subretinal injection and demonstrated preservation of cone structure and function over an 18-month, with retinal toxicity demonstrated at high doses.[125] A recent study developed *RP2* knockout and patient-derived iPSC-derived retinal organoids as a model of *RP2*-RCD. Following gene therapy using an AAV5 vector, they demonstrated increased outer nuclear layer thickness and rhodopsin expression compared to controls, supporting further investigation in a clinical trial.[126]

It has also been shown ex vivo, using RPE and 3D retinal organoids derived from patients iPSCs with an RP2 premature stop mutation, that a read-through drug can rescue RP2-associated cellular phenotypes – supporting establishing a clinical trial.[127]

6.11 | Enhanced S-cone syndrome (ESCS)

Enhanced S-cone syndrome (*NR2E3*, OMIM 604485) is a rare slowly progressive AR form of retinal degeneration, typically characterised by nummular pigment clumping at the level of the RPE, often most plentiful around the temporal vascular arcades, caused by variants in the nuclear receptor *NR2E3*.[128,129] NR2E3 plays a role in human retinal photoreceptor differentiation and degeneration.[130] NR2E3 may serve as a genetic modifier and therapeutic agent to potentially treat a range of retinal degenerative diseases.[131] In patient-derived iPSCs, correction of *NR2E3*-associated ESCS has been described using CRISPR-Cas9.[132]

6.12 | Bietti crystalline corneoretinal dystrophy (BCD)

BCD (*CYP4V2*, OMIM 608614) is an AR disease, with similar clinical symptoms to other RCD, associated with progressive RPE-choriocapillaris complex atrophy and retinal crystals, which can disappear with disease progression, resulting in greater RPE disruption.[133,134] No disease-specific treatment is currently available. Reducing free cholesterol by cyclodextrins or δ-tocopherol, and gene supplementation therapy, were investigated in an iPSC model and murine model, respectively, with promising results.[135,136]

7 | LEBER CONGENITAL AMAUROSIS (LCA) AND EARLY-ONSET SEVERE RETINAL DYSTROPHY (EOSRD)

Leber congenital amaurosis (LCA) and early-onset severe retinal dystrophy (EOSRD) are characterised by severe congenital/early-onset visual loss, nystagmus and amaurotic pupils. Below we discuss genotypes with treatment avenues being explored.

7.1 | General management of LCA/EOSRD

Management of most forms of LCA/EOSRD is symptomatic. The rate of visual loss varies, and some genes have been associated with faster progression. Affected children benefit from correction of refractive error, use of low vision aids when possible, and optimal access to educational and work-related opportunities. Infants with severe visual impairment may also have delays or difficulties with speech, social skills and behaviour, highlighting the importance of a multi-disciplinary approach.

7.2 | *GUCY2D* – LCA/EOSRD

Patients with *GUCY2D* – LCA/EOSRD (*GUCY2D*, OMIM 600179) often have relatively normal fundi with preservation of central macular architecture until late in adulthood, in contrast to most other LCA/EOSRD genotypes.[137] A phase 1/2 gene therapy trial (NCT03920007) is ongoing for subretinal administration of SAR439483.

7.3 | *CEP290* – LCA/EOSRD

OCT studies of *CEP290* – LCA/EOSRD (*CEP290*, OMIM 610142) have shown that despite profound cone dysfunction, the foveal architecture is structurally preserved until the fourth decade of life in some patients.[138,139] Phase 1/2 (AGN-151587 (EDIT-101), NCT03872479) and Phase 2/3 (sepofarsen (QR-110), NCT03913143), gene editing and antisense oligonucleotide-mediated exon skipping trials, respectively, are ongoing for patients with compound heterozygous or homozygous intron 26 variants (c.2991 +1655A>G) in the *CEP290* gene. This specific intronic variant is the most common disease-causing variant, having been identified in at least one allele in 58-77% of *CEP290*-LCA patients.[138,140]

7.4 | *RPE65* – LCA/EOSRD

RPE65-retinal dystrophy (*RPE65*, OMIM 180069) has been at the centre of intensive research and therapeutic efforts given the gene size, the severity of the disease and the relative preservation of retinal structure.[141] There is

an FDA- and EMA-approved gene therapy for *RPE65*-retinal dystrophy (Luxturna (voretigene neparvovec-rzyl (VN)-AAV), Spark Therapeutics), and an ongoing Phase 1/2 trial that has reported promising efficacy (NCT02946879, AAV5 – OPTIRPE65). VN-AAV accomplished a multi-luminance mobility test (MLMT) lux score change of 2.4 lx at 4 years and maintained an average improvement in FST, reflecting more than a 2 $\log_{10}$(cd.s/m^2) improvement in light sensitivity.[142]

7.5 | *AIPL1* – LCA

AIPL1 – LCA (*AILP1*, OMIM 604392) is a rare cause of LCA (1-2% of the cases).[143,144] Patients have no residual outer retinal structure beyond the age of 4 years.[139,145] A compassionate use gene therapy study is ongoing for *AIPL1*-LCA, aiming to rescue structure in infants and young children with residual structure.

8 | CHORIORETINAL DYSTROPHIES

8.1 | Choroideremia (CHM)

CHM (*CHM*, OMIM 300390) is an X-linked IRD characterised by degeneration of the choriocapillaris. CHM is primarily an RPE disorder followed by photoreceptor degeneration.[146]

Four Phase 1/2 gene therapy trials have been completed. A Phase 1/2 (NCT02341807) showed no benefit employing AAV2-hCHM in high and low doses, despite the vector being well tolerated. One (NCT01461213) published results on six patients who were administered fovea-involving, subretinal injections of the 1.9 kb human *REP1* transgene packaged with a chicken β actin promoter containing rAAV2 vector,[147] describing a good safety profile. The 6-month data revealed modest, non-statistically significant improvement in retinal sensitivities with a mean change of 2.3 dB. Gains in retinal sensitivity were reported in five patients, while one patient, who received an unplanned lower dose (maximum of 6×10^9 genome particles, compared to 1×10^{10} genome particles in the other patients) owing to an intraoperative surgical complication, had a mild reduction in retinal sensitivity. Visual acuity improved by more than three lines of ETDRS letters at 2 year follow-up in two patients who had advanced disease; with improvements maintained at 3.5 years follow-up.[148] The same vector was used in a subsequent trial (NCT02077361), but at a higher dose of 1×10^{11} genome particles, and another six male patients were treated.[149] There was no statistically significant change in retinal sensitivity as detected by microperimetry. The area of intact autofluorescence, used as a surrogate for residual functioning retinal tissue, was tracked longitudinally and found to decline over the 2 years of follow-up in both the treated and untreated eyes, with no statistically significant difference between these two groups. One treated eye had a ≥15 ETDRS letter gain in their BCVA at 2 years (although this was also seen in an untreated eye in a different patient). One patient experienced a serious adverse event with the presence of hyperreflective intraretinal material that improved with oral steroids, but a persistent defect in the EZ ensued, with an eight ETDRS letter reduction in BCVA. A third trial in six patients (NCT02553135) delivered the same vector under the guidance of microscope-integrated intraoperative OCT (MIOCT).[150] Two patients experienced substantial BCVA gains of 10 and 5 letters at 24 months, while the remaining four had stable BCVA. There were two incidences of macular retinal hole formation, and there were no marked changes in retinal sensitivity as assessed on microperimetry in the treated eyes. A Phase III multicenter trial (NCT03496012) using the same AAV2-REP1 is ongoing.

Although aforementioned studies have provided safety data and promising (albeit variable) results regarding BCVA, whether the gene therapy product has had an effect on rate of retinal degeneration in the condition is not yet established. A Phase I trial (NCT04483440) is investigating the intra-vitreal administration of the 4D-110 drug product. 4D-110 comprises an AAV capsid variant (4D-R100) carrying a transgene encoding a codon-optimised human CHM gene.

9 | EFFICACY END POINTS FOR GENE THERAPY TRIALS

The phenotypic and genetic heterogeneity of IRDs, as well as disease prevalence, creates significant challenges in the characterization of disease natural history. Prospective investigation of natural history should aim to establish a greater understanding of pathogenesis, to identify the window for therapeutic intervention and characteristics for potential trial candidates, as well as to investigate clinically meaningful end points and outcomes for clinical trials. End points ideally need to be easy to obtain, highly repeatable and reproducible, and clinically relevant. The evolution of functional and structural assessment of the retina has created multiple potential measurements, which can serve as surrogates of successful treatment - either improvement or slowing/halting deterioration. Well-established outcomes such as VA and ERG parameters may lack sensitivity to identify

a biological effect of treatment, necessitating the use of other (potentially novel) end points and require additional studies for their validation. Given the phenotypic variability of the IRDs many end points may be disease-specific, for example, measurement of the impact of photophobia in ACHM trials. It is important to be mindful when considering end points that the primary goal of all intervention is to have a positive impact on patients' QoL and real-world function.

We identify three categories of measurement/tests: (1) functional assessments – performance-based end points, (2) structural assessments and (3) subjective assessments. In the next paragraphs we briefly present selected assessments and metrics, with relevant IRD examples.

9.1 | Functional assessment - Performance-based end points

Clinically meaningful end points of retinal function include the mean change or mean rate of change of BCVA, CS, retinal sensitivity (including topographic analysis of the hill-of-vision volume), and electrophysiological assessments. BCVA reflects the limits of distinguishing fine details at maximal black on white contrast and reflects retinal function at the area with which the patient fixates. It can be a less sensitive primary outcome for genotypes/phenotypes in which there is preservation of normal foveal cone function (primary fixation point), albeit until late in the disease process, for example, CRD. In contrast, in conditions where the preserved retinal structure does not necessarily correlate to central retinal function, BCVA may be a potentially meaningful and sensitive outcome; including for ACHM and certain LCA/EOSRD genotypes such as *GUCY2D*-, *CEP290*- and *RPE65*-associated LCA.[137,141] Another primary aspect of central visual performance is CS that is an approximation of the modulation transfer function of the visual system and reflects the limits of distinguishing grayscale differences. A full estimation of resolution threshold of the CS function is time-consuming. The Pelli-Robson chart is widely used and a well standardised method of measuring CS, by fixing the target size close to the peak of the CS function and assessing the contrast threshold. It is not an ideal test for patients with significantly low threshold (floor effect). More sophisticated solutions include automated tests, with flexibility of testing more frequencies, colour CS, different contrast spatial frequencies, and measurements at photopic, mesopic and scotopic light levels.

Retinal sensitivity is another important functional measurement, including microperimetry, static or kinetic perimetry, and full-field stimulus testing (FST); FST being of particular value in patients with low vision.[151] Two-colour perimetry can also be employed to help distinguish rod from cone function.[152] Microperimetry can assess the foveal centre and may be easier for children to perform due to the small number of stimuli presented and the shorter testing time.[153] On the other hand perimetry can examine a greater retinal area, and might be better suited for evaluation of disease where the peripheral retina first affected, such as RCD.[154] Retinal sensitivity can be evaluated (1) as a single metric of mean retinal sensitivity, (2) using pointwise analysis or (3) volumetric hill-of-vision measurement. In addition, defined retinal areas can be evaluated, for example, the treated area.

Volumetric indices of retinal function can help visualise and sensitively quantify treatment effect, as well as natural history of IRDs.[155] Visual field modelling and analysis (VFMA; Office of Technology Transfer & Business Development, Oregon Health & Science University, Portland, OR),[156] models the hill of vision from perimetric sensitivity data, and creates visual displays, and generates volumetric indices, including the total volume (VTOT), which represented the entire field tested, as well as the volume of defined areas (eg, central 1°, 5° and 10°). The volume represents the total sensitivity across the solid angle of the base of the test grid for VTOT and the entire solid angle of the defined degrees-radius circle selection.[153-155] VFMA allows focus on regions of interest and better visualization of changes in sensitivity, which can also be used for the creation of difference topographic maps.

The cost of novel therapeutics and the safety risks of intervention create an urgent need to identify outcomes that reflect real-life changes, with an impact on day-to-day life. Such outcomes may need to be disease specific, that is, relevant to the symptoms of the disease. One likely outcome would be mobility, which can be assessed using a configuration designed to measure the ability to navigate obstacles in a maze-like environment under varying light conditions. The main metric is the time taken to travel a specific path. The ambient lighting conditions can be adjusted depending on the disease. In RCD and LCA/EOSRD, navigation is primarily tested under low levels of luminance.[157] In contrast, in conditions such as ACHM and CORD, testing under high luminance is more relevant. Validation of these assessments is necessary, including randomization, multiple maze configurations, and data collection from normally sighted individuals. It should be noted than for VN-AAV (Luxturna, Sparks Therapeutics) the improvement in the multi-luminance mobility test was supported by improvement in FST.[142]

In conditions with photophobia, light sensitivity is another outcome that can be employed. The patient is

exposed to different levels of light stimulus and their response is recorded, with quantifiable outcomes such as height and area of the palpebral aperture,[158] and visual photosensitivity thresholds (VPT)[159]; with required validation again posing challenges.

9.2 | Structural assessment

Beyond functional improvement or stabilization, structural assessment can be used for patient stratification and treatment monitoring. In progressive disorders, halt of retinal degeneration is an important potential outcome. Moreover, it is part of a desired safety profile, with no acceleration in anatomical loss due to intervention. Depending on the disease natural history, different outcomes and different imaging modalities have been explored.

OCT evaluation of the residual photoreceptor area (EZ) and of the diameter of the area (EZ width), have being explored as outcomes measurements in RP and LCA.[141,160,161] In MD and COD/CORD, quantification of the area and the width of EZ loss, can serve as outcomes and inclusion criteria.[162] Another metric that can be derived from OCT is the thickness of individual layers.[163] Outer nuclear layer (ONL)-foveal thickness has been frequently used a surrogate measurement of the number of foveal cones, even though studies employing adaptive optics cellular imaging proved the lack of correlation of ONL-foveal thickness and the actual number of foveal cones in conditions such as ACHM.[45,164,165] The thickness of individual layers can further be used for topographic map and for volume estimations. OCT can also be employed intraoperatively for optimal treatment-delivery in subretinal injections.[150]

FAF can also be used for the evaluation of structural end points. The lack of signal correlated to loss of RPE, has been proposed as a metric in MDs, including STGD, and COD/CORD.[166,167] In conditions such as CHM and RP, where there is preserved foveal signal (intact foveal structure), quantification of the foveal signal area can be a meaningful measurement to monitor disease progression and halt of degeneration.[168,169] A perifoveal ring of increased signal on FAF is a non-specific finding that can be observed in a variety of IRDs.[170] It is believed that it represents dysfunctional photoreceptors, which can be amenable to rescue.[168,171] Beyond FAF, fluorescence lifetime imaging ophthalmoscopy (FLIO) is a developing modality for further functional imaging, based on the decay time of the fluorescent molecules, and therefore FLIO is a promising tool to detect and assess varying metabolic states of different retinal areas.[172]

Adaptive optics scanning light ophthalmoscopy (AOSLO) allows for non-invasive cellular imaging, thereby helping to improve our understanding of IRDs.[173] An increasing number of natural history studies and ongoing/planned interventional clinical trials exploit AOSLO both for participant selection, stratification and monitoring treatment safety and efficacy.[173-177] Several metrics are being investigated, including cone density, peak cone density, Voronoi analysis of the regularity of the mosaics and reflectivity.[178]

9.3 | Patient reported outcomes

Objective assessment of retinal function and structure allows the clinician/researcher to recognise the biological effect (or the lack) of treatment. However, the observed changes, even if they reach statistical significance, may not translate to being meaningful for the patient.

Standardised questionnaires have been developed and validated to reflect different aspects of a patient's life.[179] The NEI VFQ-25 is a multidimensional questionnaire designed to assess the impact of eye conditions/visual problems (non-disease specific) on QoL, using 25 items across 12 subscales, such as well-being/distress, ocular pain, near, peripheral central and colour vision.[179] The Brief symptom inventory (BSI) assessing psychological stress, is not specific for eye procedures, and is administered as a questionnaire in an interview version. Several groups have developed disease-specific questionnaires such as a patient reported outcome (PRO) specific for a *CNGA3* study (A3-PRO),[180] and specific questionnaires for photoaversion in ACHM.[158] Open ended interviews can collect direct patient feedback, which can evaluate the patient's opinion towards treatment, different aspects of the disease, challenges faced during and post intervention, concerns and expectations.

10 | CONCLUDING REMARKS AND FUTURE PROSPECTS

NGS-based approaches, typically using whole exome sequencing (WES), have revolutionised genomic analysis; however, not all pathogenic variants can be detected. Complex structural changes, such as large deletions, inversions, translocations and trinucleotide repeat expansions, are mostly undetected with WES, while variants in deep intronic or regulatory regions are not sequenced.[181] Whole genome sequencing offers a comprehensive alternative for undiagnosed patients, but may be currently rejected in favour of targeted genome re-sequencing due to cost and efficiency. It is hoped that most patients will be able to have a precise molecular diagnosis soon. The growing field of clinical genetics has significantly

contributed towards targeted screening, as well as for patient counselling and advice on prognosis. Similarly, advances in retinal imaging and retinal function testing have improved knowledge of the relationship between genotype and phenotype, which is key to identifying treatment effects in clinical trials of novel therapies. Also, the development of national strategies and guidelines for IRDs may further facilitate the translation of the recent advancements into clinical practice. The remaining challenge continues to be the demonstration that novel therapies under investigation (or anticipated) slow degeneration or improve function, in a safe, durable, and patient-relevant fashion.

CONFLICT OF INTEREST

None declared.

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