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Authors

Duncan, Jacque
Bowman, Angela
Laster, Amy
et al.

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Perspective

Inherited Retinal Degenerations and Non-Neovascular Age-Related Macular Degeneration: Progress and Unmet Needs

Jacque L. Duncan[1], Angela Bowman[2], Amy Laster[2], Claire Gelfman[2], David G. Birch[3], Shannon E. Boye[4], Stephen P. Daiger[5], Lucian del Priore[6], Donald J. Zack[7], James T. Handa[7] and the Foundation Fighting Blindness Scientific Advisory Board

[1] Wayne and Gladys Valley Center for Vision, Department of Ophthalmology, University of California, San Francisco, San Francisco, CA, USA
[2] Foundation Fighting Blindness, Columbia, MD, USA
[3] Rose-Silverthorne Retinal Degenerations Laboratory, Retina Foundation of the Southwest, Dallas, TX, USA
[4] Division of Cellular and Molecular Therapy, Department of Pediatrics, University of Florida, Gainesville, FL, USA
[5] Human Genetics Center, Epidemiology Dept., School of Public Health, The University of Texas Health Science Center at Houston, Houston, TX, USA
[6] Department of Ophthalmology and Visual Science, Yale School of Medicine, New Haven, CT, USA
[7] Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Correspondence: Jacque L. Duncan, Wayne and Gladys Valley Center for Vision, Department of Ophthalmology, University of California, 490 Illinois St., San Francisco, CA 94158, USA. e-mail: jacque.duncan@ucsf.edu

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Inherited retinal degeneration (IRD) disease and age-related macular degeneration (AMD) are leading causes of irreversible vision loss and blindness. Although significant progress has advanced the field in the past 5 years, significant challenges remain. The current article reviews the accomplishments and research advances that have fueled the development of treatments for patients with IRD and AMD, including the first approved gene-augmentation treatment for *RPE65*-related retinal degeneration and complement inhibition therapies to slow progression of geographic atrophy (GA) in AMD. The article outlines opportunities to address gaps and unmet needs that should lead to additional progress toward the development of treatments for patients with IRDs and non-neovascular AMD in the future.

Introduction

Inherited retinal degeneration (IRD) diseases cause vision loss when genetic variants result in progressive dysfunction and death of rod and cone photoreceptors. IRDs share some features in common with age-related macular degeneration (AMD), including progressive loss of photoreceptors and association with genetic risk factors. Both AMD and IRDs represent some of the most challenging diseases in ophthalmology. However, advances in vision research have

expanded our understanding of the mechanisms of vision loss and identified pathways that could be targets of treatments to slow the relentless progression to vision loss. The US Food and Drug Administration (FDA) approval of two complement pathway inhibitor therapies, which slow the rate of geographic atrophy (GA) lesion growth,[1–3] represents a major research advance for AMD-associated GA, based on research demonstrating the relationship between the complement pathway and AMD pathogenesis. This achievement is impactful because both are now in the clinic in the United States, representing the first treatments shown to slow the progression of GA.

The first gene augmentation therapy in all of medicine to receive approval from the FDA, voretigene neparvovec-rzyl, was demonstrated to be safe and effective, improving vision in treated patients with IRD with a diagnosis of *RPE65*-LCA.[4] That development led to dozens of gene augmentation clinical trials for IRDs, most of which were safe, but which did not proceed to phase III trials or FDA approval due to the numerous challenges associated with development of treatments for IRDs, including enrollment of rare patient populations, relatively slow and chronic rates of disease progression, and the lack of suitable outcome measures.[5–8] Furthermore, additional longitudinal studies have suggested that gene augmentation for *RPE65*-related retinal degeneration was not a cure but was accompanied by progressive perifoveal retinal pigment epithelial atrophy in a small subset of treated eyes in the pediatric population.[9–11]

Despite remarkable progress, IRDs and non-neovascular age-related macular degeneration remain among the most important unmet needs in ophthalmology.[12,13] This article builds on prior manuscripts that have described gaps and opportunities in the IRD field[14–16] and represents a summary of the current laboratory-based translational and clinical research landscape of the spectrum of IRDs and non-neovascular AMD, as determined by members of the Scientific Advisory Board of the Foundation Fighting Blindness, the leading non-governmental research funding agency in this space. Progress and major achievements over the past 5 years, gaps in the field, and priorities for additional research are described below.

Research Advances in IRD and Non-Neovascular AMD

Since 2018, a number of significant studies of disease mechanism, natural history of disease progression, and potential therapies have advanced research in both IRD and non-neovascular AMD. The focus in this review is on non-neovascular AMD and GA given that neovascular AMD has had several approved treatments available for decades, and, up until last year, there were no treatments available for GA.

Genetic Causes of Disease

Thousands of variants in more than 300 different genes can cause IRDs, and, with advanced DNA sequencing, it is now possible to identify the underlying genetic cause in 60% to 80% of affected patients.[17,18] Estimates have suggested that approximately 20% of IRD genes are yet to be linked to human disease, although they are likely to contribute to disease in relatively small numbers of individuals[19] depending on the population tested.[17,18] The tools for understanding human genetics and genetic diseases have improved profoundly over the past 5 years.[20,21] Deep sequencing and long-read sequencing[22] have advanced to telomere-to-telomere sequencing. Single-cell sequencing and other single-cell "omics" are now commonplace and have provided new insights into cell heterogeneity and cellular responses to injury and degeneration.[23,24] Artificial intelligence (AI)-assisted modeling of protein structure and function are now in use and are likely to improve our understanding of the impact of specific mutations.[25,26] Extremely large human genetic databases are available,[27] and variant and mutation-specific databases are growing rapidly.[28] Government-funded initiatives like ClinGen Clinical Domain Working Groups establish gene-disease associations and evaluate variant pathogenicity.[29] These developments are not exclusive to IRD research, but all have advanced the field. In addition, the number of genetic factors that contribute to the risk of non-neovascular AMD have continued to expand, benefiting from genomewide meta-analyses and transcriptomic approaches,[30–32] and a major focus in AMD research should be to understand the mechanistic contributions of genetic variants that have already been associated with AMD.

Mechanisms of Disease

There has been great progress in characterizing cellular and molecular mechanisms of IRDs and non-neovascular AMD over the past 5 years. This has led to gene-specific clinical trials for approximately 20 IRD-related genes (Table 1) and FDA approval of 2 drugs to slow the progression of GA in AMD.[1–3]

Table 1. Gene and/or Mutation Specific Gene Therapy IRD Clinical Trials

Gene Target	Product	Modality	Phase	Sponsor	NCT Number
ABCA4	SAR422459	Gene therapy	1/2	Sanofi	NCT01367444
CEP290	Sepofarsen	Antisense oligonucleotide	2/3	ProQR/Sepul Bio	NCT04855045
	EDIT-101	CRISPR, Gene therapy	1/2	Editas Medicines	NCT03872479
CNGA1	VG901/AAV2.NN-CNGA1	Gene therapy	1	ViGeneron	NCT06291935
CNGA3	AAV2/8-hG1.7p.coCNGA3	Gene therapy	1/2	MeiraGTx/Janssen	NCT03278873
	rAAV.hCNGA3	Gene therapy	1/2	Tubingen Hospital	NCT02610582
	AGTC 402/AAV-CNGA3	Gene therapy	1/2	AGTC	NCT02935517
CNGB3	AAV2/8-hCARp.hCNGB3	Gene therapy	1/2	MeiraGTx/Janssen	NCT03278873
	AGTC 401/ rAAV2tYF-PR1.7-hCNGB3	Gene therapy	1/2	AGTC	NCT02599922
CLN2	RGX-381	Gene therapy	1/2	REGENXBIO	NCT05791864
CLN5	NGN-101/AAV9.hCLN5	Gene therapy	1/2	Neurogene	NCT05228145
GUCY2D	ATSN-101/AAV.hGUCY2D	Gene therapy	1/2	Atsena	NCT03920007
LCA5	OPGx-001/AAV8.hLCA5	Gene therapy	1/2	Opus Genetics	NCT05616793
MYO7A	SAR421869	Gene therapy	1/2	Sanofi	NCT02065011
ND4	rAAV2-ND4	Gene therapy	3	Huazhong University of Science and Technology	NCT03153293
	LUMEVOQ/rAAV2/2-ND4	Gene therapy	3	GenSight Biologics	NCT02652780
	LUMEVOQ/rAAV2/2-ND4	Gene therapy	3	GenSight Biologics	NCT02652767
	LUMEVOQ/rAAV2/2-ND4	Gene therapy	3	GenSight Biologics	NCT03293524
	NR082	Gene therapy	1/2	Neurophth	NCT05293626
PDE6A	rAAV.hPDE6A	Gene therapy	1/2	Tubingen Hospital	NCT04611503
PDE6B	CTx-PDE6b AAV2/5-hPDE6B	Gene therapy	1/2	Coave/Eye DNA	NCT03328130
PRPF31	VP-001	Antisense oligonucleotide	1/2	PYC Therapeutics	NCT05902962
REP1/CHM	4D-110 AAV.hREP1	Gene therapy	1/2	4DMT	NCT04483440
RHO	QR-1123	Antisense oligonucleotide	1/2	ProQR Therapeutics	NCT04123626
RLBP1	CPK850	Gene therapy	1/2	Novartis	NCT03374657
RPE65	FT-001	Gene therapy	1/2	Frontera Therapeutics	NCT05858983
	HG004	Gene therapy	1/2	HuidaGene Therapeutics	NCT05906953
	AAV2/5.hRPE65	Gene therapy	1/2	MeiraGTx/Janssen	NCT02781480
RPGR	AGTC-501 rAAV2tYF-GRK1-hRPGRco	Gene therapy	1/2	AGTC/Beacon Therapeutics	NCT03316560
	AGTC-501 rAAV2tYF-GRK1-hRPGRco	Gene therapy	2/3	Beacon Therapeutics	NCT04850118
	AAV5-hRKp.RPGR	Gene therapy	3	MeiraGTx/Janssen	NCT04794101
	4D-125/AAV.hRPGR	Gene therapy	1/2	4DMT	NCT04517149
	BIIB112	Gene therapy	1/2	Nightstar/Biogen	NCT03116113
RS1	ATSN-201	Gene therapy	1/2	Atsena	NCT05878860
	AAV.RS1	Gene therapy	1/2	National Eye Institute	NCT02317887
	LX-103	Gene therapy	1	Innostellar	NCT05814952
USH2A	QR-421a	Antisense oligonucleotide	1/2	ProQR Therapeutics	NCT03780257
	QR-421a	Antisense oligonucleotide	2	ProQR Therapeutics	NCT05085964
	QR-421a	Antisense oligonucleotide	2/3	ProQR Therapeutics	NCT05176717
	QR-421a/Ultevursen	Antisense oligonucleotide	2/3	ProQR Therapeutics/Sepul Bio	NCT05158296

Note: Inclusion in this table does not necessarily indicate that a trial is active.

Single cell transcriptomic and epigenomic maps of the developing human retina and various animal models—both normal and those with various degenerative conditions—have provided insights into the mechanisms responsible for IRDs.[23,24] Given the large number of genes and gene variants that can cause IRDs, and the challenges inherent in developing gene-specific therapies for each genetic form, an important priority is to identify downstream mechanisms and pathways that are common to multiple genetic forms of IRDs, with the hope that this understanding will aid in the development of therapies that are gene-agnostic. For example, increased understanding of outer retinal metabolism is leading to the exploration of promis-

ing new metabolism-based therapeutic approaches.[33] In addition, characterizations of several neuroprotective pathways to prolong survival of photoreceptors and RPE cells have identified novel potential therapeutic targets that could be helpful to patients regardless of the underlying genetic cause, including patients with non-neovascular AMD.[34,35]

Advances in techniques to develop retinal organoids have created novel disease models and platforms to enable understanding of disease mechanisms and drug discovery.[36,37] Organoid-based models have been generated from the cells of patients with clinically characterized IRDs. The transformational development of clustered regularly interspaced repeat (CRISPR) techniques has further enabled the development of these cell-based models in either 2D (monolayers) or 3D (organoids), driving the creation of variant retinal models without the need to procure cells directly from affected patients.[38–40] Both can be used for numerous applications, including high throughput screening of molecular tools to target specific retinal cell types (e.g. promoter screening) or to evaluate treatments for retinal diseases.[41]

Clinical Features of Disease Progression

Clinical research in AMD has benefited from a consensus definition of imaging features in AMD,[42–45] and deep learning algorithms have identified novel measures of disease progression.[46] The use of AI to characterize disease progression in non-neovascular AMD is extensive[47–53] and has been recently reviewed.[54] Because IRDs are rare, most ophthalmologists—and even most retinal specialists—have limited experience diagnosing or managing patients with these diseases. In 2016, the Foundation Fighting Blindness created a Clinical Consortium of medical centers with expertise and infrastructure to diagnose and care for patients with IRD.[6] In 2017, the Consortium launched its first natural history study of patients with autosomal recessive rod-cone degeneration associated with biallelic variants in the *USH2A* gene. Because variants in the *USH2A* gene are the most common genetic form of syndromic and non-syndromic autosomal recessive retinitis pigmentosa,[55] the Rate of Progression of *USH2A*-related retinal degeneration (RUSH2A study NCT03146078) study provided the opportunity to build infrastructure of the Foundation Fighting Blindness Clinical Consortium with a standard protocol, certified personnel, and a coordinating center to collect and analyze outcome measures in study participants over 4 years of follow-up. IRD experts at 16 study sites worldwide evaluated functional changes in visual field, structural changes as measured by optical coherence tomography (OCT), and patient-reported outcomes (PROs) in >100 patients. The results of the RUSH2A study have been shared with the scientific community[55–62] and representatives from regulatory agencies and industry by the Retinal Endpoints for Disease Initiative (REDI) working group to characterize changes in outcome measures over time that can inform clinical trial study design.[61] Along with defining outcome measures that can be deployed in multicenter natural history studies of disease progression or in clinical treatment trials, the Consortium has investigated ancillary outcomes, including measures of rod function[57,58] and high-resolution measures of retinal structure[59] and function.[56] Deep clinical phenotyping of this genetically well-characterized cohort has provided insights into the impact that different disease-causing variants in the *USH2A* gene have on retinal and auditory tissues.[63,64]

The Consortium has also launched additional prospective natural history studies of IRDs associated with disease-causing variants in *USH1F* (RUSH1F study, NCT04765345), *EYS* (ProEYS study, NCT04127006), and *OAT* (GYROS study, NCT05312736). In addition, the Consortium-led UniRare study (NCT05589714) is an ambitious combined umbrella natural history and registry study for patients with disease-causing variants in any IRD gene (with a few exceptions), which has already launched secondary longitudinal natural history studies for *MYO7A* and *RDH12*.

Clinical research advances for IRDs have further been powered by AI[65,66] and the development of PRO instruments. Data from natural history studies have been analyzed using deep learning models by reading centers to identify patterns predictive of disease progression,[67,68] which may enable smaller and shorter treatment trials. However, a treatment is only as effective as the treated patients perceive it to be. PROs are quantitative measures based on reports from patients about their health and how disease affects their experience.[69] Recently, PROs were developed specifically for patients with rod-cone degenerations that may be used to evaluate the impact of treatments on patient experience.[70–76] PRO instruments have been developed with input from participants with IRD whose visual acuity ranged from 20/20 to no light perception, and studies have reported results from participants aged 21 to 76 years[74] and in adolescents aged 13 to 18 years old,[70] representing a wide range of disease severity, but work remains to develop PROs for children younger

than 13 years old.[70–76] IRD-specific PROs were developed using the FDA guidelines,[72,73] but, to our knowledge, regulatory agencies have not approved treatments for IRDs based solely on PRO measures.

Novel Therapies

Gene and Genetic Therapies

The FDA approval of an adeno associated virus (AAV)-based gene therapy for *RPE65*-related Leber congenital amaurosis (LCA2) solidified gene therapy's place in medical practice. Where are we now? Between 2018 and 2024, there were 33 clinical trials utilizing AAV-based gene therapy that were initiated to address outer retinal disease, including *CNGA3*- and *CNGB3*-related achromatopsia; *RPGR*-related X-linked retinitis pigmentosa; autosomal recessive retinitis pigmentosa associated with variants in *PDE6B* and *RLBP1*; Choroideremia (*REP1*); *GUCY2D*, *CEP290*, and *LCA5*-related Leber congenital amaurosis; X-linked retinoschisis (*RS1*); and *ABCA4*-related Stargardt disease (see Table 1). Of those 33, there were 3 (9%) that progressed to phase III clinical trials (CHM/*REP1*, NCT03496012; *RPGR*, NCT04850118; and *RPGR*, NCT04794101), and only the 2 XLRP trials listed (NCT04850118 and NCT04794101) remain active at the time of this writing. Five clinical trials for retinal ganglion cell (RGC)-mediated disease used AAV-vectors to treat Leber Hereditary Optic Neuropathy (LHON, *ND4*); of those, four have progressed to phase III (NCT03153293, NCT02652780, NCT02652767, and NCT03293524).

Recent regulatory approval of a CRISPR-based therapeutic for sickle cell disease[77] has paved the way for clinical trials utilizing gene editing-based therapeutics for IRDs. These approaches are supported by improvements in CRISPR-, base-, and prime editing technologies and improved methods for gene editing in post-mitotic cells.[78–80] The first AAV-CRISPR/Cas9-based gene editing approach used in the eye, designed to target a common pathogenic variant in *CEP290* that causes LCA (LCA10), was launched in 2019 (NCT03872479). Reports showed that this therapy was well tolerated and demonstrated vision improvement in some patients.[8] Dual AAV-vector technologies (based on DNA- or RNA-recombination or split intein approaches) will likely be applied to deliver genes that are greater than the carrying capacity of AAV across multiple indications, including *ABCA4*-STGD[81–84] and *MYO7A*-USH1B.[85,86]

In addition to gene editing and gene augmentation, the field has also seen advances in genetically directed pharmacologic therapies, including antisense oligonucleotides[87,88] (e.g. sepofarsen for *CEP290*-associated LCA10 and ultevursen for *USH2A*-related retinal degeneration; see Table 1), premature termination codon read-through therapies[89] and RNA editing,[90] although the latter two have not yet been tested in clinical trials.

Gene-agnostic treatments were delivered using gene therapy in 15 trials (Table 2), including trials for retinitis pigmentosa, neovascular AMD, non-neovascular

Table 2. Gene-Agnostic Gene and Genetic Therapy Clinical Trials for IRDs and AMD

Disease Target	Product	Modality	Phase	Sponsor	NCT Number
Retinitis pigmentosa/LCA	OCU400 AAV.hNr2e3	Gene therapy	1/2	Ocugen	NCT05203939
Rod-cone dystrophy	SPVN06/AAV-RdCVF-RdCVFL	Gene therapy	1/2	SparingVision	NCT05748873
Stargardt disease	OCU410ST/AAV5.hRORA	Gene therapy	1/2	Ocugen	NCT05956626
Non-neovascular AMD	VOY-101	Gene therapy	1/2a	Perceive Biotherapeutics	NCT06087458
	AAVCAGsCD59	Gene therapy	2	Janssen	NCT03144999
	OCU410ST/AAV5.hRORA	Gene therapy	1/2	Ocugen	NCT06018558
	Ionis-FB-LRx	Antisense oligonucleotide	2	Ionis	NCT03446144
	Ionis-FB-LRx	Antisense oligonucleotide	2	Ionis	NCT03815825
	GT005	Gene therapy	1/2	Gyroscope	NCT03846193
Neovascular AMD	RGX-314	Gene therapy	1/2	REGENXBIO	NCT03066258
	RGX-314	Gene therapy	2/3	REGENXBIO/AbbVie	NCT04704921
	RGX-314	Gene therapy	3	REGENXBIO/AbbVie	NCT05407636
	SKG0106	Gene therapy	1/2	Skyline Therapeutics	NCT05986864 NCT06213038
	4D-150	Gene therapy	1/2	4DMT	NCT05197270
	ADVM-022	Gene therapy	2	Adverum	NCT05536973

Note: Inclusion in this table does not necessarily indicate that a trial is active.

AMD, *ABCA4*-related Stargardt disease, and rod-cone dystrophy (with the latter technically being restricted to those caused by mutations in *RHO*, *PDE6A*, or *PDE6B*). Approaches included optogenetics, anti-VEGF approaches, complement pathway modulation, and expression of the neuroprotective agent rod-derived cone viability factor. Of these, two have progressed to phase III (NCT04704921 and NCT05407636) and remain active.

Novel Medical Therapies

Advances in the understanding of disease mechanisms have resulted in the identification of several small molecule therapies aimed at preserving retinal cells and slowing the progression of degeneration[91,92] (Table 3). These therapies that are not gene- or mutation-specific include antioxidant treatments (N-acetylcysteine amide [NACA][93,94] and N-acetylcysteine [NAC]),[95,96] currently in phase II (NCT04355689) and phase III (NCT05537220) trials, respectively, measuring visual function in response to oral supplementation compared to placebo. Vitamin A pathway modulators are being tested in phase I, II, and III trials for Stargardt disease[97] (NCT02402660, NCT05244304, NCT04545736, NCT04489511, and NCT03772665) and GA (NCT04014777, NCT04465955, NCT05230537, NCT03845582, NCT05949593, and NCT05893537).

In addition to well-studied modifiable risk factors, including smoking, a series of epidemiologic studies have demonstrated that a high glycemic index diet increases the risk for developing "late" AMD, and that both a low glycemic index diet and a "Mediterranean" diet (particularly enriched in fish and lutein rich vegetables)[98] can significantly mitigate AMD progression.[99] These effects appear to be additive to the AREDS2 supplement effect.[100]

A major research advance for AMD-associated GA since 2018 includes FDA approval of two complement pathway inhibitor therapies, which slow the rate of GA lesion growth.[1–3] However, both compounds slowed progression of structural measures based on fundus autofluorescence, but no statistically significant improvements in visual function were observed; in addition, there were treatment associated adverse events not limited to those associated with intraocular injections, including increased risk of neovascularization and, rarely, intraocular inflammation with occlusive retinal vasculitis,[101–103] anterior ischemic optic neuropathy, and severe visual loss in eyes treated with pegcetacoplan.[104,105] For these reasons, pegcetacoplan and avacincaptad pegol received FDA, but not European Medicines Agency (EMA), approval.[106] This achievement is impactful because both are now in the clinic in the United States, representing the first treatments shown to slow progression of GA and will pave the way for future anti-complement therapeutics.

Regenerative and Restorative Therapies

Regenerative medicine holds the potential of restoring sight after photoreceptor loss. Twenty early phase clinical trials (Table 4) of regenerative or restorative therapies for degenerative retinal disease are underway or completed. Disease indications include retinitis pigmentosa, Stargardt disease, GA, and neovascular AMD. Numerous sources have been used for donor cells in clinical trials, including embryonic stem cell-derived RPE (ESC-RPE),[107,108] induced

Table 3. Small Molecule and Biologic Clinical Trials for IRDs and AMD

Disease Target	Product	Modality	Phase	Sponsor	NCT Number
Retinitis pigmentosa	N-acetyl cysteine (NAC)	Small molecule	3	Johns Hopkins University	NCT05537220
Stargardt disease	ALK001 C20-D3-retinyl acetate	Small molecule	2	Alkeus Pharma	NCT02402660
	Tinlarebant	Small molecule	3	Belite Bio	NCT05244304
	Metformin	Small molecule	1/2	National Eye Institute	NCT04545736
	STG-001	Small molecule	2a	Stargazer Pharma	NCT04489511
	Emixustat hydrochloride	Small molecule	3	Kubota Vision	NCT03772665
Usher syndrome	N-acetyl cysteine amide (NACA)	Small molecule	1/2	Nacuity Pharma	NCT04355689
Non-neovascular AMD	NGM621	Biologic	1	NGM Biopharma	NCT04014777
	NGM621	Biologic	2	NGM Biopharma	NCT04465955
	Iptacopan	Small molecule	2	Novartis	NCT05230537
	ALK-001	Small molecule	3	Alkeus	NCT03845582
	LBS-008/Tinlarabent	Small molecule	3	Belite Bio	NCT05949593
	CT1812	Small molecule	2	Cognition Therapeutics	NCT05893537
Neovascular AMD	AXT107	Biologic	1/2	AsclepiX Therapeutics	NCT05859776

Note: Inclusion in this table does not necessarily indicate that a trial is active.

Table 4. Cell and Restorative Therapy Clinical Trials for IRDs and AMD

Disease Target	Product	Modality	Phase	Sponsor	NCT Number
Retinitis pigmentosa	hRPC	Cell therapy	1/2	ReNeuron	NCT02464436
	CNS10-NPC	Cell therapy	1/2a	Cedars-Sinai Medical Center	NCT04284293
	CD34+ bone marrow stem cells	Cell therapy	1	University of California Davis	NCT04925687
	jCell (human retinal progenitors)	Cell therapy	2	JCyte	NCT03073733
	jCell (human retinal progenitors)	Cell therapy	2	JCyte	NCT04604899
	vMCO-1	Optogenetics	1/2a	Nanoscope Therapeutics	NCT04919473
	MCO-10	Optogenetics	2	Nanoscope Therapeutics	NCT04945772
	BS01	Optogenetics	1/2	Bionic Sight	NCT04278131
	GS030-DP, GS030-MD	Optogenetics, device	1/2	Gensight Biologics SA	NCT03326336
	EA-2353	Small molecule	1/2	Endogena Therapeutics	NCT05392751
Retinitis pigmentosa/CHM	KIO-301	Small molecule	1/2	Kiora Pharma	NCT05282953
Retinopathy	CD34+ bone marrow stem cells	Cell therapy	1	University of California Davis	NCT01736059
Stargardt disease	vMCO-10	Optogenetics	2	Nanoscope Therapeutics	NCT05417126
Non-neovascular AMD	iPSC-derived RPE/PLGA	Cell therapy	1/2	National Eye Institute	NCT04339764
	Autologous iPSC-derived RPE	Cell therapy	1	Beijing Tongren Hospital	NCT05445063
	RPESC-RPE-4W	Cell therapy	1/2	Luxa Biotechnology	NCT04627428
	ASP7317	Cell therapy	1	Astellas	NCT03178149
	OpRegen	Cell therapy	1/2	Lineage/Genentech	NCT05626114
	CPCB-RPE1	Cell therapy	1/2	Regenerative Patch Technologies	NCT02590692
Neovascular AMD	ESC-derived RPE	Cell therapy	1	Moorfields Eye Hospital NHS Foundation Trust	NCT01691261

Note: Inclusion in this table does not necessarily indicate that a trial is active.

pluripotent stem cell (iPSC)-derived RPE,[109] autologous bone marrow-derived stem cells (NCT04925687), human retinal progenitor cells (NCT04604899 and NCT02464436), and human central nervous system (CNS) stem cells (NCT01632527). Protocols and techniques have been developed to identify optimal stages of cell differentiation for transplantation to make cells more resistant to rejection. Safer, more effective immunosuppression regimens have improved cell transplant safety and survival. A single postmortem histopathological report demonstrated that allogeneic ESC-RPE transplants on scaffolds in the subretinal space can survive for 2 years with a minimal immune suppressive regimen.[110]

Recent phase I studies using ESC-RPE and iPSC-RPE for GA have shown safety with no evidence of tumor formation for at least 2 years post-treatment[111] (see Table 4). Both ESC-RPE and iPSC-RPE can be made to good manufacturing practices (GMP) specification. Prior cell-based clinical studies fall into two major categories: use of cell suspensions or use of cells seeded onto scaffolds (which include both non-degradable, as well as degradable options). Use of RPE cell suspensions have been associated with efflux and epiretinal membrane (ERM) formation (although ERM formation does not yet appear clinically).[112,113] Bolus injection of RPE into the subretinal space in eyes with AMD does not lead to RPE monolayer formation but does result in pigmentation around the edges of the atrophic area. In addition to clustering at the border, the pigment may also demonstrate a gravitational distribution.[114] Use of scaffolds leads to pigmentation under the fovea and may be associated with complications, such as proliferative vitreoretinopathy with retinal detachment but, generally, scaffold-supported RPE cell delivery has been well-tolerated.[111]

Transplantation of photoreceptor precursors has also been evaluated; intravitreal injections were well-tolerated in phase I/II studies (NCT04604899), and show promising results,[115,116] although the therapeutic mechanism is not known. Following subretinal implantation in animal models, photoreceptor transplants can establish meaningful extra-synaptic connec-

tions with host photoreceptors through nanotubes. Nanotubes can develop between donor and host photoreceptors and mediate the exchange of intracellular material in vivo, leading to host photoreceptor survival in preclinical models, including nonhuman primates.[117] Efforts to promote endogenous retinal neuron production via Muller glia transdifferentiation have shown limited photoreceptor production, but more robust bipolar and RGC production.[118,119]

Optogenetics combines genetics and optics to confer novel light-detection capabilities to inner retinal neurons, such as bipolar cells and RGCs, which typically possess non-image forming light sensitivity. This method entails the transfection of inner retinal neurons with a gene that encodes a light-sensitive protein, such as channelrhodoposin-2.[120] Optogenetic strategies are typically considered for patients with late-stage disease when most photoreceptors have been lost.

Recent advances in this area have been in opsin technology, with a focus on the use of red-shifted variants of channelrhodoposin (e.g. ChrimsonR, ReaCHR, and COMv1) to enhance light sensitivity.[121] Proteins can be responsive to natural light wavelengths (as in AbbVie RST-001, NCT02556736) or can be genetically altered to be red-shifted, thereby reducing the risk of light damage from intense white light. The latter uses eyewear to transmit an amplified signal to further stimulate ganglion cells (GenSight Biologics SA GS030-DP, NCT03326336). Nanoscope Therapeutics has developed novel multi characteristic opsins which are an ambient light-sensitive, polychromatic opsins that have the potential to restore vision in different color environments without the need for artificial light interventions (NCT04919473, NCT04945772, and NCT05417126).[122]

Five clinical trials have been launched to test various optogenetic strategies (see Table 4). GenSight reported partial restoration of visual function from one patient who could not visually detect any objects before injection with or without the goggles or after injection without the goggles. This is the first reported case of partial functional recovery in a neurodegenerative disease after optogenetic therapy.[123] Nanoscope Therapeutics also reported positive data from their RESTORE trial, including that MCO-010 achieved its primary and secondary end points, although these findings have not yet been published in a peer-reviewed journal.[124] Additional companies have announced plans for clinical trials using human rhodopsin[125] (Kubota Vision Inc.), a CoChR variant[126] (Ray Therapeutics), or chimeric rhodopsin (GCHR)[127] (Restore Vision Inc.).

Visual prosthetics are devices used to electrically stimulate cells in the visual pathway to restore functional vision in individuals in late-stage disease with partial or total vision loss. There are various types of visual prosthetics, including retinal implants, optic nerve implants, and cortical implants.[128] Several therapies have been evaluated in clinical trials, including one (the Argus 2 system) that received Human Device Exemption status from the FDA in 2017.[129] However, the company that developed the Argus 2 system discontinued production of the devices in 2019.[130] Other prosthetic devices, including the electronic retinal implant Alpha AMS, Intelligent Retinal Implant System (IRIS V2, NCT02670980), Suprachoroidal Retinal Prosthesis (NCT03406416 and NCT05158049),[131] and PRIMA high-resolution photovoltaic (NCT03392324 and NCT04676854) have been investigated in clinical trials, but to date none have advanced to market approval by the FDA for use in clinical care. Finally, suprachoroidal-transretinal stimulation (STS) has been reported in human patients[132,133] with advanced retinitis pigmentosa[134] and Stargardt disease and reported improved performance of a reaching movement in an eye with residual natural vision (UMIN000012754).

Unmet Needs and New Opportunities

Building on progress made in response to prior recommendations,[14–16] several unmet needs remain to be addressed and, in some cases, new opportunities have developed. Whereas some of the gaps described below represent limitations of understanding, many more are based on clear understanding but incomplete application or implementation of existing knowledge. These are described below, segmented by research priority area. These thematic research areas cover interdisciplinary fundamental topics (genetics, cellular and molecular mechanisms of disease, and clinical structure and function), translational approaches (gene therapy, novel medical therapies, and regenerative and restorative therapies) and a stand-alone AMD priority area.

Genetics

The primary goals of this research priority area are:

1. To identify genes and mutations causing IRDs.
2. To identify genetic factors contributing to non-neovascular (atrophic) AMD. Further-

more, a major focus in non-neovascular AMD research should be to understand how genetic variants that have already been associated with AMD contribute to the risk of disease progression.

For both, the goal is to incorporate genetic findings into clinical care, and to foster development and application of treatments and cures.

Specific Gaps for IRDs

1. What are the disease-causing genotypes in unsolved IRD cases? How do non-coding mutations, mosaicism, digenic/oligogenic inheritance, polygenic inheritance, hypomorphic alleles, uniparental disomy, and non-coding RNA and complex structural variants contribute to IRD genotypes?
2. What is the pathogenic classification of variants of uncertain significance (VUS) in IRD genes? How can the application of novel analytic methods, including AI-assisted modeling of protein structure, protein-protein interactions, and pathway analysis, facilitate VUS re-classification?
3. What are the factors contributing to clinical variation (especially in patients with identical disease-causing genotypes), including genetic, environmental, and lifestyle factors?

Specific Gaps for Non-Neovascular AMD

1. What are the genetic and epigenetic factors contributing to:
   a. the life-time risk of developing non-neovascular AMD (early AMD with drusen between 65 µ and 125 µ in diameter, intermediate AMD with drusen >125 µ in diameter, with or without pigmentary changes, and GA[135])?
   b. the pathophysiology of non-neovascular AMD?
2. How do genetic variations mechanistically contribute to AMD?
   a. Can genetic modifiers be identified that modify treatment response?
   b. What is the biologic impact of the genetic variations on the different cell types involved in AMD?
   c. How do changes in mitochondrial DNA contribute to disease?

Cell and Molecular Mechanisms of Retinal Disease

The primary goals of this research priority area are:

1. To identify and better understand the molecular mechanisms by which genetic and environmental factors lead to the development of IRDs and non-neovascular AMD, and how they influence and modify disease progression, with the goal of informing the development of treatments.

Specific Gaps for Cell and Molecular Mechanisms of Retinal Disease

1. What are the mechanisms and pathways shared across IRDs that can be targeted by gene agnostic approaches?
2. How can organoids (or other stem cell-based models) and animal models be generated or characterized to better model the macula?
3. Can the use of spatial omics approaches lead to better understanding of the macula and other topological heterogeneity in the retina?
4. How can access to fresh AMD tissue and RP donor tissue be improved to enhance the understanding of disease mechanisms?[136]
5. What is the role of nuclear and mitochondrial DNA damage in IRD pathophysiology and how can it be targeted to ameliorate disease phenotypes?

Clinical Structure and Function

The goals of this research priority area are:

1. To advance research that contributes to the evaluation of phenotypes and interventions in patients with IRDs or non-neovascular AMD. This includes developing clinical procedures to help diagnose and phenotype patients with IRDs; conducting multimodal studies to link function to underlying pathology; and developing outcome variables for clinical trials, including functional testing, retinal imaging, and candidate surrogate end points. Clinical research in IRDs should utilize imaging, psychophysics, electrophysiology, and optoretinography to understand mechanism of loss in patients with specific disease-causing variants, improve understanding of the relationships between rod and cone loss in IRDs, the

role of the RPE in IRDs, the role of inflammation in IRDs, and the causes and prevention of cystoid macular edema (CME) in IRDs. Similar approaches would benefit AMD research.
2. To improve access to accurate and cost-effective genetic testing, counselling, and clinical care for patients with IRD and their families, because IRDs affect patients from all backgrounds. This includes improved physical and financial access to expert clinical centers, broader access to less well-served communities globally, and greater access to information and resources via websites and other communication channels.

Specific Gaps for IRD Clinical Research

1. What are the adaptive responses to photoreceptor loss in the visual pathways? For example, how does Muller cell gliosis and other remodeling impact gene therapy efficacy?
2. What are the mechanisms responsible for CME? Are there mechanistically targeted treatments that can reduce vision loss associated with CME?
3. What are the roles of hormones in disease progression, including sex hormones?
4. Why is the macula resistant to degeneration? How do foveal cones survive without rods? Is their gene expression different from peripheral rods? Can RPE differences in the foveal region account for some of the foveal preservation?
5. What is the role of the immune system in IRDs, including microglial/Muller cell responses and innate versus adaptive immune responses? Do they differ by genotype? Are there less invasive ways to measure inflammation (e.g. cell free RNA/DNA) from an anterior chamber tap, or optical ways to quantify inflammation, such as characterization of vitreous cells? What is the optimal anti-inflammatory regimen in viral and non-viral interventional trials?
6. What role does noise have in denervated inner retinal cells in patients with IRDs? Is there cortical adaptation over time in patients with IRD?
7. What are the earliest manifestations of IRD? Does early degeneration and loss of acuity manifest loss of cortical development, creating an amblyopia-like effect? Is there a critical window for treatment?
8. Given that AI has been used to monitor disease progression from imaging (OCTs, fundus photographs, and autofluorescence) in natural history and treatment trials,[65,66] how can systematic application of AI algorithms be used to model disease associated with less common genetic forms of IRD? Can AI be used to predict areas of visual field loss so that testing could be more focused? Because local variations in visual sensitivity can be predicted from OCT scans, can this approach be used to test structure-function assumptions[137,138] more broadly in less common genetic forms of IRD?
9. Because patient-tailored perimetry has already been implemented in clinical trials, are there opportunities to further refine focal tests of retinal function, possibly including further development of focal ERGs, focal pupillography, or optoretinography?[139,140]
10. What can be learned about visual field outcomes from experts in other specialties, such as glaucoma?
11. In light of advances in mobility tests[141–143] and tests of visual function, such as full-field sensitivity testing (FST), how can we further improve and optimize assessments of vision in patients with advanced disease?
12. Although this represents an implementation gap rather than a knowledge gap, research in IRDs is limited in inclusion of patients from under-represented populations. Disproportionate stratified sampling and other approaches may be helpful in addressing this challenge, in addition to expanding outreach to participants that identify as members of under-represented populations to increase their participation in IRD research studies.
13. Is there a classification scheme for CME that relates to etiology and helps predict treatment efficacy?

Specific Gaps for Non-Neovascular AMD Clinical Research

1. What are the critical visual function parameters that track closely with disease progression?
2. What is the basis for the low luminance deficits seen in patients with non-neovascular AMD?
3. What are the best ways to assess rod function and dark-adapted cone function in AMD, because these parameters may be sensitive markers of disease onset and progression?
4. Can we develop a risk factor classification scale for AMD progression, similar to the Diabetic Retinopathy Severity Scale, with progression on the scale useful as an outcome variable for AMD worsening?
5. What are the genetic and epigenetic factors contributing to:

   a. clinical phenotypes and progression, including rare, high-penetrance variants,
   b. variation in AMD phenotype and disease progression.
6. How can we better integrate individual and population-based genetic findings and other contributing factors into prevention, prognosis, clinical care, and design and testing of therapies for non-neovascular AMD? Can we develop large scale genetic screens to identify genes/proteins that lead to the production or removal of subRPE deposits?
7. What functional, physiological, or molecular imaging changes complement anatomic changes in patients?
8. Can we distinguish fast versus slow AMD progressors? Which patients will progress?
   a. What imaging biomarkers predict initiation or progression of AMD, and can biomarkers be used to monitor treatment response?
   b. What functional or surrogate primary end point is suitable (to the FDA) for clinical trials testing a treatment for AMD at a stage earlier than GA, such as nascent GA?
   c. Can we develop outcome variables, other than progression to neovascular AMD or GA, for the worsening of early or intermediate AMD that can shorten clinical trials?
9. Does slowing GA growth lead to measurable benefits for BCVA, reading speed, quality of life, and do factors other than the location of atrophy (e.g. subfoveal versus extrafoveal) dictate the impact? How does the location of the atrophy affect the results of clinical treatment trials?

Gene Therapy

The overarching goal that this research priority area is to find viral and/or non-viral gene delivery system(s) to treat dominant, recessive, and X-linked retinal degenerative diseases, including evaluation of efficacy and safety using preclinical models in preparation for human clinical trials. Specific goals are to:

1. Improve gene therapy delivery methods by understanding the hurdles associated with gene delivery by subretinal injection, intravitreal injection, suprachoroidal, and subconjunctival injection, and developing tools to overcome them; develop non-viral delivery tools (e.g. lipid nanoparticles); and develop alternative viral vectors (in addition to AAV).
2. Develop a better understanding of how to modulate the immune response to gene therapy while maintaining optimal treatment effectiveness.
3. Develop tools for effectively and efficiently transducing all relevant retinal cell types (e.g. cell-specific plasmids and novel capsids) that permit improved control of expression levels.
4. Implement strategies for delivering complex constructs (large DNA, gene editing tools, mRNA, or protein).
5. Advance RNA editing techniques.
6. Establish metrics by which the efficiency of delivery (viral or non-viral) and the efficiency of editing (DNA/RNA) can be quantified and measured across delivery platforms.
7. Understand the impact of gene augmentation in a diseased retina (e.g. can delivered proteins restore protein networks/full cellular machinery/outer segment structure?).
8. Develop standardized methods for quantifying vector genomes and total protein that can be compared among groups/studies, including analysis of dose-response effects on treatment efficacy and toxicity.
9. Develop manufacturing techniques that are affordable/scalable.

Specific Gaps for Gene Therapy

1. What is the impact of gene replacement on cell biology in the diseased retina? How do proteins derived from exogenous sources integrate within multi-subunit enzymes and protein networks to restore full cellular mechanisms in diseased cells? How is this different in a diseased retina?
2. How can translation from preclinical models to humans be optimized and de-risked?
3. What are the barriers to gene delivery via multiple routes of administration (ROA) and what are the optimal tools to overcome them?
   a. For subretinal injection, what are the consequences of retinal detachment in the central versus peripheral retina?
   b. For intravitreal injection, what are the physical and biological barriers to photoreceptor and/or RPE transduction?
   c. For suprachoroidal injections, what are the physical and biological barriers for RPE transduction?

4. How do different genotypes (different disease-causing variants in the same gene) impact results of gene replacement therapies, and how do they affect clinical outcomes?
5. Are there experimental plans that would facilitate the use of previous preclinical toxicology and safety data to enable advancement of other constructs (especially for ultra-rare disease-causing gene defects)?
6. What can be learned from failed and successful gene therapy trials?
7. How can the effective dose of gene-based therapy be reduced, and how can dosing be more precisely controlled? How can purity and content of delivered therapies be assessed, monitored, and regulated to reduce toxicity and improve efficacy?

Novel Medical Therapy

The goal of this research priority area is:

1. To promote the development of new therapies (e.g. small molecules and other treatments) that slow or prevent the loss of retinal function.

Specific Gaps for Novel Medical Therapy

1. What are the appropriate models of relevant cell types for high throughput screening and drug repurposing studies?
2. What is the role of the microbiome in IRDs? Can targeting the microbiome (e.g. antibiotics and bacterial consortia) alter disease course?
3. Can therapies that improve cellular metabolism slow the progression of disease?
4. Can non-drug therapies (e.g. red light) be identified to treat IRDs?
5. What are the key challenges in developing therapies for complex genetic diseases and how can they be overcome?
6. Can we develop noninvasive delivery modalities (topical or systemic), especially for IRDs with early onset of disease?
7. How can delivery systems be optimized to control dosing to optimize efficacy and reduce toxicity?

Regenerative and Restorative Therapies

The primary goal of this research priority area is to develop strategies to rescue or replace degenerating or dead retinal cells leading towards restoration of lost vision or slowing and/or prevention of vision loss. Additional goals include in vitro determination of efficacy, and important parameters for mammalian RPE and photoreceptor rescue strategies. This could include optimizing the parameters to maximize the use of RPE and/or photoreceptor precursors as a source of transplanted cells.

Specific Gaps for Regenerative and Restorative Therapies

1. What is the optimal preparation and purification of donor tissue to maximize the probability of successful cell transplantation? Despite the existence of several preparation/purification techniques for photoreceptors, it is not known if there is an ideal production method of iPSCs/donor tissue for cells for transplantation.
2. How can the survival and function of transplanted cells before and after transplantation be optimized? Unanswered questions include which exogenous, pre-transplant factors are important to maximizing cell survival after transplantation (e.g. Lazaroids)?
3. What is the role of biomaterials in facilitating survival, integration, and organization of transplanted cells?
4. For optimal cell survival post-transplant, which immune suppression regimen is required, and how does this vary with cell source, host disease, and other specific donor/host variables?
5. How can the proper functioning of transplanted cells be enhanced and measured?
   a. How can donor RPE function be measured after transplantation into diseased eyes?
   b. How can the integration of transplanted photoreceptors be measured? Is microperimetry/multifocal ERG sufficient? What structural studies could also be used to demonstrate integration and function?
6. What is the relative importance of cytoplasmic transfer versus transplant survival? Can material transfer between cells be used for therapeutic purposes (e.g. stimulation of host Muller cells to differentiate into photoreceptor cells)?
7. Optogenetics: What is the best non-photoreceptor cell to target for optogenetic therapy to restore visual perception? How will perception of optogenetic-mediated responses to visual stimuli be integrated with input from remaining photoreceptors in macular diseases, including non-neovascular AMD and Stargardt disease? What is the appropriate control for

optogenetic studies: the untreated contralateral eye, or sham treated control subjects?

8. Device development for sight restoration: What is the potential of visual prostheses to restore sight? Prosthetic research should focus on the limitations of devices studied to date, how to improve interaction with remaining retinal cells, retinal circuitry rewiring after photoreceptor degeneration, and assessment of vision stimulated by prosthetic devices in the absence of photoreceptors.

Age-Related Macular Degeneration

The goals of this research priority area, which has a focus on non-neovascular AMD, are:

1. To understand the pathophysiology of the transition from no signs of AMD, to age-related small "hard" drusen <65 μ in diameter, to early AMD, to intermediate AMD, and to late AMD (neovascular or GA), with the goal of having the greatest impact on prevention and/or slowing progression.[144]
2. To improve approaches to address modifiable risk factors for AMD progression, such as smoking, elevated body mass index (BMI), high-risk diets or lifestyles, etc.; whereas also addressing fundus risk factors for AMD progression, other than large drusen and pigmentary changes, such as reticular pseudodrusen,[145] very large drusen (>250 μ), diffuse rod loss, nascent GA, or decreased macula lutea.[135]

Specific Gaps for Non-Neovascular AMD

1. What are the major differences between normal age-related transition to developing small "hard" drusen and the transition to developing early AMD?
2. What triggers AMD? Is there a uniform initiating trigger for developing AMD?
   a. Is AMD initiation a single disease or a spectrum of diseases, and is initiation different from progression? Specifically, are there factors related to the progression from medium sized drusen to intermediate AMD, that differ from the factors related to the progression to neovascular AMD or GA.
   b. What are the mechanistic similarities and differences between initiation and progression?
3. What are the major pathogenic pathways at each disease stage, and can they be prioritized by their contribution to disease? Are these pathogenic pathways associated with both aging and/or AMD?
4. What is the mechanistic role of lifestyle risk factors (smoking, diet, etc.) in the development and/or progression of AMD?
5. As a complex disease, how can we better integrate factors for AMD worsening, such as genetics, functional genomics, inflammation, mitochondrial misfunction, rod abnormalities, RPE abnormalities, choroidal abnormalities, Bruch's membrane abnormalities, "omics" associations, and others?[146]
6. What can we learn about the biology of the transition zone in GA?
7. How can iPSC models of AMD be used as a screen to test drugs in preparation for justifying a clinical trial? Can retinal organoids be developed to include RPE, vasculature, and microglia?
8. What features predispose to the development of reticular pseudodrusen,[145] and why do they result in greater risk of progression? Do patients with reticular pseudodrusen require a different treatment strategy than those without?
9. What are the barriers to the creation of animal models that recapitulate AMD, and how can they be overcome?
10. Can treatment be developed to reverse AMD, and, if so, at what stage?

Conclusions

Beyond the specific knowledge gaps that were identified, higher-order themes emerged across multiple areas.

Heterogeneity – multiple research priority areas noted challenges associated with genotypic, cellular, and phenotypic heterogeneity. Why do patients with the same genotype have different phenotypes? What is the role of genetic modifiers, epigenetics, stochasticity, systemic, and lifestyle factors? Does cellular heterogeneity impact regional disease processes? How might phenotypic and underlying genotypic variability affect responses to interventions?

Models – several groups noted a lack of good models (animal and/or cellular) and the need to improve iPSC models to better recapitulate aspects of human biology and disease. Can iPSC retina models be generated to include additional non-neuronal cell

types and/or a macula? What is the relevance of fetal-like iPSCs in modeling late-onset diseases? What are appropriate models for high through-put screening in vitro?

Immune System and Reactions – What is the role of the immune system in disease initiation and progression for IRDs and AMD? Is it genotype specific? How can immune reactions to genetic and cellular therapies be attenuated? Will distinct genotypes respond differently to the same therapy and/or immune modulation?

Disease Stage and Biomarkers - What are the earliest signs of disease? Are the underlying mechanisms of disease initiation and progression shared? Are there imaging biomarkers that predict onset and progression of disease? How can AI aid in their identification? Are there imaging and/or non-imaging biomarkers that can be used to monitor response to therapy?

Data Sharing and Transparency – There is a need for transparency and data sharing around pre-clinical and especially clinical data to ensure that the field can learn from successful and failed clinical trials, to expedite the pace of future trials.

Addressing the specific knowledge gaps for each of the priority areas above should lead to additional progress toward the development of treatments for patients with IRDs and non-neovascular AMD in the future. Multi-disciplinary approaches, including multimodal imaging and multi-omics approaches, and increased integration and collaboration between clinicians and translational scientists should accelerate progress toward the stated goals.

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