ASRS American Society of Retina Specialists

ASRS Provides Clinical Recommendations for Retina Specialists in Response to AAO's *Clinical Assessment of Patients with Inherited Retinal Degeneration*

The ASRS comment provided by Stephen S. Tsang, MD, PhD

I would like to commend the authors of the Clinical Statement for their compilation of recommendations to retina specialists, which provides guidelines that will enable doctors to improve their ability to diagnose and care for this heterogeneous patient population. On a few points, there are alternative approaches that the coauthors may be interested in considering, particularly in regards to pediatric protocols for ERG, autofluorescence imaging, and whole exome sequencing.

In the Clinical Statement, the authors recommend conforming to ISCEV standards for ERG protocols in pediatric patients. However, these patients likely require sedation, adding unnecessary risks to the procedure. I would like to suggest that physicians consider using the following ERG protocol (below) for pediatric cases, in which the dark adaptation is limited and sedation is avoided to reduce patient discomfort and eliminate risk of anesthesia, respectively. While this may not allow for standardization across patients as would be preferred, it is useful for approaching various differentials, such as distinguishing between congenital stationary night blindness vs Leber's congenital amaurosis, for example. It will also provide the information that parents are *most* interested in knowing - whether their child's condition is progressive. Using this protocol, pediatric ERG recordings with skin electrodes (non-ISCEV) plus five minutes of dark adaptation will avoid the risks of general anesthesia while still enabling a prognosis to be made. When the patient is older, the full ISCEV protocol can be used to refine the initial diagnosis.

Pediatric Protocol

1. Begin with photopic ERG
2. Perform a limited 5-minute dark adaptation
3. Maximum scotopic ERG should be greater than lighted photopic ERG in normal children.

Additionally, the Clinical Statement also promotes the use of reduced illumination imaging, with half illumination on autofluorescence (AF). However, physicians routinely perform fluorescein angiography, which has a much brighter illumination level than quantitative autofluorescence (qAF). Due to the lack of well-documented evidence of blue light toxicity in humans and benefits from reduced illumination fluorescence, documentation of disease progression should include qAF. If the imaging is acquired under poor illumination as recommended, it will be more difficult to quantify areas of metabolic dysfunction, for example. If the imaging cannot be quantified, the utility of the exam is nullified, in which case it simply should not be performed at all. Another reason acquiring high-quality qAF images is critical is because these images can inform diagnosis and candidate gene testing.

Finally, the Clinical Statement advises relying on whole exome sequencing (WES) more than may be necessary, at least for some retinal dystrophies. For example, if, based on fundoscopy, ERG, and AF, a patient is suspected to have enhanced S-cone syndrome or rod monochromatism, it is not cost effective to perform WES. Rather, the first test that should be run is single-gene sequencing, which costs approximately $200-300 in comparison to ~$3,000 for a panel of genes associated with inherited retinal disease. If candidate gene testing and a retina gene panel are non-revealing, whole-exome sequencing is indicated (~$6,000). Gene testing should be phenotype-driven, using ERG and other imaging modalities to direct test selection, and first-line testing should involve analyzing candidate genes rather than directly jumping to WES. This is particularly true when the testing demands such enormous costs to the patient, who is often denied coverage by insurance companies. Below are the steps that should be taken when selecting genome testing:

Genetic Testing:

1. Phenotype directed candidate gene testing
2. Retinal exome panel

3. Whole exome sequencing
4. Whole genome sequencing

Further resources on ERG protocols, imaging illumination, and genome sequencing are provided below. Using these strategies in combination with the recommendations made in the Clinical Statement, retinal physicians will be well equipped to provide high quality and cost-effective care to their patients.

Additional resources:

1. McCulloch DL, Marmor MF, Brigell MG, Hamilton R, Holder GE, Tzekov R, Bach M. ISCEV Standard for full-field clinical electroretinography (2015 update). Doc Ophthalmol. 2015 Feb;130(1):1-12. doi: 10.1007/s10633-014-9473-7. Erratum in: Doc Ophthalmol. 2015 Aug;131(1):81-3. PubMed PMID: 25502644.
2. Tsui, Irena, MD, Brian Song, BA, Chyuan-Sheng Lin, PhD, and Stephen H. Tsang, MD, PhD. "A Practical Approach to Retinal Dystrophies." *Retinal Physician*, 1 Apr. 2007.
3. Vincent A, Robson AG, Holder GE. Pathognomonic (diagnostic) ERGs. A review and update. Retina. 2013 Jan;33(1):5-12. doi: 10.1097/IAE.0b013e31827e2306. Review. PubMed PMID: 23263253.
4. Berson EL. Long-term visual prognoses in patients with retinitis pigmentosa: the Ludwig von Sallmann lecture. Exp Eye Res. 2007 Jul;85(1):7-14. PubMed PMID: 17531222; PubMed Central PMCID: PMC2892386.

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