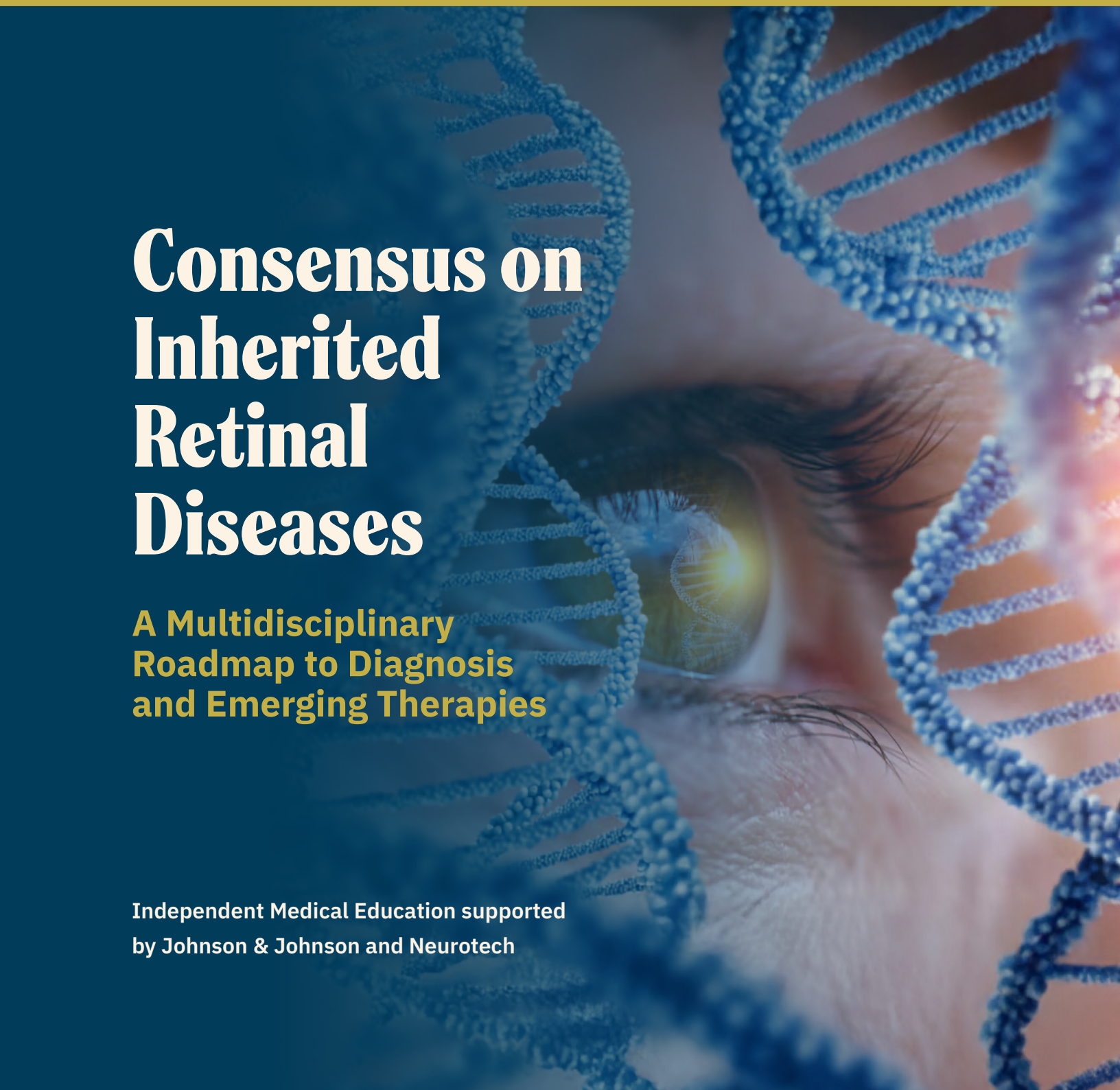
EURETINA EDUCATION PLATFORM

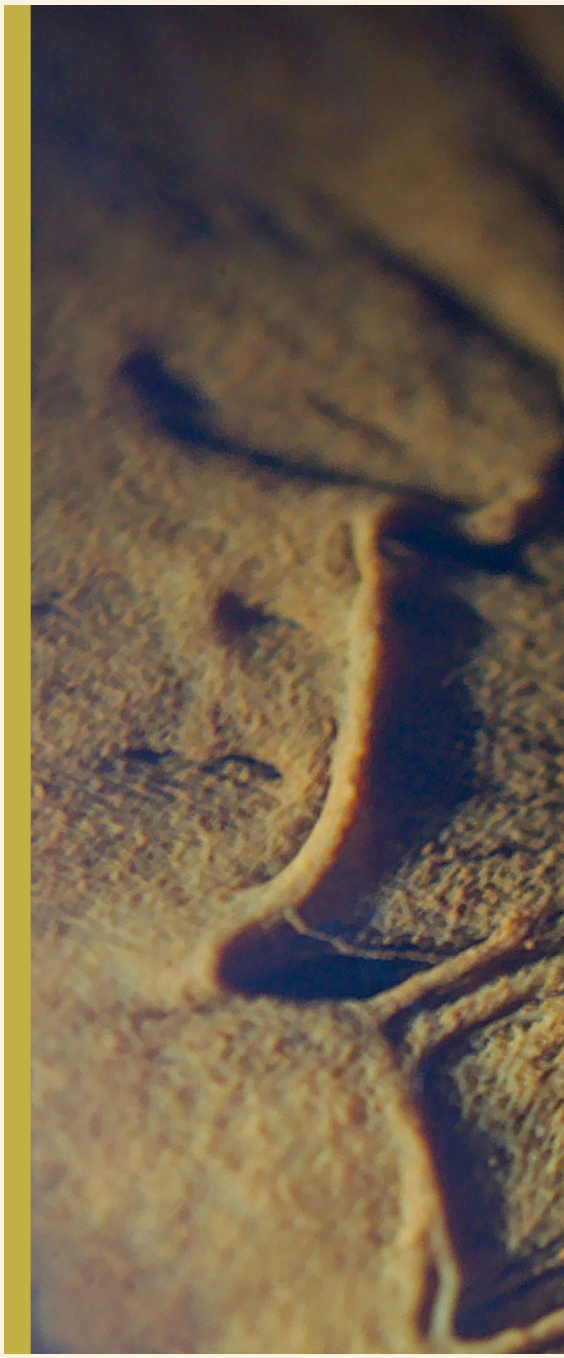


Consensus on Inherited Retinal Diseases

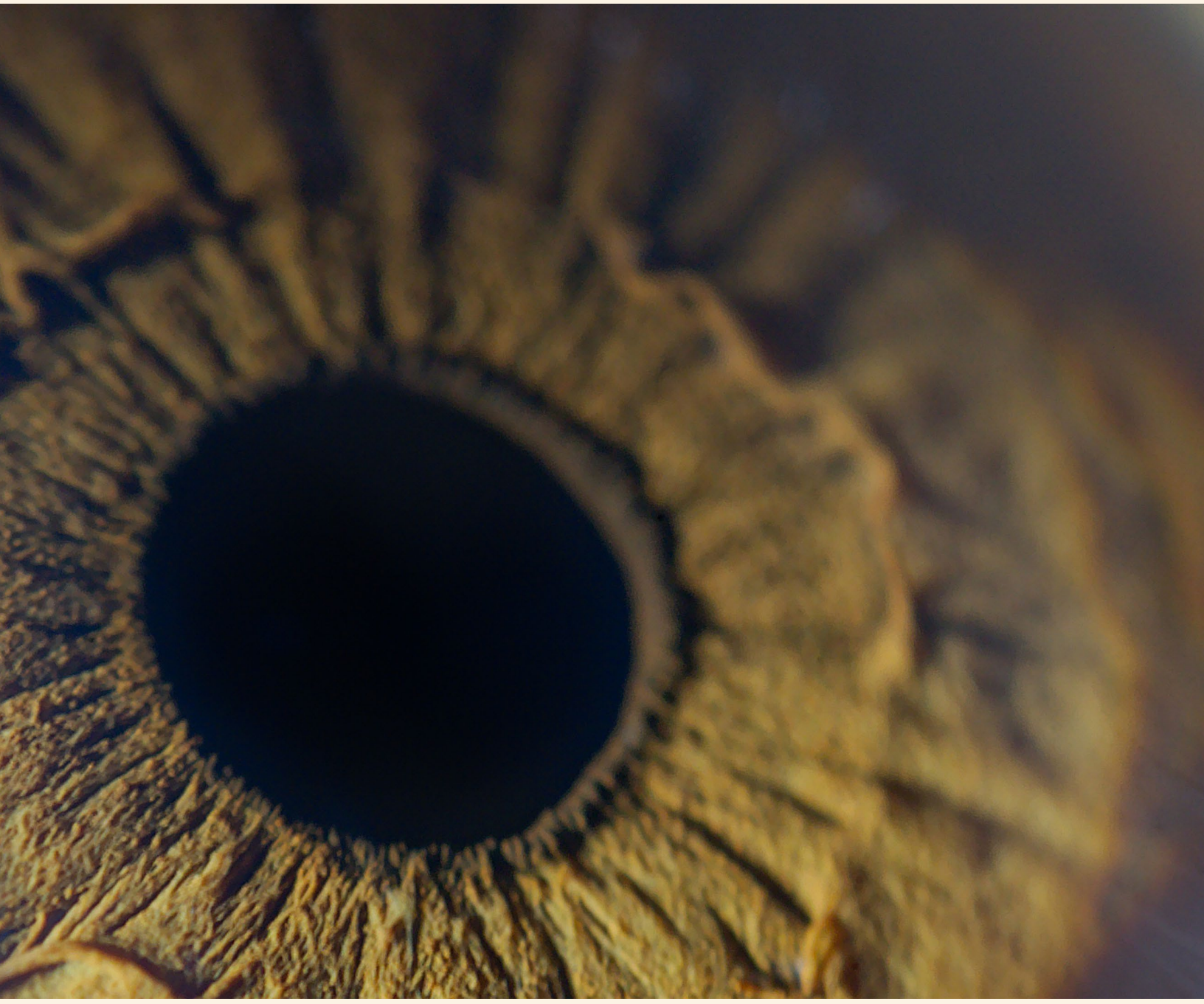
A Multidisciplinary Roadmap to Diagnosis and Emerging Therapies

Independent Medical Education supported by Johnson & Johnson and Neurotech

Inherited Retinal Diseases (IRDs)



represent a broad clinically and genetically heterogeneous group of disorders characterized by vision loss due to the abnormal development, progressive dysfunction, or degeneration of photoreceptors, retinal pigment epithelium (RPE), or other retinal structures.[1] With the increasing availability of genetic and molecular diagnostics and the emergence of gene-based therapies, IRDs have become a major focus in both research and clinical practice, giving hope to the approximately 5.5 million individuals worldwide affected with these diseases.[2]



The following consensus statement, formed through an online survey of and discussions with leading retina specialists and clinical geneticists, identifies key challenges and best practices in the diagnosis, management, and interpretation of patients with IRD. Drawing from peer-reviewed literature and the experience of the Expert Consensus Group, the following consensus statement aims to inform the ophthalmic community and reinforce the importance of a multidisciplinary and collaborative approach in the evolving landscape of IRD care.

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Etiology of Inherited Retinal Disease

IRD is one of the most genetically diverse groups of disorders found in humans.[3] Resulting from pathogenic variants in genes influencing for retinal structure and function, an IRD can be inherited as autosomal recessive (50% to 60% of cases), autosomal dominant (30% to 40% of cases), or X-linked (about 10% of cases) traits, although mitochondrial and digenic inheritance patterns may also exist.[1] The molecular pathogenesis of IRDs may involve processes that may include disruption of the phototransduction cascade, defective protein transport, altered photoreceptor development, and accumulation of toxic metabolic byproducts.[4-6]

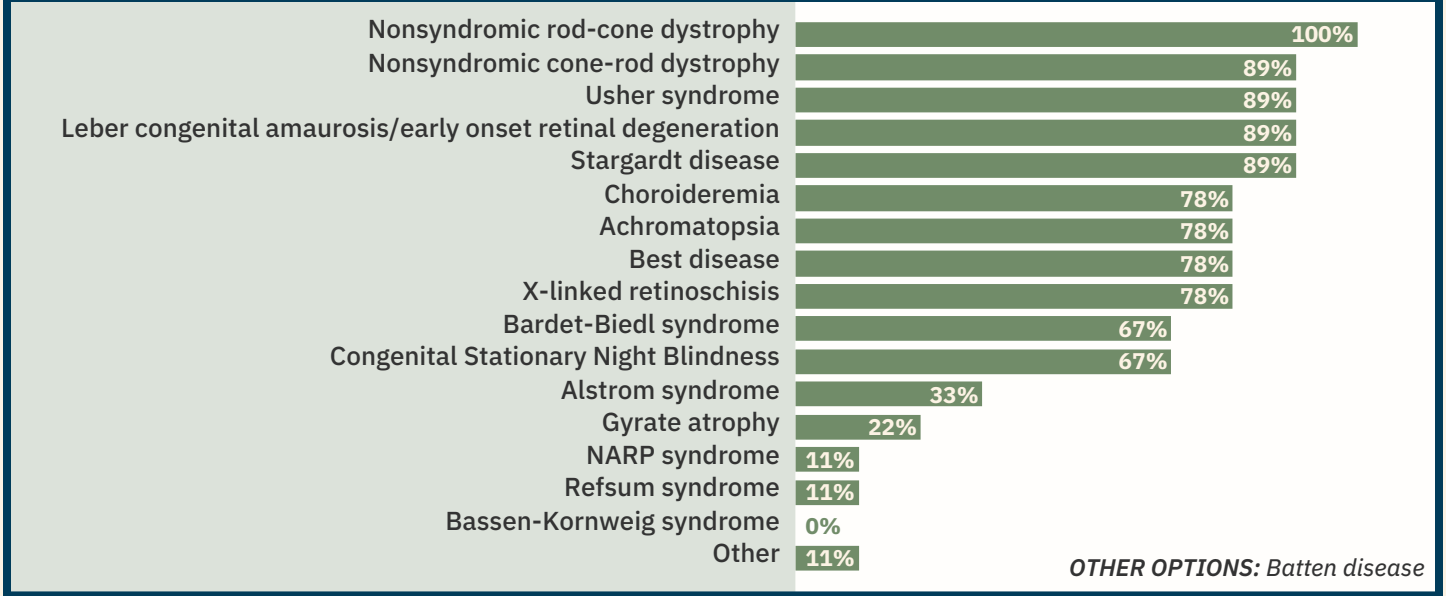
Some of the first IRD-causative genes, *RHO* and *CHM,* were identified in 1990.[7,8] Between 1988 and 2024 an average of thirteen new causative genes were identified annually, however, this growth has not been uniform and slowed down after 2018.[49] Today, over 400 genes have been implicated in IRDs.[3,9,49]

Although some rare and novel IRD genes may exist, researchers believe most IRD-causative genes have been discovered already.[7-9]

With numerous genes associated with IRD, it is not surprising that each gene's contribution to the overall prevalence of IRD is quite small. Studies indicate that more than half (65%) of identified pathogenic variants are unique to each patient,[1] and the worldwide rate of mutation identification reported ranges between 50% and 76%.[10-12]

Many IRDs are nonsyndromic and involve only ophthalmic manifestations; however, more than 300 genes have been associated with syndromic IRDs.[1,3,49] The most common forms of nonsyndromic IRDs include retinitis pigmentosa (RP), rod-cone and cone-rod degeneration, Leber congenital amaurosis (LCA), and inherited macular dystrophies.[13] Conversely, the most common syndromic IRD is Usher syndrome.[14]

FIGURE 1. What are the most common IRDs encountered in your practice? (Select all that apply)



The five most common IRDs encountered in clinical practice by the Expert Consensus Group include nonsyndromic rod-cone dystrophy (ie, RP), nonsyndromic cone-rod dystrophy, Usher syndrome, LCA/early onset retinal degeneration, and Stargardt disease. (Note: the percentages listed refer to the percentage of experts reporting having encountered a certain IRD in their practice)

Among the Expert Consensus Group, the five most common IRDs encountered in clinical practice are nonsyndromic rod-cone dystrophy, nonsyndromic cone-rod dystrophy, Usher syndrome, Leber congenital amaurosis/early onset retinal degeneration, and Stargardt disease (**Figure 1**). Patients presenting with choroideremia achromatopsia, Best disease, X-linked retinoschisis, Bardet-Biedel syndrome, and congenital stationary night blindness are also frequently seen by the Expert Consensus Group.

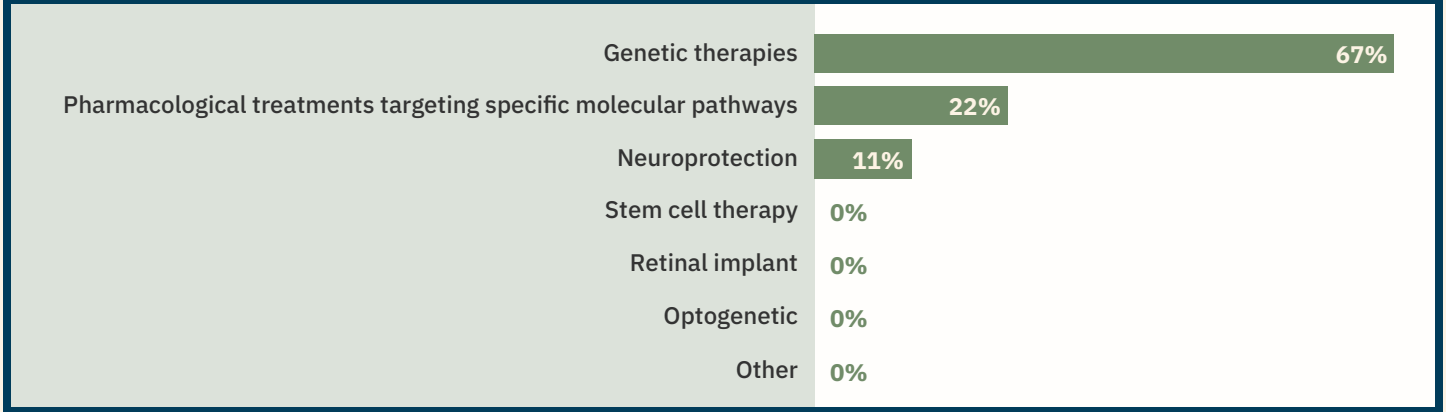
Omar A. Mahroo, MB, BChir, PhD, FRCOphth, practices at Moorfields Eye Hospital, which has the largest genotyped cohort of patients with IRDs in the world. "The single commonest gene associated with IRD is the *ABCA4* gene," he said, further noting, "We also see a lot of *USH2A*-associated syndromic and nonsyndromic RP, RPGR-associated X-linked RP, and a whole range of progressive and stationary conditions."

Pathogenic variants in *ABCA4* are responsible for the majority of Stargardt disease cases.[15] Many of the 2,000+ variants described in the literature are hypomorphic and may contribute to milder or later-onset disease phenotypes.[50] On the severe part of the spectrum, *ABCA4* mutations lead to generalized retinal dystrophies (ie, cone-rod dystrophies or rarely RP). *RPGR* pathogenic variants account for most X-linked RP,[16] while *USH2A* mutations are frequently found in both syndromic (Usher syndrome) and nonsyndromic forms of RP.[17]

Understanding the genetic basis of IRDs has direct implications for the diagnosis and treatment of patients with these conditions, for estimating prognosis and for genetic counselling. It is also important for assessing their eligibility for clinical trials of emerging therapies. In the United States and Europe, for example, biallelic pathogenic variants in *RPE65* causing a form of LCA are now treatable with an FDA- and EMA-approved gene therapy, *voretigene neparvovec-rzyl* (Luxturna, Novartis). This has sparked a paradigm shift in how clinicians may approach IRD, from phenotypic description alone to a molecularly driven model of precision care.

Several novel treatments are on the horizon, with the Expert Consensus Group identifying genetic therapies among the most promising. Other areas of interest include pharmacological treatments targeting specific molecular pathways, and neuroprotection (**Figure 2**; for more information on pipeline treatments, see *"Therapeutic Advances and the Future of IRD Treatment" on page 20*). In some countries, transcorneal electrostimulation is available to patients with retinal dystrophies; however, it is difficult to predict if and how much individual benefit it provides to the disease progression. Although retinal implants such as Argus II (Cortingent) and Retinal Implant IMS/AMS (Retina Implant AG) were approved for patients with end-stage RP, neither is currently commercially available.

FIGURE 2. In your opinion, what is the most promising treatment currently in the pipeline for IRDs?



Results of the Expert Consensus Group survey reveal that the most promising treatment currently in the pipeline are genetic therapies, followed by pharmacological treatments targeting specific molecular pathways and neuroprotection.

Prevalence and Demographics

While each IRD is individually rare, collectively they affect about one in 1,380 individuals worldwide.[1] RP, the most common IRD, affects about one in 4,000 to 5,000 people.[18] Stargardt disease is estimated to affect one in 8,000 to 10,000, while Usher syndrome and LCA occur in approximately one in 30,000 and one in 50,000 individuals, respectively.[19-21] These numbers may underrepresent the true burden of IRDs due to delayed or missed diagnoses, particularly in low-resource settings.

Philipp Herrmann, MD, PhD, FEBO, estimates that up to 70% of the patients with IRDs he treats have either Stargardt disease or RP. "These are rather challenging conditions to manage. The RP diseases start in the periphery with different symptoms and signs," he mentioned. Along with RP and Stargardt disease, the third most common IRD Katarina Stingl, MD, PhD, sees in her practice is cone-rod dystrophy.

Genetic epidemiology studies demonstrate a high carrier frequency for IRD-causing genetic variants. A 2020 population-based analysis across six global cohorts found that nearly 36% of individuals were carriers of at least one pathogenic IRD allele.[2] The study estimated that up to 5.5 million people worldwide may be affected by autosomal recessive IRDs with a potential for 2.7 billion carriers globally.

Diagnosis and Early Detection

In tertiary care settings, IRD cases are more likely to be identified in the presence of early symptoms such as photophobia, peripheral vision alteration, decreased visual acuity, and color vision alteration (**Figure 3**). Behind night blindness, the second largest red flag for Dr. Stingl is a peripheral scotoma. "But mostly there is a typical combination of symptoms for the subtypes of IRDs," she said.

According to the Expert Consensus Group, 55% report that at least half of their IRD patients initially present with mild visual disturbances and minimal impact on daily activities or occasional vision problems and slight reduction in quality of life. Meanwhile, 77% of experts report at least half of their patients to present late in the disease state with significant visual impairment and social isolation and/or major challenges in mobility and employment.

"It's probably a close call, but overall patients will seek help before they reach a late-stage diagnosis," Dr. Herrmann said. "If patients lose vision, it will bring them to see someone. There are exceptions, obviously, but overall, it's often an early-stage diagnosis."

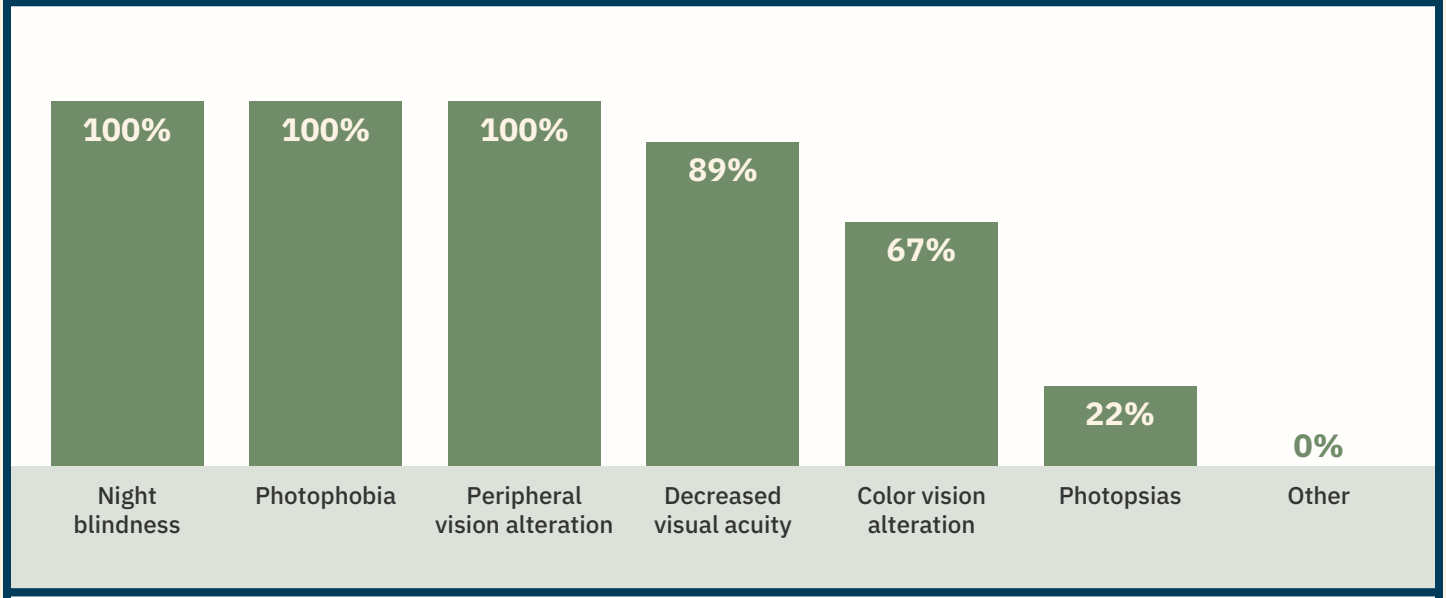
Dr. Stingl offers a different perspective. "I would say only the minority present with slight problems. If they are children with congenital visual impairment, they sometimes do not notice symptoms because they compensate well, and if they are adults, they have other things to do if they are not bothered too much," she said. "For example, a little night blindness is commonly ignored because cities are usually well illuminated at night. I would say people present when they are really disrupted later in daily life."

Demographic patterns of diagnosis vary. Some clinicians, such as Robert H. Henderson, MBBS, MD, FRCOphth, only see children. Dr. Henderson specializes in syndromic diseases in childhood such as Batten's disease, which are a group of inherited neurological disorders that typically begin in childhood and are characterized by progressive vision loss, seizures, cognitive decline, and motor skill deterioration. He is currently running two gene therapy clinical trials in this space. "As you can imagine, every single child with Batten disease in the entire United Kingdom comes to see me. That very much steers what I do," he said.

On the other hand, only between 10% and 20% of patients Dr. Stingl sees are very young pediatric cases. "For me, it's more common to see teenagers getting close to adulthood," she said, adding it is mainly because she follows patients through adulthood.

Estimates from the Expert Consensus Group on the percentage of IRD patients diagnosed in childhood

FIGURE 3. What of the following early symptoms prompt you to consider an IRD? (Select all that apply)

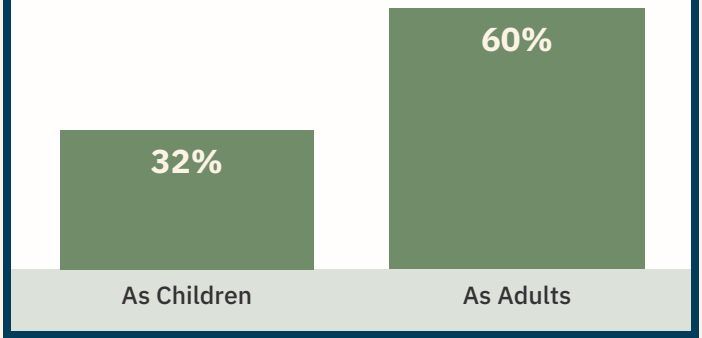


Three early symptoms, night blindness, photophobia, and peripheral vision alteration, are equally important to the detection of IRDs. Other early symptoms prompting consideration of an IRD include decreased visual acuity, color vision alteration, and photopsias.

varied significantly, but the average reported was 32% (**Figure 4**), confirming the importance of pediatric screening. When diagnosis occurs in childhood, the Expert Consensus Group indicates they perform additional screenings, including full ophthalmic, orthoptics, and refractive examinations, genomic analysis, OCT, electroretinography, and strabismus and functional amblyopia testing depending on the clinical presentation. "In many cases, patients presenting in childhood and early adolescence usually have symmetric imaging patterns in the right and left eyes," Dr. Herrmann said, adding that in some cases these may not be clearly seen due to the early disease.

More than half of the Expert Consensus Group (56%) refer young patients to a pediatrician, 33% refer to a renal specialist, and 33% and 11% order a developmental assessment and MRI, respectively, when they diagnose an IRD in childhood. The Expert Consensus Group also notes the specific work-up may depend on the phenotype and/or the genetic analysis, with some mentioning routine registration of such cases in IRD-specific databases to facilitate ongoing care and research tracking.

FIGURE 4. What percentage of your IRD patients are diagnosed as children vs as adults?



Estimates from the Expert Consensus Group on the percentage of IRD patients diagnosed in childhood represented a wide range of responses, and the average reported was 32%.

Individuals with IRDs diagnosed in adulthood often experienced years of slow progression or lack of access to genetic services. “If you took the patients who were diagnosed in adulthood and you asked them when they first knew they had problems, quite a lot of them will mention having had problems in childhood,” Graeme Black, MA, MB Bch, DPhil, FRCOphth, said. “Historically, a lot of people didn’t get diagnoses, but that is changing. I suspect the age at which people achieve diagnoses will start to come earlier as the power of imaging gets better, awareness increases, and genetic testing is offered to more people.”

For some conditions, diagnosis in adulthood is more common. Dr. Herrmann analyzed data from 1,000 consecutive patients treated at his clinic to determine the average age of diagnosis for IRDs. For RP, he found most patients were diagnosed in late adolescence or very early adulthood (unpublished personal data). “Some will be diagnosed in their 50s and 60s, and some will be at a very young age, 7 or 8 years old, but that’s not the most common presentation,” he said, adding that there is usually a significant lag between onset of first symptoms, such as night blindness and full diagnoses, because early symptoms are often subtle.

However, the Expert Consensus Group emphasized the importance of early detection for optimizing vision preservation, counseling, and treatment access. “We receive many adult patients who couldn’t attend a consultation [as children] because there were no consults developed then,” Carmen Ayuso García, MD, PhD, said. “The proportion of adult patients therefore is higher than expected. … Also, they did not receive the proper genetic counseling and reproductive options because they didn’t know what risks they were facing.”

Things in the Spanish National Health System have changed, Dr. García continued. Now, there is a published portfolio for genetic diagnosis and counseling (https://cgen.sanidad.gob.es/#/).

Accurate diagnosis of IRDs requires a high index of suspicion, particularly when patients present with subtle visual symptoms or atypical fundus findings.

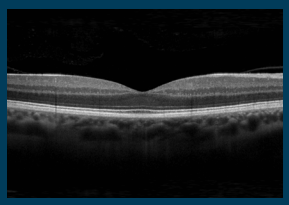
In many cases, the specific IRD is initially misdiagnosed as another IRD or in some cases a more common retinal or neuro-ophthalmic condition.[22]

"Most patients would get picked up if they presented to a medical retina clinic, but there can be what's called a diagnostic odyssey, meaning it can take people some time to get their diagnosis," Dr. Henderson said. "They may see their optician first and then their general practitioner, and then the general practitioner refers them. ... There definitely are patients who have been walking around with a retinal dystrophy for some time without a diagnosis."

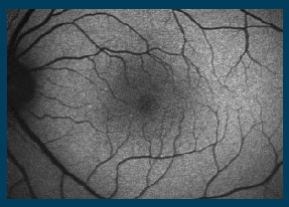
The typical presenting symptoms of IRDs vary depending on disease subtype but include nyctalopia (ie, night blindness), peripheral and central vision decline and loss, photophobia, color vision disturbances, blind spots, uncontrolled eye movements, and hyperopia. In children, nystagmus, delayed visual development, and poor fixation may prompt further evaluation.[23]

IRDs have heterogeneous clinical presentation, often resulting in diagnostic challenges. In addition to a comprehensive workup and a detailed ocular, systemic, and family history, multimodal retinal imaging, functional testing, and psychophysical and electrophysiological evaluation form the cornerstones of a diagnostic approach for IRD.[24] Key diagnostic evaluations are outlined below.

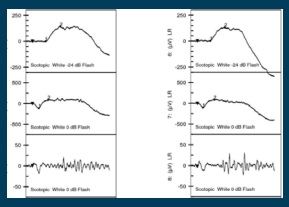
Key Diagnostic Evaluations for IRD



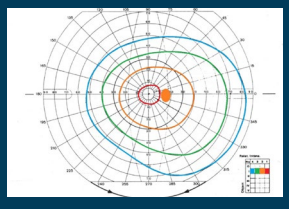
Optical coherence tomography (OCT) to identify outer retinal disruption, subfoveal deposits, and cystoid macular edema. OCT analysis is especially helpful for diagnosing Stargardt disease, cone-rod and rod-cone dystrophies, and X-linked retinoschisis.



Fundus autofluorescence (FAF) may be used to assess lipofuscin accumulation in the retinal pigment epithelium, often showing a hyperautofluorescent ring in RP or hyperautofluorescent flecks in Stargardt disease. It also may be used for retinal pigment epithelium atrophies as well as in general for almost all diseases of the outer retina.



Full-field electroretinography (ffERG), the gold standard for assessing rod and cone function, may distinguish generalized photoreceptor dysfunction from macular dystrophies.



Goldmann or Humphrey visual fields may be useful for monitoring disease progression.

Microperimetry and full-field stimulus threshold (FST) both provide sensitive measures of functional decline in clinical trials.

In terms of diagnostic tools, FAF, OCT, and ffERG were consistently ranked by the Expert Consensus Group as the most valuable for early diagnosis, followed by visual acuity, genetic testing, and fundus examination (**Figure 5A**). To monitor progression, they emphasized visual acuity, OCT, FAF, kinetic visual fields, and ffERG as key tools (**Figure 5B**). Another excellent tool to monitor progression is full-field stimulus threshold, Dr. Stingl said. "In most patients, scotopic ffERG is a flat line early, and FST is the only tool to monitor rod functional decline progression over time," she commented.

"The most innovative diagnostic tool over the past decade is the multimodal imaging approach," Dr. Herrmann said. "Genetic testing is also elementary to get good phenotyping and genotyping. You need both to be able to really pinpoint the actual problem."

Dr. Black shared that all patients presenting at genetic retinal clinics undergo a full dilated examination, imaging in the form of ultra-widefield retinal imaging, autofluorescence, and OCT, as well as genetic testing on the first visit. Electrodiagnostics are usually reserved for future visits, he said, and Dr. Mahroo agreed. "Based on OCT, FAF, and ultra-widefield imaging, if we think electrophysiology might be helpful, we order it," Dr. Mahroo said. "We do get electrophysiology on quite a lot of our patients, but not on all."

Dr. Herrmann cautions it may not always be possible to obtain full imaging on a young child. When he feels a full work-up will be difficult to do, he will prioritize OCT. Visual fields may also be helpful, but in most cases, preschool-age children are unlikely to comply, Dr. Stingl said. Although visual fields are helpful, Dr. Mahroo said they are not commonly performed in these patients at Moorfields in London.

Timely referral to a specialist is recommended for patients with suspected IRD to support diagnosis, counseling, and resource discussions as well as to improve quality of life.[25] Many specialist centers maintain IRD registries to support research and future trial enrollment.

"Nowadays, fortunately, in Spain, we can offer these kinds of options to our patients [from a younger age]. They can enter in our clinical trials, they can hear about future clinical trials or treatments, and they are ready to enter as soon as they are developed," Dr. Ayuso said. "I think the complete 360º clinical care for patients is very important."

Dr. Herrmann agrees that timely diagnosis is key, especially in young children. "It's important to help these kids so they can develop in the best way possible," he said. The first step, he explains, is setting an agenda with genetic testing and a clear diagnosis.

Role of Genetic Testing

The Expert Consensus Group widely endorses genetic testing as a standard component of an IRD evaluation. Most, including Elfride De Baere, MD, PhD, feel that a confirmed diagnosis has a positive influence on patients' quality of life because they can receive adequate care and follow-up across a variety of specialties. "Patients are better informed about prognosis and management of the disease. They can receive dietary advice and access to low vision aids," she said. "The diagnosis is also very important for family planning and reproductive options," Dr. De Baere added.

Luckily, access to genetic testing is becoming more common. "The awareness of genetic disease among medical retina and pediatric ophthalmologists is increasing, and so is the access to genetic testing. Further, budgets for genetic testing have shifted so that, broadly, if you have a genetic disease, you are eligible for testing in the United Kingdom," Dr. Black said.

In the United Kingdom, most patients receive genetic testing through a national genomic medicine service, Dr. Mahroo explained. "Before, we used to do gene panels, but now almost all of our IRD patients get it done through this route."

Nevertheless, genetic test results may take a long time to come back. About 5 years ago, it might take more than 1 year for results to be processed, Dr. De Baere mentioned. Now in Belgium, where she practices, test results are usually available in about 2-3 months. In the United Kingdom, results are typically available in about 4 months, according to Dr.

FIGURE 5A. Of the following diagnostic tests, which in your opinion are most important to accurately diagnose early stage IRD? (Select all that apply)

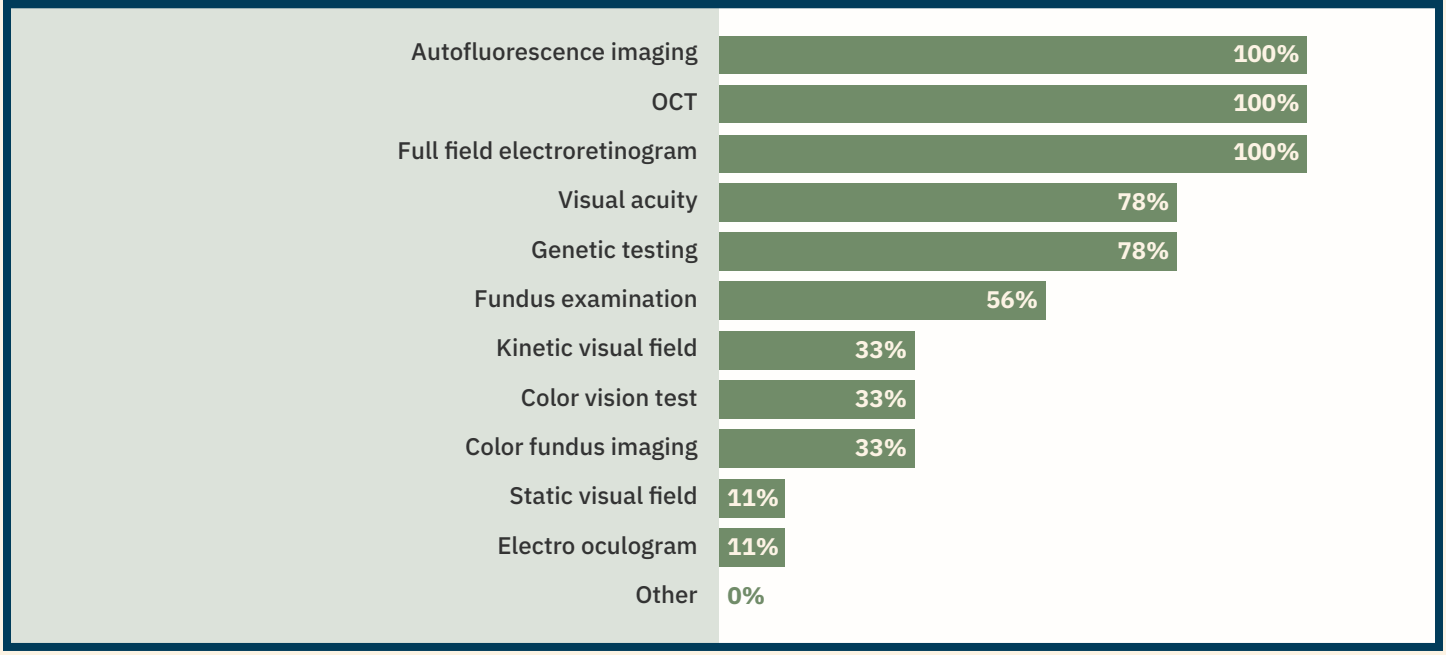
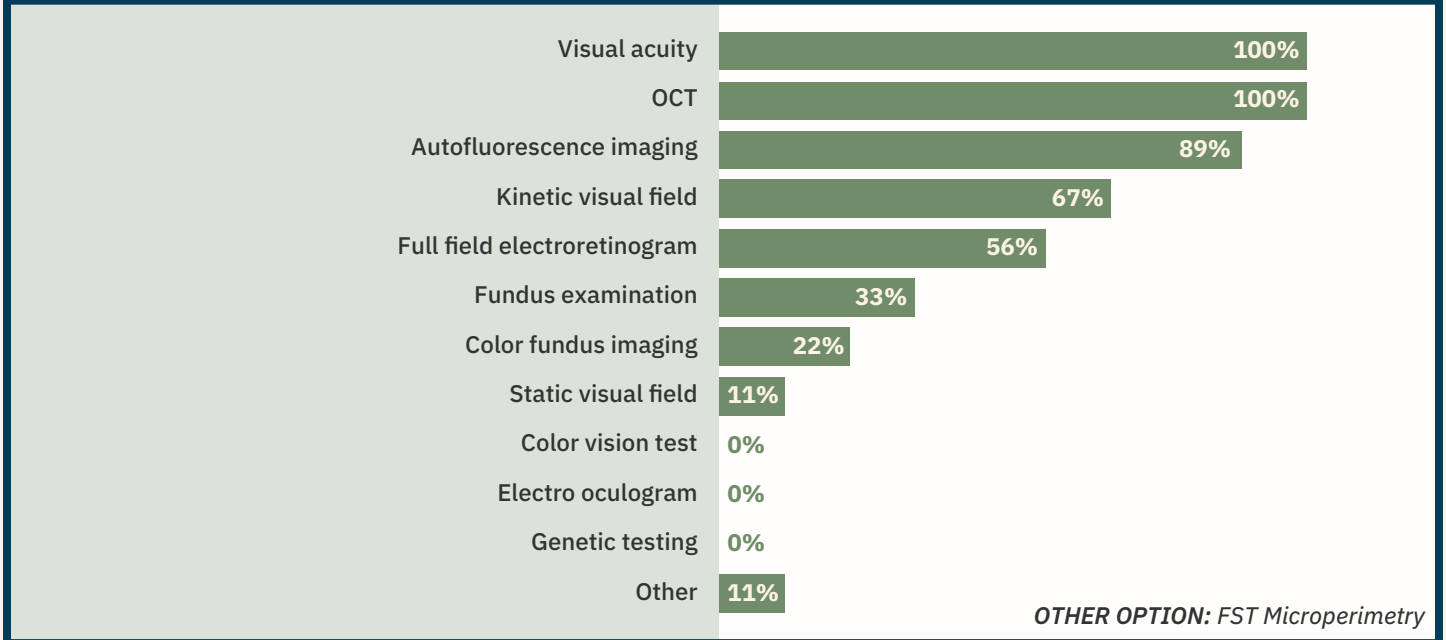


FIGURE 5B. Of the following diagnostic tests, which in your opinion are most important to accurately identify disease progression? (Select all that apply)



OTHER OPTION: *FST Microperimetry*

The Expert Consensus Group indicates FAF, OCT, and ffERG are the most valuable tools for early diagnosis (A) and visual acuity, OCT, FAF, kinetic visual fields, and ffERG as key tools to monitor progression (B).

Black. Sometimes, results may come back sooner from some genetic testing centers, but these results may not be as reliable. "I'd rather wait 4 weeks longer instead of having it back in 2 weeks' time, but not being able to really trust the results," Dr. Herrmann said.

One option for quicker and reliable test results is the Molecular Vision Laboratory in Oregon, United States. "They do over 1,000 genes, and they give us a result within a month," Dr. Mahroo said. "They're very responsive. If we ask them to check a specific gene, they are quite adaptable."

When asked what prompts them to refer patients for genetic testing, the most common responses from the Expert Consensus Group included clinical suspicion of IRD, segregation analysis of a known familial variant, electrophysiologic or imaging abnormalities, and family planning for a patient with identification of specific genetic variants associated with the disease. Even without a family history, genetic disease cannot be ruled out, Dr. Herrmann cautioned. "Often it's the clinical presentation together with the imaging that help you pin it down, and then we have a positive diagnosis rate coming back about 70% to 80% of the time we initiate genetic testing," he added.

Genetic testing may be helpful to guide management options, inform prognosis, and facilitate access to clinical trials or approved therapies.[26] Emerging next-generation sequencing panels targeting IRD-associated genes are widely available and should be considered for all patients with suspected IRD.[27-29] Today, whole-exome or whole-genome sequencing are primary tools to improve diagnostic yields, particularly if targeted panels are negative or inconclusive.[30]

Clinical geneticists in the Expert Consensus Group emphasize the importance of phenotype-guided testing, ideally interpreted within a multidisciplinary team. Variants of uncertain significance must be evaluated with caution, often requiring segregation analysis, functional studies, and reanalysis as genetic databases evolve.[31]

Interpretation of genetic results must be individualized. Some mutations exhibit variable penetrance or phenotypic heterogeneity, and compound heterozygosity, or the presence of complex alleles at a locus, is common in autosomal recessive disease.[32] Informed genetic counseling is crucial to help patients understand their diagnosis, inheritance patterns, reproductive risks, and eligibility for gene-based interventions.

Yet sometimes, patients remain undiagnosed after genetic testing. Dr. De Baere said about 40% to 50% of patients who undergo genetic testing for IRDs return inconclusive results. "In some cases, you will never find a diagnosis," she said.

Long-Term Management & Follow-Up

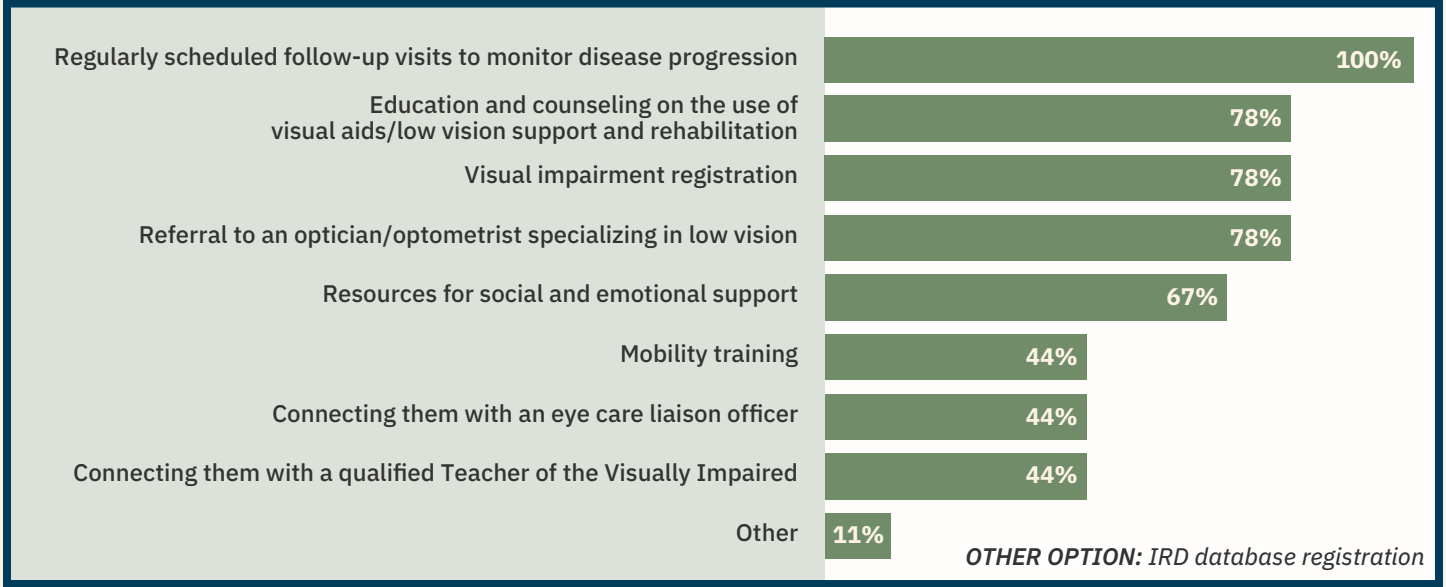
Effective management of IRDs requires a multidisciplinary, and ideally, an interdisciplinary approach that extends beyond diagnostics.[33] Experienced professionals from diverse specialties that include ophthalmology, genetics, neuropsychiatry, psychology, neurology, orthoptics, developmental therapy, occupational therapy, otolaryngology, as well as orientation and mobility must come together to provide comprehensive care and counseling aimed at helping patients and their families not only understand the condition and its side effects but also the psychological implications and the potential risks for offspring (for more information, see the section *"Collaboration Between Ophthalmologists, Geneticists, and Other Specialties" on page 18*).

While pharmacologic treatments for most IRDs are either rare or nonexistent, early diagnosis and supportive care can meaningfully improve quality of life. Emotional support, vision rehabilitation, and effective communication of the disease's prognosis are essential components of ongoing care. "You don't manage groups of people, you manage individuals," Dr. Black said. "You must manage them according to their needs."

Unfortunately, social and emotional support may not be readily available. "I think this is a little bit difficult, and maybe we don't do enough," Dr. Stingl said.

In the United Kingdom, a Certificate of Vision Impairment may be issued to certify a person has lost

FIGURE 6. **Of the following strategies, which do you use to help and manage patients with IRD effectively after they are diagnosed? (Select all that apply)**



The top strategy to help and manage patients with IRDs effectively among the Expert Consensus Group is regularly scheduled follow-up visits to monitor disease progression followed by education and counseling on the use of visual aids and low vision support and rehabilitation, visual impairment registration, and referral to an optician/optometrist specializing in low vision.

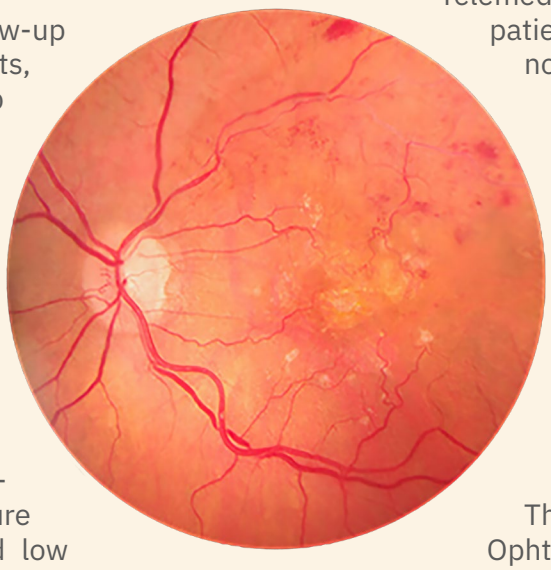
significant vision. There are two levels of impairment: sight impaired (ie, partially sighted) and severely sight impaired (ie, blind). Completed by an ophthalmologist and provided to a patient's general practitioner, their local authority, and the Royal College of Ophthalmologists Certifications Office with the patient's consent, the certificate enables a patient to access rehabilitation and habilitation services, financial concessions, welfare benefits, and other services.[34] Patients have reported, however, lack of clarity around the certification and registration processes, with investigators noting in their paper, "the lack of a joined-up process … needs to be addressed if we are able to provide the support that patients deserve in order to improve their quality of life and wellbeing."[34]

The Expert Consensus Group recommends regularly scheduled follow-up visits to monitor disease progression as the top strategy to help and manage patients with IRDs effectively (**Figure 6**), followed by education and counseling on the use of visual aids and low vision support and rehabilitation, visual impairment registration, and referral to an optician/optometrist specializing in low vision. According to Dr. DeBaere, recommending advocacy groups, such as the European Network for Rare Eye Diseases (ERN-EYE), is also welcomed by patients. ERNs are cross-border networks of health care providers that join forces to tackle rare and complex diseases such as IRDs. Charitable organizations such as the Royal National Institute for the Blind in the United Kingdom also play an enormous role in providing services and devices such as magnifiers, binoculars, and other low vision aids, Dr. Henderson said. They may also provide legal documentation to schools and businesses, ensuring students and employees are provided the right tools to succeed in their environments. Patient support organizations such as Stargardt's Connected, which is comprised of patients, clinicians, researchers, opticians, and pharmaceutical industry representatives, help individuals living with Stargardt's and other members of the community join forces to raise awareness, provide support, and seek a cure.

Follow-up strategies may be tailored to the type of IRD, disease severity, rate of progression, and patient age.[35] Follow-up intervals vary across the Expert Consensus Group, reflecting the heterogeneity of the disease course. Some respondents (33%) indicate they see patients annually, whereas some (11%) see patients every 3 years. Most (56%), however, indicate follow-up care is more nuanced, reporting it varies from patient to patient.

"We try to maintain contact on a regular but infrequent basis with as many patients as possible," Dr. Black said. "I don't like the notion that we can discharge them because there's nothing we can do. I think people appreciate being either followed regularly or to know that they could be if they chose to be. In particular, supporting them while they're adapting to their diagnosis, over that period of months or years when the emotional impact of the condition is at its greatest ... is key," he added.

Dr. Ayuso prefers an annual follow-up routine. "I think for stable patients, it is very important to follow-up at least once a year because, for these patients, they can eventually participate in clinical trials," she said. "It's important not to give them false hope, but having this follow-up can help select adequate patients to enter clinical trials."



On the other hand, 1-year follow-up intervals can also ensure patients receive visual aids and low vision training at the first sign of visual acuity loss, Dr. Ayuso said. "They urgently need this kind of care."

Dr. Henderson also recommends a 1-year follow-up pattern. "For me and the child, it's really important that we touch base because I need to know if they need additional support," he said.

Dr. Herrmann indicates he'd like to see patients more often than he does, and for younger children he prefers more frequent visits. "Every 9 months is ideal," he said, especially early in the diagnosis.

Dr. Mahroo said the interval can be even shorter for patients who have suspected but unconfirmed disease where there is a possibility of a nongenetic cause. "We might see them every few months to check things aren't changing quickly, which would be inconsistent with a genetic disease," he said. "But if we have a patient with a genetic diagnosis and we know what they're dealing with is a very slowly progressing disease, we'll offer them to be discharged if they want to be." This is done through a text-based patient-initiated follow-up process that asks if a patient wants a follow-up appointment or defer for 1 year. "That can work for up to 5 years and they don't need to see their primary care physician to get referred back," he said.

Depending on how quickly the disease is progressing, Dr. Stingl may see patients in cooperation with the local ophthalmologist once every 5 years once stability is achieved and maintained.

Telemedicine is also useful for monitoring patients with IRDs. Every Monday afternoon at Moorfields, Dr. Mahroo provides video consultations for those with suspected IRDs. "Ironically, sometimes patients have high-tech imaging, but no one's taken a proper family history," he said. "The family history can be helpful and guide us to what the likely gene is. ... I do that over video consultation and then we can arrange genetic testing remotely."

The American Academy of Ophthalmology offers a basic care schedule for patients with IRDs (**Table 1**),[35] and strategies for the management of patients after diagnosis include referral to low vision services, genetic counseling and support, trial screening, and participation in natural history studies. Additionally, the European Reference Network for Rare Eye Diseases (ERN-EYE) develops expert clinical consensus statements for particular disease states like RP and gene therapy (www.ern-eye.eu/).

Importantly, some practices may offer routine registration in institutional or national IRD databases, which not only supports longitudinal care but also facilitates therapeutic access and outcome tracking.

TABLE 1. Clinical Evaluation for IRDs[35]

ASSESSMENT	INITIAL VISIT	FOLLOW-UP (EVERY 1 TO 2 YEARS)
HISTORY		
• Ocular (including current needs)	1-4[a]	1-4
• Medical (including current medications and history of retinotoxic medication use)	1-4[a]	1-4
• Family history of vision problems	1-4[a]	1-4
PEDIGREE	1-4	1-4
CLINICAL EYE EXAMINATION		
• BCVA: ETDRS protocol (or equivalent)	1-4	1-4
• Color vision testing (optional)	1-4	1-4
• Slit-lamp biomicroscopy	1-4	1-4
• IOP	1-4	1-4
• Indirect ophthalmoscopy	1-4	1-4
IMAGING		
• Color fundus photos*	1-4	1-4
• Spectral Domain OCT	1-4	1-4
• Fundus autofluorescence: Short wavelength with reduced illumination when possible	1-4	1-4
• Infrared Reflectance or autofluorescence (when available)	1, 3, 4	1, 3, 4
VISUAL FIELDS		
• Kinetic	1-4	1-4
• Static	1-3[b]	1-3[b]
• Microperimetry	1-4[b]	1-4[b]
ELECTRORETINOGRAPHY		
• Full-field ERG[c] (when appropriate)	1-4	1-3
• Multifocal ERG[d] (when appropriate)	2, 4	2, 4
• FST (useful with unsteady fixation or when ERG is non recordable)		
GENETIC DIAGNOSTIC TESTING		
• Exome sequencing-based panel testing (standard-of-care) • Genome sequencing (shifting from research to the clinic) • Single gene vs gene panel testing	1-4	1-4 (if earlier visits did not provide conclusive results)

a) Numbers refer to clinical phenotypes:

1. *Rod-cone degenerations, such as retinitis pigmentosa. Those with stationary rod-cone dysfunction, such as congenital stationary night blindness, should be evaluated similarly at baseline, then followed with clinical eye examinations only.*
2. *Cone-rod degenerations. Conditions affecting cones that are traditionally considered stationary, such as achromatopsia, should also be evaluated similarly at baseline, then followed with eye examination annually as some cases may progress slowly, warranting ongoing follow up.*
3. *Chorioretinal degenerations, such as CHM-associated retinal degeneration (choroideremia) and gyrate atrophy.*
4. *Inherited dystrophies that involve the macula, such as cone degeneration, X-linked retinoschisis, ABCA4-associated macular degeneration (Stargardt disease), and PRPH2-associated macular degeneration (pattern dystrophy).*

b) Static perimetry and microperimetry are of uncertain value for patients with advanced disease as they may have unstable, eccentric fixation that makes interpretation difficult.

c) Full-field ERG is not necessary in Best disease, North Carolina macular dystrophy, and in cases of pattern dystrophy limited to the macula. However, if electro-oculogram testing is not available, full-field ERG should be normal in Best disease. A full-field ERG is appropriate for a patient with macular changes for whom one is considering cone or cone-rod dystrophy in the differential diagnosis. Also, a non-detectable ERG is not recommended to be repeated.

d) Multifocal ERG is of uncertain value in patients when central acuity is significantly reduced or fixation is unstable, as mentioned above.

**Abbreviations: ETDRS, Early Treatment of Diabetic Retinopathy Study*

***Fundus photos should be used sparingly in Stargardt disease and other maculopathies due to potential light toxicity, thus consideration should be given to limiting their use.*

COLLABORATION BETWEEN OPHTHALMOLOGISTS, GENETICISTS, AND OTHER SPECIALTIES

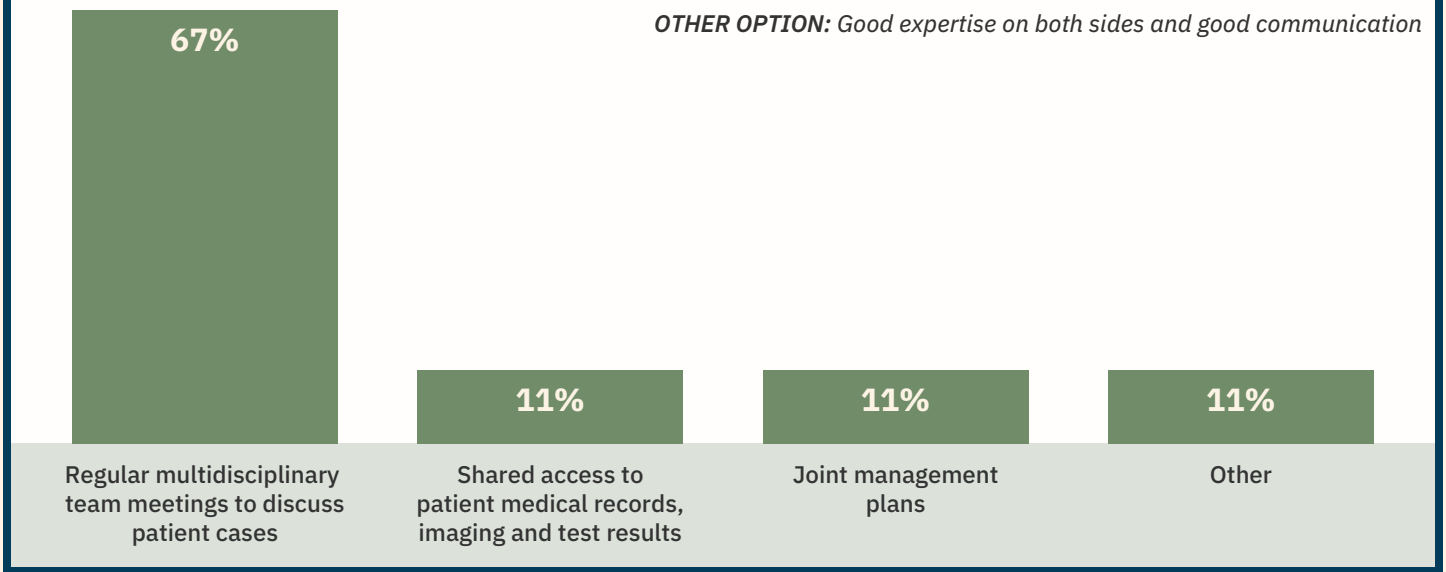
A consistent theme throughout Expert Consensus Group responses was the indispensable value of seamless multidisciplinary collaboration between retina specialists, clinical geneticists, and other specialists. The complexity of IRD diagnosis and management demands joint expertise from ophthalmologists, clinical geneticists, genetic counselors, and low vision rehabilitation specialists.

"Services for rare diseases have expanded," Dr. Black said. "The connectedness between primary care, optometrists, ophthalmologists, and pediatricians is greater than ever before."

Fortunately, the IRD community is small, and personal relationships are plentiful. "It usually comes quite naturally—working together—and it's important to have a constant exchange between experts. We have a lot of motivated people in the field. Overall, it's accepted by everyone that we need to collaborate, exchange ideas, and present cases."

The diagnostic and management complexity of IRDs cannot be addressed in silos. Best practices for multidisciplinary care and optimized collaboration suggested by the group include bidirectional communication, shared access to genetic test results and imaging, regular interdisciplinary meetings and grand rounds for variant interpretation and clinical correlation, standardized diagnostic and follow-up protocols, as well as co-developed educational tools for patients, families, and referring providers (**Figure 7**). "Not alerting the education system to the fact a child has a vision problem can impact their education more widely," Dr. Henderson said. "Psychologically, it plays into a child's sense of self-confidence. So poor vision at birth is counted as a developmental emergency. If your developmental milestones aren't checked and supported, children tend to set back on themselves. Not supporting a child can really impact who they are and their perception of themselves, and I think that's true even if patients have a later-onset form of RP," he added.

FIGURE 7. In your opinion, what is the best strategy to optimize collaboration between ophthalmologists and clinical geneticists to achieve comprehensive care for patients with IRDs?



Most (67%) of the Expert Consensus Group indicate that regular multidisciplinary team meetings to discuss patient cases is the best strategy to optimize collaboration between ophthalmologists and clinical geneticists and achieve comprehensive care for patients with IRDs.

Several of the Expert Consensus Group described successful models in which retina specialists and geneticists work side by side to ensure accurate phenotyping, timely testing, and cohesive counseling. An integrated care model, they reason, also supports natural history studies, facilitates trial enrollment, and improves continuity of care for patients living with a complex, lifelong condition such as IRDs.

Dr. Ayuso, whose center has one of the largest IRD registries with more than 8,000 patients, explains that their center has a weekly clinical session spanning across specialties to learn from each other and focus on developing the science behind caring for patients with IRDs.

"We organize patient care in a very multidisciplinary way and with a very close relationship to the different specialist ophthalmologists, electrophysiologists, neurologists, and audiologists," she said. "I think that is very important in order to develop the same interest in the disease and for our patients."

The catalog of genetic diagnoses in the Spanish National Health System offers recommendations regarding the types of genetic tests, the clinical context including carrier, presymptomatic, prenatal, and preimplantation diagnosis, and suggestions about which genes should be screened. It is updated periodically, contributing to the harmonization of genetic services across the country.

Dr. Herrmann describes a combined consent process used across universities in Germany that facilitates communication across specialties. "It really takes time to explain to these patients what is happening," he said. "It is usually not an ophthalmologist alone who will do this."

Effective communication, mutual respect for expertise, and coordinated patient care pathways are essential for delivering comprehensive and compassionate care to this vulnerable patient population. It may also be life-saving, Dr. Henderson said. "If a patient has a severe retinal dystrophy from birth or in the first months of life, making sure they've had an MRI of the brain, making sure they've had a renal opinion is crucial. Some of them will have other conditions that have a retinal dystrophy as part of that, and missing a related diagnosis would be potentially catastrophic," he elaborated.

Therapeutic Advances and the Future of IRD Treatment

The US FDA approval of *voretigene neparvovec-rzyl* for *RPE65*-related retinal dystrophy marked a milestone in ocular gene therapy. This adeno-associated virus (AAV)-based treatment demonstrated sustained improvements in functional vision for up to 7.5 years.[36] Long-term studies are underway to monitor efficacy and durability.[37] The availability of the treatment has catalyzed a surge in new investigational drugs.

As mentioned previously, gene therapy was overwhelmingly identified by the Expert Consensus Group as the most promising treatment on the horizon, although not all gene therapies have been shown to produce meaningful results, Dr. Stingl said. "Some have had safety issues."

Several gene therapy programs are in late-stage development, targeting conditions such as X-linked RP, choroideremia, and Stargardt disease. Recently, AAV5-hRKp.RPGR (*botaretigene sparoparvovec*, Janssen Pharmaceuticals) was shown to demonstrate an anticipated and manageable adverse events (AE) profile through 52 weeks in patients with RP GTPase regulator-associated X-linked RP.[38] The open-label, phase 1/2 dose escalation and expansion study enrolled 36 males 5 years or older who were randomized 1:1:1 to low or intermediate dosing or deferred treatment. Improvements in retinal sensitivity and functional vision were seen among patients treated with *botaretigene sparoparvovec* compared to those in the deferred treatment group at week 26, and similar trends were seen at week 52. A phase 3 trial, however, did not meet its clinical endpoint.

Beacon Therapeutics completed enrollment for a global, randomized, controlled, masked, multicenter phase 2/3 trial evaluating the efficacy, safety, and tolerability of laru-zova for the treatment of X-linked RP. The trial assesses two dose levels of laru-zova for improving low-luminance visual acuity and mean sensitivity, with 12-month data expected in the second half of 2026.

The safety and efficacy of ATSN-101, a subretinal *AAV5* gene therapy for LCA1 also has been studied.[39] LCA1 is caused by mutations in *GUCY2D*. A total of 15 patients with biallelic mutations in *GUCY2D* were enrolled. In a dose escalation phase, three adult cohorts (n=3) were treated with three ascending doses of a unilateral subretinal injection of ATSN-101. In a dose-expansion phase, one adult cohort (n=3) and one pediatric cohort (n=3) were treated at the high dose. Treatment was well tolerated over 12 months, with no serious adverse events attributed to ATSN-101. High-dose treatment led to significant and sustained improvements in dark-adapted retinal sensitivity (mean change: 20.3 dB; P=.012). There were modest gains in visual acuity. Half of the high-dose patients completing the mobility test achieved the maximum score in the treated eye.

Beyond gene replacement, novel strategies include antisense oligonucleotide to modulate pre-mRNA splicing. Clinical trials for sepofarsen (Sepul Bio by Théa) as an investigational treatment for *CEP290*-related LCA type 10 are underway. A phase 1b/2 multicenter, multiple-dose, dose-escalation clinical trial supported the continuation of sepofarsen development.[40] A post-hoc analysis of the results showed statistically significant improvements in visual acuity and retinal sensitivity. Other RNA-based therapies in phase 1/2 and phase 2/3 clinical trials included ultevursen (Sepul Bio by Théa) and QR-1123 (ProQR Therapeutics).[41] In April 2022, ProQR Therapeutics discontinued the development of QR-1123 and other IRD programs.

"I personally think RNA treatment for specific mutations is a good approach and partially successful," Dr. Stingl said, adding that none are yet approved but have shown promising results.

Another encouraging development, CRISPR-based gene editing, may also show promise for IRDs. "In my opinion, that's the most elegant and reasonable approach to fix a genetic problem," Dr. Herrmann said.

Subretinal delivery of an experimental CRISPR/Cas therapeutic agent developed for LCA type 10 in animal models was well tolerated and sustained productive editing rates that met or exceeded the targeted threshold.[42] Further, a dual AAV-CRISPR/Cas9 treatment designed to reprogram rods into cone-like photoreceptors has been shown to significantly rescue rod and cone degeneration and restore visual function in two mouse models.[43]

Optogenetics has also made some headway in this space. Using gene therapy strategies to introduce light-sensitive transmembrane proteins called opsins into cells other than photoreceptors in the retina, optogenetics is a mutation- and disease-agnostic approach to potentially transform the management of the more advanced stages of conditions such as RP and Stargardt disease. Current therapies in development include MCO-010 (Nanoscope Therapeutics), RST-001 (RetroSense/Allergan), GS030 (GenSight), BS01 (Bionic Sight), and RTx-015 (Ray Therapeutics). Of the optogenetic treatments in the pipeline, MCO-010 has the most advanced clinical status. A randomized, multicenter, sham-controlled, phase 2B study of the treatment demonstrated a clinically meaningful improvement in vision in 27 patients with severe vision loss from advanced RP. At 52 weeks, approximately 40% of patients experienced a statistically significant mean change in BCVA improvement from baseline of at least 0.3 logMAR. The results were sustained at 76 weeks.[44]

More clinical trial information may be found at https://www.fightingblindness.org/clinical-trial-pipeline.

"A very big priority is the mutation- and gene-agnostic therapies," Dr. De Baere said. "In my opinion, that would be the most important advance apart from gene therapy because we have over 400 IRD genes. It's not possible to develop therapy for each individual gene and also for each individual mutation."

An increasingly important challenge in clinical research in the EU and worldwide is potential bureaucracy and regulatory barriers. The system for approval of clinical trials and novel treatments has become very time- and resources-consuming, which can introduce delays. Medically, a quality control of clinical trials and therapy approval based on expert groups instead of centralized control might be more efficient and meaningful. Particularly, one current challenge is the development of outcome measures that are sufficiently sensitive to detect meaningful improvements within an appropriate time frame.

There are also new frontiers in retinal cell transplantation to regenerate retinal layers and establish new synapses among retinal cells. Currently experimental, most retinal cell transplantation approaches are in early phases of development.[45] Likewise, research into stem cell–based therapies[46] and the use of grafted tissue in retinal diseases continue, with potential applications for IRDs.[46-48]

While enthusiasm is high, challenges in IRD treatments remain, particularly regarding immune responses to viral vectors, limited gene packaging capacity, and long-term transgene expression. Real-world barriers to IRD care include limited patient access to specialized centers, variability in genetic confirmation protocols, and challenges in educating patients and payers about these novel therapies. Nonetheless, the IRD community is optimistic about the expanding treatment pipeline and the potential to transform care in the next decade.

"Some treatments are showing promising results, and we're very hopeful that they'll come to fruition and become licensed," Dr. Mahroo said. "The standard thing I say to most patients is, 'Unfortunately, there's no treatment right now, but there's lots of research going on. We hope in 5 to 10 years there will be something for you.'"

Conclusion

IRDs, once relegated to the realm of clinical curiosity, have emerged at the forefront of genomic medicine and therapeutic innovation. This consensus statement underscores the critical role of early detection, multidisciplinary and interdisciplinary diagnosis and management, and molecular confirmation in guiding care. As gene and cell therapies transition from bench to bedside, the ophthalmology community must be prepared to adopt new standards of care that integrate advanced diagnostics with patient-centered management.

Through continued collaboration, research, and advocacy, clinicians and researchers can shift the paradigm for IRD from inevitable vision loss to targeted intervention, hope, and improved quality of life.

References

1. Ben-Yosef T. Inherited retinal disease. *Int J Mol Sci.* 2022;23(21):13467.

2. Hanary M, Rivolta C, Sharon D. Worldwide carrier frequency and genetic prevalence of autosomal recessive inherited retinal diseases. *Proc Natl Acad Sci U S A.* 2020;117(5):2710-2716.

3. Tatour Y, Ben-Yousef T. Syndromic inherited retinal diseases: genetic, clinical and diagnostic aspects. *Diagnostics (Basel).* 2020;10(10):779.

4. Ullah M, Rehman AU, Quinodoz M, et al. A comprehensive genetic landscape of inherited retinal diseases in a large Pakistani cohort. *Genomic Med*. 2025;10:31.

5. Wong WM, Mahroo OA. Monogenic retinal diseases associated with genes encoding phototransduction proteins: a review. *Clin Exp Ophthalmol*. 2025;53(3):260-280.

6. Manley A, Meshkat BI, Jablonski MM, Hollingsworth TJ. Cellular and molecular mechanisms of pathogenesis underlying inherited retinal dystrophies. *Biomolecules*. 2023;13(20:271.

7. Cremers F, van de Pol DJ, van Kerkhoff LP, Wieringa B, Ropers HH. Cloning of a gene that is rearranged in patients with choroideraemia. *Nature.* 1990;347:674-677.

8. Dryja TP, McGee TL, Hahn LB, et al. Mutations within the rhodopsin gene in patients with autosomal dominant retinitis pigmentosa. *N Engl J Med.* 1990;323:1302-1307.

9. RetNet. Accessed July 15, 2025. https://retnet.org/

10. Carss KJ, Arno G, Erwood M, et al. Comprehensive rare variant analysis via whole-genome sequencing to determine the molecular pathology of inherited retinal disease. *Am J Hum Genet*. 2017;100:75-90.

11. Del Pozo-Valero M, Riveiro-Alvarez R, Martin-Merida I, et al. Impact of next generation sequencing in unraveling the genetics of 1036 Spanish families with inherited macular dystrophies. *Invest Opthalmology Vis Sci*. 2022;63:11.

12. Stone EM, Andorf JL, Whitmore SS, et al. Clinically focused molecular investigation of 1000 consecutive families with inherited retinal disease. *Ophthalmology*. 2017;124:1314-1331.

13. Schneider N, Sundaresan Y, Gopalakrishnan P, et al. Inherited retinal diseases: linking genes, disease-causing variants, and relevant therapeutic modalities. *Prog Retin Eye Res.* 2021;89:101029.

14. Fuster-García C, García-Bohórquez B, Rodríguez-Muñoz A, et al. Usher syndrome: genetics of a human ciliopathy. *Int J Mol Sci.* 2021;22:6723.

15. Molday RS, Zhong M, Quazi F. The role of the photoreceptor ABC transporter ABCA4 in lipid transport and Stargardt macular degeneration. *Biochim Biophys Acta.* 2009;1791(7):573-583.

16. RPGR gene. MedlinePlus. Accessed July 16, 2025. https://medlineplus.gov/genetics/gene/rpgr/

17. Ordonez-Labastida V, Chacon-Camacho O, Lopez-Rodriguez V, Zenteno JC. USH2A mutational spectrum causing syndromic and non-symdromic retinal dystrophies in a large cohort of Mexican patients. *Mol Vis*. 2023;29:31-38.

18. Verbakel SK, van Huet RAC, Boon CJF, et al. Non-syndromic retinitis pigmentosa. *Prog Retin Eye Res.* 2018;66:157-186.

19. Stargardt disease. Orphanet. Accessed July 16, 2025. https://www.orpha.net/en/disease/detail/827#:~:text=The%20prevalence%20is%20estimated%20at,Both%20sexes%20are%20equally%20affected

20. Leber congenital amaurosis. Orphanet. Accessed July 16, 2025. https://www.orpha.net/en/disease/detail/65?name=Leber%20congenital%20amaurosis&mode=name

21. Usher syndrome. Orphanet. Accessed July 16, 2025. https://www.orpha.net/en/disease/detail/886#:~:text=Prevalence:%201%2D9%20/%20100,with%20half%20of%20the%20cases

22. Eyes on inherited retinal diseases (IRDs). Eyes on Genes. Janssen Pharmaceuticals. Accessed July 16, 2025. https://www.eyesongenes.com/inherited-retinal-diseases/

23. Suppiej A, Marino S, Reffo ME, et al. Early onset retinal dystrophies: clinical clues to diagnosis for pediatricians. *Ital J Pediatr.* 2019;45:168.

24. Georgiou M, Fujinami K, Michaelides M. Retinal imaging in inherited retinal diseases. *Ann Eye Sci.* 2020;5. doi: 10.21037/aes-20-81

25. Mayo Clinic. Diagnosis, clinical trials and treatments for inherited retinal disease. October 14, 2024. Accessed July 16, 2025. https://www.mayoclinic.org/medical-professionals/ophthalmology/news/diagnosis-clinical-trials-and-treatments-for-inherited-retinal-diseases/mac-20556115#:~:text=Inherited%20retinal%20diseases%20(IRDs)%20vary,research%2C%20imaging%20and%20treatments%20available

26. Lam BL, Leroy BP, Black G, Ong T, Yoon T, Yoon D, Trzupek K. Genetic testing and diagnosis of inherited retinal diseases. *Orphanet J Rare Dis.* 2021;16:514.

27. Chiang JP, Trzupek K. The current status of molecular diagnosis of inherited retinal dystrophies. *Curr Opin Ophthalmol.* 2015;26:346-351.

28. Wang F, Wang H, Tuan HF, et al. Next generation sequencing-based molecular diagnosis of retinitis pigmentosa: identification of a novel genotype-phenotype correlation and clinical refinements. *Hum Genet.* 2014;133:331-345.

29. O'Sullivan J, Mullaney BG, Bhaskar SS, et al. A paradigm shift in the delivery of services for diagnosis of inherited retinal disease. *J Med Genet.* 2012;49:322–326.

30. Lionel AC, Costain G, Monfared N, et al. Improved diagnostic yield compared with targeted gene sequencing panels suggests a role for whole-genome sequencing as a first-tier genetic test. *Genet Med.* 2018;20:435-443.

31. Gupta P, Nakamichi K, Bonnell AC, et al. Familial co-segregation and the emerging role of long-read sequencing to re-classify variants of uncertain significance in inherited retinal diseases. *NPJ Genom Med.* 2023;8:20.

32. NHS. Core concepts: autosomal recessive inheritance. Accessed July 16, 2025. https://www.genomicseducation.hee.nhs.uk/genotes/knowledge-hub/autosomal-recessive-inheritance/

33. Murro V, Banfi S, Testa F, et al. A multidisciplinary approach to inherited retinal dystrophies from diagnosis to initial care: a narrative review with inputs from clinical practice. *Orphanet J Rare Dis.* 2023;223:18.

34. Pardhan S, Driscoll R, Ingleton H, et al. Confusion around certification of vision impairment (CVI) and registration processes—are patients falling through the cracks? *Eye*. 2023;37:3412-3416.

35. Guidelines on clinical assessment of patients with inherited retinal degenerations – 2022. American Academy of Ophthalmology. October 2022. Accesed July 17, 2025. https://www.aao.org/education/clinical-statement/guidelines-on-clinical-assessment-of-patients-with

36. Leroy BP, Fischer MD, Flannery JG, et al. Gene therapy for inherited retinal disease: long-term durability of effect. *Ophthalmic Res.* 2023;66(1):179-196.

37. Fischer MD, Simonelli F, Shani J, et al. Real-world safety and effectiveness of voretigene neparvovec: results up to 2 years from the prospective, registry-based PERCEIVE study. *Biomolecules.* 2024;14(1):122.

38. Michaelides M, Besirli CG, Yang Y, et al. Phase 1/2 AAV5-hRKp.PRGR (botaretigene sparoparvovec) gene therapy: safety and efficacy in PRGR-associated X-linked retinitis pigmentosa. *Am J Ophthalmol*. 2024;267:122-134.

39. Yang P, Pardon LP, Ho AC, et al. Safety and efficacy of ATSN-101 in patients with Leber congenital amaurosis caused by biallelic mutations in GUCY2D; a phase 1/2, multicentre, open-label, unliateral dose escalation study. *Lancet*. 2024;404(10456):962-970.

40. Russell SR, Drack AV, Cideciyan AV, et al. Intravitreal antisense oligonucleotide seporarsen in Leber congenital amaurosis type 10: a phase 1b/2 trial. *Nat Med.* 2022;28(5):1014-1021.

41. Girach A, Audo I, Birch DG, et al. RNA-based therapies in inherited retinal diseases. *Ther Adv Ophthalmol*. 2022;14:2515841422134602.

42. Madder ML, Stefanidakis M, Wilson CJ, et al. Development of a gene-editing approach to restore vision loss in Leber congenital amaurosis type 10. *Nat Med.* 2019;25(2):229-233.

43. Zhu J, Ming C, Fu X, et al. Gene and mutation independent therapy via CRISPR-Cas9 mediated cellular reprogramming in rod photoreceptors. *Cell Res.* 2017;27(6):830-833.

44. Boyer DS, Bergstrom L, Emanuelli A, et al. Efficacy and safety of MCO-010 optogenetic therapy for vision restoration in patients with severe vision loss due to retinitis pigmentosa: a phase 2b randomized, sham-controlled, multi-center, multi-dose, double-masked clinical trial (RESTORE). *Invest Ophthal Vis Sci.* 2023;64(8):5443.

45. Sorrentino FS, Di Terlizzi P, De Rosa F, et al. New frontiers in retinal transplantation. *World J Transplant.* 2024;14(4):97690.

46. Radu M, Branisteanu DC, Pirvulescu RA, et al. Exploring stem-cell-based therapies for retinal regeneration. *Life.* 2024;14(6):668.

47. Cotrim CC, Jorge R, de Oliveira MC, et al. Clinical studies using stem cells for treatment of retinal diseases: state of the art. *Arq Bras Oftalmol.* 2020;83:160-167.

48. Chen X, Xu N, Li J, Zhao M, Huang L. Stem cell therapy for inherited retinal diseases: a systematic review and meta-analysis. *Stem Cell Res Ther.* 2023;14:286.

49. Rivolta C., Celik E, Kamdar D, et al., RetiGene, a comprehensive gene atlas for inherited retinal diseases. Am. J. Hum. *Genet*. 2025: In press (https://doi.org/10.1016/j.ajhg.2025.08.017)

50. Cornelis SS, Bauwens M, Haer-Wigman L, et al. Compendium of Clinical Variant Classification for 2,246 Unique ABCA4 Variants to Clarify Variant Pathogenicity in Stargardt Disease Using a Modified ACMG/AMP Framework. *Hum Mutat*. 2023 Dec 26;2023:6815504.

51. Thompson DA, Jayasundera KT, Alekseev O, et al. Addressing Challenges in Developing Treatments for Inherited Retinal Diseases: Recommendations From the Third Monaciano Symposium. *Transl Vis Sci Technol*. 2025 Aug 1;14(8):37.

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