CLINICAL STATEMENT
Recommendations on Clinical Assessment of Patients with Inherited Retinal Degenerations

Abstract
This AAO Clinical Statement provides recommendations for evaluation and clinical assessment 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 sometimes require modified testing regimens or sedation for accurate assessment. Genetic testing and genetic counseling are important components of the assessment of patients with IRDs as genetic testing may be valuable to confirm the diagnosis, provide accurate information to the patient and family members and potentially to confirm eligibility to participate in clinical trials. The statement also provides information that would be of value to support and educate patients with IRD. These recommendations are intended to provide guidelines for the management of patients with IRDs. As always, final decisions will rest with the preferences of individual physicians and the needs of individual patients.

Introduction
Inherited retinal degenerations (IRDs) comprise a wide range of genetically and phenotypically heterogeneous diseases that share in common progressive loss of photoreceptor function accompanied by visual loss. Understanding of the cellular and molecular mechanisms underlying retinal degeneration has expanded dramatically, leading to clinical trials of therapies that may slow photoreceptor degeneration or restore some vision. These treatments target different genetic causes of disease and stages of the degenerative process; in some cases, treatments will be targeted for disease genes or mutations. Clinical care of patients has become increasingly sophisticated over the past decade with more and improved diagnostic tools (e.g., genetic testing, novel noninvasive functional testing and imaging studies). These guidelines are presented to highlight some of these advances for practitioners and patients, and to develop standards for best use of new technologies with the goal of optimizing patient care and helping physicians and patients better identify opportunities to participate in clinical trials and benefit from novel therapies.

Examinations for Patients with Inherited Retinal Degenerations
The objectives of patient evaluations are to:
1. Establish the correct diagnosis, which helps the patient receive appropriate care (prognosis, monitoring for co-morbidities and other system involvement, and providing supportive services such as low-vision training); this assumes that other non-genetic causes of retinal degeneration have been considered and excluded.
2. Provide information on the genetic nature and genetic transmission for the disease and its implication for other family members; and
3. Provide information about ongoing or future clinical trials and novel treatments.

A thorough ocular and medical history and pedigree documenting family history of eye disease is to be obtained at the initial visit and updated at subsequent visits. Molecular genetic testing (genotyping) of the patient and family members can be valuable to confirm the diagnosis, enable correct information to be provided to the patient and family, and is often a prerequisite for participation in various treatment trials. The clinical evaluation should include best-corrected visual acuity with standardized eye charts1 and manifest refraction,
biomicroscopy, measurement of intraocular pressure, and dilated ophthalmoscopy to identify ocular features, such as optic nerve drusen, cataract, and/or cystoid macular edema (CME) that interfere with vision; the latter two conditions may be amenable to treatment. Standard color or wide-field fundus photography should 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 autofluorescence (AF) fundus images. For patients with nystagmus 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.

Optical Coherence Tomography (OCT) provides cross-sectional imaging of the photoreceptors, retinal pigment epithelium, and inner retinal layers including the retinal nerve fiber layer if there is a suggestion of optic nerve atrophy, drusen or pallor. High-density volume scans provide a useful baseline for monitoring progression in structural features and helping to monitor CME or macular schisis.

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.2,3

Visual field testing is important to document the functional extent of vision from central to the far periphery for determination of legal blindness and disability, and to monitor for progression. Static visual field testing has advantages of automated indices of sensitivity loss, performance parameters to assess reliability, newer perimeters that can test the entire field, and digital data that can be exported into other applications for specific purposes such as modeling of sensitivity and programs to assess the function of cones and dark-adapted rods. There are perimeters that allow static testing well beyond the 60-degree range; however, we have strived with this document to not advocate any particular company’s instrument or product for any form of testing and, instead, concentrate on the merits and benefits in general for the test described. Although the static perimetry using the HVF30-2 protocol is acceptable in the federal registry for the determination of legal blindness and vision-related disability, 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 (microrperimeters) are particularly useful for measuring macular function in patients with eccentric viewing due to maculopathy.4 Patients with advanced disease and impaired fixation who cannot perform standard visual field testing can be followed with the full-field stimulus test (FST).5,6

The full-field electroretinogram (ERG) is important for diagnosis and staging of disease and is useful for many patients with diffuse photoreceptor disease to evaluate the retina-wide function of rods and cones.7 ISCEV (International Society for Clinical Electrophysiology of Vision) has published and updated standards that enable recordings to be compared between institutions and examiners (link.springer.com/article/10.1007/s10633-014-9473-7).8,9 Multifocal ERG testing can be useful for detection and monitoring disease progression for diseases that primarily affect the macula.10 However, its accuracy can be limited in those patients with notable loss of central vision who are unable to maintain steady foveal fixation.

Because IRDs comprise a variety of conditions, different examinations may be applied to patients with different types of disease. The four major types of IRDs that are most readily recognized 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.

### Clinical Evaluation: Inherited Retinal Degenerative Diseases

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Initial Visit</th>
<th>Follow Up Visit Every 1-2 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Ocular (including current needs)</td>
<td>1-4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1-4</td>
</tr>
<tr>
<td>• Medical (including current medications and history of retinotoxic medication use)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pedigree (family history)</strong></td>
<td>1-4</td>
<td>1-4</td>
</tr>
<tr>
<td><strong>Clinical eye examination</strong></td>
<td>1-4</td>
<td>1-4</td>
</tr>
<tr>
<td>• Best corrected visual acuity: ETDRS (or equivalent)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Slit-lamp biomicroscopy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Intraocular pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Indirect Ophthalmoscopy</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Imaging</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Color fundus photos</td>
<td>1-4</td>
<td>1-4</td>
</tr>
<tr>
<td>• Spectral Domain Optical Coherence Tomography</td>
<td>1-4</td>
<td>1-4</td>
</tr>
<tr>
<td>• Fundus autofluorescence: Short wavelength with reduced illumination when possible</td>
<td>1-4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1-4&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>• Infrared autofluorescence (when available)</td>
<td>1, 3, 4</td>
<td>1, 3, 4</td>
</tr>
<tr>
<td><strong>Visual fields</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Kinetic</td>
<td>1-4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1-4&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>• Static</td>
<td>1-3&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1-3&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>• Microperimetry (when available)</td>
<td>1-4</td>
<td>1-4</td>
</tr>
<tr>
<td><strong>Electroretinography</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Full-field ERG&lt;sub&gt;F&lt;/sub&gt; (when appropriate)</td>
<td>1-4</td>
<td>1-3</td>
</tr>
<tr>
<td>• Multifocal ERG&lt;sub&gt;F&lt;/sub&gt; (when appropriate)</td>
<td>2, 4</td>
<td>2, 4</td>
</tr>
<tr>
<td><strong>Genetic Diagnostic Testing</strong></td>
<td>1-4</td>
<td></td>
</tr>
</tbody>
</table>

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<sup>a</sup> 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 be evaluated similarly at baseline, then followed with eye examination only.
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) Fundus autofluorescence is not indicated for patients with achromatopsia on initial or subsequent visits.

c) Following kinetic visual fields in patients with North Carolina macular dystrophy, Best disease or pattern dystrophy, which are likely to be stationary, is of questionable value.

d) Static perimetry is of uncertain value for patients with diffusely advanced disease.

e) Full-field ERG is not necessary in Best disease, North Carolina macular dystrophy or in cases of pattern dystrophy limited to the macula. Also, a non-detectable ERG is not recommended to be repeated.

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

Pediatric Patients
Young children are often not able to perform many of the functional tests utilized in adults. Also, depending on their age and ability to cooperate, they may provide data that are unreliable. With infants, certain tests such as an ERG using skin electrodes or hand-held OCT imaging might be able to be performed on the parent’s lap, but such testing may provide limited information. Sedated exams provide the opportunity for a more definitive exam and higher quality imaging; however, the risks of sedation must be weighed against the value of the information gained at the specific age. It is important to realize that functional changes, such as reduction in the ERG, might be induced by sedation. Normative data, although difficult to obtain, is essential for proper interpretation.9 The reliability of visual fields in children less than 7 years old can be disappointing; however, with repetition, performance will often improve as the child matures.

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 60-80% of patients with inherited retinal disorders.11-17 Genetic testing is appropriate for most patients with presumed genetically caused 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. The American Academy of Ophthalmology Task Force on Genetic Testing published recommendations for genetic testing of inherited eye diseases,18 which can be viewed at this link: www.ncbi.nlm.nih.gov/pubmed/22944025.

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, clinical trials of gene therapies for multiple genetic forms of IRD are in progress, and positive results have been reported from several of these studies.19-22 Genetic testing can identify patients with retinal disease due to mutations in genes for which systemic associations have been identified. 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 exome and genome sequencing.
Multi-gene testing is typically necessary for the successful molecular diagnosis of a disease such as retinitis pigmentosa, where > 100 causative genes are known (complete gene list available at: sph.uth.edu/retnet/). Testing should include genes known to be associated with syndromic forms of retinal disease, since some patients presenting initially with only retinal disease may actually be affected with an underlying syndromic condition, such as Batten disease. Other types of testing, including single gene analyses, may be more appropriate for certain conditions. As these technologies continue to evolve, clinicians are encouraged to work with geneticists and/or genetic counselors to ensure appropriate genetic testing for their patients.

In order for the potential benefits of genetic testing in this patient population to be realized, 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 a physician or genetic counselor who is knowledgeable about inherited retinal disease, and who has the time to discuss potentially sensitive and complex findings. Genetic counseling should be provided before testing is ordered and 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.

**Patient Education**

Through discussions with their eye care team, patients should be provided with information about the hereditary and likely progressive course of disease, although some IRDs appear to be essentially stationary or minimally progressive. This can include counseling about genetic testing and diagnoses, as described above. Physicians play an important role in encouraging low vision rehabilitation, working with school personnel, and advocating for mobility training. Patients may benefit from low vision evaluation at baseline and every 1-2 years as necessary. Patients should also be informed of registries such as My Retina Tracker (www.myretinatracker.org), a registry supported by the Foundation Fighting Blindness (www.fightblindness.org), and information about research in the field, including clinical trials (www.clinicaltrials.gov).

This document also provides two websites that list contact information for blind services organizations within the United States and Canada from the American Foundation for the Blind (afb.org/info/about-the-afb-directory-of-services/5 and www.afb.org/default.aspx). 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 welcome.guidedogs.com, www.guidedogsofamerica.org/1/, and www.guidedog.org/.
Summary
Patients with inherited retinal degenerations require special attention to aspects of the history and ophthalmic examination, tests of retinal structure and function, and genetic testing to determine the correct diagnosis. Clinical and genetic testing of patients with IRDs has become increasingly sophisticated and treatment trials for IRDs are underway. This Clinical Statement provides guidelines for AAO members to help physicians select the optimal evaluations at baseline and during ongoing care of patients with IRDs.

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