AMERICAN ACADEMY OF OPHTHALMOLOGY®

CLINICAL STATEMENT

Guidelines on Clinical Assessment of Patients with Inherited Retinal Degenerations

Abstract

This Academy Clinical Statement provides recommendations and clinical genetic assessments of patients with inherited retinal degenerations (IRDs). Various testing procedures and the timing at which they are recommended are described for patients within 4 broad classes of IRD (rod-cone degenerations, cone-rod degenerations, chorioretinal degenerations and inherited macular dystrophies). Pediatric patients not infrequently require modified testing regimens or sedation for accurate assessment. Genetic testing and genetic counseling are essential components of the management of patients with IRDs as genetic testing may confirm the diagnosis, provide information to optimize management of the patient and family members, and potentially confirm eligibility to participate in clinical trials. For example, genetic testing is required to determine eligibility of patients for approved gene therapies such as voretigene neparvovec-rzyl for *RPE65*-related IRD. This document is intended to provide guidelines for the management of patients with IRDs and provides information to support and educate patients with IRD. As always, final decisions are the responsibility of the individual treating physicians and are based on the needs of individual patients.

Introduction

Inherited retinal degenerations (IRDs) comprise a wide range of genetically and phenotypically heterogeneous diseases that share a variable progressive loss of photoreceptor function accompanied by visual loss. Understanding of the cellular and molecular mechanisms underlying IRDs has expanded dramatically, leading to clinical trials of therapies to slow photoreceptor degeneration or restore some vision. Treatments target specific genetic causes of disease and stages of the degenerative process. In some cases, treatments target disease genes or mutations. The FDA (in 2017), the EMA (in 2018), and Health Canada and the Therapeutic Goods Administration of Australia (2020) approved voretigene neparvovec-rzyl for *RPE65*-related IRD to specifically treat patients in countries where it is approved. Clinical care of patients has evolved over the past decade with improved diagnostic tools (e.g., genetic testing, novel noninvasive visual function testing, and imaging studies). These guidelines highlight the benefit of recent advances for both practitioners and patients and will help develop standards for best use of new technologies with the goal of helping physicians optimize patient care.

Examinations for Patients with Inherited Retinal Degenerations

Patient evaluations aim to:

1. Establish a clinical diagnosis so the patient receives appropriate care (prognosis, monitoring for co-morbidities, and assessment of other organs that may be affected in syndromic conditions). Other non-genetic causes of retinal degeneration should be considered and excluded.
2. Provide information on the genetic nature and inheritance of the disease and communicate the implications to other relevant family members.
3. Provide information about ongoing or future clinical trials and novel treatments.
4. Help the patient and family cope with and prepare for progressive visual impairment (low vision consultation, employment accommodations, and emotional support).

What should be done

- A thorough ocular/medical history and pedigree documenting family history of eye disease should be obtained at the initial visit and updated during subsequent visits.
- Understanding the patient's mood and affect is important, being sensitive to signs of depression that may accompany progressive vision loss.
- Molecular genetic testing (genotyping) of the patient can be valuable to confirm the diagnosis and optimize management.
- Clinical evaluation:
    - best-corrected visual acuity with manifest refraction using standardized eye charts,[1]
    - biomicroscopy with measurement of intraocular pressure (assessment of cataracts and anterior segment anomalies),
    - dilated ophthalmoscopy to document features potentially related to vision loss (optic nerve and other retinal diseases, deposits, vessels, atrophy, schisis and macular edema).

- Imaging
    - Standard color or wide-field fundus photography may be performed at the initial visit to provide documentation of disease state and provide the context to align and compare data from other fundus modalities such as fundus autofluorescence (AF) images.
        - For patients with nyctalopia and/or peripheral visual field loss, wide-field imaging has advantages since the primary site of disease is not in the macula in early disease.
        - Fundus photos should be used sparingly in Stargardt disease and other maculopathies due to the risk of light toxicity. A test should be ordered only if it will be useful to monitor disease progress or determine if a patient is eligible for a clinical trial.
        - Macular or wide-field AF fundus imaging using reduced illumination (25%), longer exciting wavelengths, infrared AF or near infrared fundus reflectance are good alternatives to short-wavelength AF in patients with retinitis pigmentosa and Stargardt disease to possibly reduce the risk of phototoxicity, although near-infrared imaging provides distinct information.[2,3]
            - Near infrared fundus reflectance is a separate imaging modality from short-wavelength AF that also provides insight on RPE health.
    - Optical Coherence Tomography (OCT) provides cross-sectional imaging of the photoreceptors, retinal pigment epithelium, and inner retinal layers including the retinal nerve fiber layer.
        - High-density volume scans with documentation of central retinal thickness provide a useful baseline for monitoring progression in structural features and helping to monitor CME, epiretinal membranes or macular schisis.

- Visual field testing is important to document the functional extent of vision from central to the far periphery. This is essential for determination of legal blindness, disability, and to counsel patients on visual limitations.
    - Static visual field testing has advantages of automated indices of sensitivity loss and performance parameters to assess reliability.
        - Newer perimeters test the entire field, and digital data can be exported into other applications for specific purposes such as modeling of sensitivity, which is useful for quantitative measurement in clinical trials.
        - Although static perimetry using the Humphrey visual field (HVF) 30-2 protocol is acceptable in the federal registry for the determination of

legal blindness and vision-related disability, there are perimeters that allow static testing well beyond the 60-degree range.
        - This document does not advocate for any specific company's instrument or product.
    - **Kinetic perimetry** is the most common method used to assess peripheral vision and for licensing requirements for driving, disability evaluations, and legal blindness status.
    - **Fundus-guided perimeters (microperimeters)** are particularly useful for measuring macular function in patients with eccentric fixation due to maculopathy and to investigate structure-function correlations.[4]

- Electrophysiology
    - **The full-field electroretinogram (ERG)** is important for diagnosis and staging of diffuse photoreceptor disease, evaluating the retina-wide function of rods and cones.[5]
        - Delays in cone b-wave implicit times are an early sign of disease and reflect retina-wide involvement.
        - Young patients with disease that appears to be limited to the macula benefit from full-field ERGs to rule out retina-wide disease.
    - **Multifocal or pattern ERG** testing can be useful for detection and monitoring disease progression for diseases that primarily affect the macula.[6] However, its accuracy can be limited in those patients with notable loss of central vision who are unable to maintain steady fixation.
    - ISCEV (International Society for Clinical Electrophysiology of Vision) has published and updated standards that enable recordings to be compared between institutions and examiners (http://link.springer.com/article/10.1007/s10633-014-9473-7).[7,8]
    - Although it is not a test that uses electrophysiology, the **full-field stimulus test (FST)**[9,10] can be useful when retinal function can no longer be reliably documented by ERG and provides a test that can measure rod- and cone-mediated visual function, but does not require stable fixation or electrode contact with the eye.

Because IRDs comprise a variety of conditions, different examinations may be applied to patients with different types of disease. Four major types of IRDs that are encountered clinically include rod-cone degenerations, cone-rod degenerations, chorioretinal degenerations and inherited macular dystrophies. The table presented below describes the examinations and timing at which the tests should be considered for patients with IRDs. For syndromic diseases such as Usher syndrome, the schedule should include additional referral of the patient to an otolaryngologist or audiologist at baseline and for continued management of any audiologic and balance issues. Other syndromic retinal degenerations may need referral to a wider group of physicians for follow-up of systemic disease.

Clinical Evaluation: Inherited Retinal Degenerative Diseases

Assessment	Initial Visit	Follow Up Visit Every 1-2 Years
History • Ocular (including current needs) • Medical (including current medications and history of retinotoxic medication use)	1-4[a]	1-4

• Family history of vision problems		
Pedigree	1-4	1-4
Clinical eye examination • Best corrected visual acuity: Early Treatment of Diabetic Retinopathy Study (ETDRS) protocol (or equivalent) • Color vision testing (optional) • Slit lamp biomicroscopy • Intraocular pressure • Indirect ophthalmoscopy	1-4	1-4
Imaging • Color fundus photos* • Spectral Domain Optical Coherence Tomography • Fundus autofluorescence: Short wavelength with reduced illumination when possible • Infrared Reflectance or autofluorescence (when available)	 1-4 1-4 1-4 1, 3, 4	 1-4 1-4 1, 3, 4
Visual fields • Kinetic • Static • Microperimetry (when available)	 1-4 1-3[b] 1-4[b]	 1-4 1-3[b] 1-4[b]
Electroretinography • Full-field ERG[c] (when appropriate) • Multifocal ERG[d] (when appropriate) • FST (useful with unsteady fixation or when ERG is non recordable)	 1-4 2,4	 1-3 2,4
Genetic Diagnostic Testing • Single gene vs gene panel testing • Exome sequencing • Genome sequencing (usually research)	1-4	1-4 (if earlier visits did not provide conclusive results)

Legend:

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 or 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.

* 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.

Pediatric Patients

Young children are often not able to perform the functional tests utilized in adults or may provide data that are unreliable. It is difficult to measure visual function in infants (preferential looking, optokinetic nystagmus, pupillometry, etc.). With infants under 2 years of age, certain tests such as a full-field ERG using skin electrodes or hand-held OCT imaging can be performed after swaddling the sleepy infant in the dark, but most often sedation provides more reliable results. Sedated exams between the ages of 2 and 6 also provide the opportunity for a more comprehensive exam and higher quality imaging; however, the risks of sedation must be weighed against the value of the information gained at the specific age. In some cases, sedation may influence ERG tracings, so normative data are essential for proper interpretation.[8] Visual field measurement in children less than 7 years old can be challenging and unreliable; however, with repetition, performance will often improve as the child matures.[11]

Genetic Testing and Genetic Counseling

Methods for identifying the genetic cause of IRDs have advanced significantly in recent years, such that a causative mutation can be identified in up to 56-76% of patients with inherited retinal disorders.[12-15] Genetic testing is appropriate for most patients with a presumed genetic retinal degeneration. At risk family members can sometimes benefit from genetic testing, although the implications of genetic testing for asymptomatic individuals in the absence of established therapies must be considered and should be accompanied by genetic counseling. The American Academy of Ophthalmology Task Force on Genetic Testing published recommendations for genetic testing of inherited eye diseases[16] located at: http://www.ncbi.nlm.nih.gov/pubmed/22944025. A negative result does not necessarily mean the patient does not have the disease. Absence of a disease variant may be affected by the testing methodology.

Genetic testing that clearly identifies the genetic cause of disease does not need to be repeated but testing which was negative or inconclusive upon original testing may be revisited. The identification of new IRD genes and advances in laboratory technology can improve the detection rate.[17] Moreover, as our interpretation of variants improves, a result that was considered to be inconclusive may yield a positive result with improved interpretation of variants.[17]

Genetic testing plays an important role in improving the accuracy of diagnosis and prognosis, providing patients and families with specific inheritance risks, and guiding treatment decisions. For example, patients would need to have genetic testing to determine if they are eligible for the FDA-approved voretigene neparvovec or be considered for any of the numerous clinical trials of gene-based therapies (clinicaltrials.gov).[18-21] Genetic testing can identify patients with retinal disease due to mutations in genes with systemic associations. Genetic testing for patients with IRDs can take multiple forms, including single gene analyses,

panel-based tests that include many IRD disease genes, or more expansive testing such as whole exome and whole genome sequencing.

Because of the genetic heterogeneity of the other phenotypes (>80), next generation sequencing testing using a retinal dystrophy panel provides an efficient first step for genetic testing. Whether the patient has syndromic features or not, testing should include genes known to be associated with syndromic forms of retinal disease, since some patients may only show the syndromic features later. Some 'syndromic genes' can be associated with a non-syndromic retinal degeneration. As these technologies continue to evolve, clinicians are encouraged to work with geneticists and/or genetic counselors to ensure appropriate genetic testing.

To fully benefit from genetic testing in this patient population, results must be properly interpreted, by both the lab and the provider. Genetic tests should be interpreted and disclosed to the patient and family by an expert physician or genetic counselor who has the time to discuss potentially sensitive and complex matters. Genetic counseling should be provided after results are obtained; counseling can be provided in the physician's office, or by referral to an in-person genetic counselor (www.nsgc.org), a clinical geneticist with expertise in genetically determined eye disorders, or a telephone-based genetic counselor. Genetic counseling can help to inform patients of the implications and limitations of genetic testing for themselves and their family members, guide patients through the genetic testing process, prepare individuals for the psychosocial risks and implications of certain results, interpret complex variant findings, and provide a clear understanding of how genetic test results will affect their immediate and future care. Genetic counseling for early onset disease should be also offered again, later in life, to provide the greatest benefit.

Patient Education and Support

Through discussions with their eye care team, patients should be provided with information about the hereditary and likely progressive course of disease with counseling about genetic testing and diagnoses, as described above. Physicians play an important role in encouraging low vision rehabilitation, working with school personnel, advocating for mobility training, and assessing emotional status. Patients may benefit from low vision evaluation at baseline and every 1-2 years as necessary. Patients should also be informed of registries and information about research in the field, including clinical trials (www.clinicaltrials.gov).

This document also provides websites that list contact information for blind services organizations within the United States and Canada from the American Foundation for the Blind (https://afb.org/info/about-the-afb-directory-of-services/5 and https://www.afb.org), Retina International (https://retina-international.org), the CNIB Foundation (https://www.cnib.ca), Foundation Fighting Blindness (https://www.fightingblindness.org) and Fighting Blindness Canada (https://www.fightingblindness.ca/). These websites should be of value for contacting rehabilitation services for patients with blinding retinal diseases.

Every state has a department of rehabilitation supported by the National Council of State Agencies for the Blind. Support services include vocational rehabilitation (including job retraining), mobility training, evaluation for assistive technology devices, and individualized counseling. Local support services can be found at www.ncsab.org. Many low vision patients may benefit from use of a guide dog; information on guide dog services in the United States can be found at https://www.guidedogs.com/. Physicians should also be aware of the necessity of supporting the mental health needs of their patients, both at the onset of the diagnosis and as the condition progresses. This support may come from resources such as low vision support groups and individual counseling services.[22]

Summary

Patients with inherited retinal degenerations will benefit from evolving knowledge that may influence their outcome. Special attention to aspects of the history and ophthalmic examination, tests of retinal structure and function, and genetic testing all help to determine an accurate diagnosis. Clinical and genetic testing of patients with IRDs go hand in hand, and one should not be interpreted without the other to ensure accuracy. This Clinical Statement aims to guide Academy members and care providers to optimize evaluations at baseline and during ongoing care of patients with IRDs.

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References

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1. Early Treatment Diabetic Retinopathy Study design and baseline patient characteristics. ETDRS report number 7. *Ophthalmology.* 1991;98(5 Suppl):741-756.
2. Chun R, Fishman GA, Collison FT, Stone EM, Zernant J, Allikmets R. The value of retinal imaging with infrared scanning laser ophthalmoscopy in patients with stargardt disease. *Retina.* 2014;34(7):1391-1399.
3. Anastasakis A, Fishman GA, Lindeman M, Genead MA, Zhou W. Infrared scanning laser ophthalmoscope imaging of the macula and its correlation with functional loss and structural changes in patients with stargardt disease. *Retina.* 2011;31(5):949-958.
4. Anastasakis A, McAnany JJ, Fishman GA, Seiple WH. Clinical value, normative retinal sensitivity values, and intrasession repeatability using a combined spectral domain

optical coherence tomography/scanning laser ophthalmoscope microperimeter. *Eye (Lond).* 2011;25(2):245-251.
5. Fishman GA, Birch DG, Holder GE, Brigell M. Electrophysiological testing in disorders of the retina, optic nerve and visual pathway. In: 2nd ed. San Francisco, CA: American Academy of Ophthalmology; 2001:308.
6. Hood DC, Bach M, Brigell M, et al. ISCEV standard for clinical multifocal electroretinography (mfERG) (2011 edition). *Doc Ophthalmol.* 2012;124(1):1-13.
7. McCulloch DL, Marmor MF, Brigell MG, et al. Erratum to: ISCEV Standard for full-field clinical electroretinography (2015 update). *Doc Ophthalmol.* 2015;131(1):81-83.
8. McCulloch DL, Marmor MF, Brigell MG, et al. ISCEV Standard for full-field clinical electroretinography (2015 update). *Doc Ophthalmol.* 2015;130(1):1-12.
9. Roman AJ, Cideciyan AV, Aleman TS, Jacobson SG. Full-field stimulus testing (FST) to quantify visual perception in severely blind candidates for treatment trials. *Physiol Meas.* 2007;28(8):N51-56.
10. Klein M, Birch DG. Psychophysical assessment of low visual function in patients with retinal degenerative diseases (RDDs) with the Diagnosys full-field stimulus threshold (D-FST). *Doc Ophthalmol.* 2009;119(3):217-224.
11. Dedania VS, Liu JY, Schlegel D, et al. Reliability of kinetic visual field testing in children with mutation-proven retinal dystrophies: Implications for therapeutic clinical trials. *Ophthalmic Genet.* 2018;39(1):22-28.
12. Sharon D, Ben-Yosef T, Goldenberg-Cohen N, et al. A nationwide genetic analysis of inherited retinal diseases in Israel as assessed by the Israeli inherited retinal disease consortium (IIRDC). *Hum Mutat.* 2020;41(1):140-149.
13. Stone EM, Andorf JL, Whitmore SS, et al. Clinically Focused Molecular Investigation of 1000 Consecutive Families with Inherited Retinal Disease. *Ophthalmology.* 2017;124(9):1314-1331.
14. Whelan L, Dockery A, Wynne N, et al. Findings from a Genotyping Study of Over 1000 People with Inherited Retinal Disorders in Ireland. *Genes (Basel).* 2020;11(1).
15. 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(1):75-90.
16. Stone EM, Aldave AJ, Drack AV, et al. Recommendations for genetic testing of inherited eye diseases: report of the American Academy of Ophthalmology task force on genetic testing. *Ophthalmology.* 2012;119(11):2408-2410.
17. Goetz KE, Reeves MJ, Gagadam S, et al. Genetic testing for inherited eye conditions in over 6,000 individuals through the eyeGENE network. *Am J Med Genet C Semin Med Genet.* 2020;184(3):828-837.
18. Bainbridge JW, Smith AJ, Barker SS, et al. Effect of gene therapy on visual function in Leber's congenital amaurosis. *N Engl J Med.* 2008;358(21):2231-2239.
19. Cideciyan AV, Aleman TS, Boye SL, et al. Human gene therapy for RPE65 isomerase deficiency activates the retinoid cycle of vision but with slow rod kinetics. *Proc Natl Acad Sci U S A.* 2008;105(39):15112-15117.
20. Maguire AM, Simonelli F, Pierce EA, et al. Safety and efficacy of gene transfer for Leber's congenital amaurosis. *N Engl J Med.* 2008;358(21):2240-2248.
21. MacLaren RE, Groppe M, Barnard AR, et al. Retinal gene therapy in patients with choroideremia: initial findings from a phase 1/2 clinical trial. *Lancet.* 2014;383(9923):1129-1137.
22. Ulhaq ZS, Soraya GV, Dewi NA, Wulandari LR. The prevalence of anxiety symptoms and disorders among ophthalmic disease patients. *Ther Adv Ophthalmol.* 2022;14:25158414221090100.