RDH12-ASSOCIATED RETINAL DYSTROPHIES

STATE OF ART AND PERSPECTIVES FOR THE FUTURE (3rd edition)

A scientific and therapeutic landscape analysis

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TABLE OF CONTENTS

Foreword

Conditions of Use & Statement of Originality

Executive Summary

Acknowledgements

1. Leber Congenital Amaurosis Type 13 **9**

1.1 Introduction – LCAs 9

1.2 RDH12-LCA (LCA13): Clinical phenotype and genetics 11

1.3 Epidemiology/Population size 13

1.4 RDH12 gene expression, functions and pathomechanism 14

1.5 RDH12 scientific research 17

2. State of Preclinical Research Infrastructure **19**

2.1 Introduction 19

2.2 Animal models 19

2.3 *In vitro* disease models (human tissue) 24

2.4 Role in cell therapy 27

2.5 Commentary 27

3. Therapeutic Pipeline **29**

3.1 Introduction 29

3.2 Gene Augmentation 29

3.3 Other gene-specific therapeutic approaches: Gene Editing, Antisense Oligonucleotides (ASOs) 34

3.4 Gene/Mutation-agnostic Gene Therapies 34

3.5 Pharmacological/small-molecule approaches 38

3.6 Cell replacement therapy 43

3.7 Medical devices (visual prostheses) 45

3.8 Commentary 48

4. Clinical Translation Readiness & Infrastructure **50**

4.1 Introduction 50

4.2 Patient Identification 50

4.3 Clinical Trial Design 54

4.4 Commentary 62

APPENDIX A – Known RDH12 mutations, July 2026 (Excel file)
APPENDIX B – Transcripts of Key Opinion Leaders' (KOLs) interviews
APPENDIX C – Bibliography

FOREWORD

In early 2026, Eyes on the Future, a patient organisation for RDH12-associated inherited retinal dystrophies looking to accelerate research and therapeutic development in the field of RDH12-IRDs, engaged Cambridge Consulting Network (CCN)[i] to update the organisation's RDH12 scientific and medical landscape report. This report was originally written in 2019 by Dr Francesca Sofia and Dr Cristina Colombelli of Science Compass.[ii]

The aim of this project was to understand the current state of scientific research and clinical translation in RDH12-IRDs and the broader IRD landscape, in order to understand the progress made across various research groups and commercial entities in IRDs in the past five years, identify gaps, opportunities, and learnings, and inform the organisation's future strategy. It can also be used as a tool for stakeholder engagement.

The CCN team was led by Ruoh Wen Cheong (Cambridge, Project Leader & Manager). Team members consist of Anushka Irodi (Cambridge), Lukas Katzenberger (Technical University of Munich), Ana Mariya Nancheva (Cambridge), Barry Tsui (King's College London), and Shuya Wang (Cambridge).

[i] CCN is a global, pro-bono student consultancy based primarily in the University of Cambridge, UK. CCN's Life Sciences practice provides business and strategy consulting services to clients ranging from startups and SMEs to charities across biotech, pharmaceuticals, and medical devices. For more information, email info@cambridgeconsultingnetwork.co.

[ii] Science Compass is an Italy-based consulting firm that enables charities, research organisations and patient associations to outsource scientific office tasks. Services provided range from scientific assessment/monitoring in any given field of biomedicine (but mainly in the rare disease field), strategic planning and management of research-funding activities including design of calls for proposals, peer review and research portfolio administration. For more information, visit: www.sciencecompass.it

CONDITIONS OF USE OF LANDSCAPE

This document represents a broad literature review related to RDH12-associated retinal dystrophy and includes interviews with key opinion leaders in the subject matter. It does not represent or intend to represent a comprehensive collection of all work, whether research, clinical, or editorial on the titled subject matter. The content therein should be used to gain broad understanding on the titled subject matter, to frame thoughts and ideas, and to guide additional literature reviews. The content is subject to correction, updates, or clarification.

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EXECUTIVE SUMMARY

Leber's Congenital Amaurosis (LCA) is the leading cause of inherited childhood blindness and accounts for 5% of all inherited retinal diseases. Most LCA cases are caused by one of 29 identified genes; Up to 10% of LCA cases are caused by mutations in the RDH12 gene, which encodes a retinal dehydrogenase enzyme expressed in photoreceptors. Loss of function of this enzyme is thought to result in the accumulation of toxic metabolites, leading to cell death and hence retinal degeneration. Patients with RDH12-LCA experience progressive loss of visual function starting at age 2-4 years, culminating in legal blindness by early adulthood (18-25 years). Along with the other LCAs, it is considered an ultra-rare disease.

Significant progress has been made in the past five years. Perhaps most importantly, two RDH12-specific gene augmentation therapies are under active clinical development. Interim results from an early Phase 1 study of PUMCH-E101/IVB107 in China are encouraging, albeit heterogeneous between patients. Separately, OPGx-RDH12, an asset originally developed by Prof Jean Bennett (UPenn), received FDA IND clearance in October 2026, with a Phase 1/2 trial planned for Q4 2026. These gene therapy programmes have advanced into the clinic despite the imperfections of RDH12 animal models as the gene augmentation platform is mechanistically straightforward and relatively de-risked. Other mutation-agnostic therapeutic approaches have also entered clinical trials for other IRDs, including neuroprotective therapies for early stages of disease (e.g. RdCVF, NAC) as well as optogenetics and photoreceptor replacement therapy for advanced stages of disease. If approved, these therapies may be made available to other IRD patients, including RDH12-LCA patients, later on. Additionally, several groups are investigating the use of retinal scavengers and translational-readthrough inducing drugs (TRIDs), both small molecules, in RDH12 although this work is in the earlier stages of development.

This progress in clinical translation has been supported by a substantial expansion in preclinical research infrastructure and clinical knowledge. Several patient-derived iPSC lines covering a range of RDH12-associated phenotypes have been established and characterised, allowing testing of therapeutics in an environment that better mimics the native eye (compared to small-animal models like mice). RDH12 patient retinas have been extensively characterised to identify regions with better rescue potential and to determine the speed and variability of retinal degeneration to inform trial design, and the use of BCVA, LLVA, and 4-HNE biomarker as endpoints/outcome measures has shown promise in RDH12, alongside FST and MLMT whose use in IRD trials is now more established – albeit endpoints are still an area of active discussion for the field. Additionally, a multi-centre prospective study to investigate the natural history of RDH12 is ongoing (Uni-Rare).

Meaningful steps have been made in addressing most of the key gaps highlighted in the previous report(s), but continued efforts in preclinical model development (especially autosomal recessive RDH12 iPSC-based organoids), observational/interventional studies, and advocacy (e.g. regulator education, promoting earlier diagnosis in patients) will be required to address remaining challenges:

- The field still lacks a unifying disease model, the biological basis of regional retinal preservation are still not understood, and the systemic effects of RDH12 have not been investigated
- Overreliance on gene augmentation and a need to diversify the therapeutic pipeline. The clinical success and regulatory approval of assets currently under development are not guaranteed, and not all patients will be able to benefit, e.g. advanced patients who have already lost most/all of their photoreceptors

- Neuroprotection, cell replacement therapy, and optogenetics which are more important for late-stage patients remain more experimental than gene augmentation, and may need more extensive preclinical validation with better models
- Uncertain epidemiology/prevalence or missed diagnoses hinders study recruitment, trial design, and commercial interest/funding
- Robust long-term natural history for RDH12 is still not available, and clinical understanding remains biased to Western populations. Sharing of data remains limited
- Ideal outcome measures that capture heterogenous phenotypes/responses need to be determined

The previous editions of this report have outlined a roadmap leading to significant therapeutic progress in RDH12. It is hoped that, in addition to documenting these successes, the current report will help lay the scientific and clinical foundations for the next generation of RDH12-RD research and therapeutic development.

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1. LEBER CONGENITAL AMAUROSIS TYPE 13

1.1 Introduction: LCAs

Inherited retinal diseases (IRDs) are a class of rare, single-gene disorders that cause degeneration of the photoreceptors or retinal pigment epithelium (RPE) in the eyes, leading to vision loss/blindness. About 1 in 1380 individuals, or 5.5 million people worldwide, are impacted by IRDs.[1] To date, 351 genes have been identified to cause IRDs.[1,2]

Leber's congenital amaurosis (LCA) is the leading cause of inherited childhood blindness and accounts for 5% of all IRDs. LCA was first described by Theodore Leber in 1869, and comprises a group of severe, very-early-onset rod-cone dystrophies characterised by **vision loss, involuntary eye movements (nystagmus), and severe retinal dysfunction from birth or starting the first few months after birth (< age one).** Additional features may include high hypermetropia, markedly reduced/absent rod and cone responses at the electroretinogram (ERG), light-sensitivity (photodysphoria), eye poking (oculodigital sign), cone-shaped cornea (keratoconus), cataracts, and variable fundus abnormalities (e.g. waxy optic disc, attenuation of the arterioles, pigmentary retinopathy). The majority of LCA patients are non-syndromic, i.e. their disease manifestations/ symptoms are confined to the eye. In a minority of syndromic cases, severe early vision impairment may be accompanied by speech impairment and behavioural difficulties.

Majority of LCA cases (70-80%) can be traced to one of 29 identified genes (**Table 1**). LCA is typically inherited as an autosomal recessive genetic condition, with the exception of *OTX2*, *IMPDH1*, and *TUBB4B* which are autosomal dominant, and *CRX* which may be dominant or recessive depending on the exact mutation [iii] [3,4] Most of these genes encode retina or RPE proteins, with functions spanning phototransduction, the visual cycle, ciliary transportation, and photoreceptor morphogenesis. There remain unknown genes that cause the remaining 20-30% of LCA cases, and the LCA-causing pathomechanisms of recently-identified *USP45* and other genes are still controversial and require further investigation.

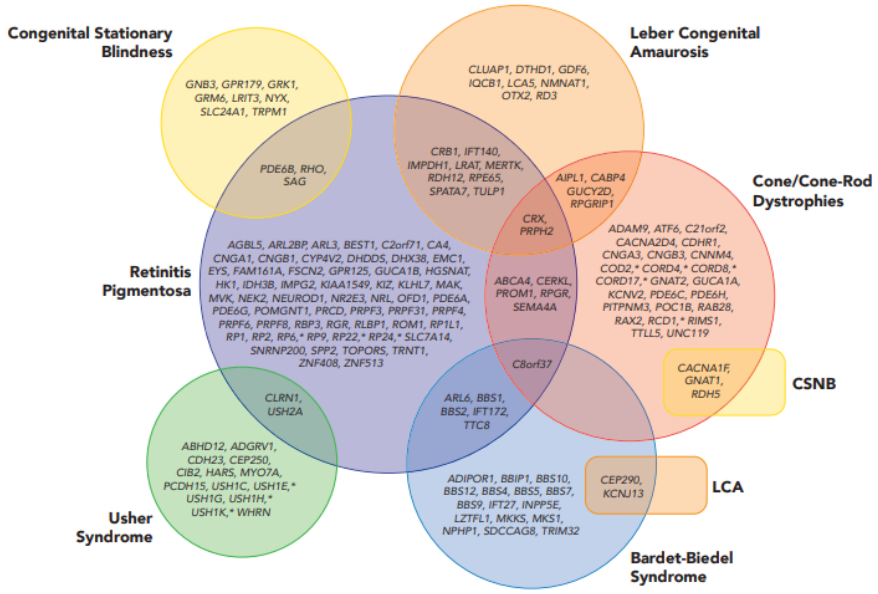


Figure 1: Genes associated with LCA and other IRDs. Adapted from Leroy et al. (2018) [5]

[iii] Note that recessive loss-of-function genetic disorders may be treated by gene augmentation therapy while dominant disorders require other methods. See Section 3.

Locus name	Gene	Protein	Function	Frequency
LCA1	*GUCY2D*	Retinal guanylate cyclase-1	Phototransduction	10-20%
LCA2	*RPE65*	Retinoid isomerase	Retinoid cycle	5-10%
LCA3	*SPATA7*	Spermatogenesis-associated protein 7	PR ciliary transportation	3%
LCA4	*AIPL1*	Aryl-hydrocarbon-interacting-protein-like 1	Phototransduction/ protein biosynthesis	1-2%
LCA5	*LCA5*	Lebercilin	PR ciliary transportation	1-2%
LCA6	*RPGRIP1*	Retinitis pigmentosa GTPase regulator-interacting protein 1	PR ciliary transportation	6%
LCA7	CRX	Cone-rod homeobox	PR morphogenesis	1%
LCA8	*CRB1*	Crumbs homologue 1	PR morphogenesis	10%
LCA9	*NMNAT1*	Nicotinamide nucleotide adenyltransferase 1	NAD biosynthesis	Rare
LCA10	*CEP290*	Centrosomal protein 290 kDa	PR ciliary transportation	15-20%
LCA11	*IMPDH1*	Inosine 5'-monophosphate dehydrogenase 1	Guanine synthesis	5%
LCA12	*RD3*	Retinal degeneration 3	Phototransduction	<1%
LCA13	*RDH12*	Retinol dehydrogenase 12	Retinoid cycle	**10%**
LCA14	*LRAT*	Lecithin:retinol acyl transferase	Retinoid cycle	<1%
LCA15	*TULP1*	Tubby-like protein	PR ciliary transportation	<1%
LCA16	*KCNJ13*	Kir7 inwardly rectifying potassium channel	Phototransduction	<1%
LCA17	*GDF6*	Growth differentiation factor 6	PR morphogenesis	Rare
	OTX2	Orthodenticle homeobox 2 protein	PR differentiation	<1%
	CABP4	Calcium-binding protein 4	Phototransduction	<1%
	CLUAP1	Clusterin-associated protein 1	PR ciliary transportation	Rare
	IQCB1 or NPHP5	IQ motif containing B1 protein	PR ciliary transportation	Rare
	DTHD1	Death-domain containing protein 1	Signaling/Apoptosis pathway	Rare
	IFT140	Intraflagellar transport 140 chlamydomonas homologue protein	PR ciliary transportation	Rare
	ALMS1	ALMS protein	PR ciliary transportation	<1%
LCA18	*PRPH2*	Peripherin/Retinal degeneration slow	PR morphogenesis	Rare
	TUBB4B	Tubulin beta 4B	PR morphogenesis	N/A
	CCT2	Chaperonin containing TCP1 subunit 2	Chaperone	N/A

	IDH3A	Isocitrate dehydrogenase 3 subunit alpha	PR energy metabolism	N/A
	SLC6A6	Solute carrier family 6 member 6	PR homeostasis	N/A
LCA19	*USP45*	Ubiquitin-specific peptidase 45	Protein turnover	N/A

Table 1. List of identified LCA genes, their function and frequency. Modified from Huang et al. (2021) [6] & RetNet [4]. Frequencies from Kumaran et al. (2018) [2]

Common mutations (frequency >10%) include *GUCY2D*, *RPE65*, *CRB1*, *CEP290*, and *RDH12*, although ethnicity-related differences exist. Mutations in *CEP290*, *GUCY2D*, and *RPE65* are generally more frequent in Caucasian populations. Meanwhile, *CRB1* is the leading causative genetic mutation in Chinese cohorts followed by *GUCY2D*, and the c.2991+1655A>G variant of *CEP290*, the most common variant in European cohorts, has not been detected in Chinese patients. *CRB1*, *NMNAT1*, and *RPGRIP1* were reported as the most common mutations in a Japanese cohort.

The LCAs are grouped together based on their severity and early onset, however, **the rate of disease progression or retinal structure degeneration varies considerably between genotypes.** Patients with *GUCY2D* and *RPGRIP1* mutations, for example, experience a rapid initial decline in vision but comparatively slow/minimal structural degeneration of the retina over time (i.e. relatively intact macular architecture, even into adulthood). Meanwhile, **RDH12-associated LCA sees significant disease progression in adolescence, both functionally and structurally**: Early, peripherally-progressive macular atrophy and bone-spicule pigmentation, and central loss of the ONL, ellipsoid zone, and disruption of RPE in OCT. This suggests a narrower and more time-sensitive therapeutic window, although some regions of the retina are relatively spared (Section 1.2).

Mutations in several LCA-associated genes also cause other retinal dystrophies such as EOSRD[iv], retinitis pigmentosa (RP; including RDH12) and cone-rod dystrophy (CORD). Certain genes (*GUCY2D, NMNAT1, CEP290, AIPL1*) are more strongly associated with LCA and others (e.g. *RPE65, LRAT, RDH12*) with EOSRD. Broadly, LCA, EOSRD, RP, and CORD are a spectrum of retinal abnormalities, with LCA-associated loss-of-function mutations at the severe end.

1.2 RDH12-LCA (LCA13): Clinical phenotype and genetics

Leber congenital amaurosis type 13 (LCA13) is a severe retinal dystrophy caused by homozygous or compound heterozygous mutations in *RDH12*, which encodes a retinal dehydrogenase expressed in photoreceptors (Section 1.4). LCA13 accounts for 3.4-10.5% of all LCA cases.[7]

Functional decline. Typical onset is in the first years of life (2-4 years). Patients commonly present with visual field constriction, reduced visual acuity, night blindness, and markedly reduced ERG responses. Visual function declines progressively, culminating in legal blindness by early adulthood (18-25 years).[8] Also commonly observed are nystagmus, sluggish/near-absent pupillary responses, mild hyperopia, and keratoconus.

Retinal structure. Retinal architecture is distorted with loss of normal lamination.[9] Macular atrophy is a prominent feature, appearing in optical coherence tomography (OCT) as disorganised retinal layers and FAF as loss of autofluorescence.[10,11] Fundus examination may be normal in early disease or show

[iv] Milder forms of disease are referred to as early-onset severe retinal dystrophy (EOSRD), severe early childhood-onset retinal dystrophy (SECORD), or early-onset retinitis pigmentosa (RP). EOSRD typically presents later than LCA, usually within five years of age, and is generally associated with better residual visual function and partially-preserved ERG responses.

yellowing, mild RPE mottling, vascular attenuation, and characteristic early dense intraretinal pigmentation. This progresses to salt-and-pepper retinopathy, optic disc pallor, retinal pigment clumping (including nummular and bone-spicule patterns especially in the periphery), RPE atrophy, and macular scarring in older patients. Petal-shaped pseudocolobomas are observed in ~1/3 of patients.[12]

Regional patterns. (1) While it is usually considered pathognomonic of Stargardt disease[13], **peripapillary sparing**, in which the region immediately surrounding the optic nerve head remains relatively preserved from degeneration, is a well-recognised phenotypic feature in a large proportion of RDH12-LCA cases.[7,14] Peripapillary sparing has since been confirmed across all RDH12-associated phenotypes (LCA/EOSRD, RP, MD, CORD) and a wide age range (5-43 years).[12] **Structurally-preserved, potentially-rescuable rod photoreceptors are observed in this region, suggesting substantial potential for functional recovery similar to treatment-responsive regions in RPE65- and GUCY2D- LCA.** This represents a target for improving peripheral and night vision. Additionally, this pattern tends to remain stable for many years constituting a longer treatment window. The biological basis of peripapillary sparing remains unknown.[15] (**2) Fovea.** A subset of patients retain a small island of structurally-preserved foveal cones despite widespread macular degeneration. However, the capacity for substantial visual improvement here is limited (unlike some other LCA genotypes), as cone function closely tracks the degree of photoreceptor loss. Foveal degeneration progresses gradually, with ONL thinning estimated at ~0.02 log/year. **Therapies targeting the fovea are more likely to slow/halt central vision loss, rather than restore vision**.[15] **(3) The peripheral retina.** Despite advanced central retinal degeneration, some peripheral rod photoreceptors remain structurally-preserved in a subset of patients. This region may represent a therapeutic target for preserving/restoring the peripheral visual field and night vision.[15] **4) Para-arteriolar RPE preservation** has also been observed in a subset of RDH12 patients (1 with RP, 4 with LCA) suggesting some overlap in the mechanisms underlying regional preservation across different genotypes.[12]

Wide spectrum of disease-causing RDH12 mutations/variants. The number of known RDH12 mutations listed in HGMD®[16] has doubled in the past seven years, from >100 in September 2019 to >211 in July 2026. This list can be found in **Appendix A**. Similarly, the number of pathogenic/likely pathogenic/variants of unknown significance listed on ClinVar[17] has increased significantly from 116 in December 2021 to 402 in September 2026. 242 of these were missense variants, 26 were nonsense, 42 frameshift, 25 splice donor/acceptor variants, and 16 were in untranslated regions (51 other). 314 of these mutations were single-nucleotide polymorphisms, 39 were deletions, and 21 were duplications (28 other).

A meta-analysis published in 2022 covering recessive RDH12-associated retinopathy (including EOSRD, arRP, LCA, CORD, MD) in 425 families found the most frequent variants to be p.(A269Gfs*2) (91/851), p.(V146D) (61/851), p.(L99I) (56/851), p.(T49M) (45/851), and p.(R62*) (33/851).[18] **These top 5 common variants accounted for 53% of families.** Ethnic-specific differences exist: The most common variant in European and Caucasian patients, p.(A269Gfs*2), is absent in East Asian patients and general populations (where p.(V146D) seems more common); p.(C201R) is the most common variant in Indian patients, and p.(L99I) is likely a founder mutation in Latino populations (Daich Varela et al. 2024, n=78 South American patients).[12] Of note, p.(T49M) and p.(L99I) have been associated with milder phenotypes. **Nonetheless, disease-relevant mutations commonly result in loss of RDH12 function. Most people with only one disease-associated allele (i.e. carry a null allele) are disease-free, suggesting that half the concentration of RDH12 protein is still well tolerated by the retina. Therapeutic aims for recessive RDH12 disease are to fully or partially restore RDH12 function.**

Most RDH12-associated disease is inherited in an autosomal recessive fashion, although certain heterozygous variants have been associated with gain-of-function disease and a mild RP phenotype inherited in an autosomal dominant fashion (adRP). These 3 variants are c.763delG, c.778delG, and

c.759delC, which all affect the same C-terminal loop and helix region in the RDH12 protein. Clinically, adRP is much milder than recessive RDH12 disease. Visual acuity ranged from -0.1 to 0.2 logMAR with constricted visual fields and reduced cone density on adaptive optics imaging. Parafoveal and peripapillary hyperautofluorescent rings can also be observed, mirroring the regional preservation observed for RDH12-LCA, suggesting that regional preservation in the retina is not limited to recessive forms of RDH12 disease.

1.3 Epidemiology/Population size

The prevalence of LCA is 2-3 cases per 100,000 live births (1:50,000 to 1:33,000).[19,20] LCA accounts for 5% of all IRDs and 20% of blindness in school age children. This disorder affects males and females in equal numbers. **RDH12-LCA is one of the more common forms of LCA (Table 1)** with the most recent and widely-quoted frequency being **3.4-10.5% of LCA cases**.[7] This suggests a patient population of up to 1,000 in the US and 800 in the EU4 countries (Germany, France, Spain, Italy), well within the classification of ultra-rare diseases.

Commercial estimates (**Table 2**) and anecdotal evidence from several KOLs interviewed for this report point to a larger RDH12 patient population, exceeding 2,000 in the US. Potential sources of discrepancy from earlier estimates may include: (1) Inclusion of other RDH12-related retinal dystrophies (e.g. EOSRD phenotypes) (2) Underdiagnosis, with some RDH12 patients not getting a genotype confirmation. This situation may improve if LCA treatments continue to advance in the clinic, motivating patients to seek genetic confirmation such that they may qualify for gene-specific treatment or trials. (3) Ethnic and geographic variation, where older prevalence estimates may be based on predominantly Western cohorts.

Gene	U.S.	EU4 + UK	Middle East/ North Africa	China	Total Prevalence by Gene
LCA5	~170	~170	~1,400	~1,500	~3,240
BEST1*	~23,600	~4,900	~3,600	~4,900	~37,000
RHO	~8,800	~4,600	~2,200	~14,600	~30,200
RDH12	~2,500	~1,000	~17,500	~9,900	~30,900
MERTK	~2,600	~460	~14,300	~4,600	~21,960
NMNAT1	~1,200	~750	~1,100	~2,200	~5,250
CNGB1	~2,100	~1,000	~5,100	~1,900	~10,100
Total Prevalence by Region	**~40,970**	**~12,880**	**~45,200**	**~39,600**	

Table 2: IRD patient prevalence estimates across several global markets, including RDH12. Analysis by Triangle Insights Group (Feb 2026).[21] Methodology not disclosed.

"I get asked that a lot […] I just feel like I've met too many people with RDH12 for it to be, 2,000. […] The patient registries are decent thanks to the [RDH12] Alliance, it's not going to be hard to enrol [patients] in these [RDH12] trials." – Dr Ash Jayagopal, Opus Genetics

"From my own reading of the literature and calculations, I estimate that there's probably around 2,000-5,000 patients in the US, and you'd expect similar numbers in the EU. […] Most of the centers out there who see these kinds of patients feel like they already have enough patients that they know of to fill the trial […]" – Dr Mathew Pletcher, RDH12 Fund for Sight

The RDH12 patient organisation Eyes on the Future tracks >100 RDH12 families across the world.[22]

1.4 RDH12 gene expression, functions and pathomechanism

Gene. The *RDH12* gene, also known as LCA13, RP53, or SDR7C2**,** was the third recessive LCA/EOSRD gene to be characterised, described by Stockton in 1998 and first cloned in 2002 by the laboratory of Krzysztof Palczewski at the University of Washington, Seattle, WA (USA).[23] It maps to the LCA13 locus on human chromosome 14 (14q23.3-24.1) (**Figure 2**). It is approximately 13 kbs in length and consists of seven coding regions (exons).

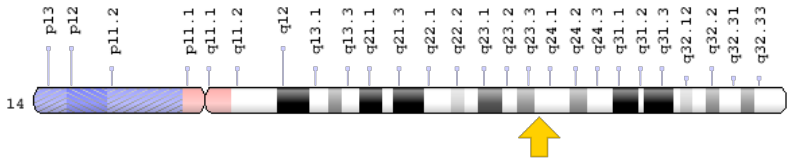


Figure 2: Cytogenetic location: 14q24.1, Molecular location: base pairs 67,701,886 to 67,734,451 on chromosome 14 (Homo sapiens Annotation Release 109, GRCh38.p12). From Genetics Home Reference NCBI.

RDH12 is expressed predominantly in the eyes, with the highest expression levels observed in the retina. In situ hybridisation in monkey and mouse retinas indicated that RDH12 localises to the inner segments of rod and cone photoreceptors.[23–25] RDH12 expression is also detected in the kidneys, brain (pineal gland), skin, skeletal muscle, liver and stomach. RDH12 transcription/expression is subject to circadian regulation, peaking early in the day, which supports the idea that RDH12 helps protect PRs against light-dependent damage from increasing concentrations of retinaldehydes.[26]

Protein. RDH12 protein is a 316 amino-acid long enzyme with a molecular mass of about 35 kDa. It is localised to the inner segments and cell bodies of rod and cone photoreceptors[23], where it is attached to the endoplasmic reticulum (ER) with the majority of its polypeptide chain exposed on the cytosolic side of the membrane.[27] The tertiary structure of RDH12 has not been experimentally resolved, but approximate models have been constructed (**Figure 3**).

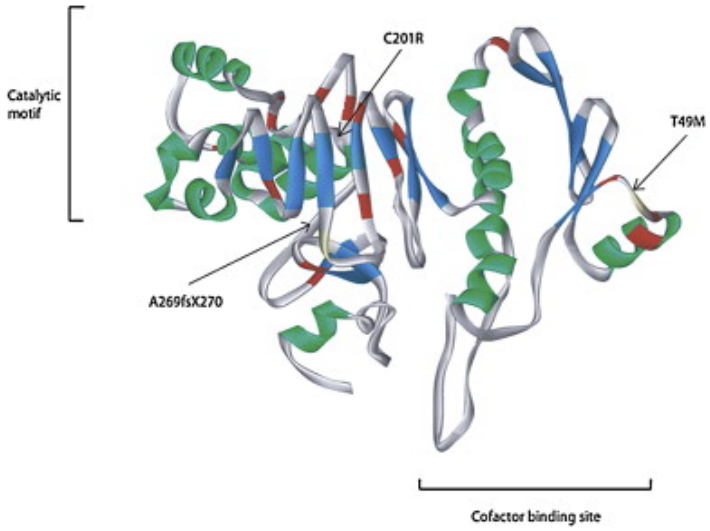


Figure 3: Model of RDH12 tertiary structure. Colour code: alpha helices, green; beta sheets, blue; random coil, grey. Several known sites of autosomal recessive, retinal-dystrophy-associated missense mutations are shown in red. Three mutations (C201R, A269fsX290 and T49M) are labelled.[28]

Function. The visual/retinoid cycle is a process that occurs in cells of the retina (PRs and RPE), which enables continued perception of visual stimuli by recycling vitamin A (all-trans retinol). This is a multi-step process that involves many different enzymes; Among these, enzymes RDH8 and RDH12 are primarily responsible for the NADPH-dependent reduction of all-trans retinal (atRAL). **As much as 30% of atRAL reduction in the visual cycle is catalysed by RDH12**, albeit its contribution is likely minimal, as atRAL reduction in the visual cycle occurs primarily in the outer segments of PRs (by RDH8) whereas RDH12 is resident in the inner segments. More importantly, it has been suggested that RDH12 functions to **reduce excessive free atRAL and decrease other toxic compounds e.g. A2E and 4-HNE, thereby protecting PRs against light-induced PR apoptosis**.[v] 4-HNE is produced by light-exposure-mediated lipid peroxidation, and 4-HNE accumulation results in cellular stress and death (apoptosis). Likewise, RDH12 metabolising atRAL has been found to be key in protecting cells from oxidative and ER stress. Maeda et al. also suggested that **RDH12 may regulate the flow of retinoids in the eye**.

A recent study in zebrafish has suggested an additional function for RDH12 in the visual cycle. In addition to catalysing 30% of atRAL reduction, **RDH12 also supplements 11-cis retinal** – which is canonically supplied to PRs by RPEs – to regenerate visual pigment in cone photoreceptors **by oxidising 11-cis retinol provided by Müller cells.**[29]

Although RDH12-associated disease is primarily retinal, expression of RDH12 in non-ocular tissues suggest potential metabolic/physiological roles. *Rdh12* knockout mice have been reported to develop a hyperuricemia phenotype.[30] RDH12 was also shown to convert dihydrotestosterone (DHT) to androstanediol, suggesting a possible involvement in steroid metabolism.[31]

[v] A2E: *N*-retinylidene-*N*-retinylethanolamine; 4-HNE: 4-hydroxynonenal

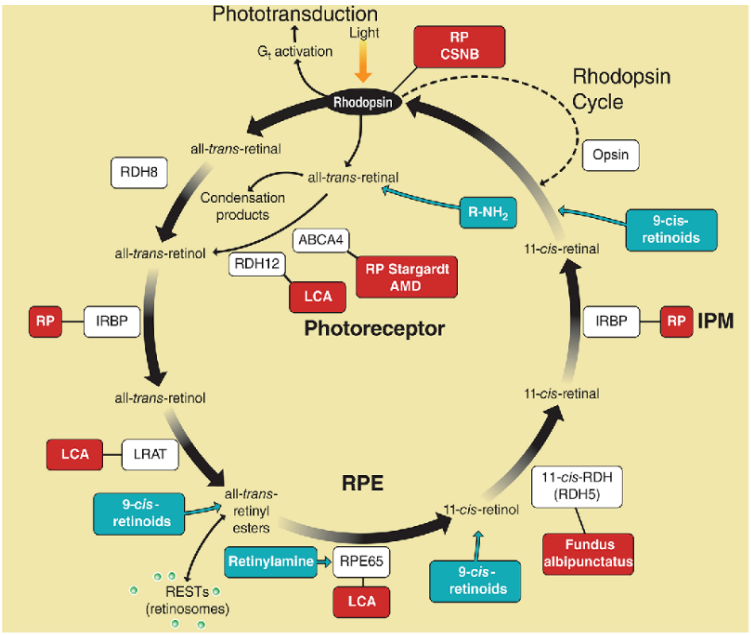


Figure 4: The visual cycle. Adapted from Kiser et al. (2014)[32]

Pathomechanisms. Impairments in the cycling of vitamin A, due to mutations in genes coding for enzymes in the visual cycle, are associated with many retinal disorders (**Table 3**). However, while the molecular mechanisms of pathogenesis/progression in RDH12-recessive LCA remain debated, the leading theory is that inactive/degradation-prone mutant RDH12 lose their enzymatic activity[8,27,33,34], resulting in **the accumulation of toxic atRAL and conjugation products (e.g. A2E and 4-HNE) in the inner segment of PRs leading to cell death, rather than visual cycle disruption.** This is evidenced by milder disease phenotypes in Rdh8KO/Rdh12KO mice compared to mice deficient in other key visual cycle enzymes (RPE65 or LRAT), and greater sensitivity to light-induced apoptosis in PRs of Rdh12KO mice compared to wild-type mice despite comparable and sufficient 11-cis retinal levels (i.e. functioning visual cycle).

Dominant forms of RDH12 disease (adRP), which typically have milder phenotypes, involve an aberrant C-terminal loop structure[18]. A gain-of-function mechanism for RDH12 has also been proposed.[35]

Gene	Protein	Disease
IRBP/RBP3	Interphotoreceptor retinoid binding protein	- High myopia with retinal dystrophy - Retinitis pigmentosa 66 (arRP66)
LRAT	Lecithin:retinol acyl transferase	- LCA14/EOSRD - Juvenile retinitis pigmentosa
RPE65	Retinoid isomerohydrolase	- LCA2 - Retinitis pigmentosa 20 (RP20)
11-cis RDH/RDH5	11-cis retinol dehydrogenase	Fundus albipunctatus
RDH12	Retinol dehydrogenase 12	- LCA13/EOSRD - Retinitis pigmentosa 53 (RP53)

ABCA4	ATP Binding Cassette subfamily A member 4	- Stargardt disease 1 or Fundus flavimaculatus - arRP19 - CORD3 - EOSRD
RGR	Retinal G protein–coupled receptor	Retinitis pigmentosa 44
RLBP1/CRALBP	Retinaldehyde binding protein 1	- Retinitis punctata albescens - Fundus albipunctatus - arRP Bothnia type - Newfoundland rod-cone dystrophy

Table 3: Diseases linked to changes in visual cycle proteins. *Modified from Travis et al., 2008*[36]

1.5 RDH12 scientific research

Since the discovery of the RDH12 gene in 2002, there has been a gradual increase in scientific interest from the research community, and this has accelerated in recent years (**Figure 5**).

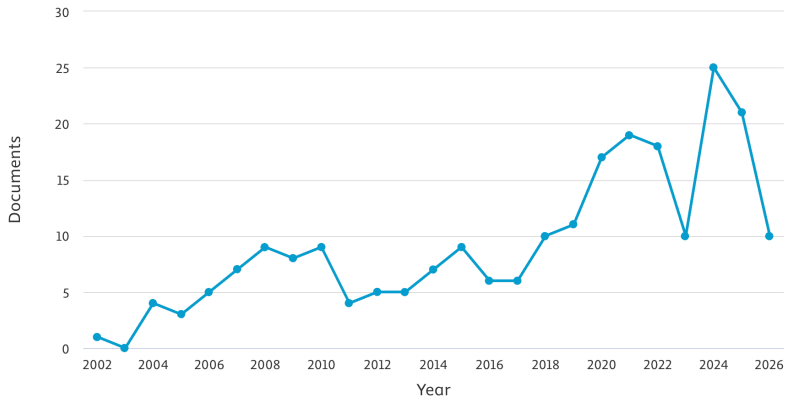


Figure 5: Number of papers addressing RDH12 per year of publication. Value for 2026 is up to July 2026.

In July 2026, 229 bibliographic items could be retrieved using Scopus[vi] search, using "RDH12" as a keyword within titles, abstracts, and paper keywords. This figure corresponds to **8.1% of the total scientific production in the LCA field** (totalling 2818 publications, Scopus, July 2026). **This represents an expansion from the 98 items and 5.6% of LCA research in March 2019.**

By geography, China has emerged as a key player for RDH12 research (53 publications), behind the US (83 publications). They are followed by the UK, Germany, and Japan. By subject area, the vast majority of publications falls in the fields of (1) Medicine (38.5%) comprising mainly clinical and case reports, (2) Biochemistry (27%), and (3) Neuroscience (11.2%).

The most active researchers within the RDH12 space, by number of RDH12 publications (Scopus, July 2026), are:

- **Debra A. Thompson** (14 publications) - Professor of Ophthalmology and Visual Science and of Biological Chemistry at the Kellogg Eye Center, Ann Arbor, MI (US). Her research continues to focus on the molecular mechanisms responsible for IRDs.

[vi] Scopus (https://www.scopus.com/home.uri) is the largest abstract and citation database of peer-reviewed literature. It features a handful of tools to track, analyze and visualize research.

- **Michel Michaelides** (12 publications) - Professor of Ophthalmology at Moorfields Eye Hospital and UCL Institute of Ophthalmology, London (UK). His group has substantially expanded characterisation of RDH12-associated autosomal dominant retinitis pigmentosa and detailed clinical phenotyping using multimodal imaging.
- **Mariya Moosajee** (10 publications) - Professor at Moorfields Eye Hospital and UCL Institute of Ophthalmology, London (UK), with research spanning clinical characterisation and molecular genetics of RDH12-associated disease, including novel dominant variant discovery.

2. STATE OF PRECLINICAL RESEARCH INFRASTRUCTURE

2.1 Introduction

Before any therapeutic candidate can be tested in human clinical trials, researchers must first establish their safety and efficacy in preclinical models, which include *in vivo* animal models and *in vitro* cell lines and organoids. It would be ideal to have preclinical models specific to the disease of interest, both to study the pathomechanism of the disease and to investigate the effects of treatment protocols. **When the previous edition of the RDH12 Landscape report was published, only stable cell lines and mice models were available for RDH12-related retinopathies, each with their own limitations,** and the lack of large animal models was highlighted as a challenge to clinical translation. The field has utilised existing small-animal model data and **developed new iPSC-based models to bridge these gaps.**

As of 2026, the two RDH12 gene augmentation therapy programmes in active development are (1) PUMCH-E101/IVB107 (Peking Union Medical College Hospital & Innovec Biotherapeutics) which has completed dosing in an early Phase 1 study in China and, according to Innovec, obtained US FDA IND clearance, and (2) OPGx-RDH12 (Opus Genetics, asset from UPenn) which received FDA IND clearance in October 2026 (**Section 3.2.1**). **From discussions with KOLs, it is understood that both programmes did not specifically require preclinical efficacy data that exactly mimic the human phenotype from large animal models to enter human testing.** The PUMCH/Innovec programme utilised cellular-level expression studies to select the best capsids, and tested them in RDH12 rat and mouse models. Because the murine models do not fully recapitulate the human phenotype, the researchers supplemented this with patient-derived iPSCs and retinal organoids to test the vector, safety, and rescue potential. Non-human primate models (normal monkeys that do not exhibit photoreceptor degeneration) were also used to evaluate in-eye and systemic safety. The Opus programme showed expression of the RDH12 transgene in photoreceptors at physiologic levels could be achieved in small animal models, as well as established studies that showed meaningful outcomes (protection of the retina) by providing a functional copy of RDH12 in small animal models even if they do not exactly mimic the human degeneration phenotype.

For a monogenic recessive disease with a clear loss-of-function pathomechanism such as RDH12 retinopathies, because gene therapy directly addresses the root cause and replaces the missing gene product, regulators have been willing to accept evidence of target engagement (transgene expression in photoreceptors) and safety data without disease-specific large animal models that more closely resemble humans. **Patient-derived tissues can also be used to show human phenotypes and are becoming more broadly available.** While **the lack of better animal models is no longer the main barrier to initiating trials for gene augmentation,** they are still valuable for disease understanding, testing other therapeutic modalities with less-direct mechanistic evidence, vector biodistribution/exposure, surgical procedures, and systemic tolerability/immune response.

In this chapter, we compare the advantages and limitations of different types of preclinical models and list the preclinical models available for RDH12-related research.

2.2 Animal models

2.2.1 Mice models

Mice are the most widely used animal model for studying human disease, as they are small, easy to maintain, grow and reproduce quickly, and relatively **easy to manipulate genetically**. As of 2026, three murine Rdh12 knockout (KO)/null lines (mice not expressing RDH12) have been generated:

- Maeda et al. 2006 (Palczewski Lab)[25]: Full Rdh12KO, by replacing RDH12 exons 1-3

- Kurth et al. 2007 (Thompson/Hübner)[24]: Full Rdh12KO, by targeted deletion of RDH12 exons 1-3
- Bian et al. 2021 (Ming Qi, Zhejiang University)[37]: Full Rdh12KO, by removing RDH12 exons 1-5 in mice carrying the light-sensitising Met450Leu RPE65 variant, which reduces RPE65 levels

The two legacy Rdh12KO mice **do not exhibit overt retinal degeneration and are able to regenerate visual pigments normally** in rods/dissected retina, suggesting that the loss of RDH12 alone does not substantially impair the visual cycle in mice.[vii] Even mice that have lost RDH8, RDH12, and RDH5 simultaneously ($Rdh8^{-/-}Rdh12^{-/-}$ double knockout and $Rdh8^{-/-}Rdh12^{-/-}Rdh5^{-/-}$ triple knockout lines) show only minor abnormalities in chromophore regeneration and develop only mild light-dependent retinal degeneration. This may be due to rodents having naturally slower retinoid regeneration kinetics than humans (rodents are nocturnal and normally exposed to lower levels of illumination than humans), making them less vulnerable to disruptions in the visual cycle (e.g. slower 11-cis retinal delivery). Nonetheless, **knockout mice are more susceptible to photoreceptor apoptosis when kept at daylight brightness**, and display delayed dark adaptation/ERG recovery and **accumulate toxic all-trans retinal (atRAL) after photobleaching.** These findings suggest that RDH12 has a protective role under conditions of excess illumination. **Overall, their phenotype is milder than that of humans carrying RDH12 null alleles, and the retinal pathology does not resemble LCA13 exactly,** limiting their utility in studying RDH12 disease mechanisms and testing candidate therapies.

The new RPE65-Met450/Rdh12KO C57BL/6 mice can better reproduce the phenotypes observed in human RDH12-IRD patients. Exposure to bright light for 48 hours induced **visual dysfunction and photoreceptor death** in the Rdh12KO mice, as shown in significantly reduced a- and b-wave amplitudes on ERG, thinner outer nuclear layer in the central retina, and yellow-white punctate retinal flecks in the fundus indicating cone or RPE cell dysfunction. This structural and functional degeneration could be slowed and even rescued using AAV2/8-mRdh12 cDNA gene therapy. Nonetheless, the mouse phenotype is still comparatively mild versus the severe phenotype observed in RDH12 patients. Additionally, hyperuricemia (high uric acid) and renal disease phenotypes were observed in these mice, suggesting that RDH12 deficiency has extra-ocular effects that may warrant clinical investigation in human patients.[30,37]

The legacy Rdh12KO mice have been used to elucidate certain aspects of RDH12 function and pathogenesis. RDH12 protects the inner segments of PRs from leakage of retinal or other toxic aldehydes from the outer segments during light exposure.[39] In particular, free atRAL can condense into the lipofuscin component A2E, which is highly accumulated in *Rdh12*KO mice retinae and increases with aging.[38] This and other very reactive aldehydes might induce toxic effects on mitochondria and other vital organelles within the inner segments of PRs.[25,39] Marchette et al. (2010) showed that RDH12 metabolises 4-HNE, a toxic molecule that accumulates in the presence of oxidative stress and upon light exposure, forms adducts with proteins in the inner segment of PRs, eventually leading to PR cell death.[40] Rdh12KO mice were significantly more affected than wild-type mice by bright light. It is theorised that loss of RDH12 function will cause 4-HNE to progressively accumulate through daily exposure to moderate light.

The **limitations of mice models**[41] include:

- While all mammalian species share the same basic retinal features, mice do not have a macula/region of high PR/cone density, and hence cannot fully model RDH12 retinopathies which involve rapid and severe macular atrophy/degradation.
- Rod-dominant retina (only 3% of photoreceptors are cones) and slower retinoid regeneration

[vii] Chrispell et al. 2009[38] provides evidence to the contrary: Retinal homogenates from the Kurth et al. 2007 Rdh12KO mice showed decreased atRAL reduction and increased A2E levels.

kinetics, due to their nocturnal nature.

- Other biological differences (e.g. gene expression, epigenetics, immune systems) that result in phenotype differences from human condition, despite knocking out the orthologous gene.
- Some uni-ocular AAV gene therapy studies in rodents have shown binocular effect (i.e. improvement is observed in both the treated and untreated eyes of the same animal, either due to AAV transfer between the eyes, elevation of neurotrophic factors, or both), unlike in canine models or humans. This would complicate studies that require a within-animal control.

In general, while electrophysiological recovery at the retina level can be studied in mice, implications for functional vision recovery may not always be readily translated to humans.

2.2.2 Zebrafish

Zebrafish (*Danio rerio*) are a powerful model for studying eye diseases and **conducting high-throughput screening**, due to[42]:

- ~70% sequence identity with orthologous genes in humans
- Ease of manipulating genetically and ease of generation/maintenance
- Diurnal nature and a human-like cone-dominated retina with a macula-like region, useful for modelling macular degeneration-like pathologies, PR-RPE interactions, and cone diseases which affect visual acuity, colour perception, and central vision
- **Rapid eye development**, with opsins expressed by 2.5 days post fertilisation (dpf) and visual responses by 5 dpf, suitable for assessing early-onset disease
- **Ease of assessing phenotypes**, as embryos and larvae can be imaged in vivo, and retina can be studied using ERG and OCT

Challenges/Limitations include:

- **Different photoreceptor distribution.** Human cones are packed in the macula and fovea, while zebrafish cone are organised uniformly across the retina[43]
- Zebrafish can regenerate PRs via de-differentiating Müller glia in response to degenerative disease, which may make disease progression appear slower than it is
- Zebrafish may have 1-2 redundant/overlapping orthologues for a single human gene, which need to be knocked down/out simultaneously (*rdh12* is not duplicated)
- Mutant phenotypes not always recapitulated in knockdown models

CRISPR/Cas9 gene editing is a popular method to introduce mutations in zebrafish, due to its ease of use, high efficiency, and availability of various techniques e.g. knock-in, base editing, prime editing.

The Zebrafish International Resource Center database[44] contains three rdh12 mutant lines: one with a LacZ insertion (ZL5093.05, Burgess and Lin Lab, NIH/UCLA), one with a point mutation that causes a premature STOP (ZL14087.07, Stemple Lab, Cambridge), and one frameshift variant in exon 1 that causes a premature STOP (ZDB-ALT-240111-13).

The latter zebrafish line (*rdh12*^{u533}) was developed by the Moosajee Lab (Moorfields Eye Hospital/UCL), originally to screen/repurpose drugs for RDH12. *rdh12* mRNA expression was significantly reduced in the mutants, implying non-functional proteins. The embryos did not reveal a retinal phenotype at 5 dpf and were comparable to wild-type fish in terms of retinal morphology, rhodopsin levels, atRAL levels, and oxidative stress markers, in contrast to human RDH12 patients who develop early onset phenotypes. At 12-16 mpf, mislocalised rhodopsin (mislocalised to the PR inner segments and ONL in

retina, while opsin expression was unchanged, consistent with a rod-cone dystrophy), enlarged phagosomes in RPE (consistent with widespread RPE atrophy in RDH12-LCA patients), and reduction of *atg12* and *sod2* expression (which may lead to increased oxidative stress and degeneration) were observed in the fish, i.e. **the zebrafish exhibited a late-onset, rod-predominant degeneration more similar to a RDH12-associated RP human phenotype which is milder than RDH12-LCA.** Similar discrepancies between human and zebrafish phenotypes have been observed previously for KCNJ13-LCA. It is hypothesised that compensatory mechanisms (other than additional *rdh12* isoforms, e.g. other RDHs) exist in the zebrafish, and/or that the cone-specific visual cycle independent of the RPE may play a more prominent role in the regeneration of the visual chromophore in zebrafish.[45] Separately, working on a zebrafish line with wild-type *Rdh12*, Kaylor et al. (2024) identified *crdh* (previously called *Zcrdh*) as an RDH that allows zebrafish cones to regenerate opsin visual pigments from exogenous 11-cis retinol; Loss of *crdh* disrupts the cone visual cycle, and RDH12 was identified as the mammalian equivalent of this gene.[29] This challenges previous knowledge that RDH12 is not duplicated in zebrafish. **A *rdh12/crdh* double mutant may present a further avenue for study.**

Because atRAL was not elevated in the *rdh12*^{u533} zebrafish up to 16mpf, its current utility in screening therapeutic candidates that act as retinal scavengers (e.g. pregabalin) is limited, although it may be useful to screen therapeutic candidates acting by other mechanisms (e.g. antioxidants), or if atRAL levels are found to be elevated after a longer observation period or light exposure.

2.2.3 Large animal models

Compared to mice and zebrafish, large animal models such as dogs, cats, pigs, and non-human primates (NHPs) have much **more similar eye sizes/anatomy and photoreceptor distribution** (presence of cone-rich visual streaks) to humans. Hence, **mutant phenotypes in these models are expected to more-closely mimic IRDs in humans**, which would benefit disease understanding and preclinical testing of therapeutic candidates for RDH12. No large animal models currently exist for RDH12 retinopathies, although some exist for other IRDs. The main constraints to widespread use of large animal models are mainly the logistics/cost and ethics, rather than scientific feasibility.

2.2.3.1 Dogs

Dogs have visual streaks (cone-rich regions) in their retina, with peak cone density comparable to human/macque retinas, as well as binocular overlap and competition, and their **disease phenotypes often mimic IRDs in humans.** Dog models are available for several IRDs (**Table 4**), including *ABCA4* mutant dogs for Stargardt disease and *GUCY2D* mutant dogs for LCA1, and famously provided the first proof-of-concept for IRD gene augmentation therapy in the development of Luxturna for RPE65-LCA (LCA2). Specifically, the dogs were used to probe whether the second eye could be successfully treated without immune responses to the vector/transgene, due to initial exposure during injection in the first eye, and whether the therapy completely halted degeneration. Of note, the ERG improvement observed in dogs was greater than that in human patients.

Dogs are not routinely genetically-engineered to induce disease phenotypes, due to ethical concerns. Instead, the medical field relies almost entirely on spontaneous (naturally-occuring) disease models identified through screening, and there are only a few centres in the world that maintain dog colonies.

Disease	Gene (Inheritance pattern)	Progress in humans
RP	*PDE6A* (AR)	Ph 1/2a
	PDE6B (AR)	Ph 1/2
	CNGB1 (AR)	Trial planned
	RHO (AD)	Preclinical
	RPGR (XL)	Multiple trials

LCA	*RPE65* (AR) - Luxturna	Approved
	NPHP5 (AR)	Trial planned
Achromatopsia	*CNGB3* (AR)	Ph1/2
Best disease	*BEST1* (AR)	Preclinical
cCSNB	*LRIT3* (AR)	Preclinical
Cone-rod synaptic disorder	*CaBP4* (AR)	Preclinical

Table 4: IRD gene therapies in human trials where a canine model was used in development[41]

2.2.3.2 Pigs

Pig models have been generated for Stargardt Disease (*ABCA4* knockout), Usher Syndrome, and autosomal dominant RP (rhodopsin P23H knock-in). Dr Ruifang Sui (Peking Union Medical College Hospital) has previously generated and characterised minipig models of Bietti crystalline retinopathy and oculo-cutaneous albinism, and has proposed generating an *RDH12* knockout or even a mutation-specific knockin minipig model. However, she does not currently have the funding to do so.

Separately, porcine-derived organs have been proposed as a xenogeneic source of transplants in patients with end-stage organ failure. In the context of IRDs, Zhang et al. (2018) have obtained allogenic RPE cells and a regenerated intact eye, which could potentially be transplanted into advanced IRD patients in the future.[46]

2.2.3.3 Non-human primates

Non-human primates (NHPs) are particularly valuable for studying macular dystrophies such as Stargardt disease, Best disease, and *RDH12* retinopathies, as they have a macula and fovea like humans do. However, unlike in dogs, very few naturally-occurring IRD models have been identified (only *BBS7*, *PDE6C*, and one ungenotyped RP), generation/validation of genome-edited disease-specific NHPs is expensive and technically challenging (only *CNGB3* and *RHO*), maintenance is laborious (slow reproductive rate, long lifespan prolong study timelines, limited number of facilities able to handle NHPs), and there are substantial ethical and zoonosis concerns around their use. Several gene-agnostic NHP models are used to mimic end-stage retinal degeneration (induced by chemicals or laser) for the testing of cell therapies, although these are not relevant to studying the initial pathogenesis of a specific genetic disease or testing treatments that target early-stage degeneration.[47]

Few IRD disease-specific NHP models are available, but healthy NHPs are routinely used in safety and toxicology studies for new drugs prior to clinical testing.

2.2.4 Invertebrates

Worms and flies have been used to model human diseases such as Alzheimer's, Parkinson's, ALS, Huntington's, and cancer. Advantages include fast generation times, large brood sizes, small size, and low cost. However, developmental pathways, organism biology, and homology to human genes is lower compared to mammals, limiting their utility in contexts where phenotype recapitulation is crucial.[48]

2.2.4.1 Caenorhabditis elegans

C. elegans does not have opsins, utilising a different mechanism for light detection.[49] Thus, nematodes have no need for production of retinoic acid or retinoid chromophores, and their RDH12 homologues probably possess different functions.

2.2.4.2 Drosophila melanogaster

Drosophila has six genes encoding short chain dehydrogenase/reductase (SDR) with ~50% identity to human *RDH12*. *Drosophila* SDRs and human RDH12 have a common ancestry and similar substrate/cofactor specificities, suggest conservation of their function in retinoid metabolism.[50] Although

Drosophila was previously thought to lack a visual cycle, the RDH pigment-cell enriched dehydrogenase (PDH) has been shown to be necessary for chromophore regeneration. Loss of PDH causes light-dependent rhodopsin depletion and retinal degeneration, possibly due to toxic retinaldehyde accumulation; These defects can be partially rescued by expression of mammalian RDH12.[51] The *Drosophila* PDH crystal structure has been determined (unlike human RDH12) and this has enabled homology modelling of human RDH12, which has provided insights into the structural consequences of disease-causing mutations in RDH12, including mutations affecting the catalytic domain, the dinucleotide binding site, and the protein-protein dimerisation interface.[52]

2.3 *In vitro* disease models (human tissue)

Animal models allow us to study disease and treatment effects in a whole organism, but are fundamentally limited by anatomical and biological differences to humans (~90% of drugs, which pass preclinical testing in animals, still fail clinical trials in humans or later development). Hence, *in vitro* models utilising human tissue with the disease of interest are used where possible.

2.3.1 Retinal explants/organotypic cell cultures

Diseased/affected tissues can be obtained from patients (e.g. through a biopsy) and cultured as models for various diseases. However, we cannot surgically obtain ocular biopsies (retinas) from living patients without destroying their remaining sight (the procedure damages the retina, which is not capable of regenerating). Therefore, only post-mortem samples from late-stage disease are available for IRDs, with limited utility in studying disease pathogenesis or early/mid-stage therapeutic interventions.

2.3.2 Stable cell lines

COS-7, Sf9,[viii] and HEK-293 cells, which do not normally express RDH12 as they are not retinal tissues, have been transfected with wild-type and mutant RDH12 by various groups to study the expression and activity of different disease-causing RDH12 variants *in vitro*. In some cases, the mutation can nearly completely abolish RDH12 activity either due to disruptions of the active site (e.g. p.(C201R)) or reduced protein stability/accelerated degradation (e.g. p.(T49M), p.(Ala269Glyfs*2)).[27,33,34,40]

The Moosajee Lab has developed HEK-293 cell lines expressing wt RDH12 and 3 LCA-associated mutants (p.(Y226C), p.(A109P), and p.(S13*)). The wt RDH12 cells have been confirmed to express functional wt RDH12 that is correctly localised to the ER. The p.(A109P) mutant line showed reduced RDH12 expression, while the p.(Y226C) and p.(S13*) mutant lines showed no protein expression. All mutant lines had significantly reduced RDH12 activity as measured by all-trans retinol production from all-trans retinal. **These cell lines have been used to establish oxidative and ER stress as key disrupted pathways in RDH12 retinopathies, and to screen retinal scavenger compounds as potential therapeutic candidates,** by assaying their ability to reduce atRAL-induced cellular stress/restore cell viability.[45]

More recently, Pavlova et al. (Sirius University, Sochi, Russia) have established ARPE-19 and HEK-293 cell lines expressing wt, p.(T155I), and p.(M1*) RDH12. **The ARPE-19 models may be more clinically relevant than HEK293, as these are retinal pigment epithelium (RPE) cells although it should be noted that RDH12 is a primarily a disease of photoreceptors.** Wt/mutant RDH12 activity was assayed by cell viability following treatment with 100 μM 4-HNE, a RDH12 substrate. ARPE-19 cells expressing wt and p.(T155I) RDH12 were protected from the cytotoxic effects of 4-HNE, while p.(M1*)

[viii] Not human cells; COS-7 derived from African green monkey and Sf9 from fall armyworm. These *in vitro* models are well-understood and easy to work with/control for. They are especially useful for studying protein interactions/disease pathways, drug-target engagement, and toxicity and isolation.

RDH12 lost its activity. This study also established AAV7m8 as the most efficient vector for transducing RPE cells (ARPE-19) with RDH12, compared to AAV5 and AAV.PHP.S, in an in vitro context.[53]

2.3.3 hPSC-derived photoreceptors and retinal organoids

Photoreceptor diseases are best studied in photoreceptor cells carrying the relevant mutation and in a functional retina. Induced pluripotent stem cells (iPSCs) can be generated from somatic cells (e.g. skin or blood)[ix] obtained directly from patients. Hence **they already carry the disease-causing gene variants and can be readily differentiated into the relevant ocular cells/tissues (e.g. RPE, PRs)**, providing an ideal model for disease modelling, drug screening, and/or personalised/regenerative medicine that overcomes the limitations of both retinal explants and stable cell lines.

2.3.3.1 RDH12 hPSC lines

Several RDH12 patient iPSC lines have been established in recent years, covering a range of retinal degeneration phenotypes (**Table 5**).[x]

Name	RDH12 mutation	Description	Source Lab
UCLi014-A	p.F254fs (c.759delC)	32yo male, ADRP, heterozygous	Moosajee (UCL)
UCLi015-A	p.N207D (c.619A>G)	40yo female, AR LCA, homozygous	Moosajee (UCL)
ERPLi002-A	p.S13* (c.38C>A)	11yo male, LCA, homozygous	Eyestem (India)
UGENTi003	p.R234H, c.(-123C>T;701G>A) & p.A269Gfs*2, c.806_810del	38yo female, intermediate rod-cone dystrophy, compound heterozygous	Coppieters (UGhent)
UGENTi004	p.R234H, c.(-123C>T;701G>A) & p.A269Gfs*2, c.806_810del	20yo male, intermediate rod-cone dystrophy, compound heterozygous	Coppieters (UGhent)
PUMCHi018-A	p.R62* (c.184C>T) & p.V146D (c.437T>A)	13yo male, LCA, compound heterozygous	Sui (PUMCH, China)
BTHBIOi006-A	p.V146D (c.437T>A) & p.S175L (c.524C>T)	39yo female, LCA, compound heterozygous	Beijing Tongren Hospital, China[56]
SKLOi005-A, SKLOi005-B	p.S175L (c.524C>T) & p.A269G (c.806C>G)	30yo male, LCA, compound heterozygous	Sun Yat-Sen University, China[57]

Table 5: Available RDH12 patient-derived iPSC lines

From the previous report, Dr Jean Bennett (UPenn) was also planning to develop patient-specific RDH12 iPSCs, in order to generate PR models to test her lab's RDH12 gene therapy (now being developed by Opus Genetics). No public updates have been provided on the progress on iPSCs for this programme.

The UCLi014 iPSC has been used to successfully generate retinal organoids (see Section 2.3.3.2) modelling autosomal dominant RDH12-related retinitis pigmentosa, which has a milder, late-onset phenotype compared to LCA.[58] Additionally, two iPSC control lines (UCLi016, UCLi017) have been generated from healthy donors with no known ocular conditions.[59] Note that these control lines are not isogenic to the patient-derived iPSCs, which may complicate results/comparisons. It would be ideal to create isogenic control lines by gene editing the existing RDH12-patient iPSCs, such that the genetic background/cells are identical apart from the presence/absence of the RDH12 mutation.

In contrast to patient-derived iPSCs which naturally carry the disease-associated RDH12 mutations, **mutations can also be engineered into stem cells carrying wtRDH12 genes.**

[ix] Protocols for generation of iPS cells require that a skin biopsy is collected by a non-invasive and safe procedure. Then, patient-specific fibroblasts are derived, maintained in culture, and stored in appropriate cell banks. These cells can be reprogrammed to iPSCs through a mixture of key factors. The time lag from biopsy to validation of the best iPSC clone may take 2-3 months.

[x] Cellosaurus[54], hPSCreg[55]

David Gamm's Lab is building RDH12 hPSC models by engineering specific RDH12 mutations into hPSC lines. They aim to differentiate these cells into retinal organoids and **establish a potency assay that directly measures RDH12 function by measuring the autofluorescence signatures of different retinoids (i.e. atRAL and atROL).**[xi,60] This would be an assay that **directly quantifies wt/mutant RDH12 activity in real-time and in live organoids, rather than downstream effects which may have more confounding factors** e.g. cell survival, PR/organoid morphology, **addressing a gap in existing functional assays.** This assay can be used to test therapeutics of various modalities (gene augmentation, gene/base editing, translational read-through drugs, small molecules) where the therapeutic mode of action is to restore/rescue RDH12 reduction/clearance of atRAL in PRs; It is not relevant for other modalities e.g. optogenetics, cell replacement that do not act on RDH12 metabolites in PRs. The same can be done with RDH8, which has the same role as RDH12 in the visual cycle but is localised to the outer segment of PRs, although RDH8 mutants are rarer.

Separately, the South China Agricultural University has also been generated a CRISPR/Cas9 RDH12 knockout iPSC line SCAUi001-A modelling cone-rod dystrophy, obtained from blood cells from a 35-39yo healthy male.

2.3.3.2 Differentiating hPSCs into PRs and retinal organoids

Stem cells (human/murine embryonic stem cells (ESCs) or iPSCs) can be differentiated into photoreceptors, for the study of RDH12 dysfunction and treatment candidates in PRs. The technology for generating RPE cells is more mature than PRs, but nonetheless various protocols have been published for differentiation of ESCs and iPSCs *in vitro* towards photoreceptor lineages. **Older methods produced 2D PR cultures in a dish, which do not replicate the complex environment of the native retina** (cell organisation/layering (lamination), intercellular/synaptic interactions of PRs and RPE cells, etc) and are hence not "authentic", fully functional/photosensitive photoreceptors.

Retinal organoid technology – in which entire **3D, multilayered structures containing all seven major cell types (including photoreceptors and their relevant interactions), develop and organise like native retina, and have partial light-responsive function** are grown from stem cells – **present improved disease models for IRDs**, and have enabled discovery of novel variants (for *ABCA4, CNGB3*), study of pathogenesis (for *USH2A, CEP290,* and *CRB1*), and evaluation of therapeutic candidates (**Table 6**).[61,62] As mentioned in Section 2.3.3.1, the Moosajee Lab at UCL have successfully generated retinal organoids modelling RDH12-adRP from a patient's iPSC cells, and the Gamm Lab at UW Madison is developing a RDH12 functional assay measuring atRAL and atROL levels in live retinal organoids containing RDH12 mutations.

Disease	Gene & mutation	Therapies screened
RP	CRB1 c.3122T>C	AAV
	PRPF31 c.1115_1125_del11	CRISPR/Cas9
	PRPF31 c.709_734dup	AAV
	RPGR c.1685_1686delAT	CRISPR/Cas9
	RPGR Exon 14	CRISPR/Cas9
	RPGR Frameshift mutations in exon ORF15	AAV
	RHO Structural variant	Small molecule
	USH2A c.2276G>T	CRISPR/Cas9
	NR2E3 c.166G>A	CRISPR/Cas9
	RP2 c.358C>T	AAV
LCA	CEP290 c.2991+1655A>G	ASO, small molecule
	AIPL1 c.834G>A	TRID, AAV
	AIPL1 c.466-1G>C	CRISPR/Cas9

[xi] Interview with Dr David Gamm (July 2026)

	CRX c.264G>T	AAV
	NPHP5 c.421_422delTT	AAV

Table 6: Retinal organoids generated from patients with RP or LCA used for therapeutic screening. Adapted from Lee & Jo (2025)[61]

Currently, 5 primary protocols are used to generate retinal organoids from patient-specific iPSCs. It is important to note that **retinal organoids are still only imperfect, semi-physiologic models**. Limitations include:

- Retina light-sensing/function may not be fully recapitulated; The eye-brain connection is not modelled
- Microenvironment: These organoids do not have vasculature (blood vessels) or an immune system, cannot recapitulate nutrient/oxygen delivery and inflammatory/immune responses
- Lack RPE-PR interface/intercalation, which are held together by intraocular pressure and fluid movement across the RPE *in vivo*
- Variability between iPSC lines during the differentiation process hampers consistency and reproducibility
- Time-consuming, high-touch process

Work is under way to further improve retinal organoid technology (e.g. retina-brain assembloids, organ-on-a-chip).

2.4 Role in cell therapy

Apart from disease modelling and therapeutic candidate testing, the ability to grow obtain/grow retinal cells *ex-vivo* provides a source of transplantable cells that may be used to replace cells that already have degenerated in IRD patient eyes (see Section 3.6). **Healthy PRs/RPEs or their precursor cells could, in theory, be obtained from animals** (see Section 2.2.3.2), **cultured human eye tissues** i.e. retinal organoids or directly differentiated from donor stem cells, or adult/foetal retina.

The most clinically-advanced work in the photoreceptor replacement field, which is more relevant to RDH12-LCA, is the PR precursor cell therapy OpCT-001 (Opsis Therapeutics, BlueRock Therapeutics, FUJIFILM Cellular Dynamics) which is in Phase 1/2a trials for late-stage primary photoreceptor diseases (see Section 3.6). The cells used in this therapeutic protocol are obtained from iPSCs and administered to the back of the eye as a suspension. Separately, retinal organoid sheets have been transplanted into human patients with advanced RP, and showed improvement in visual function tests for severe visual impairment, although visual acuity did not improve.[63] Both of these programmes use allogeneic grafts, which are obtained from healthy donors without IRDs, hence should not degenerate like the patient's own photoreceptors did. However, allogeneic grafts run the risk of immune rejection; This is circumvented by using HLA-matched graft cells from a clinical-grade iPSC haplobank. Another approach is personalised medicine, in which the patient's own iPSCs are gene-edited (to replace the mutant RDH12 with wild-type RDH12) and differentiated into photoreceptors to be transplanted back into their own eyes (autologous graft). However, feasibility, cost, and resource intensity are challenges; Additionally, not all patient iPSC lines can generate retinal organoids/transplantable material with equal efficiency. **For rare diseases like RDH12 retinopathies, haplobanks may not contain suitable cell lines, hence patient-derived iPSCs remain valuable.**[61]

2.5 Commentary

The preclinical research infrastructure available for RDH12-associated retinopathies has expanded substantially since the previous edition of this report. Among animal models, a zebrafish

model (RDH12-adRP-like phenotype) and a light-sensitised RDH12KO mouse model that exhibits visual dysfunction and PR degeneration have been generated and characterised. Additionally, ARPE-19 lines (derived from RPE, hence may be more clinically relevant than existing HEK-293 lines) expressing wild-type and mutant RDH12 have also been established. While useful for early-stage, high-throughput screening (to evaluate target engagement and extent of functional rescue) and potentially in studying disease biology, **these small-animal/stable line models still do not faithfully mimic/reproduce the severe, cone- and macula-predominant, early-onset RDH12-LCA phenotype in humans.** Large animal models (e.g. pig, dog, non-human primates) would be more suitable for these purposes given their similarity to humans in terms of eye anatomy (e.g. size, compartments, photoreceptor distribution in retina, ocular dominance columns, more similar immune systems), as well as studying whole-organism effects of a treatment, but disease-specific large animal models are costly and logistically challenging to establish and use. Among the large animal models, RDH12 minipigs would be the most feasible to create, as specific mutations can be engineered into the animals (unlike dogs where gene editing is not routinely used) and they are cheaper to handle than non-human primates. **Several patient-derived iPSC lines covering a range of disease phenotypes have been established and characterised by multiple groups and may be used to bridge this gap,** in particular to test rescue potential/disease modification in humans, vectors and safety as has been used in the ongoing PUMCH-E101/IVB107 gene therapy programme and to observe the retinal reduction activity of RDH12 in human photoreceptors, as they more closely mimic the live, native human eye. Retinal organoids have been a breakthrough in this context, although there are still many areas for improvement.

The absence of a RDH12-specific large animal model is no longer the most urgent problem to solve; Two RDH12 gene therapy programmes (OPGx-RDH12 and PUMCH-E101) are already underway as regulators increasingly gain confidence in the gene therapy platform and recognise the lack of representativeness/transferability of animal data. This shift has been facilitated by ongoing dialogue between regulators, clinicians, and researchers. For other challenges in translation and progress in addressing them, see **Chapter 4**.

Nonetheless, the ideal preclinical package would still include different models for different purposes – small animals for screening and initial proof-of-concept, stem cell derived retinal organoids/tissue for human phenotypes, and large animals for safety/tolerability, delivery methods, exposure/biodistribution (does not necessarily have to be disease-specific models), and functional rescue (in disease-specific models). Additionally, current *in vivo* models that do not faithfully recapitulate the human phenotype may not be sufficient **for other therapeutic modalities that are less straightforward/de-risked than AAV-mediated gene augmentation. The pathomechanism of RDH12-associated retinopathies also remains unresolved, with conflicting data from studies in different systems** (mice/zebrafish/HEK-293). Studying alternative models may provide better insight into this and potentially lead to better therapeutic interventions.

To conclude, our current recommendations in the RDH12 disease model space, in priority order, are (1) Continued use of existing models/assays to validate current RDH12-specific or mutation-agnostic small-molecule leads (see **Section 3.5**) (2) Development of RDH12 AR LCA (LCA13) retinal organoids (by knock-in or patient-derived iPSCs), for studying disease biology and compound screening (3) Establishment of the corresponding control lines (4) Establishment of a pig model for RDH12.

3. THERAPEUTIC PIPELINE

3.1 Introduction

Luxturna (voretigene neparvovec-rzyl, Spark Therapeutics), the first FDA-approved gene therapy product for a genetic disease (2017), is now an established standard of care for RPE65-associated retinal dystrophies such as LCA2 and RPE65-RP. As of August 2026, it remains the only approved ocular gene therapy, but various therapeutics are under clinical development for other IRDs across a range of modalities.

Different individuals may be better suited to different treatment approaches, depending on their genetic diagnosis and extent of retinal degeneration.

- For patients presenting at an early stage of disease, the treatment aim would be to arrest and prevent vision loss, for example by gene augmentation or gene editing.
- For patients with significant vision loss but residual photoreceptors at the time of presentation, a mix of gene augmentation and neuroprotection might be useful.
- Patients that have already lost their vision due to photoreceptor cell death will not benefit from gene augmentation therapy. Other kinds of therapies like cell replacement therapy, optogenetics, or a retinal prosthesis might be suitable.

Management of most forms of LCA/EOSRD is symptomatic. Affected children benefit from correction of refractive error, use of low vision aids, when possible, and access to educational and work-related opportunities.

An assessment of therapeutic approaches under investigation for IRDs with emphasis on RDH12 is reported in the following paragraphs. A summary table of the therapeutic pipeline (**Figure 7**), including the stage of development, can be found at the end of this chapter.

3.2 Gene Augmentation

Gene augmentation (gene replacement) is currently the most clinically advanced therapeutic strategy for IRDs. It involves delivering a functional copy of a damaged or nonfunctional gene to surviving retinal cells, most commonly using an adeno-associated viral (AAV) vector. This augments the production of functional protein in the diseased cells, and is particularly suited to monogenic recessive loss-of-function disorders, including RDH12-LCA, where the coding sequence (~2kb) is well within the carrying capacity of AAV vectors.

The eye is broadly considered an excellent target for gene therapy. It is accessible, and contains an enclosed, immune-privileged subretinal space where a bolus of therapeutic solution can be delivered without leakage into the systemic circulation and lower chance of immune responses/inflammation.[64] Additionally, the retina is small and does not divide (in adulthood), so only small amounts of the therapeutic are required. Furthermore, surgical procedures/ treatment administration is well-established, and real-time monitoring via OCT and fundus imaging is available.[65]

Structure-function dissociation, i.e. evidence for physical existence of PRs that lack normal function implying biochemical recovery of the visual cycle pathway/ activation of the residual photoreceptors is theoretically possible, is a prerequisite for gene augmentation therapies.[66,67] In other words, gene augmentation is most effective when viable photoreceptors remain and therefore depends on early diagnosis and treatment before advanced retinal degeneration has occurred.

Emerging evidence suggests that the eye's immune privilege is not absolute. Vector immunogenicity is dependent on dosage and administration route. Yiu et al. (2020) found that for AAV8 in non-human primates, local inflammation was lowest for intravitreal administration, followed by subretinal AAV8 (delivered transclerally).[68] Superchoroidal AAV8 led to the strongest local inflammation. Maidana et al. (2025) found that for subretinal injections in mice, both transscleral and transvitreal injection induce similar levels of reactive gliosis (i.e. immune cell infiltration), but the transscleral approach leads to higher eventual PR cell death.[69] Systemic antibody response was highest for intravitreal AAV8 compared to subretinal or suprachoroidal delivery.[68,70]

In the previous RDH12 landscape report, it was concluded that while AAV2 is the most common vector used in ocular gene therapy at the time, AAV5 and AAV8 would be more adequate for RDH12-LCA where the primary damage is located in the PRs, due to efficient transduction of PRs in murine and primate retina (AAV5) and high tropism to PRs when administered in the subretinal space. There is also a need to select optimal driver promoters, which relates to long-term sustainability of the therapeutic effect, a learning from post-marketing studies for Luxturna.

3.2.1 RDH12 Gene Therapy Programmes

Significant progress has been made in this field since 2021. As of August 2026, two RDH12 gene therapy products are under active development.

PUMCH-E101/IVB107 is a gene augmentation therapy targeting RDH12-associated retinal dystrophies, jointly developed by Peking Union Medical College Hospital (Dr Ruifang Sui) and Innovec Biotherapeutics, a biotech based in Beijing, China. This therapeutic candidate utilises Innovec's AAV.IVT18 vector, which can be administered intravitreally to transduce photoreceptors. The product has completed unilateral (single-eye, with the fellow eye serving as the control[xii]) Phase 1 studies at Peking Union Medical College Hospital (NCT06749639). The company has also stated that they have obtained US FDA IND clearance and Fast Track designation.[71]

The investigators have reported interrim safety and preliminary efficacy results from 10 participants in IOVS[72] and presented these results in several conferences including the ARVO Annual Meeting and the FFB's Innovation Summit. Key results are summarised below:

- IVB107 was well tolerated. No dose-limiting toxicities (DLTs) or serious adverse events (SAEs). All treatment-emergent adverse events (AEs) were mild or moderate. The most common AEs were mild inflammation and steroid-related intraocular pressure elevations.
- Encouraging BCVA improvement at Week 36. Treated eyes improved +7.5 letters (vs -0.1 letters in fellow eyes, difference 7.6 letters, p=0.00184). 3/10 eyes achieved ≥10-letter gains. LLVA demonstrated similar treatment-specific benefit.
- Biochemical evidence of target engagement. 4-HNE levels in the aqueous humour were evaluated as an exploratory biomarker. From an elevated pre-treatment baseline (mean 756pg/mL vs healthy controls 144pg/mL), 4-HNE levels decreased to 459pg/mL (mean reduction 297pg/mL, p=0.0255). Two of seven patients normalised to control levels.

While there was a spread in treatment benefit in individual patients as measured by BCVA and LLVA, patients who had more retained photoreceptors, as seen in thicker retinas in pre-baseline examinations, saw greater treatment benefit (visual function improvement), consistent with expectations

[xii] Dr Sui's lab has conducted natural history studies (unpublished) that showed good symmetry in both eyes of individual RDH12 patients, supporting the use of the fellow eye as a treatment control.

for gene augmentation therapy. Hence, the earlier the patients received the gene therapy, the greater the rescue potential. Because most RDH12 patients are early-onset and severe, the investigators are looking to enroll patients as young as 6 years old in upcoming real-world studies for PUMCH-E101/IVB107 (see below).

All 10 patients have undergone more than 1 year of follow-ups, with the longest at 1 year 10 months (as of August 2026). Eight participants who were eligible for the second phase of treatment were subsequently treated in their second eye and are currently undergoing follow-ups, with some patients having completed 9 months. The preclinical data from this study has now been published[73], and the clinical results will be published afterwards. Anecdotally, there has been significant patient-reported functional improvements.

Given demonstrated safety and efficacy from the 18 eyes and preclinical data, PUMCH-E101/IVB107 has been approved as a real-world therapy in the Bo'ao Lecheng Medical Special Zone, Hainan, China. Patients who have a confirmed RDH12 diagnosis and are evaluated to have potential treatment benefit outweighing the risks can receive the treatment in Bo'ao, under close supervision by the pilot zone's Medical and Pharmaceutical Regulatory Authority, before formal Phase 2 and 3 trials are carried out.[74,xiii]

OPGx-RDH12 is an AAV-mediated gene augmentation therapy originally developed by Dr Jean Bennett at the University of Pennsylvania. The asset has been licensed to Opus Genetics (NASDAQ: IRD), a clinical-stage biopharmaceutical company with seven AAV-based gene therapies under development for different IRDs, including OPGx-RDH12 for RDH12-LCA. FDA cleared the IND in October 2026.[204]

The IND-enabling work for this asset was co-funded by the Global RDH12 Alliance (led by the RDH12 patient organisations RDH12 Fund for Sight and Eyes on the Future) in a strategic partnership that includes a risk-sharing structure, performance-based milestones, and co-development e.g. clinical and regulatory strategy.[75] Preclinical studies demonstrated that OPGx-RDH12 delivered functional RDH12 enzymes in vivo and restored structure and function in a small animal model. **The programme is expected to begin a Phase 1/2 trial in the US in Q4 2026**, with funding supported by the RDH12 Alliance.[76]

Opus's RDH12 gene therapy will be administered subretinally, and utilises the same photoreceptor-targeting AAV8 capsid as Opus's lead asset (OPGx-LCA5, in Phase 3 trials). The advantages of this are that the capsid is clinically de-risked for safety (with several ongoing/completed AAV8-mediated IRD gene therapy safety trials) and some synergies in terms of manufacturing knowledge. Opus may also incorporate learnings from clinical trials in LCA5 to RDH12-LCA, e.g. in clinical dosing and patient management.

In terms of next steps for the programme, if safety can successfully be established in Phase 1 trials, Opus will explore clinically-meaningful visual function and structural improvements as endpoints, both established (e.g. BCVA, microperimetry) and novel (e.g. the virtual reality orientation and mobility test used in the LCA5 trial). Patient recruitment should not be an issue, thanks to patient registries from the RDH12 Alliance. A potential area for improvement would be direct preclinical proof of efficacy, however, this would require large animal (e.g. canine) disease models, which are not available for RDH12[xiv] and are unlikely to recapitulate the disease progression in humans. Nonetheless, animal data is no longer a hard requirement from the FDA prior to clinical trial commencement for genetic diseases.[xv]

[xiii] Interview with Dr Ruifang Sui, August 2026
[xiv] Interview with Dr Ash Jayagopal, August 2026
[xv] Interview with Dr Mathew Pletcher, July 2026

A third RDH12 gene therapy asset – which was discussed in the previous RDH12 Landscape report – was previously developed by Dr Debra Thompson at the University of Michigan. This is a subretinal administration of rAAV2/5 carrying a human RDH12 cDNA driven by a human rhodopsin-kinase promoter. Preclinical studies showed the vector reconstitutes the reductase activity in the retina and decreases susceptibility to light-induced retinal damage in Rdh12KO mice.[77] The asset was later licensed to MeiraGTx (NASDAQ: MGTX)[78], a clinical-stage genetic medicine company. Further studies (AAV5 vector development, toxicology studies for IND filing, assays to clear batch release) were subsequently performed, however, **the company later discontinued its RDH12 natural history study and has not released updates on the RDH12 programme since.**[79]

3.2.2 Gene augmentation for other forms of LCA

For some of the most prevalent LCAs, i.e. LCA1 (10-20% of LCA patients), LCA10 (15-20%), LCA2 (5-10%), gene therapies are under clinical development with one approved therapeutic. Progress on clinical-stage gene augmentation programmes for LCAs are summarised below.

- **RPE65-associated LCA (LCA2):** Luxturna (voretigene neparvovec, Spark Therapeutics) is now an established standard-of-care gene augmentation therapy, with approximately eight years of post-marketing experience. Long-term follow-up demonstrates sustained improvements in functional vision in many patients, with pharmacovigilance analyses reporting maintenance of clinically-meaningful functional gains in approximately 70% of treated patients at four years, although retinal degeneration continues and visual acuity may gradually decline over time despite treatment. Long-term safety has remained favourable, with most adverse events related to the subretinal surgical procedure (including transient inflammation, cataract progression, elevated intraocular pressure and retinal tears/detachment). More recently, chorioretinal atrohy has emerged as an important long-term observation in some treated eyes.[80]
- **AIPL1-LCA (LCA4):** MeiraGTx has reported results from the first-in-human paediatric interventional study of rAAV8.hRKp.AIPL1 in the UK. All 11 children treated who were blind at birth gained visual acuity in the treated eyes. Functional vision measures include observation of the children's visual behaviour and ability to perform simple vision-guided tasks. As of early 2025, MeiraGTx was in discussions with the UK MHRA for marketing approval without further clinical data, and similarly engaging with the FDA to discuss a path forward for expedited approval in the US. In November 2025, the company announced a strategic collaboration with Eli Lilly to commercialise its genetic medicines in ophthalmology.[81,82]
- **LCA5:** Opus Genetics has recently completed patient enrolment (n=8) for its Phase 3 trial of OPGx-LCA5. The investigators will begin dosing patients in Q4 2026, with topline six-month efficacy data anticipated by the end of 2027. The primary endpoint for this study is a mean improvement of at least 7 decibels (dB) in retinal sensitivity across central 16 test loci in microperimetry; Results from the previous Phase 1/2 trial showed a mean improvement of ~10.5dB.[83,84]
- **GUCY2D-associated LCA (LCA1):** Atsena Therapeutics' ATSN-101 has reported encouraging Phase I/II data demonstrating improvements in retinal sensitivity and functional vision with an acceptable safety profile, making it one of the leading next-generation LCA gene therapy programmes currently in clinical development.[85]

CEP290-LCA/LCA10 accounts for 15-20% of LCA patients, but the CEP290 gene is too large to be packaged into conventional AAV vectors, hindering the development of gene replacement therapy for LCA10. Preclinical research at Astellas Gene Therapies is underway to deliver miniCEP290 constructs, i.e.

only amino acids 580-1180 of the full CEP290 gene, in mice. The studies show improved electroretinogram (ERG) response and structural and functional rescue of PRs.[86]

3.2.3 Gene augmentation for other IRDs

Several gene therapies for other IRDs have also progressed substantially. Several ongoing/completed programmes are listed below.

- **ND4-Leber hereditary optic neuropathy (ND4-LHON):** Phase 3 trials (REFLECT) have concluded in 2025 for Gensight's lenadogene nolparvovec (Lumevoq). Safety and clinically-meaningful VA improvement (15+ ETDRS letters) was sustained at 5 years. Early access programmes are currently available in the US and France while the company runs additional trials to support regulatory applications.[87,88]
- **RPGR-associated X-linked RP:** Botaretigene sparoparvovec (bota-vec) completed Phase 3 testing. Although the primary endpoint (Visual Mobility Assessment) was not met, meaningful improvements in low-luminance visual acuity and other patient-reported measures have prompted MeiraGTx to re-acquire the asset from Johnson & Johnson and pursue regulatory submission to the US, EU and Japan, with a potential launch targeted for 2027.[89]
- **PDE6B-RP:** AAV2/5-hPDE6B (eyeDNA/Coave Therapeutics) is in Phase 1/2 trials, with positive 12- and 24-month follow up results presented at the ARVO 2024 meeting.[90]
- **ABCA4/Stargardt Disease:** The large size of the ABCA4 has traditionally been a roadblock to AAV-mediated gene replacement therapy (~6.8kb, exceeding the AAV carrying capacity of ~4.7kb). Three ongoing gene replacement trials (SpliceBio SB-007, VeonGen VG801, AAVantgarde Bio AAVB-039, all in Phase 1/2) utilise protein splicing, i.e. delivering two parts of the ABCA4 gene in separate AAV vectors, allowing them to fuse in the cells to form the full ABCA4 gene. Several other trials are ongoing for Stargardt Disease utilising different modalities.[91]
- **Usher Syndrome Type 1B (MYO7A):** AAVantgarde Bio has completed enrollment in Phase 1/2 trials for AAVB-081. Like AAVB-039 for ABCA4, this programme uses a dual-vector setup (two AAV8 vectors) to deliver replacement copies of the target gene.[92]
- **Achromatopsia:** STZ Eyetrial **(**Tübingen University Hospital, Germany) has demonstrated long-term safety in ongoing Ph1/2 trials for subretinal delivery of AAV8.CNGA3. AGTC is carrying out clinical development for CNGB3 gene replacement (AGTC-402, Phase 1/2) while discontinuing CNGA3 due to limited efficacy. MeiraGTx demonstrated favourable efficacy readouts in Ph1/2 trials for AAV8.CNGB3, but the Janssen collaboration covering it ended in 2023.[93]
- **Batten Disease:** Tern Therapeutics' TTX-381 (AAV9.CLN2) demonstrated preserved photoreceptors throughout the macula, including the fovea, through 24 months of follow-up (Ph1/2) vs rapid progressive degeneration in untreated fellow eyes.[94] Meanwhile, Neurogene has paused development for its NGN-101/CLN5 programme as they did not obtain RMAT designation from the FDA.[95]

Several programmes discussed in previous versions of this report are no longer in active therapeutic development or have been absorbed. The UPenn RDH12 programme led by Dr Jean Bennett is now the ongoing OPGx-RDH12 programme (Opus Genetics). The UMich RDH12 asset from the lab of Dr Debra Thompson was in-licensed by MeiraGTx, but more recently appears to have been deprioritised. Nightstar/Biogen's AAV2-REP1 programme for choroideremia was discontinued after the Phase III STAR trial failed to meet its primary efficacy endpoint. Oxford BioMedica's lentiviral StarGen programme for ABCA4-associated Stargardt disease ended following early-phase evaluation, with participants transferred to long-term safety follow-up, contributing to the subsequent shift towards alternative large-gene delivery platforms such as dual AAV vectors.

3.3 Other gene-specific therapeutic approaches: Gene Editing, Antisense Oligonucleotides (ASOs)

LCA13 (RDH12-LCA) is caused by loss-of-function mutations in RDH12, making it amenable to treatment by gene replacement therapies (Section 3.2), as the treatment leads to the production of wild-type, functional RDH12 protein without having to suppress the patient's own non-functional RDH12 protein. Meanwhile, for dominant-negative/gain-of-function genetic diseases, gene replacement therapy is insufficient because the continued presence of the patient's diseased protein continues to cause harm. For example, certain rare mutations in RDH12 e.g. c.763delG or c.778delG) lead to a mild, late-onset form of RP53. In addition to expression of the wild-type gene, dominant diseases require the removal of the disease-causing gene (CRISPR-Cas9 gene editing) or suppression/augmentation of its expression (gene silencing e.g. by antisense oligonucleotides or RNA editing).

Gene editing/silencing approaches may also be applied to loss-of-function IRDs, including RDH12-LCA. Both of these approaches are currently under clinical development for LCA10 (CEP290-LCA).

- **QR-110/sepofarsen (Sepul Bio, Phase 3):** Sepofarsen is an RNA ASO injected intravitreally to mask the IVS26 mutation in CEP290 and hence restore production of the functional protein. The original Phase 2/3 ILLUMINATE trial reported its primary results in 2022. While it missed its primary visual acuity endpoint against a sham-treated parallel control group, a post-hoc paired-eye analysis suggested treatment benefit compared against the untreated fellow eyes of the same patient. Sepofarsen is now in global Phase 3 HYPERION trials (Sepul Bio/Laboratoires Théa), which uses the paired-eye trial design from the outset.[xvi, 96]
- **EDIT-101 (Editas Medicine, Phase 1/2 complete[xvii]):** The first CRISPR-based in-vivo retinal gene-editing programme, consisting of an AAV5 vector encoding SaCas9 with a PR-specific GRK1 promoter plus 2 guide RNAs, designed to permanently remove the pathogenic IVS26 sequence from the CEP290 gene. No treatment-related serious adverse events or dose-limiting toxicities were reported, and 11/14 patients showed improvement in at least one of BCVA, red light sensitivity, mobility, or vision-related quality of life. However, Editas paused development of this programme in 2022, due to a small potential responder population (~300 homozygous IVS26 CEP290 patients in the US), to seek a collaboration partner. No updates have been announced since.[97,98]

Within the broader IRD landscape, Sepul Bio is also developing an ASO for USH2A Usher Syndrome (Ultervursen, Phase 2b ongoing), which induces the skipping of mutant exon 13 during pre-mRNA splicing to produce a truncated but functionally normal usherin protein in the PRs.[xviii] Other editing strategies apart from CRISPR-Cas9 gene editing are also being explored, including Ascidian Therapeutics' ACDN-01 (Phase 1/2, STELLAR), which replaces the pathogenic sections of ABCA4 RNA copies, allowing functional proteins to be produced.[99]

3.4 Gene/Mutation-agnostic Gene Therapies

Gene-agnostic therapies have been gaining increasing attention in recent years. These therapies target common pathways of retinal degeneration, rather than correcting a single faulty gene. Hence, **gene-agnostic therapies originally developed for other forms of retinal degeneration (e.g. RP, Stargardt's) may also have potential to be applied to RDH12-LCA.** Different strategies are better suited to different stages of degeneration. The rest of Chapter 3 details different gene-agnostic therapeutic modalities; In Section 3.4, we describe two of these strategies, both of which utilise gene therapy to express specific

[xvi] NCT03913143, NCT06891443
[xvii] NCT03872479
[xviii] NCT06627179

proteins in retinal cells.

3.4.1 Optogenetics

Optogenetics is the approach in which genes encoding a light-sensitive protein (opsins) are introduced into surviving, but normally non-light-sensing, neurons in the inner retina. This effectively converts secondary (bipolar cells) and tertiary (retinal ganglion cells) neurons into PRs, bypassing the PRs themselves (**Figure 6**). Early data has suggested that some degree of vision can be restored, even if PR degeneration is severe, and some patients with advanced RP have seen improved mobility, object recognition, and functional vision tasks. Nonetheless, sample sizes remain small and visual acuity gains are modest; The current generation of optogenetics therapies also require optimised light delivery (most often via bulky light-enhancing goggles) for maximum benefit.[100]

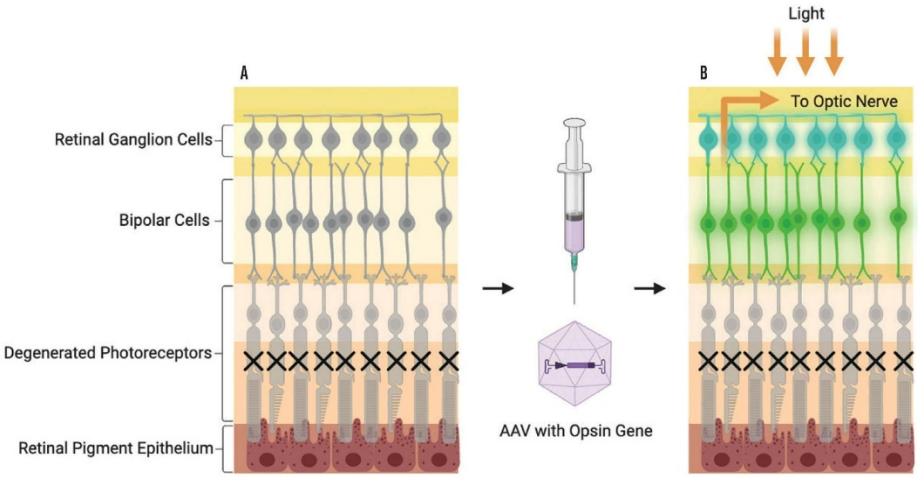


Figure 6: Optogenetics: AAV-mediated delivery of opsins to bipolar or ganglion cells leads to the restoration of light-driven output. Figure adapted from Retina Today.[100]

Two types of opsins have dominated development: Microbial opsins (e.g. channelrhodopsins, halorhodopsins) and mammalian/human-based opsins (rhodopsin, cone opsins, melanopsin). Both allow the generation of electric signals (membrane potential) when light is detected, but through different mechanisms. Microbial opsins are light-gated ion channels/pumps, while animal opsins control ion channels via GPCR signalling cascades in response to light. Retinal rod and cone PRs can adapt their range and adjust their sensitivity to light. Hence, animal opsins are more sensitive to light than microbial opsins, i.e. they may be able to function at normal/physiological levels of light, bypassing the need for light-enhancing goggles which may damage the eyes. More recent development has focused on animal opsins.[101]

Because AAVs are the main delivery vector in optogenetics to transduce retinal cells, the same considerations from Section 3.2 apply here: Some AAV serotypes show tropism to particular neurons (AAV2, 5, 7-9)[102] and they are delivered to the retina via two principal routes: subretinal and intravitreal. Contrary to gene augmentation therapies, most ongoing optogenetic trials utilise intravitreal delivery.

By using different cell-specific promoters or a ubiquitous promoter, expression of these opsins can be triggered in specific cells (PR/bipolar/RGC). **Which retinal cell(s) to target depends on the individual's state of degeneration**; This can be assessed using high-resolution, non-invasive imaging. All else equal, cone targeting is expected to produce optimal results, followed by bipolar cells and lastly ganglion cells. The overall outcome will depend on many factors, such as the degeneration state of the retina, the ability of the patient to learn the new retinal language driven by the "optogene", and the

rehabilitation program provided.[103]

Optogenetic approaches have yielded promising results in preclinical studies.[104] For example, efficient expression of optogenes in cones and ganglion cells has been demonstrated in the retina of non-human primates and post-mortem human retinal explants *in vivo*, while optogenetically restored retinal ganglion-cell responses have also been demonstrated in living primates.

Various optogenetics programmes have entered clinical development. Most target the retinal ganglion cells.

- **MCO-010** (sonpiretigene isteparvovec, Nanoscope Therapeutics): The most advanced programme we identified. MCO-010 is an AAV2 vector delivering a synthetic multi-characteristic opsin to **bipolar cells**, requiring no external light-amplifying hardware. The Phase 2b/3 RESTORE trial (NCT04945772), in advanced RP patients, met its primary best-corrected visual acuity endpoint in both dose groups at 52 weeks against sham control, with sponsor-reported gains averaging more than 0.3 logMAR. The sponsor also reported maintenance of visual-acuity gains and no serious adverse events in treated eyes through three years of follow-up. MCO-010 has received FDA Fast Track and Orphan Drug designations, and the FDA accepted its Biologics License Application for review in September 2026. If approved, MCO-010 would be the first FDA-approved gene-agnostic optogenetic therapy for a retinal disease.[xix,105–107]
- **BS01** (Bionic Sight): Delivers the channelrhodopsin ChronosFP to **retinal ganglion cells** using an AAV2-CAG-ChronosFP vector and received FDA RMAT designation in February 2025. In its Phase 1/2 dose-escalation trial in advanced RP patients (NCT04278131), sponsor-reported results indicated that 5/5 participants receiving the lower doses showed an increase in light sensitivity of at least 100-fold. 10/11 participants treated at the two highest doses showed improvements in best-corrected visual acuity. Interim Phase 1/2 results were reported in 2025.[xx,108]
- **RTx-015** (Ray Therapeutics): Delivers a modified rhodopsin to **retinal ganglion cells** via a AAV.7m8 vector. Received FDA RMAT designation and EMA PRIME designation in April 2026, currently being evaluated in the Phase I ENVISION trial (NCT06460844) in patients with RP or choroideremia.[xxi,109]
- **GS030** (GenSight Biologics): An rAAV2.7m8 delivered red-shifted channelrhodopsin targeting **retinal ganglion cells**, paired with light-stimulating goggles. Currently undergoing Ph1/2a trials (PIONEER, NCT03326336) in subjects with non-syndromic RP.[xxii]
- **AGN-151597/RST-001** (RetroSense; now AbbVie): An AAV2 delivered channelrhodopsin-2 (ChR2) targeting the retinal ganglion cells, evaluated in patients with advanced RP (Ph1/2a NCT02556736). The study is now completed, efficacy was not demonstrated, and no subsequent clinical development of the programme has been publicly identified.[xxiii]

Several therapeutic candidates are also under clinical development in China:

- **ZM-02** (Zhongmou Medical/Augelux Therapeutics): An AAV-delivered PsCatCh2.0 (an

[xix] NCT04945772, NCT06162585
[xx] NCT04278131
[xxi] NCT06460844
[xxii] NCT03326336
[xxiii] NCT02556736

engineered channelrhodopsin that requires 100x less light intensity than its predecessor) targeting **retinal ganglion cells**. Demonstrated safety and significant BCVA improvement, supported by MLTs and an unexpected bonus in colour perception at week 52, in Ph1 studies in 8 patients with advanced RP. The study is still ongoing, although a new multi-country Phase 1/2 trial has now been registered.[xxiv, 110]

- **UGX-201** (UGenex Therapeutics): An AAV2.7m8 delivered chimeric opsin (fusion of human MW-opsin and G-protein-coupled mGluR4) targeting **retinal ganglion cells**. Early trials are ongoing in 9 patients with advanced nonsyndromic RP. Sustained and meaningful visual acuity gains were observed in both patients with and without light perception at week 52.[111]
- **IVB105** (Innovec Biotherapeutics): Delivers the human opsin OPN3 to **bipolar cells** using the company's proprietary AAV capsid. The programme received FDA Orphan Drug and Rare Pediatric Disease Designations in late-2024 and is expected to enter first-in-human testing in September 2026, initially in patients with late-stage RP and very limited residual vision.[xxv, 112]

Applicability to RDH12-LCA: Unlike gene augmentation, which requires sufficient surviving PRs to be rescued, optogenetics may restore some degree of vision in patients with medium-advanced degeneration where PR degeneration has progressed beyond the therapeutic window for gene replacement. No RDH12-specific optogenetic programmes are ongoing, although optogenetics products approved for other indications can in theory be used for RDH12 patients, so long as the bipolar or retinal ganglion cells remain intact and functional.

Other known challenges in optogenetics include (1) uncertainty regarding the quality of vision that can be restored, and (2) the possibility of immune reaction to ectopically-expressed proteins. However, compared to visual prostheses (Section 3.7), these strategies use a more naturalistic form of light stimulation and the clinical application can be less invasive. Optogenetics should be used at medium-advanced stages of retinal disease.

3.4.2 Neurotrophic & transcription factors[113]

The retina is a neural tissue. As such, it is (in theory) amenable to neuroprotective interventions that aim to prolong cell survival or promote function. Such treatments may slow the loss of PRs and RPEs, especially in the early stages of retinal degeneration. Hence, they are most often used in the early stage to **slow disease progression and preserve useful vision**, although they can serve as adjunctive treatments throughout the course of disease. Currently no neuroprotective therapies are known to fully prevent/halt LCA or RP progression or restore vision; They do not directly correct the underlying cause of disease. Neuroprotective approaches include neurotrophic factors and various small molecules (Section 3.5).

Neurotrophic factors are endogenously-secreted small proteins with short half-lives. In the eye they are generally synthesised by Müller glia and RPE. Therapeutic strategies focus on continuous expression/delivery by gene augmentation or implants of engineered cells, rather than supplying the proteins directly. Several neurotrophic and growth factors have been **shown to be effective in protecting PRs across multiple IRD animal models, regardless of the underlying mutation.** The most studied are: CNTF, BDNF, GDNF, bFGF, PEDF, LIF, NGF, RdCVF and LEDGF. **At least 3 clinical trials are ongoing**:

- **CNTF:** NT-501 (Neurotech) is an intravitreal implant containing engineered RPE cells that produce

[xxiv] NCT06292650, NCT07282457
[xxv] Interview with Dr Ruifang Sui (August 2026)

CNTF. Early trials in RP patients showed limited functional benefit [114, xxvi], but subsequent clinical development has focused on patients with macular telangiectasia type 2, for which it was approved by the FDA as ENCELTO in March 2025. This implant is currently being evaluated in glaucoma. [xxvii,115]

- **RdCVF:** SPVN06 (SparingVision) is an AAV gene therapy that transduces RPE and cone cells, promoting the expression of RdCVF (neurotrophic factor, promotes glucose uptake and metabolism in cones) and RdCVFL (enzyme that reduces oxidative stress). As of Feb 2026, SPVN06 has completed patient dosing in PRODYGY, a Phase 1/2 study in adult RP patients with mutations in RHO, PDE6A, or PDE6B, with the initial data readout expected in 2027.[116,117] While SPVN06 is not being evaluated specifically in RDH12 patients, **RdCVF-based approaches are relevant for RDH12 as they act to protect PRs against photo-oxidative damage.**
- **jCell/famzeretcel:** jCell (jCyte) is an allogeneic retinal progenitor cell therapy. It does not replace host retinal cells but functions to release a range of neuroprotective/neurotrophic factors, e.g. PEDF, bFGF, humanin, etc. The Phase 2 JC02-88 trial (NCT06912633) on adults with RP (irrespective of genotype) is ongoing and expected to complete in Q1 2027.[118] **While not evaluated in LCA patients, this therapeutic is gene-agnostic so may be relevant for RDH12 patients.**

AAV delivery of CNTF, as well as the anti-apoptotic XIAP and BiP factors, have also been tested in RP mouse models, with positive results.[119–121]

Neuroprotective gene therapies can act synergistically with gene replacement therapy. For example, the use of an AAV vector carrying the glial cell line-derived neurotrophic factor (GDNF) in combination with a vector carrying the causative genes of two types of RP led to significant improvements in two models of RP, suggesting that in the future a combination approach of gene replacement and neuroprotective factor therapy may provide enhanced rescue over either treatment alone.[122]

Another similar mutation-agnostic strategy is the delivery of modifier genes. The most advanced programme in this space is **OCU400** (Ocugen), which delivers nuclear hormone receptor NR2E3 to retinal cells. NR2E3 regulates photoreceptor development and maintenance, metabolism, phototransduction, inflammation, cell survival, and other physiological functions. Hence, this therapy aims to reestablish healthy cellular homeostasis lost in RP retinas. Phase 3 studies are ongoing, with topline data expected in Q1 2027, after which Ocugen plans to submit a BLA (targeted for Q2 2027).[123,205]

3.5 Pharmacological/small-molecule approaches

Neuroprotective small molecules are most often used in the early stage to slow disease progression and preserve useful vision but can serve as adjunctive treatments throughout the course of disease. Currently no pharmacological therapies are known to fully prevent/halt LCA or RP progression or restore vision, as they do not directly correct the underlying cause of disease.

Several classes of pharmacological agents have been tested in retinal disorders:

- Neurotrophic factors (Section 3.4.2)
- Anti-apoptotic agents
- Antioxidants
- Retinal scavengers

[xxvi] In the previous report, KOLs interviewed have suggested potential explanations: CNTF may not have been the best factor, or the patient selection/outcome measures might need improvement.
[xxvii] NCT04577300

- GPCR agonists/antagonists
- Translational readthrough inducing drugs (TRIDs)

Most are gene-agnostic, but some (e.g. retinal scavengers) only work in pathologies where all-trans retinal is elevated, including RDH12-LCA; TRIDs are only applicable to certain types of mutations, but can be on any gene (see Section 3.5.5). Preclinical work has advanced on all fronts for IRDs broadly since the publication of the 2021 report, but only neurotrophic factors and NAC (an antioxidant) are currently in human trials for retinal degenerative diseases. **Most of the RDH12-specific small-molecule preclinical advancement has been in retinal scavengers.**

KOLs interviewed for the 2021 edition of the RDH12 Landscape Report confirmed that **PR cell death in RDH12 is likely a multimodal process**, such that both neuroprotective agents and antioxidants may play a role in preserving PRs.

"We probably have to hit many different targets. Neuroprotection is very complicated, and any one therapy alone may not be sufficient, you have to have several different therapies hitting different pathways to really get good neuroprotection." – M. Pennesi

3.5.1 Anti-apoptotic agents

It is hypothesised that PR degeneration in LCA and RP mainly occurs through apoptosis. This is supported by (1) a certain degree of PR preservation when anti-apoptotic agents were tested in RP animal models, and (2) for RDH12, increased apoptotic cell death in the retinas of Rdh12-deficient mice when exposed to high-intensity illumination.[25]

Recent work using RDH12-mutant HEK293 cell lines demonstrated that the loss of RDH12 function triggers apoptosis, via accumulation of all-trans-retinal (atRAL) and increased oxidative and ER stress (e.g. activation of the pro-apoptotic mediator CHOP).[45,124] **Additional studies to confirm the role of apoptosis in PR degeneration in human patients (e.g. using iPSCs) would further strengthen the case for the use of anti-apoptotic factors in RDH12-LCA.**

Many anti-apoptotic compounds (caspase inhibitors or otherwise) have been identified, but few have been tested in patients for ocular diseases, and none have reached Phase 3 trials. Small-molecule anti-apoptotic compounds include:

- **TUDCA (tauroursodeoxycholic acid):** A water-soluble bile salt that interferes with the upstream mitochondrial pathway of cell death, hence reducing oxidative and endoplasmic reticulum (ER) stress. Found to have protective effects in the eye, especially concerning retinal degenerative disorders, when tested in models of neural and retinal degeneration.[125,126] Clinical trials for ocular diseases are not reported.[127] **TUDCA has been tested by the Moosajee Group at UCL in RDH12-mutant cell lines, but failed to reduce ER stress, as measured by expression of sXBP1, CHOP, and ATF4, involved in apoptotic signalling.**[124]
- **Norgestrel:** A synthetic progesterone derivative commonly used in hormonal contraception. Showed neuroprotective effects in different animal models of RP[128], likely through bFGF and LIF, one of the key survival factors in retinal cells under stress conditions. Nonetheless it has not been tested in humans yet.
- **Myriocin:** A serine palmitoyl-CoA transferase inhibitor. Reduces ceramide, which is an important component of apoptosis signaling. Shown to rescue PRs from death when injected intraocularly in a mouse model of RP.[129] Subsequent investigations made use of a non-invasive transcorneal drug delivery system based on eye drops of a suspension of solid lipid nanoparticles loaded with

myriocin. This system is patented by Nanovector, has received ODD, and is suitable for pharmaceutical development, warranting further clinical evaluation.[130] It has also been found that upon longer treatment cone morphology and function were well preserved even after major rod death. The authors speculate that myriocin can have a direct effect onto mechanisms that influence cone survival, maybe due to its immunosuppressant activity (through inflammation lowering).

3.5.2 Antioxidants

As **oxidative damage is implicated in PR degeneration,** there is a plausible biological rationale to investigate antioxidants as therapeutics for RP and LCA.[131] **Several antioxidants have been investigated for retinal degenerative diseases**, including:

- **N-acetylcysteine (NAC) & its amide (NAC-A):** NAC is mainly used to treat drug toxicity/overdose and more recently has received interest as an adjuvant for psychiatric disorders. NAC achieves its antioxidant activity primarily by stimulating synthesis of glutathione, the body's master antioxidant.[132] Oral and topical applications have been shown to prevent retinal degeneration in preclinical studies of RP.[133,134] **Oral NAC at 1,800mg twice daily to slow vision loss is being evaluated in the NIH-funded Phase 3 NAC Attack trial (NCT05537220) involving 485 RP patients.** The study is expected to be completed in May 2030.[135]
- **Carcinine (β-alanyl-L-histamine):** A natural peptide derivative that can scavenge reactive aldehydes produced by lipid peroxidation thus preventing them from reacting with cellular proteins. Available as an OTC dietary supplement in the US. Oral and intravitreal administration of carcinine in mice was found to reduce 4-HNE – a toxic metabolite elevated in RDH12-LCA eyes – to non-toxic alcohols, protecting PRs from light-induced apoptosis and protects against light-induced PR degeneration.[40,136] However, as of 2021, the authors had no plans to further develop carcinine as a therapeutic for retinal dystrophies as they do not have a patent on it.
- **Vitamin A, docosahexaenoic acid (DHA), lutein:** The retina is enriched in such diet-derived compounds, and the effects of vitamin A, DHA and lutein supplementation have been studied in large-scale, long-term randomised trials, but with no evidence for efficacy.[122] For RP, a formal evidence review by the American Academy of Ophthalmology (15 studies, 1993-2022) concluded that **no high-quality evidence supports any form of dietary supplementation, including vitamin A, for slowing RP progression**.[137] It should be noted that dietary supplementation of vitamin A can actually be deleterious and speed PR degeneration in some retinal disorders such as Stargardt disease.

Rdh12KO mice studies suggest that **RDH12 deficiency makes the retina more vulnerable to light-induced oxidative injury**, although not to the extent of spontaneous retinal degeneration under normal cyclic light[24,39], as RDH12 protects cellular proteins in the inner segments of PRs from oxidative modification.[25,38,40] Because mice models of RDH12 do not fully recapitulate human LCA pathology, the **pathomechanisms downstream of all-trans retinal (atRAL) accumulation have been elucidated in mutant RDH12 HEK-293 and zebrafish models**, causing **upregulation of the sXBP1, CHOP, and ATF4 pathways**.[124]

The Moosajee Group at UCL/Moorfields has investigated the use of NAC, NAC-A, and carcinine in their RDH12 HEK-293 and zebrafish models. **Of these antioxidants, NAC-A was shown to reduce ER stress markers (atRAL-induced upregulation of HO-1 expression) in three RDH12-mutant stable cell lines**, and significantly in the p.S13* mutant line. Since the publication of these results, the group has tested NAC-A for toxicity in vivo in wild-type animals, and work is ongoing to test for efficacy in RDH12 mutant

mouse models.[124, xxviii]

3.5.3 Retinal scavengers

Such compounds can directly react with all-trans retinal, which is toxic at elevated levels, as seen in RDH12-LCA and other retinopathies, as it condenses to form byproducts like A2E leading to oxidative stress. Chemical groups that can react with aldehydes (the reactive group in atRAL) include primary amines, thiols, and hydrazines. Of these functional groups, **primary amines exhibit the best potential**, as thiols form a complex mixture of products which have foul odours and could disrupt the redox balance, while hydrazines often display toxicity.[138]

Krzysztof Palczewski's lab has previously investigated the effect of 24 primary-amine-containing compounds in mouse models of different retinopathies. **16 of these primary-amine-containing compounds produced protective effects against light-induced acute retinal degeneration**, by sequestering excess atRAL through formation of Schiff base conjugates, without inhibiting the regeneration of visual pigments (i.e. normal function). The compounds tested were selected from FDA-approved drugs (and a subset of analogues) and therefore have good safety and bioavailability profiles.[138]

One of these compounds is **pregabalin**, a drug commonly used to treat epilepsy, nerve pain, and anxiety. **In Rdh12KO mouse models, pre-treatment with pregabalin prevented retinal degeneration** after bright-light exposure (10,000 lx, 60 min).[138] In subsequent studies undertaken by the Moosajee Group, **pregabalin was shown to significantly reduce atRAL-induced ER stress in three RDH12-mutant stable cell lines.**

Apart from NAC-A (Section 3.5.2) and pregabalin, **the Moosajee Group has also shortlisted the primary amines hydroxylysine and polylysine as potential therapeutic candidates** using their RDH12-mutant stable cell lines. The group has tested these compounds for toxicity in vivo in wild-type animals, and work is ongoing to test for efficacy in RDH12 mutant mouse models.[xxix]

3.5.4 Calcium channel blockers and GPCR modulators

Oxidative stress promotes excessive Ca^{2+} influx into cells and their mitochondria, which further promotes the formation of reactive oxygen species (ROS). **Increased Ca^{2+} influx has been observed in PRs upon cell death.** Ca^{2+} influx may be modulated directly using calcium-channel blockers or indirectly through G-protein coupled receptors (GPCRs). Preclinical studies in RP models have provided evidence for both these approaches in delaying retinal degeneration.

Among calcium channel blockers:

- Oral nilvadipine significantly slowed RP progression in small clinical trials, specifically in the central 10° but not the central 2° of the visual field[139]
- Intraperitoneal nicardipine was able to preserve PRs in PDE6B mutant mice, although less effective than nilvadipine. No effect from nifedipine.[140]
- D-cis-diltiazem failed to slow PR degeneration in canine and mouse models of PDE6B RP[140–142]
- Verapamil hydrochloride largely inhibited light-dependent degeneration of PRs in the rdgB mutant of Drosophila[143]

[xxviii] Interview with Dr Vitalii Kalynovskyi (August 2026)
[xxix] Interview with Dr Vitalii Kalynovskyi (August 2026)

The GPCR strategy is mainly being advanced by Krzysztof Palczewski's lab. As hundreds of FDA-approved GPCR modulators with proven safety already exist, the repurposing of these drugs may represent a quicker route to a retinal degeneration treatment than de novo development.

Using systems pharmacology, Palczewski's group has identified a low-dose combination/"cocktail" of metoprolol, tamsulosin, and bromocriptine (all FDA-approved drugs for different diseases) that could safely slow light-induced retinal degeneration in *Abca4*$^{-/-}$*Rdh8*$^{-/-}$ mice when administered orally or intraperitoneally. Preservation of rod and cone structure and function, as well as preservation of bipolar and horizontal cells, was observed.[144,145]

This drug combination has now been tested in various other preclinical models including *Pde6β*^{rd10} and *Rho*$^{P23H/WT}$ RP mice (where it improved cone function and slowed degeneration), *Pde6A*$^{-/-}$ dogs (where it modestly mitigated cone degeneration after a 7-month-long drug infusion), and *Rpe65*$^{-/-}$ mice (where it improved rod pathway function and metabolic function but did not protect from cone degeneration).[146] **To conclude, not only has this therapeutic strategy advanced into large animal models for RP (canine), its mutation-agnostic efficacy across different genetic forms of RP as well as one form of LCA (RPE65) has also been shown**.

The biological half-life of these drugs in human serum could enable once- or twice-daily oral administration for effective treatment of retinal degenerative disorders.[144,145] Another possibility would be to formulate the mixture as eye drops and test their efficacy experimentally to further minimise side effects.

3.5.5 Translational readthrough inducing drugs (TRIDs)[147,148]

For the 12% of IRD patients that carry specific types of mutations – nonsense variants, which result in a premature stop codon and therefore a truncated protein – TRIDs cause the ribosomes to skip this premature termination codon (PTC) and therefore synthesise the full-length, functional protein. To date, >30 TRIDs have been developed and preclinically validated. No severe side effects have been reported in human trials.

Ataluren (PTC Therapeutics), which was originally developed for Duchenne Muscular Dystrophy (DMD), has been tested for USH1C-, USH2A-, MERTK-, and RP2- related IRDs in patient-derived retinal cells or fibroblasts, with positive results.[148–150] Next-generation TRIDs (NB30, NB54) have also been tested for USH1C.[149] In the 2021 report, Jogin Desai intended to test ataluren in iPSCs from a RDH12 nonsense-variant patient. **The Gamm Group at UW Madison is building RDH12-mutant retinal organoids with PTCs, partly because the group has parallel work on TRIDs and wants to apply those learnings to RDH12.**[xxx]

Unfortunately, clinical trials for other diseases (e.g. DMD, cystic fibrosis, epidermolysis bullosa) have yielded disappointing results. One potential gap in previous trials is in disease-specific functional assays and large animal models, which may provide better predictions of clinical outcomes.

3.5.6 Miscellaneous

In this section, we provide a list of small-molecule therapeutic candidates that have shown PR-protective effects in animal models of RP, but do not fall under any of the previous categories. **Due to their specific modes of action, they are not applicable to RDH12-LCA.**

- **Zuretinol/9-cis-retinyl acetate:** Substitutes for 11-cis-retinal, which is absent in some forms of retinal dystrophies, leading to rod degeneration. Phase 1 studies in RPE65- and LRAT-LCA patients

[xxx] Interview with Dr David Gamm & Dr Celia Bisbach (July 2026)

confirmed safety and efficacy.[151] The asset is currently being developed by Eluminex Biosciences (2022).

- **Valproic acid:** A GABA-inhibitor/antiepileptic hypothesised to correct misfolding of RP-mutant rhodopsin.[152] Results on visual field/acuity improvement from small clinical studies have been mixed (Bhalla et al., 2013; Kumar et al., 2014 Iraha et al., 2016; Sandberg et al., 2011; Shanmugam et al., 2012).[153–157]
- **Isopropyl unoprostone:** A prostaglandin analogue/BK potassium channel activator used to lower intraocular pressure in glaucoma patients. Showed dose-dependent improvement in central retina sensitivity of RP patients in a Phase 2 trial[158], but its efficacy could not be proven in subsequent Phase 3 trials (NCT01786395).

3.6 Cell replacement therapy

PRs cannot be endogenously regenerated in humans once lost. Cell replacement therapy aims to replace these lost retinal cells to restore vision in mid- to late-stage patients. **Cell replacement therapy can be applied across different IRDs, although the specific genetic defect informs (1) The type of cell that needs to be transplanted (PRs, RPEs, or both)** – this also depends on the stage of degeneration, **(2) Choice of autologous vs donor cells, and (3) Likelihood of success, i.e. transplanted cells able to integrate into neural circuitry.**[159,xxxi]

Photoreceptor (rods and cones) degeneration may be a result of defects in the PRs themselves (mainly RP), or dysfunctional retinal pigment epithelium/RPE cells (mainly macular degeneration). **For RDH12 patients, whose primary defect is in the PRs, a transplant of immature PR cell (progenitor) suspension or RPE cells plus PR tissue would be needed.**

Most retinal cells (PR/PR progenitors/RPEs) used for transplantation are obtained from stem cells (SCs), particularly induced pluripotent stem cells (iPSCs), but also embryonic SCs (ESCs), bone marrow SCs, iris pigment epithelium cells, etc. Some approaches use foetal or adult retina (not stem cells).

PR replacement therapy has long been hampered by difficulties culturing the cells and integrating them into the eye, but significant progress has been made in the space in recent years. PRs cannot be grown individually. Instead, retinal organoids have to be grown in a way that mimics natural development of the eye (the optic vesicle or optic cup stage, and containing neural retina and RPE cells), from which enriched transplantable PRs are derived and transferred. This is a high-touch process. In recent years, several protocols for culturing PRs from the differentiation of ESCs and iPSCs have been developed.[160] Even then, these organoids are still not a real retina, as they lack a proper RPE-PR interface/intercalation, which are held together by intraocular pressure and fluid movement across the RPE in vivo, which is challenging to reproduce in vitro (and still not yet achieved). Nonetheless, David Gamm's Group (UW Madison) has shown that retinal organoid derived PRs were able to show robust, complex function similar to ex-vivo adult primate fovea.[161]

Graft PRs need to establish synaptic connections with host bipolar dendrites to be functional. In general, this is difficult, either with the PRs in a suspension or organised in retinal tissue grafts. In one case, Lamba et al. (2009) reported improved electrical response to light after transplantation of suspended human ESC-derived PRs in a mouse model of LCA7.[162] **More recently, the Gamm Group has shown that retinal organoid derived PRs are able to integrate into host neural circuitry and that the results are reproducible across different species.**

[xxxi] Discussion with Dr David Gamm (July 2026) & Public talks given by Dr David Gamm

"Our biggest challenge was being able to make at scale authentic human photoreceptor precursors, and to be able to tune those towards cones and rods, and then to test them in multiple different systems. So we tested them in up to five different animal systems and showed that they survived, showed that they made connections." – D. Gamm

Recently it has been demonstrated that instead of, or in addition to, integration of donor cells into the host retina, photoreceptor precursors transplanted into animal models of retinal degenerative disease showed transfer of cytoplasmic material from donor to recipient PRs. Thus, transplanted donor cell integration and material transfer between transplanted and host cells may both underlie the therapeutic benefits associated with transplantation therapy.

The Gamm Group's work on iPSC-derived PR precursor cell therapy (OpCT-001) has entered clinical development via Opsis Therapeutics, in collaboration with FUJIFILM Cellular Dynamics and BlueRock Therapeutics (Bayer subsidiary), two of the largest cell manufacturers in the world. This collaboration enabled commercial-scale manufacturing of the iPSC-PRs, requiring industrial platforms and know-how in scaling, cryopreservation, etc.

"We are in a position where we can produce pretty much any cell type in the retina at scale and cryopreserve it." – D. Gamm

OpCT-001 received FDA Fast Track Designation in February 2025 and Orphan Drug Designation for RP in January 2026. Phase 1/2a trials are ongoing and recruiting (NCT06789445); the first patient received the therapy in July 2025. The trial is expected to enrol ~54 adults with genetically-confirmed primary photoreceptor diseases, including RP, rod-cone or cone-rod dystrophy. Specific eligible genes have not been publicised, although eligibility requires a confirmed genetic diagnosis and retinal regions suitable for cell administration. This represents the first clinical study of an iPSC-derived cell therapy for primary photoreceptor diseases.[163–165]

Other PR cell therapy programmes include Eyestem's (Jogin Desai) Eyecyte-PRP. This is an iPSC-derived PR progenitor cell therapy intended to replace PRs lost in RP and dry AMD. The company has obtain preclinical proof-of-concept in animal models and announced plans to repeat the experiments in animal models before applying to the Indian regulator start human trials in Q4 2023.[166] However, as of August 2026, no registered clinical trial or peer-reviewed product-specific in-vivo publication has been identified for Eyecyte-PRP. The company is also currently evaluating RPE cell replacement therapy (Eyecyte-RPE, NCT06394232) for GA secondary to Dry AMD in Phase 1/2a trials in India.

Theoretically, PRs will last the human lifespan (they do not normally divide), so the long-term viability of the implanted PRs depends on their destruction by the host's immune system and the retinal environment they are implanted into.

Most retinal degeneration cell therapy trials to date use allogeneic (i.e. donor) cells. This requires systemic immunosuppression of HLA matching to prevent immune rejection and improve long-term viability. Most clinical regimens utilise short-term local immunosuppression (oral prednisolone and perioperative corticosteroids). Autologous grafts, where the cells for transplant are derived from the patient's own cells, reduces rejection risk but is prohibitively expensive. Additionally, for loss-of-function diseases such as RDH12-LCA, the disease-causing gene in the transplant cells needs to be rectified prior to transplantation, either through gene editing or augmentation (such as in Zynteglo, Lyfgenia, and Casgevy approved for blood-related disorders).[167]

Some retinal degenerative diseases lead to toxic environments that cannot sustain PR

survival. For cell replacement therapy to succeed in such cases, the retina may need to be primed, for example by using neuroprotective factors to reduce toxic metabolites, and this is a key topic for the next generation of research within this field. However, in the short term, because combination therapies of cell replacement and neuroprotection are unlikely to be approved by regulators less both treatments are separately shown to be safe and efficacious (no approvals so far), the **initial cell replacement therapy studies will focus on patients who have healthier retinal environments**, to maximise the chances of observing meaningful clinical benefit. Candidates will have their retinas imaged (e.g. OCT), which is non-invasive and relatively easy to do in the eye. The patient pool may be expanded later on after safety and efficacy are proven.

The field of regenerative medicine is still clinically nascent. As a note of caution, there have been reports of severe visual loss, including complete blindness, after intravitreal injection of autologous adipose tissue-derived stem cells from unregulated clinics in the US.[168,169] The transformation of intravitreal stem cells into myofibroblasts was suspected to have caused proliferative retinopathy and retinal detachment in those cases. Any cell replacement therapies must be rigorously evaluated for safety and efficacy. Other potential concerns not addressed above include:

- Ethical problems for ESCs and foetus-derived cells
- Potential malignant transformation
- Limited source of the graft (especially from cadavers or autologous grafts)
- Donor-to-donor variability for allogeneic transplants

3.7 Medical devices (visual prostheses)

In the context of retinal degenerative diseases such as RDH12-LCA, unlike the approaches described in Section 3.2-3.5 which largely aim to preserve PRs and cell therapy which aims to replace lost PRs, prosthetic approaches seek to substitute the lost PRs using artificial hardware. **Visual prostheses are mutation-agnostic and one of the few therapeutic options (along with optogenetics and cell therapy) for patients with end-stage retinal degeneration where PR rescue is no longer feasible,** provided downstream neurons/pathways are still functional.

These surgically-implanted devices capture visual information using an external camera, convert it into stimulation patterns, and pass them to surviving neurons in the brain, optic nerve, or retina via electrode arrays. These stimuli generate visual percepts ("phosphenes") that can help users perform basic vision-guided tasks. **Despite some functional benefit, current devices do not restore normal vision and visual acuity remains substantially lower than that of a healthy eye.**

Most visual prostheses were developed for patients with end-stage retinitis pigmentosa (RP), geographic atrophy secondary to age-related macular degeneration (AMD), or profound blindness of other causes. The visual implants can be divided into three main categories, depending on the site of implantation:

- Retinal prostheses
- Optic nerve prostheses
- Cortical prostheses

3.7.1 Retinal prostheses[170,171]

Connected to the inner retinal layers (retinal ganglion cells, which must retain their function), bypassing normal phototransduction involving PRs.

The first generation of these devices were inorganic technologies (micro-photodiode or micro-electrode arrays). **None are currently available to new patients, despite past regulatory approvals** for Argus II (Second Sight, 2011), Alpha IMS and Alpha AMS (Retina Implant AG, 2013 and 2016 respectively), and IRIS II (Pixium Vision SA). While some of these devices did successfully restore vision in patients, they ultimately fell short of expectations and were withdrawn from the market. Argus II was the most successful retinal prosthesis system. More than 350 people were implanted worldwide, and the best visual acuity reported in an individual patient was approximately 20/1260. Clinical studies also documented functional improvements, persisting to five years and beyond.

Depending on where they are implanted, retinal prostheses are categorised as epiretinal (directly adjoining the RGC layer), subretinal (between the sclera and bipolar cells), or suprachoroidal (between choroid and sclera).

	Advantages	Disadvantages
Epiretinal	• Less risky to implant • Long-term stability • Allows for heat dissipation	• Eliminates use of eye movements • Requires external camera • Does not recapitulate topographic organisation of the retina
Subretinal	• May utilise intact middle retinal layer processing pathways • Preserve natural eye-head coordination in vision	• Retinal remodelling, gliosis • Long surgery times • Risk of thermal injury • Limits on device size
Suprachoroidal	• Safer, more stable location • May be less invasive, accessible for repair (does not require transvitreal surgery)	• Implant site highly vascularised, risk of haemorrhage and fibrosis • Distance from retina, may need higher power

Several inorganic retinal prostheses are reached clinical development. These include:

- *NR600 (epiretinal, Nano Retina, Israel)*
- IMIE 256 (epiretinal, Golden Eye Bionic & IntelliMicro Medical, US & China)
- EPI-RET3 (epiretinal, RWTH Aachen)
- *PRIMA (subretinal, Science Corporation)*
- *Gen 2 suprachoroidal device (suprachoroidal, Bionic Vision Australia)*

Italicised items indicate programmes with active clinical development ongoing. PRIMA demonstrated prosthetic central visual perception while preserving residual natural peripheral vision in an initial 5-patient feasibility study. The subsequent PRIMAvera study (NCT04676854) enrolled 38 patients with geographic atrophy. 32 participants completed the primary 12-month evaluation, of whom 26 achieved an improvement of at least 0.2 logMAR in prosthetic visual acuity. Natural peripheral visual acuity was not significantly reduced. Serious adverse events occurred in 19 participants, most shortly after implantation and subsequently resolving. A second-generation 44-channel prosthesis developed by Bionic Vision Australia was evaluated in four subjects with end-stage RP (NCT03406416). During follow-up extending to approximately 2.7 years, the devices remained functional and no device-related serious adverse events were reported. Improvements were observed in visual localisation and, in some subjects, motion discrimination and object identification. PRIMA received a CE mark under the European Union Medical Device Regulation and is therefore commercially available in 30 European Countries. The US FDA review is ongoing.[172,173]

Preclinical programmes include:

- IMTC HARP4K (subretinal, Iridium Medical Technology, Taiwan)
- POYRETINA (epiretinal, Ecole Polytechnique Lausanne)
- Bionic Vision Australia (suprachoroidal, Bionic Vision Australia)
- STS (intrascleral, Osaka University, Japan)

Organic retinal prostheses are electronic devices based on combinations of semiconductive and conductive polymers. They can overcome some of the problems of inorganic devices, such as limited biocompatibility of the rigid chips, inability to cover large retinal areas (narrow "tunnel vision"), and heat production. Examples of organic retinal prostheses include laser micro-structured diamond electrode arrays[174], liquid crystal polymers[175], or a composition of a passive substrate (silk fibroin or polyethylenterephthalate), an organic conductive layer of PEDOT:PSS and a light-sensitive semi conductive layer of P3HT.[176] This latter device proved safe and able to rescue visual functions (evaluated as pupillary reflex, visually driven behavior, visually evoked potentials and visual acuity) in a rat model of RP.[177]

Organic retinal prostheses have several convenient features:

- They are tissue-friendly because of their conformability and intrinsic biocompatibility
- They are fabricated with straightforward and inexpensive processes
- They are ultrathin, lightweight and deformable
- They have greater longevity and chemical stability than inorganic counterparts
- They don't need a power supply or an external camera
- They can potentially cover large retina areas

As of August 2026, **organic retinal prostheses remain at the preclinical stage**, and no fully organic retinal prosthesis has entered established human clinical testing or received regulatory authorisation.

3.7.2 Optic nerve prostheses

Connected to the optic nerve, bypassing the retina; Patients must have functional retinal ganglion cells (RGCs). As of August 2026, only one preclinical programme, AV-DONE (NIDEK, Japan) is known.

3.7.3 Cortical prostheses

Connected directly to the visual cortex of the brain, bypassing the optic nerve and retina. Earlier systems used electrode arrays positioned on the surface of the visual cortex, required relatively large electrical currents while providing low spatial resolution of the signals and risk of adverse effects e.g. seizures. More recent approaches use intracortical (penetrating) microelectrode arrays, which provide more localised stimulation at lower current levels.

- Orion Visual Cortical Prosthesis System (Second Sight Medical Products) was evaluated in a small early-feasibility study in six participants with profound acquired blindness from 2017 to 2025.[xxxii] The implants remained technically functional over several years, although explantations and an early seizure were reported.
- Cortivis (Biomedical Technologies, Spain) is undergoing a pilot study from 2019 to 2028. No results have been released yet.[xxxiii]

[xxxii] NCT03344848
[xxxiii] NCT02983370

- The Illinois Institute of Technology has developed the Intracortical Visual Prosthesis progamme, which is in clinical trials with its third participant receiving the implant in May 2026.[xxxiv,178]
- Neurotechnology/brain-computer interface company Neuralink's Blindsight programme received an FDA Breakthrough Device Designation in 2024, with clinical trials expected to begin 2025/26, although no updates have been released by the company.

Questions remain regarding long-term tissue responses, electrode stability, and the durability of the visual percepts.

Unlike hearing/cochlear implants, which provide reliable speech recognition to many deaf patients, visual prostheses are still unable to recreate the complex processing capabilities of the visual system for blind patients. While some devices have proven functional benefit, commercial barriers remain, and improvements in hardware sophistication alone have not consistently led to better outcomes, due to biological (e.g. retinal remodelling, gliosis, neuronal loss, inter-patient variability in disease progression) and technical factors (e.g. device useful life, surgical complexity, etc). At the same time, biological therapies for IRDs are rapidly advancing, with distinct advantages for early-stage patients compared to mechanical aids. As such, visual prostheses are relatively attractive to late-stage IRD patients.

3.8 Commentary

Comparing the 2021 Landscape Report and the current document, it is clear that the field is reaching a major inflection point. Significant progress has been made in almost all therapeutic modalities for retinal degenerative diseases, and clinical programmes are ongoing for many modalities. Perhaps most importantly, **two RDH12-specific gene augmentation therapies are under active clinical development.** The Mendelian nature of RDH12-LCA, as well as a relatively de-risked delivery platform (local administration, AAVs well-studied, safety and biodistribution tested in non-RDH12-specific animal models), have given investigators the confidence and regulatory go-ahead to start gene therapy clinical trials, despite the lack of RDH12-specific large animal models to definitively prove human-like phenotypes (Chapter 2). Early results from the PUMCH-E101/IVB107 trial for RDH12, as well as other forms of LCA, suggest that functional improvement is possible and may be clinically meaningful even when measured using standard endpoints (e.g. BCVA), despite patient-to-patient heterogeneity. For IVB107, **the magnitude of improvement was related to the state of retinal degeneration** (i.e. the more retained photoreceptors that could be rescued, the better). Hence the earlier these therapies can be tested and potentially approved, the better the outcomes for patients.

Neuroprotective therapies, which aim to slow the process of degeneration, are also being developed. Neuroprotective agents themselves do not cure the disease, but **may extend the therapeutic window** for patients for definitive interventions. This includes neurotrophic factors delivered by gene or cell therapy and the oral antioxidant NAC. While these therapies are mutation-agnostic in their mechanism of action, they are currently only being investigated in advanced RP patients who have the best risk-benefit from taking an investigational therapy. This also increases the chances of success for the trial. **If approved, these therapies may be made available to other retinal degeneration patients later on.** Other approaches, such as **retinal scavengers** and TRIDs, **are in RDH12-specific preclinical development** (i.e. tested in RDH12-mutant models). Because these approaches may not directly restore function of the wild-type protein as in gene replacement therapy, large animal models that recapitulate the human phenotype may prove more important to show treatment efficacy for further development.

[xxxiv] NCT04634383

For patients in advanced stages of disease who have already lost substantial amounts of PRs, **photoreceptor replacement therapy, optogenetics, and visual prostheses are more relevant. These approaches have also entered clinical trials, mostly for late-stage RP.** These approaches are mutation-agnostic (barring some specific considerations, such as the ability of the retina to support implanted PRs, which may necessitate combined cell replacement + neuroprotective therapy) and so could potentially be made available to RDH12-LCA patients in the future, if approved.

Substantial challenges still remain in many approaches, and a successful IND filing is not a guarantee of safety and efficacy, and indeed regulatory approval. Additionally, good trial infrastructure such as a pool of diagnosed patients, natural history data, and validated endpoints are necessary to improve the chances of translational success. Advancements in these areas, for RDH12 and other IRDs, will be detailed in Chapter 4. Nonetheless, the science has moved in a short period from theoretical possibility to clinical reality, and RDH12 is now one among a growing number of IRDs for which meaningful therapeutic intervention appears achievable in the near future.

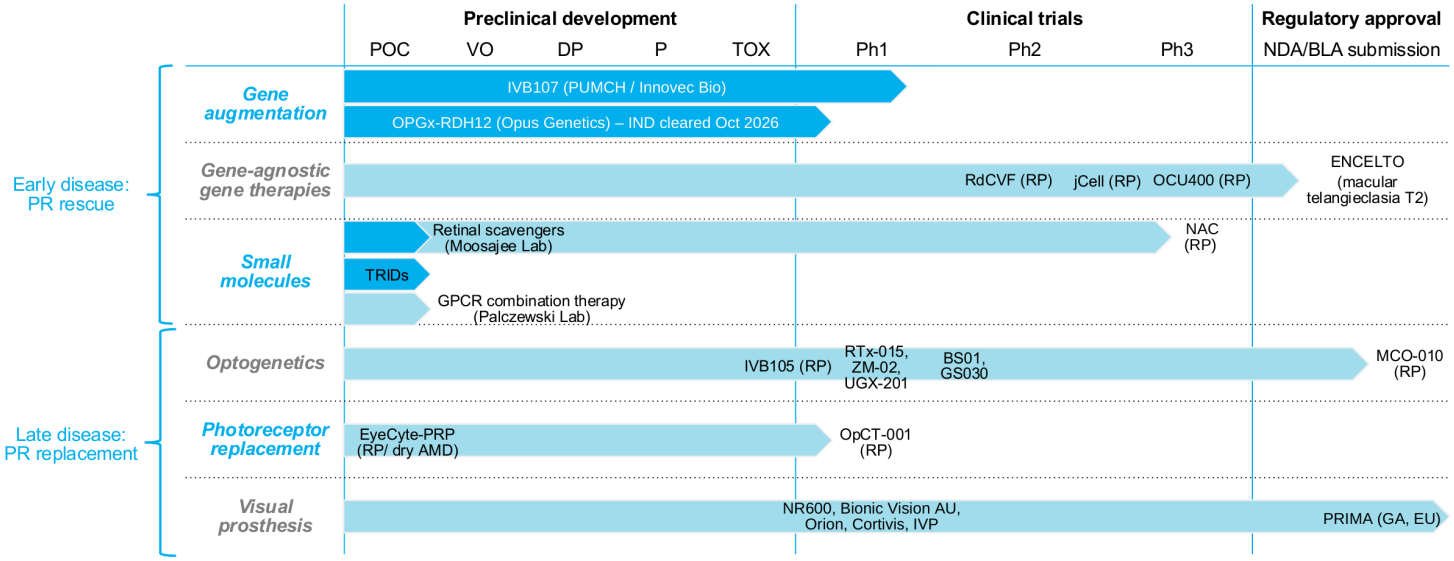


Figure 7: Summary of RDH12 Therapeutic Pipeline as of October 2026. Dark blue items indicate RDH12-specific development, while light blue items indicate development for other IRDs with potential to be applied to RDH12.

4. CLINICAL TRANSLATION READINESS & INFRASTRUCTURE

4.1 Introduction

The previous chapters examined the clinical characteristics and disease biology of RDH12-associated retinal degeneration, the state of preclinical research infrastructure, and the therapeutic pipeline now entering clinical development. Successful translation of these therapies requires not only preclinical proof of biological efficacy: Investigators must be able to recruit appropriate patients, select outcome measures capable of demonstrating clinically meaningful benefit, and design studies that meet regulatory requirements, all within the constraints of RDH12-associated disease (low prevalence, high phenotypic variability, and late diagnosis when the disease has already progressed substantially).

In this chapter, we review the state of clinical translation readiness for RDH12-associated disease, covering patient identification/recruitment, population studies, clinical trial endpoints and other trial design considerations.

4.2 Patient Identification

Given the low prevalence of RDH12 and other IRDs, a relatively large proportion of patients need to be identified and genotyped in order for a sufficiently large trial population to be recruited (a challenge highlighted in RPE65-LCA/Luxturna trials[179]), and to strengthen the case for commercial investment.

4.2.1 Diagnosis

Patients may be diagnosed with LCA/EOSRD based on several **clinical presentations/ observations, typically in the first years of life**:

- Poor visual function and sluggish/near-absent pupillary responses
- Severely decreased visual acuity and constricted visual field
- Other behavioural/structural signs: Franceschetti's oculo-digital sign (eye poking, pressing, and rubbing), nystagmus (roving eye movements), hyperopia
- Variable retinal phenotypes at fundoscopy, ranging from a relatively normal appearance to various degrees of pigmentation and Coats-like exudative vasculopathy.

Markedly reduced or non-detectable ERG responses (photopic and scotopic) are considered diagnostic of LCA. There is a progressive decline in the visual function of all patients.[180,181]

In the case of RDH12, patients often retain useful vision in childhood and have mild to no hyperopia, **while fundus abnormalities can be observed relatively early**, with macular and peripheral RPE atrophy in early childhood followed by bone-spicule pigment in late childhood/early adulthood.[182]

As different IRD/LCA subtypes overlap substantially in their clinical presentation, definitive diagnosis requires genetic/molecular testing. Genetic testing – most commonly NGS-based panel tests covering known IRD genes or LCA/EOSRD genes, which has largely replaced earlier techniques such as APEX chips – is commercially available[xxxv] at a USD500-2,000 out-of-pocket cost. Segregation analysis in family members is used to confirm the biallelic inheritance in recessive RDH12-associated disease. Patients with an LCA/EOSRD diagnosis may also be referred to the Foundation Fighting Blindness (FFB)'s My Retina Tracker Genetic Testing Programme. which provides genetic testing (PreventionGenetics), genetic counselling (InformedDNA) and access to the FFB's IRD patient registry at no cost to the patient.[184]

[xxxv] 39 clinical tests from 12 labs cover the RDH12 gene, including RP and LCA panels. See the NLM Genetic Testing Registry [183]

Targeted familial variant testing is also available to blood relatives of the diagnosed patient. Separately, prenatal diagnosis is offered by specialised laboratories for at-risk couples with identified disease-causing mutations. AI-based methods (Eye2Gene) are also available – currently for research purposes only – for diagnosing IRD genotype based on three types of retinal scans and show good accuracy.[185]

Apart from more accurate prognosis and disease monitoring, a genetic diagnosis allows for patients to potentially qualify for interventional trials and/or gene-specific therapeutics in the future.

4.2.2 Population Studies

Understanding the natural history[xxxvi] and spectrum of disease[xxxvii] is crucial for trial design: in endpoint selection/development, establishing the baseline/control arm, informing patient selection/eligibility, and quantifying the inherent variability of phenotypes and responses in the patient population (**Section 4.3**).

Due to the rarity of RDH12-associated dystrophies, clinical knowledge of the disease is largely limited to single-centre studies or case reports, and while informative, the data collected in these studies cannot be shared widely or made available to external investigators. Several new studies have been published since the previous Landscape report. Recent single-center RDH12 population studies are grouped by research group and summarised below:

- **PUMCH: Zou et al. (2018)**, n=38 patients: Reported six new variants of disease-causing RDH12 mutations, self-reported nyctalopia in 55% of patients especially older patients independent of BCVA loss, and nystagmus in only 16% of patients but correlated with hyperopia (37% of patients) and reduced BCVA independent of age.[186]
- **PUMCH: Wang et al. (2022)**, n=29 patients: Reported five novel variants of disease-causing RDH12 variants. Confirmed early-onset, severe, generalised retinal degeneration in most patients (83%) impairing both rods and cones. Patients with the hypomorphic p.(A269G) variant (17%) which is relatively common in East Asia saw slower degeneration and were characterised as late-onset cone-rod dystrophy with central macular atrophy; These patients did not progress to severe/LCA forms of disease.[18]
- **UPenn: Aleman et al. (2018)**, n=21 patients (paediatric cohort): Confirmed early-onset, severe disease on various functional measures (VA, visual fields, FST, ERG), with a more severe impact on cones than rods. Predominantly affects the central part of the retina, while there is evidence of structure-function dissociation in the pericentral and peripapillary retina.[187]
- **UPenn: Aleman et al. (2024)**, n=46 patients (paediatric cohort): Severe, early-onset retinal degeneration, with VA loss at a rate of 0.04logMAR per year, and photoreceptor loss in the fovea. Peripapillary retina could be retained and showed structure-function dissociation. More severe impact on rods than cones in terms of sensitivity.[187]
- **UCL: Fahim et al. (2019)**, n=57 patients: Confirmed early onset, with all affected individuals presenting macular atrophy, significantly reduced or absent ERG, and loss of retinal structure and function by the age of 10 as measured by VA, visual field, and OCT. Sparing of the peripapillary area was recorded in 18 subjects.[7]
- **UCL: Daich Varela et al. (2024)**, n=8 patients: Despite early macular atrophy, residual cone photoreceptors were detected in patches, often with preservation of a subfoveal ellipsoid zone, even in advanced disease. AOSLO imaging revealed cone densities of 12,620-23,660 cells/mm² at 0.5° from the fovea, appearing either as scattered islands or a central subfoveal remnant.[188]

[xxxvi] The progression of a disease process in a patient over time, in the absence of treatment
[xxxvii] The range of symptoms and severities across different patients

- **Wuhan University, Jin et al. (2022)**, n=46 patients. 69% of patients were classified as RP while 24% were classified as LCA. A macular petal-like atrophy was characteristic of the fundus of RDH12 patients. As the fundus type increases in severity the BCVA decreases significantly, and types I and IV fundi are associated with night blindness.[189]

The most recent meta-analyses that pool data from multiple centers/ smaller studies are:

- **UMichigan: Fahim & Thompson (2019)**, n= 134 patients. Great variability in VA although all declined with age; universal reduction in ERG rod and cone responses; and universal visual field constriction (notwithstanding only 21% of patients had visual field results recorded). Common observations that were recorded include pigment migration (90%) as young as 4 years of age, macular atrophy (78%) as young as 3 years of age, optic nerve pallor (23%) and posterior staphyloma (18%).[182]
- **PUMCH: Wang et al. (2022)**, n=425 families. Age of onset ranged from 2 months to 26 years (median 3 years); For autosomal recessive disease, BCVA ranged from no light perception to 0.8, but majority (88%) had BCVA ≤ 0.3 and 57% ≤ 0.1 (Figure 8). Recorded fundus changes showed macular-predominant retinal degeneration.[18]
- **UCL: Daich-Varela et al. (2023)**, n=78 patients: Macular and midperipheral atrophy observed from age three; Slower disease progression (measured by BCVA and progression to legal blindness) associated with the p.(L99I) variant (homozygous). This data includes the first large South American RDH12 cohort.[12]

Variations in phenotype and severity may partly be explained by the many disease-causing variants of RDH12 and/or genetic modifiers in the RDH12 gene, visual cycle genes, and other interacting proteins. Several dominant variants (c.763delG, c.778delG, c.759delC) have been associated with adRP while p.(T49M), p.(A269G), and p.(L99I) with later-onset disease, but severe, LCA forms of the disease can be caused by many different variants that have not been fully characterised phenotypically. Additionally, ethnic-specific variations exist. For example, the most common variant in European and Caucasian patients, p.(A269Gfs*2), is absent in East Asian patients and general populations, where p.(V146D) seems more common.

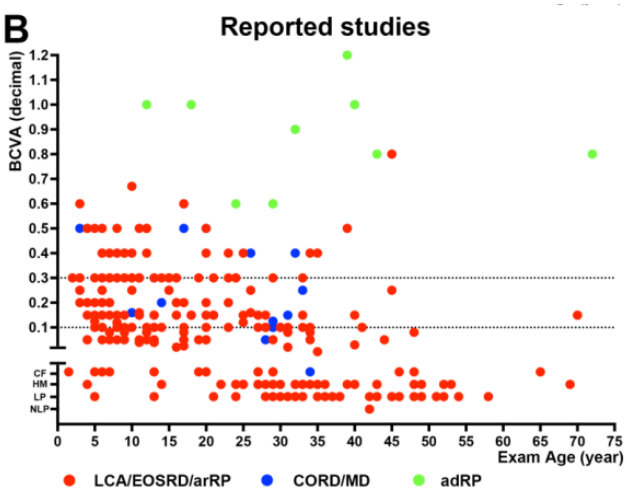


Figure 8: BCVA of RDH12 patients in the literature, stratified by clinical classification, prior to 2022. Taken from Wang et al. (2022)[18]

A natural history study was conducted at UCL/Moorfields Eye Hospital in London between 2021 and 2023, sponsored by MeiraGTx. Most of the data has not been published, but it established adaptive optics scanning laser ophthalmoscopy (AOSLO) as a method to observe cone PRs and structural change over time in patients with EOSRD, even for young patients with nystagmus, and early macular atrophy.[188] Patients were also assessed using visual field modelling and analysis and a multi-luminance navigation path.[190]

To overcome the issue of non-standardised study protocols from different centres/IRDs, the Universal Rare Gene Study, or UniRare (NCT05589714), was started in 2022. UniRare is a registry and prospective natural history study for various IRDs conducted by the Foundation Fighting Blindness Clinical Consortium and coordinated by the Jaeb Center for Health Research. The study aims to enrol c. 1,500 participants with retinal dystrophies associated with >300 rare genes, across 36 clinics in North/South America, Europe, and Australia. Standardised data will be collected, including functional measures (e.g. visual acuity, static/microperimetry, FST, ERG, contrast sensitivity, colour vision), structural measures (OCT ellipsoid zone area, ONL thickness, and RGC cell layer thickness; FAF), and patient-reported outcome measures (MRDQ, ViSIO-PRO, PROMIS-29 for adults; ViSIO-ObsRO and LVP-FVQ II for children). The observation period lasts four years; The final patient(s) are expected to be enrolled in December 2026, and the study completed in December 2030. ***RDH12*** **is one of the two genes where a further prospective longitudinal study has been confirmed**, funded by Opus Genetics. Specifically, the study aims to (1) Characterise disease progression over four years by functional, structural, and patient-reported measures, (2) Determine if structural measures are valid surrogates for functional measures (e.g. OCT ellipsoid zone for BCVA, FST, and microperimetry) which are typically preferred by regulators, and (3) Investigate factors that affect disease progression (e.g. age of onset, visual acuity at baseline, specific variants/mutation characteristics, and vitamin A/DHA/lutein supplementation), which may help identify patients most suitable for trials and the optimal time window for intervention. For aims (1) and (2) above, results from at least 20 patients are needed for the results to be meaningful; for aim (3), at least 40 patients are needed. The maximum cohort size for each gene is 100 patients.[191]

4.2.3 Patient Registries

Patient registries (also known as clinical/disease registries) are databases containing standardised information about patients who have a disease, including clinical (e.g. medical records, diagnostic images, clinician or patient reported outcomes or surveys) and other data. These registries may be managed by researchers, or patient organisations with guidance from a scientific advisory board. The databases may be used to pool data for epidemiological and natural history studies, recruit patients for observational or interventional studies, improve/monitor the quality of care, etc. Registries may be disease-specific or cover various conditions (e.g. ClinGen, My Retina Tracker).

The Foundation Fighting Blindness (FFB) established **My Retina Tracker, a global patient registry for IRDs**, in 2014. The primary objective of this registry is to provide de-identified patient and disease data for IRD observational or interventional studies by academic or industry researchers. The registry is patient-controlled, meaning that each patient uploads and maintains their own records. However, for reasons related to its design, the registry does not presently allow longitudinal studies. The ongoing **Universal Rare Gene Study (UniRare)** aims to collect data from 1,500 patients across >300 IRD genes, including functional, structure, and patient-reported outcomes. This multi-center study is coordinated by the Jaeb Center and funded by the FFB, and is expected to conclude in December 2030.

The UK RDH12 patient organisation Eyes on the Future runs a **RDH12-specific community registry**, which collects contact details and medical information directly from affected individuals/families, such as age at diagnosis, affiliated hospital/ophthalmologist/healthcare provider, visual acuity score,

clinical symptoms, and genotype (variant). Provision of medical information is voluntary and data will be anonymised before it is shared with trusted researchers.[192]

Additionally, KOLs interviewed for past editions of this report have suggested that a RDH12 biobank – i.e., a repository of patient biological samples – would be helpful for **basic and preclinical research**, but face challenges in logistics (collecting, transporting, and storing samples), funding, and expertise. Currently, **several patient-derived RDH12 hPSC cell lines are available**, covering a range of RDH12 mutations and retinal degeneration phenotypes (**Chapter 2.3.3.1**).

4.3 Clinical Trial Design

4.3.1 Outcome measures/endpoints[193]

Endpoint selection is crucial to demonstrating treatment efficacy. Conventional outcome measures like central visual acuity (VA) and OCT of the macula are well-suited to capture disease and treatment outcomes in AMD or diabetic retinopathy, where macular atrophy and central vision loss occurs rapidly. However, these endpoints may not be clinically meaningful for IRDs, given the different disease phenotypes/progressions (e.g. in some IRDs, peripheral vision is lost first which is not reflected by central VA) and the fact that trial participants are often already at advanced stages of vision loss. Notably, the Biogen Phase 3 STAR trial of an AAV2-REP1 vector for choroideremia failed to meet its primary endpoint (proportion of patients showing 3-line (≥15 letters) improvement in BCVA at 12 months) despite 4 patients in the high-dose arm gaining ≥15 letters and 14% gaining ≥10 letters (vs 0 and 2% in the control). Hence **endpoints need to be tailored to the clinical characteristics of these unique subsets of patients**, and clinical trials for IRDs have had to design novel specialised endpoints for this purpose.

Clinical endpoints include safety, functional, anatomical/structural, and patient-reported outcome measures (PROMs). FDA approvable primary and secondary outcome measures for ocular clinical trials are shown in **Table 7: FDA approvable primary and secondary efficacy outcome measures for ophthalmology.** .

Type		Measure	Comment
Primary	Functional	VA	≥15 letters (3 lines) improvement in BCVA/LLVA
		Perimetry	≥7dB improvement at ≥5 of pre-selected loci (HVF, OVF, MP)
		Mobility	≥2 levels improvement in MLMT
	Structural	OCT, FAF	Decreased progression of EZ layer, EZ area, retinal atrophy
Secondary	Functional	FST	Full-field scotopic threshold test
		ERG	ffERG, mfERG
		Photosensitivity, pupil, etc	
	Structural	AO-SLO	Adaptive optics
	PRO	PRO	Patient-reported outcomes (NEI VFQ, etc)

Table 7: FDA approvable primary and secondary efficacy outcome measures for ophthalmology.

The FDA prefers functional or direct clinical endpoints to measure efficacy. A 15-letter/3-line improvement in best-corrected visual acuity (BCVA) using the ETDRS protocol and static or kinetic perimetry to assess visual field have historically been the gold standard for measuring efficacy in ophthalmology and are the FDA's preferred primary endpoints. However, **surrogate structural measures may be used** when reasonably likely or expected to predict clinical benefit by epidemiological, therapeutic, pathophysiologic, or other evidence. Ultimately, **the FDA needs to agree that the selected endpoints have been sufficiently validated for use** before an IND can be approved.

To date, the primary outcome in published IRD trials has been mean change from baseline in BCVA, microperimetry, and ambulatory navigation/mobility mazes. Secondary outcomes vary widely and have included LLVA, visual field, FST, visual perception by QoL questionnaires, ERG, microperimetry, fundus photography, nystagmus testing, OCT central retinal thickness, pupillary light reflex response, and photophobia testing. In this section, we discuss endpoints used in IRD trials and their relevance to RDH12-associated disease.

Note that as the OPGx-RDH12 Ph1b/2a trial is primarily a safety/tolerability study, the primary endpoints are dose-limiting toxicity events, treatment-related adverse events, and a qualitative assessment of OCT and fundus/FAF images. Efficacy endpoints are listed as secondary endpoints.[xxxviii]

4.3.1.1 Functional endpoints

Functional endpoints include assessment of visual function (how well the eye detects stimuli) and tests that assess patients' ability to execute vision-aided activities of daily living.

Best-corrected visual acuity (BCVA): Currently included in all IRD trials as a primary or secondary endpoint. However, BCVA loses sufficient sensitivity on both ends of visual function, with a basement effect at the threshold of count fingers (CF) and a ceiling effect due to foveal sparing in IRDs such as RP where central vision declines later in the disease course.

Low-luminance visual acuity (LLVA): Adjusted BCVA protocol with lower luminance. More sensitive (declines before any detectable change in BCVA in early stages of choroideremia and RPGR-RP) and a better predictor of future acuity loss. The best applications of LLVA as an endpoint are thought to be rare maculopathies and rod-cone dystrophies.

Perimetry/microperimetry: Measures rod degeneration which leads to progressive loss of visual field. Common metrics are mean sensitivity (MS) and mean deviation (MD) of visual field sensitivity, vs age-matched controls, expressed in decibels (dB). The observation period needed to calculate a statistically significant decline in MS/MD may be 2-3 years but this may vary between diseases. Microperimetry (MP) is especially useful in cases where central vision and fixation are poor due to macular pathology, and has strong test-retest reliability. MP has been used in trials across choroideremia, LCA, AR Stargardt disease (STDG1), X-linked retinoschisis, RP, and achromatopsia. Limitations include lengthy and challenging testing as well as a wide range of methods/devices/reporting metrics used in different trials.

FST: Important measure of residual vision when perimetry cannot be performed (e.g. due to severe VF constriction, inadequate fixation due to nystagmus or severe blindness) originally developed for LCA but now widely used in IRD trials. Dark-adapted FST can distinguish between cone and rod deficits, while light-adapted FST can distinguish between cone subpopulations. Correlates closely with MLMT and able to assess visual function below a luminance of 1lux, which is a drawback of the MLMT. However not considered as a primary endpoint measure and lacks applications beyond LCA. It has been recommended to develop a consensus document establishing guidelines for the clinical application of FST, vis-à-vis the ERG standardisation guidelines developed by ISCEV. ATSN-101 in GUCY2D-LCA showed a stronger response in FST than in BCVA[85] while FST (and MLMT) improved in Luxturna trials even though BCVA did not.[194]

[xxxviii] NCT07681778

Pupillometry: A valuable metric in advanced vision loss. Used as a secondary measure in some studies, but the criteria for meaningful efficacy change has not been determined. A recent study identified statistically significant differences in pupillary responses among different RP genotypes.

MLMT/MLoMT: The multiluminance mobility test (MLMT) is a physical obstacle course performed at different light levels (1 to 400 Lux). Patients are assessed on accuracy and speed of completing the task. MLMT was originally developed for the Luxturna trial, and has since been adopted for use in other trials. Luxturna was a landmark approval as it was based on improvements in MLMT and FST rather than BCVA, and MLMT is currently the only performance-based test that is approved as a primary endpoint. A key concern expressed by KOLs interviewed for the previous version of this report was that MLMT was very limited in its accessibility, as the test could only be conducted in Philadelphia and Iowa. Since then, a VR-headset version of the MLMT, **MLoMT**, has been developed and validated.[195] VR assessments have the advantages of being safer, more standardised, offer unlimited course variability, and are easy to deploy given standardised data collection and less space requirements. MLoMT is being used in both the OPGx-LCA5 and OPGx-RDH12 studies (NCT05616793, NCT07681778).

Functional measures not used in RDH12 studies:

- **FrACT:** Able to measure clinical changes in visual acuity down to hand motions (HM), therefore more sensitive than the BCVA ETDRS protocol in settings of very low vision. FrACT has been used in optogenetics trials where patients have already experienced advanced vision loss (MCO-010 for RP; patients with BCVA lower than 1.9 logMAR or 20/1600 on the Snellen scale). Not used in RDH12 trials; OPGx-RDH12 recruiting patients with up to 0.5 logMAR BCVA.
- **Contrast sensitivity** (Pelli-Robson charts, Ora-VCF, Ora-CST). Widely used as a secondary endpoint and FDA has indicated that CS would be an acceptable primary endpoint if clinically and statistically significant differences were detectable at multiple spatial frequencies and cycles.
- **ERG:** Widely used for clinical diagnosis and monitoring of retinal function in IRDs. However, ERG responses are often extinguished in the early stages of many IRDs including LCA, while BCVA and perimetry are still measurable, limiting its utility as an outcome measure.
- **Colour vision:** Colour vision deficits can be detected in the early stages of many IRDs. Not yet used as a primary endpoint as efficacy signals have not been demonstrated in Ph1 and Ph2 trials.
- **Photoaversion:** Often presents as an early symptom of IRDs especially cone and cone-rod dystrophies. However, quantifying its severity and progression has been challenging.

Other functional tests not used in RDH12 studies:

- **Ora-VNC:** A mobility test developed by Ora Inc similar to the MLMT which is currently in use as an endpoint in multiple Phase 2 and 2/3 IRD trials.
- **LDNA:** A newer functional assessment with improved sensitivity compared to the MLMT, able to evaluate visual function between 0.04-500 lux, allowing inclusion of participants with early to advanced stages of disease. Developed by Ocugen in collaboration with the FDA for OCU400 Ph3 trials for RHO-mediated and gene-agnostic RP.
- **FLORA:** Assesses mobility, activities of daily life, reading, and other measures of independence. Designed for administration before and after implantation of the Argus II retinal prosthesis.
- **Reading Performance testing and Radner Reading Charts:** Used to evaluated functional reading vision in IRD settings.

- **MLSDT:** Assesses near-object recognition. Has been used as a key secondary endpoint in optogenetics (Nanoscope's Ph2b trial of MCO-010).
- **StreetLab:** An indoor simulation environment designed to mimic the complexities of a real urban street – a situation which IRD patients consistently report as one of the most challenging aspects of their visual disability.[196]

It was previously noted that MLMT and FST may not be feasible in young children (e.g. below 8 years old) as they require active patient participation. While alternative child-friendly functional tests (e.g. a toy table) have been proposed, development and regulatory qualification of new outcomes would require substantial time, expertise, and resources. Nonetheless, Aleman et al. (2024) demonstrated that FST can be performed reliably in paediatric RDH12 patients, but careful interpretation of the results are needed as FST performance seems to naturally increase with age (e.g. due to better compliance) independent of treatment.[15]

4.3.1.2 Structural endpoints

Structural endpoints are biomarkers based on retinal imaging designed to substitute for clinical biomarkers. As such, they must be validated to demonstrate that they correlate with, and have predictive value for, meaningful functional changes. **Structural endpoints are objective and can be resolved at the cellular level in some cases** – especially useful in IRDs as interventions are often intended to restore or preserve specific cell populations. Additionally, **in some cases e.g. adaptive optics imaging of cone density, structural changes can be observed prior to functional changes**. However, **interpretation may be complex, and their utility depends on disease stage**; In more advanced disease where the retina has already degenerated significantly, measurable structural change within residual cells may be too slow to detect over the course of a trial.

FDA guidance recognises the rate of photoreceptor loss measured by OCT or fundus autofluorescence (FAF) as a possible efficacy endpoint.[197] In AMD, in particular, slowing the growth of geographic atrophy measured by fundus autofluorescence supported the US approvals of Syfovre and Izervay (although this surrogate was not accepted by the EMA).[198] Qualitative assessment of OCT and fundus/FAF images are listed as a primary endpoint in the OPGx-RDH12 safety trial.

Some structural endpoints used in trials are discussed below:

- **Optical Coherence Tomography (OCT)**
  - Measures of macular thickness are widely used in diabetic macular oedema and AMD trials
  - Disruption of the inner segment ellipsoid zone layer (EZ) has been shown in many IRDs to correlate to a loss of retinal function. EZ width and EZ area are under evaluation as endpoints in RP, XLRP, LCA, Stargardt, and other IRDs
  - Measures of PR loss include hypertransmission defects, contiguous RPE layer loss, and outer retinal atrophy, which are under development to determine if OCT can be more sensitive than FAF as a measure of atrophy
- **Fundus autofluorescence (FAF)**
  - The preferred method for measuring RPE/PR atrophy due to high resolution and contrast
  - Used to calculate rate of atrophy progression in GA and AMD trials and Stargardt disease
- **Adaptive optics (AO)**
  - Able to image the retina at the cellular level (resolution of 2μM vs SD-OCT is 5-7μM)

- Currently there are no AO metrics acceptable as endpoints in Ph3 trials. However**, AO-SLO techniques can provide numerous measures of PR health** including cone density, cone spacing, and cone regularity, which is especially important for gene therapies that aim to rescue PRs, as structural changes have been shown to precede major functional loss, and the cone mosaic was shown to be preserved following a therapeutic intervention.
- Studies describing the reliability and variability of cone structure and function are essential to validate AO-SLO-derived metrics for use as longitudinal outcome measures. The drawbacks of AO-SLO are that it requires specialised instruments and trained personnel, and AO is not possible to obtain in patients with poor fixation.

For RDH12-associated dystrophies, Aleman et al. (2024) has published structural and functional characterisation of the retina in a study of 46 patients (see Section 4.3.1.5) while Daich Varela et al. (2024) published AO-SLO based features in 8 patients.[15,188]

4.3.1.3 Molecular biomarkers[199]

Molecular biomarker development for IRDs is an active area of research. Martinez-Fernandez De La Camara et al. (2013) have measured the levels of different oxidative stress markers in the aqueous humour and blood of RP patients.[200] Elevated SOD3 activity was found in the aqueous humour and reduced SOD3 activity and increased TBARS formation in peripheral blood. Serum cGMP levels are also known to be elevated in patients with RP albeit with a relatively high false positive rate.

Retinal cell death may also be quantified by measuring molecules released from dead neurons into ocular fluids such as neurofilament proteins in the vitreous body and anterior chamber fluid (an invasive procedure) and fluorescent cell death markers visualised by confocal scanning laser ophthalmoscopy (non-invasive). Cordeiro et al. (2010) used Alexa Fluor 488-labelled Annexin V and propidium iodide to identify apoptotic or necrotic cells in the retina, and proof-of-concept has been obtained in a Phase 1 clinical trial for glaucomatous neurodegenerative disease.[201] While PR death may be driven by apoptotic or other mechanisms, molecular probes may be developed to detect markers of these processes e.g. cytochrome c and caspases (for apoptosis) as well as HDAC, PARP, calpains, DNA-methyl-transferases. It may be possible to develop in vivo biomarkers that can be imaged using fluorescent scanning laser ophthalmoscopy.

RDH12 converts all-trans retinal (atRAL) into all-trans retinol (atROL) and dysfunction causes the accumulation of toxic 4-hydroxynonenal (4-HNE). **4-HNE in aqueous humour was evaluated as an outcome measure in the PUMCH-E101/IVB107 trial**; RDH12 patients had markedly elevated 4-HNE levels pre-treatment (756pg/mL) compared to controls (144pg/mL), and 4-HNE decreased to 459pg/mL 36 weeks post-treatment with two patients normalising to control levels.[72] atROL levels have been also shown to increase after administration of the gene therapy in preclinical studies, indicating restoration of RDH12 activity (17.4ng/mL in untreated Rdh12KO mice retinas to 193ng/mL in the high-dose group).[73] Quantification of retinoids is usually done ex vivo using chromatography, thus limiting its utility to preclinical studies. However, **a recent study using multiphoton autofluorescence lifetime imaging studies demonstrated the ability to quantify atRAL and atROL non-invasively in retinal tissue and human retinal organoids[60], which could potentially be adapted for in vivo use using FLIO**, which is already used to quantify lipofuscin in the RPE.[202]

4.3.1.4 Patient-reported outcome measures (PROMs)

There are currently no FDA-approved PROs for use as a primary outcome measure. They are not required in trials, but regulatory guidance recommends their use, and they are common secondary endpoints. PROMs that are widely used in ophthalmology but are not IRD-specific include the NEI-VFQ, IVI, VLV-IVI, MRDQ, MVAQ, ViSIO-PRO and its observer-reported version, ViSIO-Ob-RO, which is suitable for children under 12 years of age.

Several IRD-specific PROs are available. A 2017 review identified nine for RP, one for CSNB, and one for STDG. The review, however, found that these questionnaires were limited by inadequate validation, small sample size, and narrow scope, with specificity limited to a small subset of IRDs. No RDH12-specific PROs are available.

The FDA has issued guidance on PROM development/validation.[206] During the Second Global Scientific Conference on Clinical Trial Design and Outcome Measures for RDH12 organised by Eyes on the Future and the RDH12 Fund for Sight, it was highlighted by KOLs that in order for a PROM to be more acceptable to regulators and payors, (1) A conceptual model of disease, which collects information about pertinent symptoms or impacts on a patient's quality-of-life from patient interviews, needs to be constructed. (2) The PROM should be mapped to the EuroQoL-5 Dimension (EQ-5D), which facilitates the calculation of quality-adjusted life years for reimbursement decisions by payors.[79] Once developed, the PROM should be evaluated using data from clinical trials and modified if necessary.

4.3.1.5 Summary & Relevance to RDH12

Given the inherent phenotypic variability in patients, no single endpoint is sufficient to capture potential treatment benefits. **A multimodal approach combining functional and structural measures is needed, and treatment targets/ endpoint measures need to be tailored to each individual based on their pattern of retinal degeneration obtained through retinal imaging.**

Aleman et al. (2024) performed extensive structural and functional characterisation of the retinal regions (**Figure 9**) and function of 46 RDH12 patients.[15]

- BCVA declines slowly at an average rate of ~0.04 logMAR per year. Foveal structure by OCT (n=16 patients with at least one eye with 0.6 logMAR or better) showed detectable but abnormal ONL at the fovea that thinned at ~-0.02 log/year. Foveal sensitivity losses were consistent with foveal cone photoreceptor losses (no structure-function dissociation)
- The peripapillary retina is relatively preserved, as seen from NIR-AF and OCT (e.g. ONL thickness). Little structural degeneration is observed over time, although rod sensitivity/function is much lower than expected from the structure. Cone densities (from AO-SLO) were either normal or borderline normal despite sensitivity/function loss.
- The mid-/far-peripheral retinal regions were also relatively spared both in structure (as seen in FAF) and function (measured by kinetic visual fields).

Overall, the study suggests two complementary therapeutic strategies for RDH12 disease: preservation of the remaining foveal cone photoreceptors to slow progression of central vision loss, and restoration of function in retained peripapillary rod photoreceptors to improve night vision.

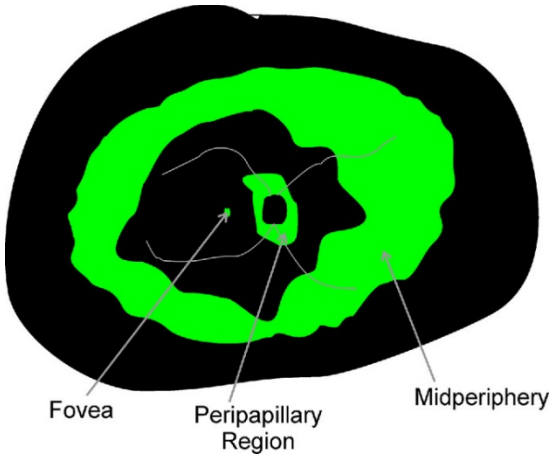


Figure 9: Retinal regions reported to be relatively preserved (green) in RDH12-LCA. Figure taken from Aleman et al. (2024).[15]

Functional measures remain foundational to demonstrate clinically meaningful benefit in IRD clinical trials. Both ongoing RDH12 trials utilise BCVA, LLVA, and visual field mean sensitivity (perimetry). OPGx-RDH12 also lists kinetic visual fields, FST (light- and dark-adapted), pupillometry, and MLoMT as efficacy measures. While central vision loss occurs early on in RDH12-associated disease compared to other IRDs, BCVA only measures function in a small retinal area and therefore may only provide a partial/ incomplete representation of treatment effect. However, **the PUMCH-E101/IVB107 Ph1 trial showed that BCVA and LLVA may be able to capture improvement in RDH12 disease** – BCVA +7.6 letters on average and 3/10 eyes achieving ≥10-letter gains, and LLVA +8.1 letters on average with 2/9 eyes achieving ≥15 letters increase at week 36.[72] It was shared by Dr Ruifang Sui that with longer follow-up, more patients achieved ≥15 letter gains on both metrics which would meet a commonly used benchmark. Meanwhile, static visual field MS showed no significant difference, consistent with floor effects in advanced disease. Nonetheless, **visual acuity should not be the only functional measure**; Dr Sui also shared anecdotal evidence that patients were better able to perform activities of daily life, indicating improvement in functional vision, and thus **MLMT/MLoMT and FST which were instrumental to the approval of Luxturna should also be used to reflect treatment benefit.**

Structural endpoints have been accepted by the FDA in some trials, but they are disease specific. OCT changes may occur too slowly to be measured in a 1-2 year trial (unlikely functional measures), especially if significant PR loss has already occurred by the time of treatment which is often the case for RDH12. Adaptive optics could in theory measure PR-level changes, but requires stable fixation, and many RDH12 patients have nystagmus or poor fixation and therefore cannot be imaged reliably. Nonetheless, imaging is still crucial to patient selection and retinal mapping: According to Dr Sui, patients who had thicker retinas and more preserved PRs tended to show greater treatment benefit as measured by BCVA and LLVA. **Structural integrity may predict treatment response in RDH12 even if functional endpoints are the easier way to demonstrate efficacy.**

4-HNE in aqueous humour has been explored as a mechanistically relevant molecular biomarker in RDH12 disease. However, further validation may be necessary before it can be used as a primary endpoint. Furthermore, in theory, atRAL and atROL (which provides a direct probe for RDH12 function) could be quantified non-invasively, but much more development is needed before this biomarker can be considered in clinical trials. Lastly, patient-reported outcome measures (PROMs) should be used as secondary endpoints, as they are accepted by regulators and can help substantiate efficacy, although they are not a substitute for clinical measures. The OPGx-RDH12 trial utilises MRDQ which is specific for

retinal degeneration and PGI-S, PGI-C, and PGI-I which broadly assess the patient's overall health, functioning, and symptoms. No RDH12-specific PROM is available, however development of IRD-specific PROMs is expected to be extremely resource-intensive and take several years, so this should not be a bottleneck to starting clinical trials.

4.3.2 Other considerations in trial design

Control strategies. The PUMCH-E101/IVB107 trial utilised a paired-eye design, i.e. one eye was treated first with the other eye serving as the control, and the BCVA/LLVA gains were reported on this basis. The second eye was treated in a later phase of the trials. Dr Ruifang Sui shared that in natural history studies conducted by her group prior to the trial, good interocular symmetry was observed, which substantiates the use of the contralateral eye as a within-subject control. Paired-eye trials are more efficient than one-eye trials because they require fewer trial participants to detect a treatment effect with adequate power, especially for IRDs with small trial-eligible populations.[179]

The FDA discourages paired-eye designs in retinal disorder trials[197], as the treated and contralateral eyes may be in different disease stages at baseline and disease progression may differ between the two eyes during the clinical trial period (asymmetric deterioration) and therefore may not serve as a reliable control. Additionally, the FDA prefers that both eyes of a patient are treated; based on biostatistics designs used in FDA-approved trials, patients should be the unit of randomisation and comparison, not individual eyes, especially for later registration trials/pivotal studies.[203] Furthermore, having different procedures in both eyes (treatment vs sham) may lead to unmasking, which can confound study results with functional outcomes (although this should not affect structural outcomes which are independently assessed).

That said, a study for STGD1 showed that intra-patient variability was consistently smaller than inter-patient variability, and even with asymmetric disease progression (worst-case scenario of intraclass correlation coefficient = 0.00), it is still more efficient to conduct a paired-eye design trial as the number of available eyes is doubled. Aleman et al. (2024) showed that for RDH12 there was generally interocular symmetry with a median BCVA difference of 0.18 logMAR between eyes. There were exceptions, however, with up to one eye being 3.4logMAR worse than the other.[15]

Intervention window and patient selection. The experience of PUMCH-E101/IVB107 shows that RDH12 patients who had more retained photoreceptors at baseline (as seen in thicker retinas in pre-treatment examinations) saw greater treatment benefit (visual function improvement as measured by BCVA/LLVA at week 36), consistent with expectations for gene augmentation therapy as seen in Luxturna.[203] Hence, the earlier the patients received the gene therapy, the greater the rescue potential (see **Chapter 3**). This may necessitate recruiting younger patients, who may not necessarily be suited to outcome measures that require active patient participation like FST and ML(o)MT. Regardless, patients should have their retinas imaged (retina morphology) and functionally assessed to determine the state of PR degeneration and which retinal regions have the greatest treatment potential for a subretinal injection of a gene augmentation therapy.

Long-term effects. Current evidence for Luxturna suggests treatment benefit is durable and maintained for up to 4 years as measured by MLMT and FST. The most significant safety concern is chorioretinal atrophy, which was reported in 13-50% of treated eyes, particularly in younger patients and often near the injection site. Although the underlying cause remains uncertain (surgical trauma, vector toxicity…), it has recently been suggested that altered retinal metabolism following successful gene therapy may lead to metabolic imbalance that also results in degeneration of the surrounding retina/RPE/choroid. Other safety risks include elevated risks for retinal tears or detachment, intraocular pressure changes, ocular haemorrhage, and inflammation. No systemic toxicity was identified.[80] A long-term (15 years)

observational follow-up study is ongoing (NCT03602820). These observations highlight the importance of long-term structural and functional monitoring in IRD trials.

4.4 Commentary

In this chapter, we address progress made on some of the challenges highlighted for RDH12 in the previous Landscape document.

Given the rarity of IRDs, trial recruitment was previously identified as a key challenge for gene-specific gene therapy trials (in the case of Luxturna for RPE65-LCA). However, given the relatively high prevalence of genetically-confirmed RDH12 patients today, we believe this is less of a barrier to starting clinical trials. The challenge here may now be more on early diagnosis and treatment, as it has been shown that the earlier a patient gets treated, the better the treatment outcome.

"…for RDH12, talking to folks, most of the centers out there who see [RDH12] patients feel like they already have enough patients that they know of to fill the trial..." – M. Pletcher

The scarcity of RDH12 natural history studies to inform trial design was also highlighted in 2021. While 10-year disease progression is still not available, shorter-term studies that are relevant to clinical trials have been published by the UPenn and PUMCH groups and have been used for the trial design of the OPGx-RDH12 and PUMCH-E101/IVB107 programmes. Additionally, a multi-centre prospective natural history study for RDH12 is ongoing under the Uni-Rare programme. Natural history studies have shown good symmetry in terms of disease progression/severity between the two eyes of an RDH12 patient, which would allow for a paired-eye trial design, although such trials are discouraged for later trial stages. Furthermore, there is more clarity on outcome measures/endpoints that can reflect disease progression and treatment benefit in RDH12-LCA; FST and ML(o)MT should be used in conjunction with BCVA/LLVA (FDA's preferred endpoint) as visual acuity may only reflect specific aspects of disease/treatment. For example, in both RPE65-LCA and GUCY2D-LCA trials, significant improvements were made on MLMT and FST while BCVA did not show significant improvement. Nonetheless, BCVA/LLVA may be more useful for RDH12: Clinically-meaningful BCVA and LLVA improvements were observed in patients treated with PUMCH-E101/IVB107 meeting the FDA's threshold of 15 letters in some (albeit this was in contralateral eye studies, which the FDA discourages, only data up to week 36 is currently published, and outcomes were heterogenous between patients). According to Innovec Biotherapeutics, they have since obtained IND authorisation from the FDA. Progress has been made to address challenges around the use of FST and MLMT that were raised in previous discussions (requirement for active patient participation may complicate use in paediatric patients and inaccessibility). In the case of MLMT, a virtual version of the test (MLoMT) has been developed and deployed in other IRD trials. Given that functional outcome measures are expected to show benefit for RDH12, further development of structural outcome measures is not an urgent priority, but retinal imaging is key to identifying the retinal regions showing the greatest improvement potential that should be targeted by gene therapy. 4-HNE has also been explored as a mechanistically relevant biomarker for restoration of RDH12 function. RDH12-specific PROMs may be useful, but should not be a bottleneck to starting trials in the near-term.

Constructive engagement between scientists, industry, and regulators is paramount to preparing a field for clinical translation. KOLs interviewed for this version of the RDH12 report were overall positive on this: Dr Amy Laster (Foundation Fighting Blindness) noted that the FFB actively works to educate regulators on specific IRDs, and that regulators increasingly engage with rare disease sponsors through

orphan, paediatric rare disease, and related designation programmes, although global alignment is still needed as different regulators may have different preferences (e.g. on structural vs functional endpoints). Dr Ash Jayagopal (Opus Genetics) expressed that Opus has consistently collaborated closely with the FDA e.g. in terms of trial design. Dr Mat Pletcher (RDH12 Fund for Sight) highlighted the FDA's regulatory flexibility, which allowed Opus to move its RDH12 programme forward given strong mechanistic rationale of AAV-delivered gene therapy for a monogenic disease. Dr Ruifang Sui (PUMCH) mentioned that strong support from Chinese regulators was critical to advancing the development of IVB107, including bringing it from clinical trials to supervised real-world treatment in Hainan province. Overall, regulators recognise the urgency to find treatments for rare diseases and the practical considerations of running trials for them.

A key challenge in rare disease drug development beyond the scope of this document is the financial/commercial considerations: Despite favourable policies (e.g. rare diseases being exempt from negative IRA provisions) and growing evidence that the therapies can show clinical benefit, large pharmaceutical companies may still find rare diseases commercially unattractive. New financing models have emerged to fill this gap, including the collaboration between Opus Genetics and the RDH12 patient organisations RDH12 Fund for Sight and Eyes on the Future.

Appendix B: Interview Transcripts

Amy Laster, PhD
Chief Scientific Officer, Foundation Fighting Blindness
30/07/2026

Q. How would you characterise how the IRD field has moved over the past five years? Have any specific programmes advanced faster than expected, or been disappointments? And where does RDH12 sit relative to the rest of the IRD field in terms of progress?

A. The IRD field has moved from a predominantly gene-discovery, single-gene-therapeutic mindset toward a broader translational ecosystem. Gene-specific approaches remain important, especially for diseases like RDH12/LCA13, but the field is increasingly focused on endpoints, natural history, mutation-agnostic therapies, late-stage disease strategies, regulatory alignment, and the infrastructure needed to make rare disease trials feasible. Given how many LCA-type diseases exist, it is difficult to single out any one programme as a specific standout or disappointment.

Q. Thinking specifically about gene-specific therapies, several are already in the clinic and arguably scientifically de-risked. What do you see as the remaining challenges?

A. Gene augmentation remains foundational, but the next wave of genetic technologies is broader: RNA-based approaches, gene editing, optogenetics, and cell-based or regenerative strategies, alongside small molecule approaches. Many patients, particularly those with advanced retinal disease or genes that are difficult to target with a gene-specific therapy, need more than one therapeutic option. The biggest bottleneck in clinical translation is not the science itself. For most ultra-rare IRDs, infrastructure matters as much as the intervention: diagnosed patients, standardised testing, longitudinal data, qualified sites and investigators, and outcome measures that both regulators and trial sponsors can trust. Building that infrastructure is one of the field's central bottlenecks in translating science into treatment.

Q. Following up on that, is there any unpublished work you're aware of that you think is promising, or that we're likely to see in the literature in the next few years?

A. One lesson from the field is that working gene by gene requires shared infrastructure. Studies like our Clinical Consortium and the Uni-Rare project are designed to help us learn across many IRD genes, particularly where no single gene has enough patients to answer every clinical question on its own. UniRare is an international, seven-year study designed to characterise IRD patients and use standardised data collection to examine disease mechanisms shared across genes.

Q. On the preclinical side, are there specific lab groups within the IRD field you expect to see advance in the near term?

A. Looking across our funded portfolio and the wider landscape: a group at Radboud University in the Netherlands is developing antisense oligonucleotide therapies and assessing how to modulate splicing effects. Several groups at Mass Eye and Ear are working on gene editing, including HITI-based approaches and CRISPR-based editing. The group at UC Irvine led by Dr. Krzysztof Palczewski, a well-known biopharmacist, is developing both editing approaches and small molecule approaches. On delivery, beyond

AAV, groups at Oregon Health & Science University and the University of Wisconsin-Madison are developing nanoparticle delivery for editing machinery, including for LCA programmes specifically.

Q. Of these technologies, which do you think has the most plausible applicability or transferability to LCA13 specifically?

A. There is real potential in gene therapy and gene editing where retinal integrity is still in place, since preservation or restoration is achievable in that window. There are also gene-agnostic small molecule strategies, such as N-acetylcysteine, designed to slow disease progression, and Sparing Vision's RdCVF programme, also intended to slow vision loss. These may be options for individuals who are not eligible for gene-specific approaches. More broadly, cell-based strategies become relevant when disease is more advanced; BlueRock has a cell-replacement technology currently in the clinic. Depending on disease severity, optogenetic approaches from a couple of companies anticipating product approval may be another option for someone with more advanced disease.

Q. You mentioned some patients may not be eligible for gene-specific gene therapies. Beyond disease progression, what other exclusion criteria are there?

A. It varies, but it is often baseline visual acuity, the structural condition of the retina, and where degeneration is occurring and whether it can be reliably measured over time. Trials typically have several exclusion and inclusion criteria because the goal is to optimise the cohort toward the individuals most likely to respond, in order to test whether the treatment works. That said, falling outside a trial's inclusion or exclusion criteria does not mean someone would be unable to receive the treatment later if it becomes commercially available.

Q. Validated clinical endpoints remain one of the biggest challenges for IRDs, given how differently each one manifests. The Foundation Fighting Blindness has committed to establishing three validated clinical outcome measures within five years. Can you tell us more about that work?

A. Many treatments that have made it from bench to clinic have failed not because the treatment did not work, based on patient-reported outcomes, but because the primary endpoint was not met. That has driven an increasing focus on endpoints across the field. Within our five-year strategic plan, we are using our Clinical Consortium, more than 40 centres-of-excellence globally using standardised protocols and equipment, to identify biomarkers of disease progression, treatment windows, and disease hallmarks, and to determine which functional endpoints are most useful.

Best-corrected visual acuity is standard, but full-field stimulus threshold testing, where points of light are presented across the retina to detect where a patient can respond, is becoming important for some diseases and not others. No single endpoint covers every retinal disease, because they manifest so differently. For dry AMD and geographic atrophy, for example, it is useful to look directly at lesions in the eye, but that approach breaks down if lesions fall outside the area that can be demarcated, which is sometimes the case for diseases like ABCA4.

On the structural side, OCT can measure the margin between healthy and diseased retina. The FDA has accepted one such measure, the ellipsoid zone, but which diseases it is appropriate for, and whether area or length is the right metric, are still being worked out per disease. Answering that requires trial-ready cohorts tracked over a meaningful period to understand progression and identify likely responders.

Globally, some regulators are more comfortable with functional endpoints, others with structural ones, so alignment matters: we do not want a situation where patients have access to treatment in one country but face delays or no access in another. Creating that alignment is one of our strategic plan's activities.
Regulators are also pushing for endpoints that capture clinically meaningful difference in a patient's own terms, for example, going from being unable to drive to being able to drive. But retinal disease is rarely that clear-cut; someone with LCA may never have driven in the first place, so that is not a useful measure. We are working to identify what genuinely affects quality of life through more patient-reported outcomes work, understanding what is meaningful to patients directly. This is uncovering some of these endpoints, but it will take significant time, identifying the endpoints is one step, validating them is another, and both take years rather than months.

Q. For the patient-reported outcomes work, what is the end goal? More questionnaires, given tools like the VFQ and general quality-of-life instruments already exist in ophthalmology, or something else?

A. We are revisiting some existing questionnaires, which have evolved and remained meaningful, but we also want to understand patients' daily lives before they are in a treatment, to bring their voice and experience into therapeutic and trial design from the start. Beyond that, we are excited about using VR technology to simulate everyday environments and measure how disease progression affects real-world navigation, capturing things patients might not think to mention in an interview or questionnaire. If we then place someone in the same simulated environment after treatment, we can measure the difference directly. That is a new tool I think will help generate real-world data.

Q. Is there any major work underway right now that you are aware of? What are the major challenges to getting these questionnaires approved, validated, or standardised? Is questionnaire design itself the main challenge?

A. Right now, what I am most aware of is ongoing conversation with clinicians about which questions best capture information relevant to clinically meaningful differences that can be measured with the tools we currently have. About the main challenges, it is more about standing up the full process around the questionnaire: IRB approval, training staff on collection, and defining how the information will be shared and evaluated once collected. Beyond that, there is a communication plan for getting patients to respond, accessibility, since many respondents are visually impaired, and logistics, including who covers the cost of a clinic visit. There are real operational steps that need to be in place before this can move forward.

Q. You mentioned regulators differ in their comfort with functional versus structural endpoints, and that you are working toward alignment. The FDA is the most important of these. How has the FDA's stance shifted in recent years, in terms of openness to different endpoints and trial designs? We are also aware of the Plausible Mechanism Pathway, though that relates more to therapeutic modality than endpoints.

A. Over roughly the last 18 months, the FDA has restructured in ways that have benefited the rare disease space. There are now more designations available, pediatric rare disease designation, orphan drug designation, among others, that let trial sponsors engage with the FDA more frequently, bring trial design ideas to them, and get specific feedback on what would make a design acceptable. This calendar year we

have seen a genuine uptick in trials receiving these designations. The FDA has also started accepting combined phase 1/2/3 trial designs, which shortens the path through what is historically the hardest stage, Phase 3.

Part of what helps here is direct regulator education: in rare disease, the FDA may not have the same familiarity with a given condition that they would with a larger disease area like cancer, so we spend time explaining the endpoints, the challenges, and what we have learned, either by bringing them into relevant meetings or going to them directly. I would describe myself as cautiously optimistic about FDA engagement over the past year. Over the next 24 months we should see whether that engagement translates into more approved trials.

Q. Given the science is relatively de-risked and regulators are more open to different endpoints, what do you see as the biggest remaining challenges we have not covered?

A. One major gap is genotype-confirmed diagnosis. As therapies become available, a significant number of individuals have had a genetic test but no confirmed diagnosis, which excludes them from trial enrolment before eligibility criteria are even applied. More trials only help if there are enough genotyped, treatable patients. We also need more longitudinal natural history data; through UniRare, our goal is to enrol around 1,500 individuals across 110 genetic diseases, which is significant but still not enough, we cannot cover every gene at once. We need better disease models, since rodent models typically do not capture human disease well. And, as before, we need infrastructure that can support multinational rare disease studies.

Q. Is there anything about the IRD landscape more broadly that we have not touched on?

A. For RDH12 and other ultra-rare IRDs, the path forward depends on matching scientific innovation with trial-ready infrastructure, I cannot overstate that. There are many promising modalities in development, but the next breakthroughs will require rigorous natural history studies, meaningful endpoints, diagnosed and engaged patients, and collaboration across the entire ecosystem: academia, nonprofits, regulators, and industry.

Ash Jayagopal, PhD, MBA
Chief Scientific and Development Officer, Opus Genetics
30/07/26

Q. Could you please tell us about the background of Opus's RDH12 program – how it came to be, how the collaboration with the RDH12 Fund For Sight happened, and maybe a bit about the nature of the collaboration? If you're able to disclose any details on milestones, profit sharing, or governance structures, anything like that would be quite helpful for us to know.

A. I'll do my best. In 2021, Opus was founded in collaboration with the Foundation Fighting Blindness and Dr. Jean Bennett, the developer of Luxturna. Dr. Jean Bennett at Penn had also developed an RDH12 asset now called OPGx-RDH12, that had IP sublicence from the University of Pennsylvania. when developing that asset, we sought non-dilutive funding to further the IND-enabling work. And that's where we met the RDH12 Alliance. I used to work with Mat Pletcher, who is a co-director of the Alliance. We worked in pharma together at Roche. So that was probably the first route of introduction for me –the fact that I already knew one of the members of the leadership team of the nonprofit organisation. And from there, we spearheaded a collaboration to try to raise cost share and co-fund the development of the asset. As part of that, there's a joint steering committee. There are milestones that we've previously agreed upon, which underscores our commitment to each other to execute and develop the asset towards IND enabling studies and dosing of patients.

Q. Could you please update us on the current state or the latest progress on the RDH12 asset, if there is anything that you can disclose at this point in time?

A. Our latest guidance is that it's headed towards the clinic in Q4 2026, and I don't think we've announced where the trial sites will be – I think that's still in progress with the clinical team.

Q. Could you tell us about how the RDH12 asset fits into the rest of Opus's portfolio? Are there any synergies across the different assets?

A. Our first program was OPGx-LCA5, which is now in a pivotal trial, and that uses an AAV8 capsid, which is the same capsid the RDH12 program uses. So there are synergies in terms of manufacturing knowledge with that capsid. Also, AAV8 then is clinically de-risked for safety in many ways. So, we take those learnings from clinical trials in LCA5, which is also a form of LCA, to RDH12 and there may be learnings there with respect to informing clinical dosing and management of patients treated with the AAV8 capsid, so definitely some synergies there.

Q. What are the biggest challenges in advancing this program? Scientifically, as you mentioned, we are relatively derisked, the modality and rationale are somewhat proven. What other challenges have there been, maybe also in a commercial sense, in the context of rare disease – trial design, recruitment, endpoint selection?

A. Sure. Trial design and endpoints are fairly well-established thanks to well-documented natural history studies and treatment experience with LCA. Since the approval of Luxturna, we've gained a lot of knowledge about these patients in paediatric and adult settings. But translation has been hampered by a limited commercial opportunity, with major strategic pharma not considering the prevalence of RDH12 high enough to garner commercial interest. That said, companies that are able to stack rare disease assets together like us, like Opus or Rocket Pharma or someone like that, may be able to enjoy commercial success

because as rare diseases assets are stacked up into a large portfolio, the economics can be realised. And that's kind of what Opus was founded on. But on its own, as a single indication, it can be tough to raise money for that. Until a company is clinical stage, it's especially hard to raise venture financing or public financing for a program such as a rare disease asset. Opus, fortunately, is now clinical stage with at least two programs. And so that has improved our reputation, and confidence, conviction in the scientific community has allowed us to more readily obtain funding for these new programs like RDH12. We've largely overcome some of those barriers to commercialization.

Q. Just to drill down on the point that you made on having different assets for different rare diseases, as a form of diversification that reduces the risk commercially. From my understanding, many of these are gene therapies and if there is a correlation in terms of the scientific risk that makes the economics less attractive to investors, because there is the perception that if one asset fails, other assets may fail along with that – Is that just a perception, that's maybe not true in reality?

A. We don't know if it's true or not until we do the clinical trial, but there is a perception out there that one ocular gene therapy's failure may read through to another program. However I think experts know that each of these inherited retinal diseases is a completely distinct indication – different gene, maybe similar cells, different phenotypes, different outcomes, severity, rate of progression, age of onset. And so when you look at them all, kind of as uncorrelated in that way, but maybe with some commonalities with cell type or capsid or technology, I guess we meet in the middle, acknowledging that there are always risks to any new therapy. I think 90% of any therapy of any modality fails to get approval. So is ocular gene therapy higher risk than that? I would say no, because we have a local route of administration which minimises complications. That route has been explored for over 20 years now, so it's a de-risked route of administration. AAV manufacturing has become far more advanced such that the purity and safety of those drug products has been established. Toxicity of AAVs increases with dose, however, subretinal gene therapy is inherently a very low-dose administration compared to systemic gene therapies. And so some of those levers that we pull can actually overall lower the risk of an ophthalmic rare disease gene therapy program relative to other extraocular chronic or rare disease programs.

Q. You mentioned the subretinal delivery method, maybe this is an old perception, but we understand there is a risk of retinal detachment. Would you say that's something that has been addressed in terms of de-risking?

A. Subretinal administration detaches the retina, we must detach the retina in order to deliver the subretinal gene therapy, so I wouldn't call that a risk, that's a necessity of the procedure. However, within 24 hours, the retina sits back down, generally it does not stay detached unless there is a surgical complication. But that's not considered, in our view, a risk of the procedure, but rather just kind of a necessity. The retina can be safely detached for quite a period of time before vision-threatening complications ensue.

Q. The other gene therapy that is in the clinic for RDH12, the Chinese programme, uses a different delivery method, that one is intravitreal.

A. Innovec has an intravitreal capsid that has the potential advantage of penetrating the inner limiting membrane and getting delivered to the retina without the need for the subretinal injection or retinal detachment, so that's an exciting development in the field, we're going to see how that goes. The data that has been presented so far has been mixed, showing good tolerability, but not necessarily efficacy in all patients. Maybe some of the patients were too severe, at which point any therapy intervention may have

been too late. I haven't looked closely enough at the data to say for sure, but it's promising to see multiple treatment options for this indication, so we're happy to see that being developed.

Q. Moving on back to Opus, how receptive has the FDA been towards, maybe new endpoints or outcome measures, or anything novel that you're doing with the trial?

A. The Phase 1 trial is a safety trial so it's too early to say what endpoints we'll be using. We're always exploring novel and established endpoints such as BCVA and microperimetry. We're not going to shy away from anything that's established, but as we learn more about our treatment population for each disease, we're always willing to explore new endpoints. For example, for LCA5, we developed a virtual reality orientation and mobility test with Dr. Bennett at Penn, which had never been tried before and showed a treatment benefit for LCA5 patients in terms of their ability to identify more out of nine objects than pre-treatment, at various luminance levels. So we're always looking to innovate in that area if it shows clinically meaningful benefit for patients, but it's still too early to say for RDH12, what we're going to be doing there yet.

Q. Taking a step back to the regulators, would you say there has been a shift in the regulatory science over the past few years – Are they becoming more receptive towards new trial designs and outcome measures, is there more engagement between the sponsors and the FDA, etc?

A. I don't have too much insight on that because from our perspective at Opus, we've always enjoyed close collaboration with the FDA. The FDA funded our first clinical trial for LCA5. We've received all the paediatric disease and rare disease designations such as RMAT *(Regenerative Medicine Advanced Therapy)* and RDEP *(Rare Disease Evidence Principles)* from the FDA, which enabled close collaboration, so we've kind of always known them to be willing and collaborative participants in bringing about the best therapies for patients. I don't know if they're *more* receptive than they used to be, I feel like they've always given us the time of day and valuable input. You could really tell they're rooting for us. They realise that there aren't enough new treatments and there's a big unmet need here, and they've been willing to work with us on high-quality trial designs to advance these therapies. I have nothing but compliments for the FDA, they've been excellent to us.

Q. That's good to hear. Going back to the previous iteration of this report, which was written in 2021, one of the challenges spotlighted at the time was the lack of good preclinical models – it's a well-known problem in the ophthalmology field that rodent models are very poor models of the human eye, for example – and this sounded like a very insurmountable challenge at the time, but now we have two assets for RDH12 and many more assets for other IRDs in the clinic. So how do we reconcile these facts, that preclinical models were the big barrier to filing an IND but now we have quite a few assets that are already in the clinic.

A. It's not that any new models came around, but there are multiple ways to show that the therapy that one is developing has a reasonably likely benefit predictably in patients. For example, if we can deliver to an RDH12-deficient mouse the normal complement of RDH12, with gene therapy, to what should be the endogenous wild type level, that's something we could say is reasonably likely to predict some sort of benefit in the RDH12 patient, who is lacking any functional copies of RDH12 in a recessive disease. So those are the kind of extrapolations we're making with the models we have. No model is ever going to be great in terms of small animals for retinal diseases because these small animals lack a human macula with the cone-rich structures needed for central vision. The dog, pig, and NHP do have those structures, however, it's very challenging and not cost effective to develop disease models in these large animals. So we pull all

the levers we can to demonstrate safety and efficacy. We're not always going to hit perfection in terms of biology proof of concept, like in RDH12, but when we can deliver an enzyme specifically to photoreceptors at a physiological level, that's a good bet for us provided we can show that that's also safe.

Q. Moving on from gene therapies, knowing that Opus's bread and butter is gene therapies, but do you have any comments on other therapeutic modalities for the LCAs, for example, cell therapy, neuroprotection, optogenetics?

A. All of these patients are going to be at different stages of disease, which may obviate certain treatments and necessitate next-generation therapies, and late-stage patients are not going to benefit, of course, from gene augmentation to the extent that an early-stage patient or mid-stage patient would. So I'm really excited about the photoreceptor replacement clinical trials which are just underway at BlueRock/Opsis, and waiting to see the kind of treatment benefit we can see from next-gen optogenetics therapies. And it's great for providers to have more than zero options for their patients, but more ideally, patients at every stage will have some treatment option that can benefit their visual function. So I think there's a place for all of these technologies in the portfolio.

Q. Going back to RDH12, how big do you think the patient pool is for this specific asset?

A. I get asked that a lot but I wouldn't have access to anything that a thinktank or you guys don't have. But I'm going to say I don't believe the prevalence – I just feel like I've met too many people with RDH12 for it to be, 2,000, I think it's got to be 5,000-7,000, although I have no proof for this.

Q. One of the problems that we have heard of is that a lot of people don't get a genetic diagnosis, they just get an LCA diagnosis and stop there. I imagine that would be a huge barrier to any gene-specific gene therapy.

A. If you're at the NHS you should get a free genetic test, and I think the EU is better about it. But in the US it's mixed because the private and public providers are mixed, are disconnected, there's no centralised system. But the Foundation Fighting Blindness, for example, provides free testing to any patient that is referred for an IRD genetic test.
I think genetic testing will pick up when providers know that there is a potential intervention for their patient. Right now if the provider knows the patient doesn't have RPE65, or if this is some late-onset RP patient, it's highly unlikely that there's an approved therapy available for them, and maybe that's demotivating testing. But I think that's going to change in the next five years with treatments coming online for XLRP, hopefully Best disease, Rho, adRP, and several LCAs such as LCA1 from Atsena and hopefully LCA5 from Opus. Hopefully treatment options getting approved will improve the likelihood that someone will get tested.

Q. If I had a clinical diagnosis of LCA and I don't get a referral to the FFB, does that mean I would have to pay out of pocket to get tested?

A. It depends on your insurer, but generally your IRD specialist will know to contact the FFB if the insurance does not accept the testing. But generally, it's becoming more widespread, the adoption of genetic testing.

Q. Is it very expensive to get tested?

A. I think it's $2,000+ a test – don't quote me on that, but it is not trivial, especially when a patient doesn't even know what they have, so we have to do better there.

Q. Looking towards the future, what would you say are the next steps for this program?

A. I would like better prevalence estimates for sure, that would help make a better commercial case. The patient registries are decent thanks to the Alliance, it's not going to be hard to enrol in these trials. We don't have the preclinical proof of disease-modification that we'd like, because we don't have good large animal models. In many of our other programs, we have canine models of the IRDs that we can test – we don't have that here. So now it will just be the hurdle that everybody faces, which is demonstrating safety. Once we have established safety, there's a lot we can do in terms of exploring clinically-meaningful visual function improvements and structural improvements in patients, but it has to be safe before we can really investigate any of that.

Q. Beyond the RDH12 asset, looking at the IRD landscape in general, is there anything that we have not discussed that you think is important to capture?

A. No, we've touched on the hot issues of how do people get tested, where do we find these patients, and how do we accelerate rare/ultra-rare disease therapies that don't have as strong a proof-of-concept as we'd like. Those are the big ones.

Q. What are the priorities for Opus over the next few months or years?

We need to get four more programs into the clinic in the next two years, so that's going to be our focus, and we need to get LCA5 approved. It's going in a pivotal trial now, so everything's just about clinical execution now.

Q. We've mentioned optogenetics and cell therapy, neuroprotection, etc, what are your views on what you've seen in these other fields that might be applicable to RDH12?

A. Some of the gene agnostic therapies, the antioxidants, the N-acetylcysteines, and some of these agnostics would be good to investigate. There are some things that are naturally neuroprotective which could be useful.

Cecile Mejecase, PhD & Vitalii Kalynovskyi, PhD
Moosajee Lab, UCL/Moorfields Eye Hospital
5/8/2026

Q. Now that we have two therapies for RDH12 in the clinic, what's the importance of developing more/better RDH12 models, or is what we have now sufficient for the field's needs?

A. That's a good question. Definitely with more patients with RDH12, it's always better to have broad knowledge of what's exactly going on to treat patients. But it's still a good start to start with what we've got, definitely.

And I believe whatever models are currently available, they're not enough, because what we see in animals, for example, there are some mutant animals that don't completely recapitulate the phenotype of patients, so they're not perfect models, so there's still a long way for improvement.

Q. Just to take stock of what models your lab works on, there's the zebrafish, which may have been some time ago, there's patient-derived iPSCs, retinal organoids, is there anything that I've missed?

A. We also have stable lines (mutant RDH12) and recently we received a mutant mouse model, which we are currently adapting. We'll be using it in a month.

Q. Could you tell us a bit about your work on the pharmacological small molecules assessed with your lab's assay? Understand that there is NAC and a few primary amines but this is not published, so if there is anything that you can share.

A. That's exactly why we developed the mutant stable lines, several lines with several mutations for RDH12. We used these cells to test a range of different primary amines or some other small compounds which can potentially be used. We tested not only N-acetylcysteine (NAC), but N-acetylcysteine amide (NAC-A). So we tested on known cells, and according to our results, we selected the most promising candidates, which are NAC-A and two primary amines, which are hydroxylysine and polylysine. We tested their toxicity in vivo on wild type animals, and our next step is to test their actual effectiveness on mutant mouse models that we're going to do in the near future.

Q. Besides the amines, are there any other small molecules that you have tried on your assays? Is there a list of what worked and what didn't work?

A. The list of what worked is kind of short, it's just the three compounds we selected. Everything else didn't work. But it wasn't just amines, it was beta-cyclodextrin, which is a kind of vehicle compound for drug delivery, tauroursodeoxycholic acid, alanyl-histamine, and something else, and there was another compound that's used generally as antiepileptic, it just escaped from my head right now, but that data is published, but [pregabalin] was tested on zebrafish, so it was quite experimental.

Q. Are there plans to use the assays or compounds in other LCAs or IRDs, or other modalities for RDH12?

A. We're currently testing only on the RDH12 model, and depending how these molecules show effectiveness on the RDH12 model, we'll decide whether or not we should apply them to other models, because these small molecules, generally if we have retinal diseases, the first thought about small molecules

should be something like an antioxidant for general support, but this stuff that we use is more targeted towards RDH12-specific pathogenesis, that way it won't be directly applicable to all of the diseases, but if we find them effective in vivo for RDH12 retinopathy, possibly, maybe we will test them on other types of retinal degeneration.

Q. For the RDH12-specific compounds, do they target the protein directly? Is there a certain mechanism that you are testing?

A. It's not directly RDH12-specific, but in case of RDH12 retinopathy, the problem is under-functioning RDH12 protein, which causes the accumulation of all-trans retinal which is the toxic compound. So our small molecules are focused on detoxification of all-trans retinal, but with very different mechanisms.

Q. Looking at the lab's priorities over the next three years, how are you prioritizing RDH12 versus other IRDs?

A. In general, we have always one postdoc working on the project, so it's always in parallel to work for the other IRDs' projects.

Q. Would you say you still focus more resources on testing more small molecules with what you have now, or would you focus more on developing models?

A. Right now, it's more of testing those small molecules.

Q. Since we have some promising leads already, what would be the next steps, if it is successful in the mouse model?

A. If it's not successful in the mouse model, obviously we'll need to take a step back and look for other compounds to be tested and try it. And if they are successful, it will depend on the actual outcome how quickly they can be translated into some actual clinical trials. I cannot give any solid estimates, but if it works, we'll try to push them to clinical trials as soon as possible. But it will depend on the actual outcome that we receive.

Q. Do you have any comments or thoughts on other therapeutic approaches for RDH12? At the moment, we have two gene therapies that are already in the clinic. How would you rank the potential of small molecules versus other things like cell therapy, gene therapy?

A. I wouldn't rank them because our approach is not a substitution to gene therapy or cell therapy, it's more like augmentation, because again, these small molecules are designed to counteract altered retinol. So ideally if everything works perfectly for any interested parties, small molecules could be used in the whole process of retinal degeneration until the actual gene therapy is developed and applied. So, it's more like a first line of defence, first line of action in a case of the RDH12 retinopathy diagnosis. And later, the gene or cell therapy can be applied.

Q. In terms of the patient pool, the neuroprotective small molecules can be applied to any (early or late stage) patient?

A. We don't know yet. Again, it should be tested. But potentially, hopefully, yes. Because it will not cure the disease, but it will stop the progression of the disease. So, it can be stopped either on the early stage or on the late stage, but it just can be stopped in general, hopefully.

Q. Is there anything else about the LCA or IRD landscape in general, or your lab's work, that we haven't talked about that you think is important to mention or discuss?

A. Just in general, when you're working on RDH12 disease or like another IRD disease, it will always have a positive impact on all the diseases of the eye, because you could provide information of a therapeutic approach or something like that. So, whichever disease we are working on, it will have a positive impact on the general research and therapeutic approaches.

Q. So there's potential synergy between research for different diseases?

A. It's more of, a therapeutic approach that we can find that could be successful for another disease, for example, a specific AAV working better or non-viral therapeutic approach working well for one IRD, we can decide to try to apply it for other IRD diseases. So, it's more in general, it doesn't have to be specific in terms of the mechanism of RDH12. Like in our lab, we are working on specifically on the mechanism of RDH12, but all the research on eye disease can benefit from it.

For example, even those two gene therapies you mentioned which are currently in trials, they differ by the modality of delivery, like whether it's intravitreal or subretinal. Therefore, given the outcome, which will work best, which will be more effective, it will inevitably shape what will be our choice for choosing the therapeutic modality for other IRDs, by knowing which in general works better in the retina. So, if we at least know which works better for one IRD, we will improve our knowledge for all of them, in a way.

David Gamm, MD, PhD
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27/7/2026

Q. You mentioned that you and Dr. Celia Bisbach are developing an RDH12 project based on a new high-throughput live-imaging readout. Could you walk us through what this assay measures and what model system it's being applied to?

A. Yes, it's something that we've been looking at for a while now. So one of the things that we do is, obviously we're interested in cell therapies, and I'm essentially a cell manufacturer. What I do is manufacture retinal organoids, different retinal cell types. And I'm always interested in trying to make them more authentic, more high throughput, more reproducible, more rigorous. So essentially that's what my lab focuses on. And as we're able to do that better and better then we look for applications. And so the vast majority of what my lab actually does is developmental and disease modelling. So a lot of what we do in the laboratory is we look at what our cells can do, what our tissues can do, what we can do in vitro. We don't try to force a round peg into a square hole, there are certain things that are easier or that we can measure, and there are things that are harder to measure, a prime example being the very first disease I ever modelled, which was gyrate atrophy. And the reason I chose that was because it was an RPE based disorder, and RPE was at the time easier for us to grow in a model. It was easier to isolate in a pure form. And there was an assay available that was a colorimetric, biochemical assay and that you could use to measure ornithine aminotransferase levels. And so it fit. So as opposed to saying, I am going to model X and then do everything I possibly can to model even when it's not really in the cards for what we have available to us now, we tend to say, what can we do and what diseases are there out there that we think we have reliable measures for? And one of them is retinoid recycling.

We can do a retinoid turnover. And we published a paper with Melissa Skala some years back looking at optical metabolic imaging. And the retinoids have different autofluorescence, they have different lifetime fluorescence. And so that can be measured in real time in live organoids. And we can measure that very accurately, quantitatively. And so RDH8, RDH12 are enzymes that oversee one of those conversions that we can actively quantify and measure in an intact organoid. So that's where our interest began. We also have interests in certain diseases because we have patients or patient groups that come to us and say we'd really like you to develop something for us for that. So we don't necessarily develop gene therapies or genome therapies themselves. We work with people who do so. And we develop models for them that hopefully get them from a preclinical stage, R&D, to preclinical all the way to BLA because you really have to look at the entire landscape because you can get to a Phase 1 without having a release assay or a potency assay, but you can't get past that. So you've got to be able to have a lot of release tests and all these various things. And so for most companies, and even now, federal agencies to really be interested in taking a therapeutic all the way to Phase 3 and BLA, they need to be able to see that there aren't going to be any roadblocks along the way. And one of the main things for that is our availability of potency assays. And so those have traditionally been done in animal models, and that's being at least in the United States more discouraged, but still possible. But there's also limitations to those as well, too.

My personal view is that there's a role for every one of these model systems. There's a role for HEK cells for certain things, depends on what you want to measure and what your objective is. There's certainly a role for in vivo testing because it's a whole organism. But then there's myriad in vivo systems that you could choose from all of which have pluses and minuses. So the fact that we lean into one versus another doesn't make a whole lot of sense either. There's nothing that's magic about any particular one of them. We tend to do what's easy or what's publishable. And then from an organoid standpoint, they're human. So we work on human organoids and they have limitations and strengths as well. And so we try to broadly improve the strengths and address the weaknesses, but it can't be catch-all for everything.

But RDH12 is one that we think that does have the possibility for organoids to have a strong role in moving therapeutics forward. And again, it's agnostic in terms of it doesn't matter what the therapeutic is. It could be pharmacologic, could be a gene augmentation, could be a gene edit, base edit, read through, could be whatever it is. That could be built into the line. So for read through we could build a nonsense mutation and if it's a gene edit we can particularly build in a particular type of gene edit into a line. So if we can develop the potency assay and if we can understand and measure rigorously, quantitatively the effect of a therapeutic, then genetically we can build in whatever we want into that line and therefore have it be kind of a catch-all for whatever therapeutic you might be interested in measuring. So that's kind of our general approach. And in the process of doing that, we have active projects in gene augmentation, genome editing, base editing, read through, all these with companies and with other academics. That's our angle. And so when you contacted us, we were interested in doing this because we have what we think is a good hammer for this.

Q. So is this an organoid model of RDH12, this is what you're building. Are you aware of some of the work that has already been done in this space, because we actually funded work at UCL to exactly do the organoids?

A. Yes, we build our own. We've used other people's lines before. But our focus is on the assay.

Q. The work, for example from UCL, which was published didn't necessarily conclude that that was a good assay to be used moving forward. Now, you're saying we think we have a better way to do it?

A. We do.

Q. Okay. And why have you chosen RDH12, because you think it is amenable to this approach?

A. We have a paper out with Melissa Skala, so it's probably best to look at the paper, and we also presented it in at the last ARVO as well.[60] The conversion of retinol and retinal is the conversion that RDH8 and RDH12 oversee. So because we can assay that, we said, okay, how can we apply this assay? Because we're asked to model diseases all the time. And so we really have to have a hook. We have to have something that we think will really contribute in order to be able to kind of dig our heels into it. IMPG2 is something similar to that. We published a number of papers on IMPG2 and we now have a very extensive program directed at IMPG1 and IMPG2, essentially because we could build a good model system and that attracted funding and that attracted interest from other people. And so we kind of built around that. And then also I had a connection with somebody who was affected, whose actually daughter was affected by IMPG2 as well too. So these kinds of things kind of coalesce to form a focus. And so they happened relatively organically.

(Dr. Celia Bisbach) I'll add just another piece of why we wanted to make our own organoid model. We're engineering in a different mutation and that just kind of also dovetails into different therapeutic testing that we're doing in the lab because we have some existing other projects where we're trying to use read through therapeutics. And we figured we can engineer this line with a premature termination codon and apply what we've learned in those projects to RDH12.

Basically what we're looking at is the conversion of all-trans retinol to all-trans retinal. And what we discovered was that they have very distinctive fluorescence lifetime spectra. So we can measure all-trans retinol, all-trans retinal over fluorescence lifetime, and they have very, very discreet, almost punctate regions where they autofluoresce. So we're not feeding them anything necessarily and we're not fixing the tissue. These are live tissues, live organoids. And so what we're able to do then is to see in whole organoids where these are applied, a shift. So we can apply light. And we compared our organoids to explants from

mouse to show that they essentially acted exactly the same. And this can be measured so that we can take pure all-trans retinal, we take pure all-trans retinal, so we know what their signatures are in fluorescence lifetime. And we can show that they move on fluorescence lifetime and we can measure the amounts that they have. Essentially what we can do, so essentially what we can do is we can measure how much we have of one or the other. Now these are all wild type organoids that we published on here. So these all have normal RDH8, RDH12 in them. And we know that they have them because they're converting it. And the plan is to build in specific mutations into RDH12. We could also do the same for RDH8, but it's exceedingly rare. And then be able to use different therapeutics to show whether we've actually restored that and to what degree we have restored it. Because we're looking at the absolute function of the protein. We're not looking at something down the line. We're not looking at whether a photoreceptor has survived or doesn't survive because that doesn't really make a lot of sense because these are all late-stage foetal organoids and so people don't lose their vision. They're not born blind essentially with these diseases. So it doesn't make sense that they would have degeneration of their photoreceptors at such an early stage of development. But the biochemical defect is there from day one. And so the biochemical defect, we should be able to measure. And if we can fix the biochemical defect, then that becomes a potency assay that we can use to advance therapeutics. So too often in retinal organoid modelling, people divorce the actual defect from what they're looking at. They look at something way down the line. Outer segments being longer, shorter. Things that are completely indirect and that we can see in wild type organoids if we look at enough of them. So we like to take whatever the genetic defect is, whatever the protein product is of that gene and then assay that to the extent that is possible. And then if we can assay that, then we'll look at the next thing down the line and the next thing down the line. But not go from: here's a genetic defect, now we're going to look if the organoid is bigger or smaller with no connection in between. In this case, we have a direct connection with an assay specifically for what RDH8 and RDH12 do. So we have a system set up that should be able to help in the development and advancement of therapeutics that hopefully will have good predictive value.

Q. Thank you. That's very comprehensive and very detailed. I really appreciate you sharing this paper with us. So another question from me is that some of the researchers we spoke to for the previous iteration of this report back in 2021 mentioned that photoreceptors derived from iPSCs were unable to interact with the RPE cells. Is this still an unsolved problem currently?

A. So there's a lot of things it doesn't do, it's not hooked up to a brain. The answer to your question is yes. We have scaffolds set up to functionally integrate photoreceptors in RPE. There's no RPE that's growing. From an embryologic standpoint, it makes sense because the way that the eye is formed as an optic vesicle and then an optic cup, that's not how these organoids form. So if the question is are retinal organoids perfect retinas, the answer is no. They're not perfect. We grow them in a dish. They have never seen the inside of a living thing. It's amazing what they can do, but you have to be able to understand what their limitations are. So if your assay requires a functional intercalation between the photoreceptor outer segments and the apical processes of an RPE cell, we're not there yet. That's not something that we were able to do. Mice don't have a macula. But people still do AMD studies on them. So you have to be able to look at what the pluses and minuses of any system are. In this case, we're measuring the biochemical assay directly for RDH8 and RDH12. That does not require an RPE cell. Now if you want to be able to look at the whole retinoid recycling along the way, then you'd have to do some sort of addition to the model system so that you can make up for the fact that you don't have this intercalation between the two. But that's not what we're measuring. If we're moving on to a broader question between what can organoids do and what can't they do, you're absolutely right. There is a functional interface between RPE and photoceptors that we've looked at. I started doing this 20 years ago, and one of the first things we did was trying to grow these things together. And because it's a potential space, because there's no synapses there, there's no direct interaction. That's why when you get a retinal detachment, you always separate between the photoreceptor outer

segments and the RPE, because they're not held together by anything except internal ocular pressure. And if your ocular pressure drops, if you get phthisis, what happens? Your RPE and your neural retina fall apart. You need internal pressure within the eye to do that as well as fluid flux across the RPE. So it's the combination of passive and active forces that hold them together. That makes it difficult to do in a simplified in vitro system. You can make it very complex, but then the problem with making it very complex is then it becomes very expensive, difficult to assay and things like that.

Q. Regarding cell therapy in general, there are many ways you could think of how it could be improved. In principle you could prime the retina to make it easier for the photoreceptors to rebuild their connections, or you could inject photoreceptors and RPE cells simultaneously. What do you see as the main challenges and future directions for cell therapy for IRDs?

A. Yes, so those are all very good points and things that we're currently working on. So you look ahead to where are we now and where do we think we're going to need to be able to improve? I mean, technology or cell technology is no different than anything else. When people started making computers, they didn't make them initially on your wrist to do all the things that they do. They're giant clunky computers but then they had a purpose and they seemed to work. And so people worked on them and made them better and better. So the idea that everything has to be perfect day one is something that just doesn't work in technology anywhere, whether it's biologic technology or it's engineering or what have you. So you start where you think things can be safe and have a potential for improvement and then you look ahead to how can we refine this a little bit further. Being a cell manufacturer myself and having an interest in essentially making authentic cell types and human cell types out of the retina. Our biggest challenge was being able to make at scale authentic human photoreceptor precursors and to be able to tune those towards cones and rods and then to test them in multiple different systems. So we tested them in up to five different animal systems and showed that they survived, showed that they made connections. And then that was the basis for moving forward and having BlueRock and Bayer pick up the option and then currently doing the CLARICO trial. So along the way, we can dream up a thousand ways to do things better. But there's pluses and minuses.
So you have got to say, well, I can do these three things over here. But now that is going to cost millions and millions of dollars more money, maybe take five more years to do. People aren't going to do that. They don't have the runway to do that. So they want to know what the simplest thing that we can do that's safe and that has the potential of helping patients is. And if that shows promise, then we'll make things a little more complicated. Or we'll find the areas there that maybe fall a little short, put R&D into trying to making those better. And that's a long answer to get to your question, which is what do I think the biggest area for improvement is. And that's the retina we're putting it into. We know exactly the cells we're putting into patients. We know everything about them, we know how to grow them, how to freeze them, how to thaw them, we know how they act. We know how long it takes them to mature, we know how long their axons grow. We know what types of synapses they make. We know when they make the synapses. We know all these various things about the cells we're putting into patients. What we can't control is the retina that's going to accept them. We're limited. Because we can do an OCT, we can do imaging, we can do functional testing, and we're blessed to be able to do a lot of that, a lot more than a lot of other tissue systems are capable of doing and doing it non-invasively. So we get more information from about the patient's retina that we're hoping to treat than most folks get in cell therapies for their brain or their heart or their liver or whatever it is. Although they can biopsy those, so that helps sometimes and we're not in a position to be able to biopsy tissues. So the idea of being able to better pick patients that have a better opportunity to be able to accept donor cells and be able to create new connections and function afterwards to some degree that improves their activities of daily living. Or if that's not possible, trying to make them so, like you said, priming. And so those are all things that we're currently working on. And we think show promise. But then that makes the whole process much more complex. So now you're talking about perhaps a gene therapy

plus a cell therapy. And the FDA and the European agencies aren't going to look at combination therapies like that if the individual therapies don't show safety and efficacy. So it's a very good point that you're making. There's a long way to go, just like the Wright Brothers' first glider off of a sand dune. There's a long way between that and supersonic jets. But there's an iterative process for doing that that is more economically viable. And we're more likely to understand what we're doing as opposed to just throwing things against the wall and hoping that they work.

Q. Coming back to the production of photoreceptors. As we understand, they are a lot harder to produce at scale compared to RPE cells. Could you comment on what the main challenges were in that regard and how the collaboration with Fujifilm helped overcome these problems?

A. Well, the company I started, Opsis Therapeutics, is a subsidiary of Fujifilm Cellular Dynamics (CDI). And so we're all based here in Madison. James Thomson, who is kind of the father of embryonic stem cells and also one of the co-founders of IPS cells, he's retired now, but he's at UW Madison. He was one of my mentors. And he started Cellular Dynamics International here in Madison. The idea there was to take all the knowledge we had here at UW Madison, all of James's knowledge, and be able to create at scale a wide variety of different cell types and to be able to cryopreserve them and use them for research purposes. And then in 2016, Fujifilm bought CDI and it became Fujifilm CDI or FCDI. And they just built a giant facility here in Madison. And then BlueRock is also an IPS-based company. And so they also manufacture IPS-based cell type products. And those are probably the two largest IPS cell manufacturing companies in the world. And we combine forces to do this particular trial, to generate photoreceptors. My laboratory had built a lot of internal IP on how to do that. And then what FCDI had was scalability. So they had a lot of IP on how to scale and cryopreserve cell types. And they've done it across multiple cell types, but they've never done it for the retina. So we combined what we knew from retina through Opsis therapeutics, which is again, the subsidiary of FCDI that handles ocular cells in particular. And then we were able to combine all of that knowledge. And then when we partnered with BlueRock, they brought in all of their knowledge as well, too. So it's decades of experience and hundreds of IPSC scientists all working together. So it was a really, really incredible opportunity and experience that we had to be able to do this. And we've learned a ton from it. And so we are in a position where we can produce pretty much any cell type in the retina at scale and cryopreserve it.

Mathew Pletcher, PhD
Chief Scientific Officer, Arbor Biotechnologies & Board member, RDH12 Fund for Sight
13/07/2026

Q. Since 2021 there has been quite a lot of encouraging progress in the space. We understand the disease biology more now, and importantly there are two gene therapy candidates that are in the clinic right now. To what extent do you feel that the challenges in RDH12 therapeutic development highlighted in the previous report (e.g. no consensus outcome measures/endpoints, lack of good preclinical models) have been solved in progressing these programmes?

A. Part of the answer to that question is: Do we actually need them? Where we've headed is in a positive direction, from a regulatory standpoint, and in how we think about progressing genetic medicines like the gene therapies we're doing for RDH12.

For instance, when we talk about animal models, really the question becomes, what are we trying to de-risk or understand with an animal model? And at one point, these were quite useful, particularly when we're trying to understand the basic biology of human disease. But when we're talking about developing a genetically-targeted therapy for genetically-defined Mendelian disorder, these models become much less important. Because with a gene-replacement therapy, there really isn't a question that you're asking of these animals other than, are you able to get the therapeutic to the site of action at a physiologically relevant level? And you don't really need a true animal model to do that. In fact, actually, I would say using a mouse in that system is always going to be an imperfect system. Even if you had a great representation of disease biology, the mouse eye isn't anything like the human eye. That's why so much of work in therapeutics for ophthalmology are done in animals like rabbits, for instance, just because the eye is so much different than the mouse. And so, when you want to talk about biodistribution or exposure levels, the mouse probably isn't the right animal system to use anyway. So, I think that's the thing. These are great tools for learning, but for therapeutic development, particularly for the kind we're talking about, I don't know if it's terribly useful.

And then on the other thing, as far as endpoints go, there too, I would say it depends on the outcome that you're looking for. The interesting thing in the therapies we're talking about, in the conditions we're talking about, you know, gene therapies for LCAs, what we've seen across the board in all of these trials across different genetic forms of diseases that actually don't need really sensitive endpoint measures to be able to detect the efficacy of these gene therapies. If you've seen the videos of the individuals treated with Luxturna, the gene therapy for RPE65, you know, this is a situation where you go from an individual who can barely stumble their way through a simple maze on the floor to someone who can easily navigate it. It's not something that actually requires a statistical test to show efficacy. When I was at Roche, I was fortunate enough to be part of a program for spinal muscular atrophy (SMA), for risdiplam, the small molecule risdiplam. And there too, it was one of those things where you did not need a statistical test. These were infants that normally passed away within the first year and a half of life, let alone be able to support themselves, sit up, stand, walk. And so the moment you saw these infants be able to reach all these developmental milestones, you already knew that you were having an impact well beyond anything that you would expect for the disease's natural course. So that's where, you know, that's where I say, I don't think these are the challenges holding back RDH12 drug development.

Well, okay, I'm going to take a step back and be really critical of the space. I would say that these are the kind of things that have been put in front of patient organisations as a way to make it feel like they're doing something because they can fund it. It's something that an academic can go to a patient organisation and

say, okay, here, you give me a grant and I can make this mouse for you, or I can do this thing because this is what you need to eventually get a drug, as opposed to actually having them contribute to making the drug.

Q. From your involvement with the Opus programme, what was the FDA's guidance in terms of the requirements for preclinical models, as well as the statistics from the trials?

For the animal model, this is where I'm really happy to see the evolution in regulatory science. When Opus first met with regulators, they really insisted on some kind of efficacy study in an animal model for them to progress. It would have been a hugely expensive model, or it would have been a hugely expensive study in an animal model that in no way represented the natural course of RDH12-LCA in humans, but it was something that they insisted on, almost as a checkbox exercise, to move to the clinic.

What changed between then and now is really this understanding that, in fact, that is a waste of money and time that really does not provide meaningful guidance on whether or not a drug is going to work in a human being. And that includes, you know, [this] year the FDA released new guidance around this idea of a probable mechanism. And it really gets at that idea that if you're treating a genetic disease, and you're treating it by actually directly addressing the genetic cause of the disease, you don't need to do an animal model. And so we went back and said to the FDA, we meet the standard, we do not need to do additional animal work. Plus, there's already work in the literature by other people that shows that even in this imperfect animal model, gene replacement can protect the retina, so there's no need for us to waste the animals to waste time doing it, and they read it, and so we were able to move that programme forward without showing directly efficacy with that specific drug product in an animal model.

So that's where I say I think we're moving in a very positive direction in recognising the limits of these animal models, and the fact that actually it's not particularly useful to spend the time and effort and money to develop them and demonstrate any kind of benefit in them with our drugs.

And so the second part of your question, the statistical, that's a little bit easier to answer just in the fact that they don't get into those details until you have data. You can talk loosely about, you put forward the different kinds of tests that you're going to do, and here we're talking about, again, using a floor maze test. In fact, actually, we're using a virtual version of that, that floor maze. But what's going to be sufficient to see approval, that's a conversation to be had once you've run the trial and have data. And there too, I think we've seen a great deal of flexibility. You know, in the Duchenne muscular dystrophy space, right, we have multiple programs that have been approved solely on the fact that they've been able to increase dystrophin levels. They haven't ever, in fact, some of those products have never, ever demonstrated any impact on the disease itself. Just the fact that the biomarker that is directly related to the underlying cause of the disease was sufficient for approval. The fact that they increased that biomarker.

Q. That's great progress. Going forward, what are the challenges for gene therapies, and especially these two programmes? Is it recruitment for trials, funding, etc?

A. You mentioned funding. I think the most frustrating thing is that with genetic medicines, we have the tools now to treat a wide range of genetic diseases, genetic retinal diseases just being one of them. But we lack a commercial model that can support the development of these therapies. And I think that's the real shame of it, is that there's sort of always this understanding that actually if we knew how to cure disease, there would always be a way to do it, to fund it, to finance it, to bring it forward, because, of course, why wouldn't you? If the science supports it, there's always a path. But what we're finding is, particularly in the

rare disease space, the economics are such that both from the cost of development and then the value on the other side once you get it approved and commercialise it, those two sides of the equation aren't equaling out in a way that allows for investment and development of these therapies, despite the fact that we have ample proof that they work, that they could save vision, save lives. And so I think funding is by far the number one issue.

The second one, which is more scientifically-related, is delivery, exposure. In the case of the work that we're doing with the RDH12 gene therapies, you're talking about delivery by a subretinal injection, which means that you're only covering a small portion of the retina with the drug. And so a significant portion of the retina will see no benefit and would continue to deteriorate with time and so you're not really getting the full benefit of that. And then additionally, subretinal injection does cause a retinal separation, potentially you do lose some of the retina from that standpoint as well. It's not a completely benign procedure. The benefit outweighs the risk of the procedure, we've seen that across all of these different gene therapy programs, is that the benefit you get from the delivery of the AAV certainly is much more significant than any damage you get from the surgical procedure. But it's a retinal separation that has its own issues associated with it, but it's the best way we have to deliver the virus right now. People have been trying for at least a decade now to come up with an AAV that can transduce the back of the eye through an intravenous injection that would be both less disruptive and also give you a much broader coverage of the eye. Largely, our ability to evolve a virus that does that efficiently has not resulted in success. There is the one programme coming out of China that uses an intravitreal injection. The results from that trial, I'd say, overall are positive, but are quite heterogeneous in the sense that there are some patients that look like they respond quite well, some that don't seem to get any benefit at all. I would suggest that that's likely due to inefficiency of transduction through the inner limiting membrane to the retina. That just goes to show that we still don't have a virus that can efficiently do that. And so, from patient to patient, you get this wide variability in benefit due to that fact. Typically, it's more immunogenic to inject directly into the vitreous, so some of the viruses that have been developed in the past, you get really strong immune responses if you do intravitreal injection with them. So we don't really have that solved. And that goes for most of the other targets in the body. If you're talking about developing gene therapy for the CNS, you know, the SMA gene therapy, that's delivered intrathecally because we don't have a good way across the BBB. And so you don't get an even biodistribution across the brain. AAV has been fantastic. It's really creating an avenue for us to develop these therapies in a way we wouldn't have without it, but it's also still limiting as well. So I think the biggest challenge we have in really making maximum use of genetic medicines is we're still looking for the perfect delivery mechanism for that. People would love to have a non-viral way of delivering it, but we still haven't found a way to get non-viral delivery to work pretty much anywhere other than liver. And so, we're just continuing to scramble for any sort of way to effectively deliver these large biological payloads.

Q. Going back to the issue on funding, the general commercial model for drug development is an asset that comes out of a lab, an academic lab, goes into a commercial entity, maybe a biotech, and then it gets hopefully bought out by a big pharma company in order to run trials. The funding model with Opus doesn’t work that way?

A. There's lots of different ways that these things can be brought forward. We've seen that actually you can develop these therapies, particularly for rare diseases, outside of a big pharma environment. The first approved gene therapy in the US, Luxturna, was developed by Spark Therapeutics, a venture-capital backed biotech, and they were able to take that all the way through to approval prior to being bought by a large pharma, in this case Roche. So they saw that from beginning to end as a biotech. And so there's lots of paths, it doesn't necessarily require that, and there are lots of interactions along the way to keep these things alive and going. Luxturna was heavily funded, in the early days, both by research grants but also through

foundations. Foundation Fighting Blindness was essential in funding a lot of that early work that eventually became Luxturna, and seeing it through those early research-based stages.

Opus at this point is a publicly traded company, so they're able to access financing from different kinds of markets than just venture backed capital. I think the semi-unique aspect is that we, the patient organisation, are directly partnering to help fund that, but I'd say that too is not entirely unique. We've seen across industry lots of unique models where patient organisations have gotten heavily involved. The Cystic Fibrosis Foundation is one of the more famous ones because they've got one of the best success stories there with Trikafta. They funded all of that early work that Vertex did on those drugs and participated in funding that all the way through clinical trials, and as a result have participated in some of the financial benefits that came from developing the drug and then used all of that money to then spin off and pay for new drug development programmes.

FAST is a patient organisation for Angelman Syndrome. They decided to spin off their own company to start developing an oligonucleotide therapy that was first developed in an academic lab, so they built a small biotech that they directly funded, developed some initial data, and then eventually sold that company to Ultragenyx. And Ultragenyx is now starting a pivotal trial to get that therapeutic approved. Ultragenyx itself is a company built by Emil Kakkis, a longtime researcher/scientist in the lysosomal storage disease space, who has developed numerous drugs himself, enzyme replacement therapies for those lysosomal storage diseases, and was able to build that into an entire company now that in turn is working with patient organisations like FAST to develop new drugs. So it's an interesting ecosystem with a ton of different kinds of models.

At the same time, too, we've seen this go horribly wrong. A year or so ago, there was a lot of press around Taysha, a venture-backed biotech company who had licensed a whole huge portfolio of gene therapy programs from Steven Gray's lab, and most of those programs were directly funded by patient organisations. When that company was founded, they were raising money and they were telling these patient organisations they were going to move all ~30 programs into the clinic. It very quickly became clear that Taysha was not going to have the resources to move all of these forward so they started to announce that they were not moving these programmes forward but at the same time, similar to some of the stories we've had in RDH12, they announced that they were not giving those programmes back either. So it began a very public fight over the ownership of those programs, because even though they were built out of an academic lab, they only existed because of patient funding, and now they sat in this biotech that wasn't willing to let them go, and it's not a terribly uncommon because really that entire portfolio of programmes that Tayshia had shrunk down to a single one because that's all the money they had to support, so they're just moving forward their Rett Syndrome therapy right now, while the rest of those just sit on the shelves.
So lots of paths in this space, but it all really comes down to the fact that everyone is scrambling to find the dollars to bring these things forward, despite the fact that there's ample evidence that they're going to work.

Q. What about compassionate use programs, or Expanded Access as the FDA calls it, which doesn't need a full clinical trial for the asset to be brought forward?

A. The thing is, you still need a drug to do that. The cost just to manufacture a clinic-quality gene therapy runs into multiple millions of dollars. You could apply for Expanded Access but the company that owns the programme doesn't need to do it, because there's lots of risks that make it unattractive but you still have to find a couple million dollars to make the drug anyway. You also have to find a physician or a center that's willing to administer a highly experimental drug that may not have all of the safety de-risking and other sorts of assurances that makes these facilities comfortable to administer such a treatment.

So I think Expanded Access seems like a good idea, but there's just so many obstacles in the way that ultimately it really hasn't been a path that's been particularly useful to folks.

Q. You said that just manufacturing the product, for it to be of clinical quality, it's a multi-million dollar cost. What does that cost go into? If you already have a factory, I assume that's not the problem, and if you already have an asset that is in trials.

A. If the asset is already in trials, then there's very little incentive for a company to make the drug available through compassionate use because it actually endangers the success of the trial. The clinical trial is tightly controlled, tightly monitored, the criteria for the patients is thoughtful and directed to trying to produce a signal that can actually demonstrate the benefit of it. You have all the safety controls in place and you can ensure that those safety controls are happening.

Now you take that drug out and you give it to someone else who doesn't meet the inclusion criteria, who may have pre-existing conditions that could cause issues that don't have the same safety controls, and you give it to them and they have some kind of adverse event, that can completely shut down your clinical trial as a result. So in fact, what most companies ask is to let the trial run, because that's the surest way to actually grant access to the broader community, is to let them complete the trial, because if the funding is there and the trial is already running, that legitimately is the best chance to make it broadly available to the greatest number of patients. So that's where I say if that's the case, then you don't really need compassionate use and it potentially endangers the entire effort.

Where you'd hope for a compassionate use is where there is no trial and no other access to it, but then you have all these other barriers that get in the way.

Q. Looking beyond gene therapy at the other modalities, especially the next-generation modalities like cell therapy or optogenetics, how would these fit into the RDH12 landscape?

A. With optogenetics, there's a lot of promise there, a lot of hope in the idea that you could potentially grant sight back when there is no light sensitive/light sensing cells left in the retina, that you could be completely devoid of photoreceptors and still be able to restore vision and that it's mutation-agnostic, that it doesn't matter what genes are responsible, what the issue is, they can be applied to everyone. So there’s a huge benefit there. I think the question that still remains is what kind of sight does that actually return? What's the quality of that sight? What's required for it? The first generation of optogenetics, it was the light-sensing proteins they used that were not the most efficient, as a result you had to wear big goggles that actually had to really intensify the light and focus it on the back of the eye, and just that process itself actually did damage the back of the eye because putting really intense light on the back of the eye is a risk factor, so it wasn't great. And even then you're not really getting true vision. They have sort of next-generation versions of these light-sensing proteins, but it's early days. And I think we're still trying to understand what that actually is going to give you from a vision standpoint. I think the promise of these next-generation proteins is they get rid of the goggles, just normal ambient light is sufficient, but it’s early days, we don't know if that's going to be the case or not. So, we’ll see.

Cell therapy is an interesting one, I'd say, but very slow-moving. For the longest time, the only thing that you could do was RPE cells, the retinal pigment epithelial cells, those were the only things that you could really culture in a dish and think about transplanting into the eye. And even then we still haven't really been able to run a successful trial with an RPE cell therapy, even though, I remember when I was at Pfizer, we had an RPE cell therapy effort going on and that was 15 years ago. So it's been a while and we're still

struggling to make that work. But what you really need is the ability to transplant photoreceptors, if you really want to restore sight in a large majority of these diseases. Because even if you have an RPE defect, what that ends up manifesting is the death of the photoreceptors. And that's where you lose vision. So you ultimately need to be able to replace photoreceptors. It seems like we might be getting close to being able to culture photoreceptors, but I don't believe we're close to having that at an industrialised scale, let alone turning that into a therapeutic., thinking about how long we've been working on RPEs and still not getting there. I'd say that's still, seems still quite a bit off into the future.

Q. Could you point us to which labs are culturing the photoreceptors?

A. So there is one company in India that I'm aware of, it's founded by an RDH12 family, EyeStem. I believe that's the name of Jogin's company. But there's others as well.

Q. Eyes on the Future has a patient registry, and there's been quite a few natural history studies done in the past five years, and there's one very large-scale study Uni-Rare. Could you give some comments on the progress in this space, any challenges, or a general overview?

A. I take a bit of a contrarian view here as well. I would say this once again falls into the space of busywork that's given to patient organisations. When it comes time to recruit patients, the interesting thing is you can do all this prep work trying to build a patient registry, but the reality is once a clinical trial actually starts, patients come out of the woodworks. A lot of these families who are largely quiet and don't get involved in advocacy, that you don't even know about will show up once there's actually something that could be done. And if the patient numbers are there, you'll be able to recruit quite easily. I think like something for RDH12, talking to folks, most of the centers out there who see these kinds of patients feel like they already have enough patients that they know of to fill the trial that we're talking about.

On the natural history side, until just recently every regulator insisted that you do a placebo control trial, so natural history. In my work in the past, we did use natural history studies to do power calculations to try to understand how many patients would be necessary to see a certain improvement on a certain metric. And so it gives you an idea of what the cost of a clinical trial would be. But ultimately, those were really useful in edge cases where maybe because the patient numbers were low and the commercial case was low, then potentially you could suggest that actually the degeneration was fast enough that you can see it in a clinical trial. But honestly, what those data tended to do more often than not was give companies a reason not to run the trial. That it was one of those things where we would do the analysis, we would look at the natural history, say the disease was too slowly progressing and the patient number would be too large that it didn't make sense to do the trial. So something like SMA, certainly we use the natural history to be able to show and clearly demonstrate the kind of gains we're seeing, you couldn't possibly expect to see this just randomly, because again these patients are so severe, but ultimately we ended up having a placebo control in one of the trials. And that was the same thing I know with Biogen's oligonucleotide, eventually they just did a placebo control and that's ultimately what allowed them to be approved independent of the natural history study. It's a great academic exercise, it can be useful somewhat in planning and thinking through clinical trial design. But is it absolutely necessary? I don't think so.

Q. On a related point, there was a number that Opus quoted in terms of the prevalence of RDH12-LCA, do you have any thoughts/comments on the prevalence or the epidemiology of the disease?

A. From my own reading of the literature and calculations, I estimate that there's probably around 2,000-5,000 patients in the US and you'd expect similar numbers in the EU. Across the LCA landscape, RDH12

is not the rarest, it's very close to RPE65 actually. There's one gene in particular, CEP290, that has by far the largest prevalence in the LCA space. But RDH12 is not the rarest of those. And so I think we're still talking about a couple thousand patients.

Q. Is there anything that you think we've missed in the RDH12 or general LCA space? Also, what are your priorities as RDH12 Fund for Sight in the next few years?

A. I am incredibly hopeful for what the next couple of years will bring. It's been a long time coming, but I do fundamentally believe we're on the verge of having a transformational therapy for the first time for our kids and other kids like ours. I think the experience of all the other gene therapies for LCA tells us that this has a high likelihood of working. I think the data coming out of the Innovec/China trial tells us this is going to work. It goes back to what I was saying, they had highly variable results, but there are patients where it clearly worked, indicating that the type of results that we've seen in RPE65 LCA, in GUCY2D LCA, in AIPL1 LCA, in LCA5, all of it, we're seeing the same kind of response in all of those. And I think from the Innovec trial data, we're going to see the same kind of results in RDH12 as well, that it is not just going to be the freezing of degeneration, the halting of the progression of disease, it's actually going to be restoration of some degree of sight. That seems to be a common feature across all of these and everything that we know about RDH12 and everything that we've seen so far says that that is possible here as well. So I am so incredibly anxious for us to start treating patients and see whether or not that plays out to be the case, but I think everything is lining up to tell us that's true.

What's the future for us? I think that the key is how quickly can we get this out as broadly as possible? That if in fact we start treating patients in the clinic and we start to see the kind of results that I just described, how can we work with Opus, with regulators to turn that into a broad approval as quickly as possible? Because that's the thing where ideally we're not running this trial for a year and a half, two years, and then want to run another pivotal trial for another couple of years and only then launch it as a commercial product that everyone can access. My hope is, is that we can generate the data necessary in this Phase 1, that we could already start to have conversations about a quick accelerated approval on this.
And again, here, I think this is moving faster than the industry is typically used to, but I think there's precedent for it now. And I think we should continue to push on that as patients. And that's where I think we play a big role in that too, is to make sure that our voice is heard, not just by the regulators who approve this, but by the companies that put it forward to put pressure on them to actually challenge and try to get that approval sooner than maybe they usually do. Because I think that's the key, the reality is we're talking about a small handful of patients that are going to get treated in the clinical trials, and there's so many more that are waiting for this. And every day that goes by, they're going to lose more of their vision. They're going to lose more of their world that's never coming back. And so we need to make that happen as soon as possible.

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5/8/2026

Q. Before we go into the results of the IVB107 trial, could you tell us about the background of the asset, about how and when you started developing this asset and how the collaboration with Innovec happened?

A. As mentioned by Sylvia, we have been in this track for many years. I remember my first RDH12 patient who was diagnosed by me, both clinically and molecularly, about 15 years ago, or more than that. So we are together with our patients and we find if we couldn't do anything, they will lose their vision gradually. That's why we started trying to find something we can do to help. Our team has led the development of IVB107, also known as PUMCH-E101 – the first part, PUMCH, is the initials of our institute, and E means eye, 101 means the first generation/ the first one – which is a gene augmentation therapy for RDH12-associated retinal degenerations. This program was collaborated with Innovec because in the past years they have this engineered AAV capsid, which we can have the intravitreal injection and get a very good transduction of photoreceptors. That's what we needed.

So we started this program about four years ago. First we tried different capsids to find the best one, and then we did cellular level expression studies and then picked the best two and then two animal models with both rat and mouse. And eventually, we did have good efficacy and safety and then we moved to a non-human primate, and the last stage is investigator-initiated trials, and now we have finished two stages. In the first stage we enrolled 10 patients, with single-eye injection. The longest follow-up is one year and 10 months, up to now. And the second stage is after all the 10 patients finished one year follow-up, after review by our independent group of scientists and our IRB, we are approved to start the second stage, which is the second eye treatment, and there are eight participants which are suitable for the second eye treatment.

We have eight participants for the second eye as a contralateral eye studies. And now we have finished nine months for some of our eight patients, and we still need more time for the follow-up. And last month, the special medical zone in Hainan province announced our translational studies will be continued as real-world studies in Hainan province. So we are looking forward to have more participants all over China and all over the world maybe to get more data from different cohorts to let us have more data to approve confirmation of both safety and efficacy.

Q. You mentioned that Innovec engineered the AAV capsid that is able to target photoreceptors even though you inject it intravitreally. Most of the IRD gene therapies that are being trialed right now are delivered subretinally. Could you comment on the pros and cons of intravitreal versus subretinal injection?

A. For the typical RP, retinitis pigmentosa, the degeneration starts from rods, the fovea, and progresses centrally. At the mid or late stage, patients still have enough cells around the macula area, and also most of the patients will have a good retina structure. But for RDH12, this is not the case. RDH12 patients begin very early. In our patients, 80% of them are diagnosed as LCA or early onset severe cone-rod or rod-cone disease. Especially the macular involvement, which have the typical atrophic layers in the central area, begins very early. So for that anatomical structure, if we do subretinal injection around that area, it will not help the patient, and we have a high risk of retinal break, because it's very thin, that area is very thin. That's why other groups, they started very early trying to find a cure of RDH12 gene therapy. If the route of

administration is subretinal, it will have failed. So finding the right vector was the key for our development, the vector capsid we used can meet our needs. That's why we can do this successfully.

In addition, actually we have a series of capsids, engineered capsids. For RDH12, we want photoreceptors to be transduced, but for other indications we may need the RPE cells or Müller or bipolar cells to be transduced. We have different vectors, different capsids. So up to now, we have trialed different indications besides RDH12, which give us confidence that the vector, the engineered capsid by intravitreal delivery is generally safe.

Q. Innovec is also running an optogenetics trial, IVB105 for retinitis pigmentosa. We were wondering if this asset is applicable to other IRDs besides RP, either LCAs or RDH12, since optogenetics is meant to be mutation-agnostic?

A. For optogenetics, which is for late-stage patients even when they have no photoreceptors, when a gene augmentation will not work for late stage RP. In China, optogenetic studies, I think there are several that are undergoing clinical trials in Phase 1/2.

For Innovec, they use their own capsid, they expressed a wide band spectrum of opsins, which can cover a wide frequency of light. So I think that will be another potential treatment for most of the patients. IVB105 will be going to a trial later this year, maybe in September, we are in the IRB process now. But for optogenetics, the advantage is we don't care what kind of gene, and even you do not have any photoreceptors, that's the advantage for optogenetics. However, because it bypasses the normal phototransduction, the vision may remain at a lower resolution than the natural vision because we have so many photoreceptors normally. And also, some need external visual devices like, I cannot remember the name, but a company from France. Also, because the phototransduction is different, cortical adaptation and rehabilitation may be required for some time because we don't know the patient experience. I have heard some patients' experience when they have this optogenetics therapy, but different patients have different experiences.

Q. So for the trial, in the immediate next steps, you're saying it's starting in September, is this specific to RP patients only?

A. Because this will be the first trial, for safety reasons and for consistent results or analysis, in this stage, only late stage RP will be enrolled, yes.

Q. Moving back to the RDH12 trials, what we have seen published online is the week 36 interrim results. As you mentioned, the trial has continued since then, but what you've reported is already quite encouraging. One of the challenges in IRD gene therapy trials is that the best corrected visual acuity (BCVA), which is the FDA's gold standard outcome measure, might not capture the degeneration phenotype of different IRDs, so it's not always the best outcome measure to measure the treatment effect for IRD therapeutics. A lot of effort has been put into designing new outcome measures, including the MLMT and structural endpoints established using OCT. IVB107 has shown quite good improvement versus the contralateral eye on BCVA, a 7.5 letter improvement and some of the patients even got 10 letters. For LLVA, I think there were some with 15 letters, so I understand that this is actually good enough for the FDA. Does this mean that BCVA is actually a good enough measure for RDH12, or do we still need to develop other LCA-specific outcome measures?

A. For this study, there are two parts, preclinical and clinical. So we submitted our data, and then we thought we will publish the preclinical first, and then the clinical. We submitted our [preclinical] paper to the journal, they reviewed it and we did all the, answered all the questions and the modifications. I think it's all ready to be published, and then one reviewer said, we feel no. We don't know why. And then we went for another round of submission, and now we are doing revisions, but for the clinical part, we have already finished the draft, so, sometimes I don't know the journals, their thought process, but we surely want to share our data.

With the longer follow-up period, we are more confident. For example, we have one 10yo child, we treated the worse eye first, after one year, and now after one and a half years, the treated eye in the first year is going up, the highest improvement for BCVA and LLVA, both more than 15 letters, and the untreated better eye are going down, up to 19 letters within one year. That's very good evidence to show you both the natural history of the untreated eye and the efficacy in the treated eye. That's not the only case, we also have a patient with very bad baseline vision, who cannot see any letters at all on the baseline. But after a year, and now a year and a half, the treated eye improved to seven letters. Also both the patient and the caregiver reported good orientation, they're happy because for example, before treatment, when they go to their garage, the boy cannot find the car, and now the boy can find the car, and it was difficult for the boy before treatment to get the food he liked using chopsticks, but now it's very easy for him. It is difficult to quantify these findings, that's one of the challenges, as we call it outcome measures as you mentioned before.

In our studies, we enrolled both adults and children. It's difficult for us to sometimes measure, younger patients with nystagmus, it's very hard. Now only basically a visual acuity or low luminance is one of the outcome measures, but there may be some others easier for the kids. For example, we will start a trial, a clinical study for differentiating different items, different shapes and different sizes, and this can be quantified, so maybe it will be a good outcome measure.

But particularly for RDH12 patients with LCA or early severe onset cone-rod dystrophy, it's very hard to measure the structural change. It's not that that means no structure change, but we do not have a sensitive tool to measure it. For example, OCT is not sensitive enough. Now we have adaptive optics which they say can measure the photoreceptors, but it needs good fixation. If you cannot fix well, you cannot have a good scan, you cannot measure the photoreceptors. So it's still a problem for us trying to find some structural evidence for improvement. But for some disorders, for example, I'm also doing a trial for RPGR patients. They are typical RP. They have some preserved fovea, the central macular photoreceptors. In the beginning at the baseline, we can see the OCT is blurred, but after treatment, both with the improvement of visual function, we can see the change of the photoreceptors even under OCT.

So, the challenges for RDH12 are a lot. For example, the patient, we do not have a strong natural history data set, but we are doing this, and we hope we can share our data for RDH12 retinopathy, Chinese patients, natural history results also for different subtypes. We still need more tools to quantify this.

Q. Your trial uses a contralateral control. In the past few years, much has been said about the lack of natural history studies, both as a control in trials, and also to understand the disease in general. The first part of that might be solved by a contralateral control using the untreated eye, but we still need natural history studies to understand the progression of the disease in general?

A. Yes. During our development of this gene augmentation therapy, we did have our own natural history data. We didn't share it because we are still doing analysis, but we do have that in hand. We did on both eyes, symmetrical analysis, and we have the results that in both eyes the symmetry is very good. Based on

this, even though the disorder may be different in different patients, but for a particular single patient, if both eyes are symmetrical, we can use the contralateral as a control.

Q. Still on the outcome measures, this trial also uses 4-HNE in the aqueous humor as a clinical marker. We see that the results are encouraging as well. 6 out of 7 patients showed a very big reduction in the 4-HNE levels, and 2 of the patients normalised to control levels. Would this marker would be applicable to other modalities e.g. optogenetics and cell therapy for RDH12 and maybe other LCAs if they also have elevated 4-HNE levels?

A. I think so. This biomarker is generally an indicator of retinal photoreceptor toxicity and damage. It will be a general indicator, but I do not know for sure for optogenetics, because for optogenetics it's not to cure anything, it's just to bypass the regular phototransduction, so I do not know about that. But for other gene augmentation, if we rescue the photoreceptors, if we make a disease photoreceptor get healthy, I think we can have the biomarker showing the biological improvement for the photoreceptors.

Q. Going back to BCVA, you published that there were 2-3 patients that showed a very large treatment benefit (10-letter improvement). Is there anything in common between these 2-3 patients that benefitted the most, is there any explanation or is it just the phenotype heterogeneity?

A. Generally, if a patient has more photoreceptors preserved, we will have better results. For example, in our Phase 1, we have an adult near 30 years old, with a very narrow central visual field. It's like 1-2 degrees, very narrow, but there was enough photoreceptors in that area for rescue. After injection, his visual acuity increased dramatically. Around month 9, he gained 30 letters, but only in that area. There was no improvement of visual field, but under that narrow tunnel vision, the visual acuity improved. Also for the patient when we do pre-baseline examinations, if a patient has a thicker retina, it means they have more photoreceptors, the visual function improvement will be better. That's one indicator for a better outcomes/ results.

Q. So the earlier we get these patients treated, the better the potential improvement.

A. Yes, that's what we want to say. But because most RDH12 patients are early-onset, only 20% of the patients' phenotypes will be like typical RP, most of them are early and severe. That's why when we started the real-world studies, we will enroll patients as early as six years old, if they are LCA or early severe.

Q. We note that the adverse events were quite mild, or moderate at worst. Would you have any further comments on the adverse events that were observed?

A. Yes, we are happy to see that the drug is generally well-tolerated. There were no DLTs, there were no severe adverse events, the events we observed, one is mild inflammation. So under our steroid strategy, both with oral and the topical, it's under control. And the second is intraocular pressure elevations, which are related to steroids, but it's also under control. There are no other adverse events related to treatment. For example, there's someone who said, during the period of follow-up, they have a headache, maybe it's not related to the drug, because they have a cold, something like that.

Q. Looking back, what have been the biggest challenges in this programme?

A. So during this development, we did not have a good disease model, because both the mouse model and the rat model, they can show some biological defect, but there is no phenotype showing as the humans, so

it's one of the challenges. That's why we also use patient-derived iPS and retinal organoids as one of the disease models to test the vector, the safety, and the rescue potential.

Another one is funding, where you do not have money, you only have ideas. That's why I want to thank our patient organisation for their support. The funding for these studies come from, some part from the patient organisation and some part from our institute's support. Without them, we could not have done anything.

Also, for a rare disease, commercialisation of the product is also a big challenge. So we want to thank the policy of the Chinese regulators for this rare disorder. They allowed us to translate our novel technology, this gene augmentation therapy, into a real-world setting. So patients who are qualified, if they have a biologic RDH12 defect/mutations and after evaluation we think they have more benefit than risk if we give them the treatment, they can get the treatment in Hainan province, in Bo'ao.

Q. Is this a special zone where you can run certain clinical trials? What makes it special?

A. [For the RDH12 therapy] It's not a clinical trial, it will be a real-world therapy. All our data of these 18 eyes and all the preclinical data was revealed and we were approved to treat patients in Bo'ao.
It's a medical intervention and under the regulation/supervision of Hainan administration, and also, we'll report all the data. For example, if a patient goes there to be treated – we will have all this, how to get there, what's the treatment, how can we do the follow-ups – we will have all this released soon, and we'll report all this data to the government, and if there are any severe adverse events happen maybe it will be stopped, but it's a treatment under close supervision. It's hard for a rare disease, for the patient, they do not have time to wait for another five years, get this drug to be approved after, you know, Phase 2, Phase 3 and all these long periods of times. The other thing is we do not have the funding to finish all these trials. So this is a special circumstance, for this rare disease and this novel technology, but we are not allowed to do the treatment in [the rest of] China.

Q. You mentioned that you used a mouse model and a rat model. In 2021, you highlighted the importance of preclinical models, especially animal models for therapeutic development. You also said if the funding allowed, you would want to create a pig model or a knock-in mouse model for RDH12. Has there has been any progress on that front?

A. If we can create a pig model, it will be valuable because the size of the eye, surgical anatomy, and retina structure are closer to those of a human being than rodent eyes, but we did not get that funding. That's why we used organoids from patients, we'll get blood or a small piece of skin from the patient and we reprogramme it into iPSC and differentiate it into a retinal organoid. But it's not a replacement for animal models, it's only a supplement because we do not have a good animal model. I don't know if there are any groups in the world that created a large animal model, like a pig or something else. But if they do have one, we are happy to share our vectors to try to see what happens.

Q. You mentioned there were non-human primate models that you used in the IVB107 work. Am I understanding correctly that this is just a general NHP model? So it's not RDH12-specific and it was just used to test the vector, the transduction of the photoreceptors?

A. For the non-human primate, they are normal monkeys. We use these models to test safety only because they do not have photoreceptor degeneration, so for example the safety within the eye and the whole body.

Q. What are the main gaps, in terms of preclinical models for RDH12, that are left? The pig model would be one because of the similarities to human eyes, while organoids are still not a replacement for animal models. So it would still be worthwhile to develop animal models?

A. The traditional retinal organoids were only the neurons. There were no immune cells and no vasculature, which is not a real mimic of the retina. Now we can do complicated retinal organoids, we can have a retinal organoid and a layer of RPE, and also vascular growth into the organoid, which is more like a real human retina. It's complicated and time consuming, but it's possible now.

So for a preclinical package, I think if we can use a small animal, e.g. a mouse or rat, and a large animal e.g. a pig, plus the human tissues, it will be perfect.

Q. What are your R&D priorities for the next few years, in the next five years or so? It can be RDH12 or other conditions.

A. Based on the advantages of this intravitreal-injectable vector, we'll do choroideremia which is also a blinding condition for patients. Also we'll do cell therapies. We will try cell therapies for RP patients later this year. It will be a Phase 1, and once restarted, this one is restarted because it was granted as fast track in China by Chinese regulators. We'll use iPS-derived photoreceptors, immature photoreceptors injected under the retina where it would mature and connect to the bipolar cells and also underlying RPE. We are looking forward to doing the trials and to see the safety and efficacy, for both the gene therapy and the cell therapy. And also optogenetics, as we mentioned before.

Q. Is there anything that we've missed? It doesn't have to be RDH12-specific, for example, mutation-agnostic approaches are also getting more progress. So is there anything about the general IRD landscape that you think we've missed, but is important to capture?

A. For the general landscape, they are reports of gene editing for some particular phenotypes, if they have a dominant disorder with a hotspot mutation, we can correct this mutation by editing the genome. It will be a method of rescue. Currently there are no ongoing trials, but I think there will be. Also for some dominant disorders, gene augmentation will be not enough. There are trials for reduction. It's a dominant disorder. Their trials will do, step one is suppression of the toxic protein, and then give a replacement of the good wild-type protein. Uh, I think this will be, you know, another good choice for patient-based reduction.

And there are also small molecules. For example, there are small molecules which can correct the misfolding proteins, that will be nice, I'm looking forward to that. There are a lot of things coming soon. We think, because our patients will have early stage, mid stage, late stage, and some will have virulent stage. For the virulent stage, maybe we'll use the neural links, help them to percept that, the vision and see the world. I think there are a lot of new stuff coming.

I'm also interested in the patients in Europe, outside China, if they are interested in the trials we are doing. And the real-world studies will come soon in Hainan, how can we help them? We are interested in that because we have something good for patients. I think it's good to have the availability for everyone.

Q. Since we're talking about genetic variants and hotspot mutations, are there certain RDH12 variants that are correlated with disease severity/progression or treatment response?

A. I don't think there are specific mutations that will cause a more severe phenotype, but for the treatment outcomes, it's closely related to the severity and the stage of the disease when the patient gets treated.

Q. Thank you so much, Dr. Sui. We will reflect your comments in the report, especially that final point about getting your work more widely known outside of China, in Europe, possibly to make the therapies available to patients outside of China, so we hope that this report will be helpful to that and a step to bringing the science out of China as well.

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17/8/2026

Q. Taking stock of the work that has been done in endpoint/outcome measure validation for IRDs since 2021, how would you describe the work that has been done in this space? Has there been an acceleration, and if so what factors caused this, or has it been more of a culmination of work that has been coming along since a decade ago?

A. I'm not so sure if it has accelerated. There are many more papers out there today than there were a decade ago, but most of the outcomes have been not only designed but also validated over the last 20 years, so it's not recent. For RDH12, we recently published an updated look at the disease, I believe it was in IOVS, you can look into it, where we use a number of readouts, both structural as well as functional readouts. That's probably your best way of getting precise information of what's happening for RDH12 specifically. You have to be careful with RDH12 on what type of readout you end up using in a clinical trial, and that is true for most retinal degenerations, of course. But the readouts are already available to us. And they include, as I said, structural readouts such as optical coherence tomography, as well as functional readouts. Specifically for RDH12, it will have to be colocalised to the structure, and that's what we published in the paper. Whether that's accepted by the FDA in a clinical trial or IND submission or not is still to be tested.

Q. To follow up on that, you have characterised the specific regions of the retina that are more preserved relative to other LCAs. As you mentioned just now, we may have to adjust for this – Is this done at the outcome measure level or is this done at a patient-by-patient level?

A. It's patient-specific.

Q. So that involves imaging the retina?

A. Importantly, the functioning of the retina, the areas where there is preservation will have to be examined. And in general we know the areas that are relatively preserved and the areas that could be targeted with a subretinal intervention if we get to do it. So it's not only the areas that have preservation, but the areas that have preservation that are accessible to the procedure, and they will have to be described both structurally as well as functionally.

Q. Does this have implications for treatment windows?

A. Yes, so patients who enter a clinical trial, maybe not the sentinel patients, but the patients where you expect to test a readout of efficacy, will have to be carefully selected.

Q. Could you comment on the pros and cons of structural endpoints versus functional endpoints?

A. Structural endpoints are, by definition, objective, so that's probably a good thing. Usually the transitional zones of degeneration are complicated. In a disease like this they are not yes/no transitions. They are transitions with a lot of structural complexity which makes interpretation, for example, complicated. The interpretation of that is complicated, and that is a negative. And the second negative, which is relevant to trials, is the speed of change over time. So the rates of change are not necessarily within the typical window of a clinical trial of two years. They do change over time, of course, and that also depends on the window of time where you're looking at the disease. If you're looking early enough, things happen, basically. If you

are viewing the disease at the time point where things have already happened, then the changes in those transitional zones that everybody wants to have as readouts is very slow over time. If you've read the paper, the hope is that functional readouts may be able to detect acute changes in vision. If the history of gene augmentation in LCA tells us anything, it is possible that that can be detected in weeks, not years. So that's the beauty of doing functional assessments. The negative part is that not every patient is going to be able to do the needed assessments, so they will have to be carefully selected as I have said before.

Q. Moving on to the functional measures, we know that there have been some assets that are being advanced even though they didn't meet their primary endpoint, which is mostly BCVA, one of them was MeiraGTx, they're moving forward with their X-linked RP asset even though it failed on vision-guided mobility. We were wondering if you have any comments on this kind of situation, when they fail to meet the primary endpoint but have good enough data on other endpoints.

A. Well, that's a very complicated conversation with the agency. They have expectations that not necessarily meet what we see in the clinic, what we see in these diseases. For example the expectation that you should include acuity, even low-contrast acuity. The expectation has to be based on science. Unfortunately in diseases like this, specifically RDH12, the change in acuity is not reflective of the primary mechanism of disease, so it would be great if we have a change in acuity, but I wouldn't be expecting that. It depends on many things. Acuity is a very imperfect measure. And it has a major issue in the sense that it is reflective of where the patient is doing that task for visual acuity, so I suspect that's the same thing that happened with X-linked RP. If the expectations are unrealistic from a scientific point of view, then you don't get an improvement.

Q. Would it be fair to say that, we're hoping that with better degeneration-phenotype-specific endpoints as the primary endpoints, it would hopefully result in a better-designed trial with better chances of success?

A. Right, the problem is that it may not be accepted by the FDA, but there's nothing that we can do about it. We have been struggling with that with every single one of our gene therapy trials.

Q. One last question on outcome measures before we move on to natural history studies – We've talked about structural endpoints, do you have any comments on patient-reported outcome measures, for example the VFQ or more broadly things like the WHO quality-of-life measures?

A. Those are great and they have to be used, and it's one way of, not bypassing, but addressing the issue of having an approved treatment – to combine multiple measures to substantiate efficacy and of course safety as well. Patient-reported outcomes are at the top and are accepted, so they have to be used for sure in the design of a trial.

Q. Is there still work to be done here, either in science or advocacy?

A. There is always work to be done. But there are tools that can be used today, and if you have a trial that should not be the rate-limiting step. We should use the tools that are available instead of spending the next 5 to 10 years developing a wonderful patient-reported outcome that will never be used. I would favour using any of the ones that are available rather than developing a new questionnaire. Validation of these is not trivial. Patient organisations can do that with proper instructions, they can help develop things that are specific to the disease.

Q. But perhaps that's not the immediate priority?

A. If things move forward, you should not wait for perfection.

Q. Moving on to natural history, in the last report there were only short-term natural history studies and retrospective data for RDH12. What do we have now and what do we still not have? Is this still a major priority?

A. What we have is enough in my view.

Q. From conversations with other KOLs the FDA seems a bit less worried about having a placebo control for trials now. Also we can use the untreated eye as a control.

A. The FDA does not, in general, accept the contralateral control. But yes, the contralateral control is what we use in the clinic for disease that is otherwise infrequent. The contralateral would be ideal but is typically not accepted by regulatory bodies.

Q. Do we know why?

A. No, and that is a question for them of course.

Q. We're also aware that there is a Uni-Rare study. It is an international, multi-centre, prospective, longitudinal natural history study, and RDH12 is a key target for that. It is going to end in 2029/2030. This is the largest natural history study for RDH12 that we're aware of. Is this the catch-all experiment? What other remaining blind spots are there, or what else do you think is not covered by this study?

A. The Uni-Rare study is approaching these diseases with a set protocol. Whether that protocol would be useful in a clinical trial, I don't know. I suspect that that could be the limitation, that you're obtaining data is that is very useful and wonderful but not useful for the specific questions of a trial. And that is a question for the Foundation Fighting Blindness. We are part of Uni-Rare and I know the protocols, and the protocols are appropriately rigid because that's what you want, to standardise it and to have comparison with other diseases and it will portray the natural history appropriately. Whether you can use that information in the design of the trial or use the same readout, the information for sure, the readout, that I am not so sure.

Q. Looking at the overall landscape of RDH12 as well as other IRDs, do you think that there is anything that we have missed that you think is important to capture?

A. Again in the last paper that we published in May we made the case for the things that are needed. It is important to fine-tune some of the readouts thinking about the eventual clinical trial. How to fine-tune it? Probably in a short few months of observation of patient-specific readouts that are specific to RDH12. But it's pretty much what we published. But for example, the [interrater] variability of some of the readouts that would end up in the protocol would have to be explored in the short. Again this is something that can be done even as you are conducting the trial.

Q. You mentioned that we have enough information on natural history. Something that is also relevant in that context is quantitative systems pharmacology and computational models in general, which can also help with dose-response estimations. Do you see a role for that in RDH12?

A. It's wonderful to have a computational model to predict where the next change would occur but that's not going to make or break a clinical trial for this disease. But it's the idea, if you could for example estimate where the change is going to occur within the window of a clinical trial, the window of observation in a clinical trial, that would be fantastic. I'm not so sure with the information that has been collected if that is possible in the short term. We are talking, if this is going to happen, it is going to happen within a year. And I don't think we have that luxury. For the most part we are missing critical windows because of the severity of the disease. The windows of intervention that could be critical, we are missing it, which is early in life. But that, again, is not relevant for the trial because in this type of design you won't include, at least initially, younger patients. You're going to start with first adult, and then young, perhaps adolescent patients. But modelling the early disease is critical to understand the disease better and to deliver the treatment at the right time. But I'm afraid we are missing that and that is not an easy thing to solve. And I know that there are proponents, colleagues of ours that are very invested in trying to model. And we have done it, both with AI and without AI. We have modelled retinal degeneration behaviour in various diseases. The paper we published recently explored the movement of the transition zones, not in RDH12 but in general. So that is something that can be modelled, for sure.

Q. So if I understand you correctly, there's great potential, but it's probably not going to be very consequential in the short term.

A. That is correct. For sure, the answer is yes, there is potential. So if you can make a prediction that is consistent across the spectrum of severity of these diseases, then that's fantastic. But it's not going to be easy.

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