I. Infants with poor vision

1. Infant with poor vision without nystagmus—Debbie Costakos

Case #1:
An ex 27-week CGA (Corrected Gestational Age) BW 1050g baby girl was referred at age 30 weeks for ROP. ROP resolved spontaneously but the patient was noted to have poor eye contact and no fix and follow at 6 months of age. PMHx was significant for prematurity, intraventricular hemorrhage (grade 3) and periventricular leukomalacia
FHx was negative for poor vision
Alignment was orthotropic
CRx was +3.00 sphere in both eyes
DFE revealed normal optic nerves, macula and vessels

Case #2:
A 6-month-old baby girl was referred at age 6 months for lack of eye contact and no fix and follow.
PMHx was not significant
FHx was negative for poor vision, strabismus or developmental delay
Visual acuity was blinks to light both eyes
Alignment was variable intermittent exotropia up to 40 PD X(T)
CRx was +5.00 +1.00 x 90 and +4.50 +2.00 x 90
DFE revealed poor foveal reflex in both eyes with a blond fundus

Use clinical findings, history and family history to guide the work up.
Differential Diagnosis may include:
Differential Diagnosis for Infant with poor vision, no nystagmus:
Delayed Visual Maturation (DVM)
Cortical Visual Impairment (CVI)
Albinism
Seizure disorder
Metabolic disorders
Prematurity with PVL, other CNS involvement (with or without ROP).

Note: strabismus alone is not a diagnosis for bilateral poor vision
Imaging tools are available

Workup to consider:
OCT—“normal” appearance varies by age
ERG
Referral to other specialists
Brain mri
Genetic testing, or not, depending on differential diagnosis and probably yield
2. *Infant with poor vision with nystagmus*—Alina Dumitrescu

**Case #3:**
A baby girl is referred due to poor visual responses, nystagmus and photophobia. Fine, rapid nystagmus present since shortly after birth. Squints in bright yet but at times stares at lights. Visual acuity Fix&Follow OU. CR +1.00 +1.50 x90 OU. Fundus exam: normal optic nerves, foveal reflex present.

**Differential diagnosis of poor vision, photophobia in a baby with infantile nystagmus:**
Achromatopsia  
Blue cone monochromacy (variable photophobia)  
LCA (for example RPRGIP1, GUCY2D)  
Albinism (variable photophobia)  
CHED (congenital hereditary endothelial dystrophy)  
Congenital glaucoma  
Optic Nerve Hypoplasia (photophobia less likely)

**Workup to consider:**
ERG  
pachymetry  
IOP  
fundus photography  
Clinically guided genetic testing

**Case #4:**
A baby boy is referred due to poor visual responses, roving nystagmus, possibly worse vision in the dark; baby seems to see them approach when lights are on but not when lights are off. Visual acuity Blinks to light, fixes and follows at near. CR +5.00 OU. Fundus exam: normal optic nerves, foveal reflex present, grossly normal retinal pigment. No family history of poor vision.

**Differential diagnosis of a baby with poor vision, nystagmus, worse vision in darkness:**
LCA (for example RPE65, Senior-Loken syndrome due to NPHP genes, many other genetic types)  
Optic Nerve Hypoplasia  
Congenital Stationary Night Blindness (rare to present with nightblindness; usually myopic)
Joubert syndrome
Zellweger syndrome
Other syndromic retinal dystrophies and degenerations

Workup to consider:
ERG
OCT
fundus photography
Clinically guided genetic testing

3. Approach to infants with poor vision with or without nystagmus—Arlene Drack

a. Infants with poor vision without nystagmus Differential Diagnosis
i. Often neurologic or developmental
   1. Prematurity sequelae
ii. Delayed visual maturation
   1. Albinism (not all patients have nystagmus)
   2. Other causes of decreased vision
iii. Cortical vision loss
iv. Seizure disorder
v. Masquerade syndromes, e.g. ophthalmoplegia, oculomotor apraxia
   1. Work up
      a. Brain mri
      b. Visual evoked potentials (VEP)
      c. Electroretinogram (ERG)
      d. Referral to medical genetics, peds neurology

b. Infants with poor vision with nystagmus Differential Diagnosis
i. Complete eye exam to evaluate for optic nerves anomalies, cataract, corneal opacities, retinal dragging or detachment causing sensory nystagmus
ii. If no obvious anomaly, or retinal anomaly, and normal head circumference, growth and development
   1. ERG
      a. If ERG abnormal, genetic testing guided by pattern of ERG
      b. If ERG normal, consider OCT, under anesthesia if necessary
         i. If OCT abnormal, genetic testing for albinism, PAX6, Stickler, get history of prematurity, other
         ii. If OCT normal, consider brain MRI
   iii. If optic nerves, HC, G and/or Development abnormal
      1. brain MRI
c. Why is diagnosis important?
   i. Some causes of poor vision with nystagmus are treatable
      1. FDA approved Luxturna for RPE65 LCA
2. Gene therapy clinical trials for CEP290 LCA
3. Gene therapy clinical trials for achromatopsia
4. Gene therapy clinical trials for XLR
5. Other gene therapy trials being developed all the time

ii. Many cases are genetic
   1. Family planning

iii. Prognosis

II. Anterior Segment Anomalies

1. Ectopia lentis—Mary Whitman

   Case #5:
   A baby presents with poor vision and eccentric pupils. DFE shows ectopia lentis. CR -15.00 through the decentered crystalline lens. Fundus examination normal. The baby appears normal, no arachnodactyly apparent.

   Differential diagnosis:
   Marfan
   Ectopia lentis et pupillae
   Homocystinuria
   Buphthalmos due to glaucoma, megalocornea, other

   Workup to consider:
   genetic testing
   blood and urine amino acid screen
   IOP
   cardiology referral

   Management:
   genetic counseling, refract the aphakic space and use aphakic contact lenses if space is large enough, consider risks/benefits and ideal timing for lens extraction/IOL placement (may need anterior chamber IOL, or scleral sutured lens)

2. Anterior Segment Dysgenesis/Peter Anomaly—Alex Levin

   Case #6:
   A baby presents with poor vision, opaque corneas. Vision is blinks to light both eyes. Ultrasound demonstrates attached retinas.

   Differential diagnosis:
   Why is it white: sclerocornea is not a diagnosis!
   Spectrum of anterior segment disorders – which is it?
   Phenotypic vs genotypic heterogeneity
Remember:
Glaucoma risk
Amblyopia risk (cornea, cataract, pupil) – manage appropriately

**Workup to consider:**
Clinical vs molecular genetic workup
Bilateral Peter anomaly often associated with systemic disorder—refer to medical genetics

**Management:**
Surgery or no surgery?
Amblyopia risk if surgery is delayed, rejection risk with early surgery

3. **Cloudy corneas/Congenital glaucoma—Ginny Utz**

**Case #7:**
A 4-day old full-term infant male presents with cloudy corneas in both eyes.

Exam findings:
- Blinks to light OU
- Anterior segment: 1-2+ corneal edema, HCD=9.5-10 mm, deep AC, Immature iris, irregular pupil
- Posterior segment: C/D 0.9 in each eye, otherwise normal
- IOP 54 mm Hg and 57 mm Hg (tonopen while feeding)
- Pachymetry: 964 OD, 922 OS

**Differential Diagnosis:**

<table>
<thead>
<tr>
<th>Epiphora/Red Eye</th>
<th>Corneal Clouding</th>
<th>Corneal enlargement</th>
<th>Optic nerve cupping</th>
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<tbody>
<tr>
<td>- Conjunctivitis</td>
<td>-Corneal dystrophies (CHED, PPMD)</td>
<td>-Megalocornea from congenital glaucoma</td>
<td>-Physiologic</td>
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<td>- NLDO</td>
<td>-Metabolic storage disorders (e.g. MPS-H/S, etc)</td>
<td>-Buphthalmos from congenital glaucoma</td>
<td>-Optic nerve malformation</td>
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<td>- Keratitis</td>
<td>- Keratitis</td>
<td></td>
<td>- Prematurity-associated</td>
</tr>
<tr>
<td>- Uveitis</td>
<td>-Congenital anomalies (Peters anomaly, sclerocornea, choristomas)</td>
<td></td>
<td>(transynaptic degeneration from PVL)</td>
</tr>
<tr>
<td>- Corneal abrasion/trauma</td>
<td></td>
<td></td>
<td>-optic atrophy</td>
</tr>
<tr>
<td>- Chemical burn</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- CHED</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- HSV</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adapted from Chpt 22, Pediatric Glaucomas, Pediatric Ophthalmology and Strabismus Section 6, p 281.

**Clinical Management:**
- Acute medical management to lower IOP (Diamox po, timolol 0.5% bid, dorzolamide TID, Xalatan QHS OU) with EUA/surgical intervention (trabeculotomy performed OU)

**Workup to consider:**
- Define ocular and systemic phenotype
- Patient underwent combined appointment with ophthalmic geneticist, medical geneticist and genetic counselor

4. **Approach to child with congenital/infantile glaucoma/anterior segment dysgenesis--Chris Lloyd**

Careful history and examination (ocular and general)

Provide “deep” phenotyping - but note phenotypic variability in ASD (example PAX6)

Parental examination very important
Informed genetic investigations/systemic management – liaison with geneticist/dysmorphologist/paediatrician

Discussion of common responsible mutations and utility of gene panels/whole exome sequencing/whole genome sequencing

Important role of microarray/karyotyping

Prognosis and glaucoma risk

III. Older children with poor vision

1. Older child with decreased vision: previously normal vision—Melanie Schmitt

Case #8.
A 7-year-old male with new onset of developmental delays & seizures. He denies any changes in vision. MRI revealed severe cerebellar & mild cerebral atrophy. VA was 20/40 OU. The ERG showed flat scotopic & moderately reduced photopic responses. Fundoscopic exam was consistent with a bull’s eye maculopathy and peripapillary pigmentary mottling. The OCT showed significant disruption of the outer retina.

Differential diagnosis:
Bardet-Biedl syndrome, Batten disease/NCL, Stargardt disease, spinocerebellar ataxia, mitochondrial disease, & adult-type Refsum disease.

Workup to consider:
ERG, OCT, metabolic testing, brain mri, skin biopsy/leukocyte smear, genetic testing, referral to medical geneticist.

Case #9.
A 11-year-old male with severely reduced vison and previous diagnosis of RP. Nyctalopia was noted for 6 years. In addition, he had an onset of light sensitivity 1 year prior. VA was 20/400 OD and 20/300 OS. He had a large XT & upbeat nystagmus on exam. His ERG was flat. On fundoscopic exam diffuse pigmentary changes, blunted foveal reflex, & vascular attenuation were seen. On OCT a grossly distorted foveal contour was observed with the disruption of all retinal layers, but most severely affecting the outer retina.

Differential diagnosis:
LCA, early-onset retinitis pigmentosa, Senior-Loken syndrome, & Batten disease/NCL.

Workup to consider:
ERG, OCT, metabolic testing, genetic testing, skin biopsy for EM, leukocytes for inclusions on smear, referral to medical geneticist.
Case #10.
A 11-year-old male with decreased visual acuity found on routine eye exam by an optometrist. Patient with a history of depression & flat affect. VA was 20/70 OD & 20/50 OS. ERG revealed a moderate reduction in the scotopic response and a severely reduced photopic response. Fundoscopic exam showed pigmentary atrophy and mottling most prominent in the posterior pole involving the macula and arcades. OCT was significant for severe disruption of the outer retina & deposits at the level of the RPE.

**Differential diagnosis:** Stargardt disease, fundus autofluorescence, Batten disease/NCL, & cone-rod dystrophy.

2. **Older child with decreased vision; never totally normal vision** -- Wadih Zein

*Case #11:*
A 7-year-old male who failed school vision screening. Initial optometry exam indicated an acuity of 20/60 in each eye and bilateral hyperopic astigmatism (+1.00+1.50x90 OU). Received a diagnosis of bilateral amblyopia; glasses failed to correct vision. Referred to our clinic by maternal uncle with retinal dystrophy. Fundoscopic exam, OCT, and ERG characteristic of underlying diagnosis.

**Differential diagnosis includes:** Stargardt disease, albinism, XLRP, and XLRS.

**Workup to consider:** ERG, OCT, fundus autofluorescence, genetic testing.

*Case #12:*
A 20-year-old female has a history of frequent otitis media during childhood. Vision in the 20/25 range despite best efforts of local optometrist to correct her to 20/20. No history of nystagmus or ocular misalignment. Granulated neutrophils incidentally noted on a blood smear. Iris transillumination and retinal pigmentary changes noted on exam.

**Differential diagnosis:** Syndromic albinism, albinism, more than one diagnosis.

**Workup to consider:** OCT, genetic testing, platelet testing.

*Approach to the older child with decreased vision* — Debby Alcorn
Differential diagnosis, Workup, management, clinical trials for vision loss with later onset or later detection:

Electroretinogram

**Electronegative ERG**
- Juvenile X-linked Retinoschisis
- Batten Disease (Neuronal Ceroid Lipofuscinosis)
Congenital stationary night blindness
Muscular Dystrophy
Retinal vein or artery occlusion

Abnormal but not electronegative
Bardet Biedl Syndrome
Alstrom syndrome
Stargardt Disease
Usher syndrome
Zellweger spectrum (infantile Zellweger, Refsum, etc.)
LCA/Retinitis pigmentosa/SECORD

Normal ERG, abnormal OCT
Albinism/albinism syndromes
Aniridia/PAX6 spectrum

Abnormal brain MRI
Spinocerebellar ataxia
Joubert syndrome
Optic nerve hypoplasia

Other
Partial list of clinical trials for genetic eye diseases as of February, 2019 (www.clinicaltrials.gov):

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene</th>
<th>Status</th>
<th>Treatment</th>
<th>Age Range</th>
<th>Contact Information</th>
<th>Phase</th>
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<tr>
<td>Achromatopsia</td>
<td>CNGB3</td>
<td>Recruiting</td>
<td>rAAV2tYF-PR1.7-hCNGB3</td>
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<td>Jill Dolgin, PharmD <a href="mailto:advocacy@agtc.com">advocacy@agtc.com</a></td>
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<td>Achromatopsia</td>
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<td>Genetic Eye Disease</td>
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<tr>
<td>Cerebrotendinous Xanthomatosis (CTX)</td>
<td>CYP27A1</td>
<td>Recruiting</td>
<td>Prevalence study in early-onset cataracts</td>
<td>2 y.o to 21 y.o.</td>
<td>Retrophin 1-877-659-5518 medinforetrophin.com</td>
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<td>Leber Hereditary Optic Neuropathy (LHON)</td>
<td>G11778A</td>
<td>Recruiting</td>
<td>AAV2-P1ND4v2</td>
<td>15 y.o.</td>
<td>John Guy, MD <a href="mailto:jguy@med.miami.gov">jguy@med.miami.gov</a></td>
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<td>Smith-Lemli-Opitz-Syndrome</td>
<td>DHCR7</td>
<td>Recruiting</td>
<td>Cholesterol &amp; antioxidant supplements</td>
<td>None</td>
<td>Ellen Elias, MD 720-777-5401 <a href="mailto:Ellen.elias@childrenscolorado.org">Ellen.elias@childrenscolorado.org</a></td>
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<td>6 y.o.</td>
<td>Jill Dolgin, Pharm D <a href="mailto:advocacy@agtc.com">advocacy@agtc.com</a></td>
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Identifying Genetic Eye Disease in Children 2019

The Genetic Eye Disease Committee has recommendations for which children to test and refer

**Genetic Eye Disease in Children**
Many of the significant genetic eye disorders in children have at least a partial genetic basis. Juvenile onset refractive error and strabismus, by far the most common reasons for referral to a pediatric eye doctor, have a large genetic component but do not exhibit classic Mendelian inheritance in which abnormalities in one gene cause one disorder and are passed on directly from parent(s) to child. Many of the most serious causes of vision loss in the pediatric age
group, however, are monogenic, meaning the cause in a given individual can be attributed to mutations in one gene. These conditions are individually rare, but taken together constitute a large portion of patients seen by pediatric ophthalmologists on a daily basis. Recognizing genetic eye disorders affords patients and doctors the opportunity for very accurate diagnosis and prognosis, genetic counseling about the risk of recurrence in future children, and potentially gene replacement or causative-gene directed treatment. It is important for pediatric ophthalmologists to recognize which ocular disorders in children are possibly genetic in order to institute the appropriate workup or refer to a subspecialist for further evaluation.

**Which pediatric patients are most likely to have a genetic eye disorder?**

Pediatric patients with congenital nystagmus have a very high risk of having a genetic cause for their eye movement disorder. Congenital nystagmus should be considered a sign, not a diagnosis. Other disorders likely to be genetic include congenital or developmental cataracts, congenital or juvenile glaucoma, high myopia present prior to preschool, ectopia lentis, pigmentary and flecked retinal disorders optic atrophy and retinoblastoma, whether unilateral or bilateral. Albinism is a genetic disorder with a broad spectrum of cutaneous and ocular pigment. Some types of albinism are associated with life-threatening systemic features.

**What types of testing are used to diagnose genetic eye disorders?**

Diagnosing genetic eye disorders often requires electroretinography, visual evoked potential testing, optical coherence tomography, fundus autofluorescence, visual fields, and other testing as well as molecular genetic testing.

**What are the potential benefits and harms of evaluating patients for genetic eye disorders?**

There is an FDA-approved gene therapy treatment for one type of retinal degeneration that typically presents with congenital nystagmus. There are specific treatments or surveillance protocols for many other genetic eye disorders. Benefits of diagnostic workup for genetic eye disorders include delivering the best care for that individual’s underlying condition and allowing the family to understand the prognosis and recurrence risk. Risks include equivocal or non-diagnostic results, misdiagnosis and stress related to receiving a genetic diagnosis. There may be instances in which having a genetic diagnosis increases bias. Depending on the disorder and type of test, non-paternity may be discovered.

**What is the recommendation of the AAPOS Genetic Eye Disease Committee with regard to which children should be evaluated for genetic eye disorders?**

Pediatric ophthalmologists should inform patients/parents that the following disorders are likely to be genetic and can be more precisely diagnosed, and in some cases treated, based on further evaluation:

- Congenital/infantile nystagmus
- Congenital/developmental cataracts
- Congenital/juvenile glaucoma
- Albinism
- High myopia before pre-school age
- Ectopia lentis
Low vision or legal blindness without known cause
Retinoblastoma

This list is not complete, and any patient with a family history of an eye disorder should be considered as having a possibly genetic condition.

**What is the recommendation of the AAPOS Genetic Eye Disease Committee with regard to how children should be evaluated for genetic eye disorders?**

Pediatric ophthalmologists with the necessary facilities and expertise to institute a workup for genetic eye disorders often complete the workup on their patients. It is strongly recommended that genetic testing be obtained and discussed with patients in collaboration with a medical geneticist or ophthalmologist specializing in genetic eye disorders as interpretation of testing and counseling are highly complex. Pre- and post-test genetic counselling is essential. Retinoblastoma patients should be managed in concert with an oncologist. Even unilateral retinoblastoma may be genetic and should be considered so unless genetic testing determines otherwise. Pediatric ophthalmologists without the requisite facilities or expertise may inform patients of the potentially genetic nature of the disorder and refer to an ophthalmologist specializing in genetic eye disorders, or a medical geneticist with experience in ocular genetics.

**KEY POINTS**

- Pediatric ophthalmologists should be able to identify common conditions as potentially genetic and refer or evaluate
- Some examples include:
  - Congenital/infantile nystagmus
  - Congenital/developmental cataracts
  - Congenital/juvenile glaucoma
  - Albinism
  - High myopia before pre-school age
  - Ectopia lentis
  - Low vision or legal blindness without known cause
Retinoblastoma

- Referral to an ophthalmologist with genetic expertise and/or a medical geneticist, often in collaboration with a genetic counselor, is crucial to determine:
  - Accurate diagnosis
  - Surveillance and/or treatment if indicated
  - Family planning

- Suspect a genetic diagnosis and need guidance? Please submit inquiry to AAPOS Genetics Committee via the AAPOS website