Survey of practice patterns for the management of ophthalmic genetic disorders among AAPOS members: report by the AAPOS Genetic Eye Disease Task Force

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To better understand AAPOS member pediatric ophthalmologists' knowledge and needs regarding genetic eye disorders, the AAPOS Genetic Eye Disease Task Force developed a 16-question survey that was circulated to national and international AAPOS members. Responses to questions on practice patterns, baseline knowledge, and educational interests regarding patients with suspected ophthalmic genetic disorders were collected. A majority of respondents (93%) evaluate patients with suspected genetic disorders. Knowledge gaps were present in heritability of certain conditions, genetic testing strategies, and referral to clinical trials. Most respondents expressed interest in further education in these areas. A model for care is proposed as a first step in the education process.

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In response to requests by members of the American Association for Pediatric Ophthalmology and Strabismus (AAPOS), the Genetic Eye Disease Task Force (the Task Force) was formed in 2016. To begin, the Task Force developed a survey to evaluate baseline knowledge of heritability of common pediatric eye disorders, practice patterns for evaluating such patients, understanding of genetic testing strategies, and ability to identify genetic patients for clinical trials and/or treatment.

Materials and Methods

A 16-question survey with branching algorithm was developed and distributed via email to all AAPOS members through the website Survey Monkey (www.surveymonkey.com). See eAppendix. If no response was obtained, two additional reminder emails were sent. Survey responses were deidentified. Questions focused on the understanding of heritability and work-up or referral of patients with disorders such as congenital/infantile nystagmus, infantile/juvenile cataracts, pediatric glaucoma, and congenital malformations. In addition, the ability to understand and use genetic testing modalities and to counsel patients was addressed. Respondents' interest in further educational opportunities on these topics was queried.

Results

Responses from 264 of 1,489 surveys (18%) were received. Of these, 77.3% (204/264) came from the United States. Forty-seven percent of respondents were in private practice (71% in a multispecialty group and 29% in a pediatric ophthalmology practice), and 49% were in a university-based practice (53% in a multispecialty group and 47% in a children's hospital). The rest were in managed healthcare practices.

Of the 264 respondents, 93% reported treating at least 1 patient per week with a genetic disorder; 57%, 1-5 patients/week; 28%, saw 5-10 patients/week; and 9.1%, >11 patients/week (eSupplement 1A, available at jaapos.org). Those in a university setting were more likely to order genetic testing than those in private practice ($P = 0.0007$ [Fischer exact test]). Of those ordering testing, 90% worked with a genetic counselor at least part time. The majority of clinicians who did not order genetic testing themselves referred to a medical geneticist, pediatric ophthalmologist with genetic expertise, or a retina or other specialist with genetic expertise; 14% did not pursue further genetic work-up and simply monitored the patients

Table 1. Baseline understanding and interest in further education on the various genetic testing strategies used in clinical practice

Testing strategies	Baseline understanding, no. (%)	Interest in further education in this area, no. (%)
Targeted mutation (allele-specific) analysis	77 (29.0)	194 (73.5)
Next-generation sequencing	43 (16.2)	192 (72.7)
Sanger sequencing	31 (11.7)	169 (64.0)
Microarray	72 (27.3)	191 (72.3)
Deletion/duplication analysis	90 (34.1)	175 (66.3)
Whole exome sequencing	65 (24.6)	183 (69.3)
Whole genome sequencing	77 (29.1)	188 (71.2)
No	128 (48.5)	N/A

clinically. In evaluating patients with suspected malformations or syndromes, 76% of respondents referred to a medical geneticist for further work-up, whereas the rest completed the genetic testing without further consultation.

Of the respondents 95% properly identified congenital/juvenile cataract as potentially genetic, while only 85% identified pediatric glaucoma as potentially genetic, and 75% identified congenital/infantile nystagmus as potentially genetic (eSupplement 1B). Baseline understanding of genetic testing ranged from 11.7% to 34.1%, depending on the testing modality (Table 1), and 48% reported that they had no understanding of any genetic testing modalities. A majority reported interest in further education in genetic testing (Table 1).

Physicians' ease in communicating the results of genetic testing also varied among respondents, with a majority (81%) responding they were either "a little" or "not at all" comfortable explaining the results to patients (eSupplement 1C). Those in a university setting were more likely to be comfortable explaining testing results than those in private practice ($P = 0.003$).

Forty-two percent of respondents reported being able to identify and refer genetic patients for clinical trials. Of

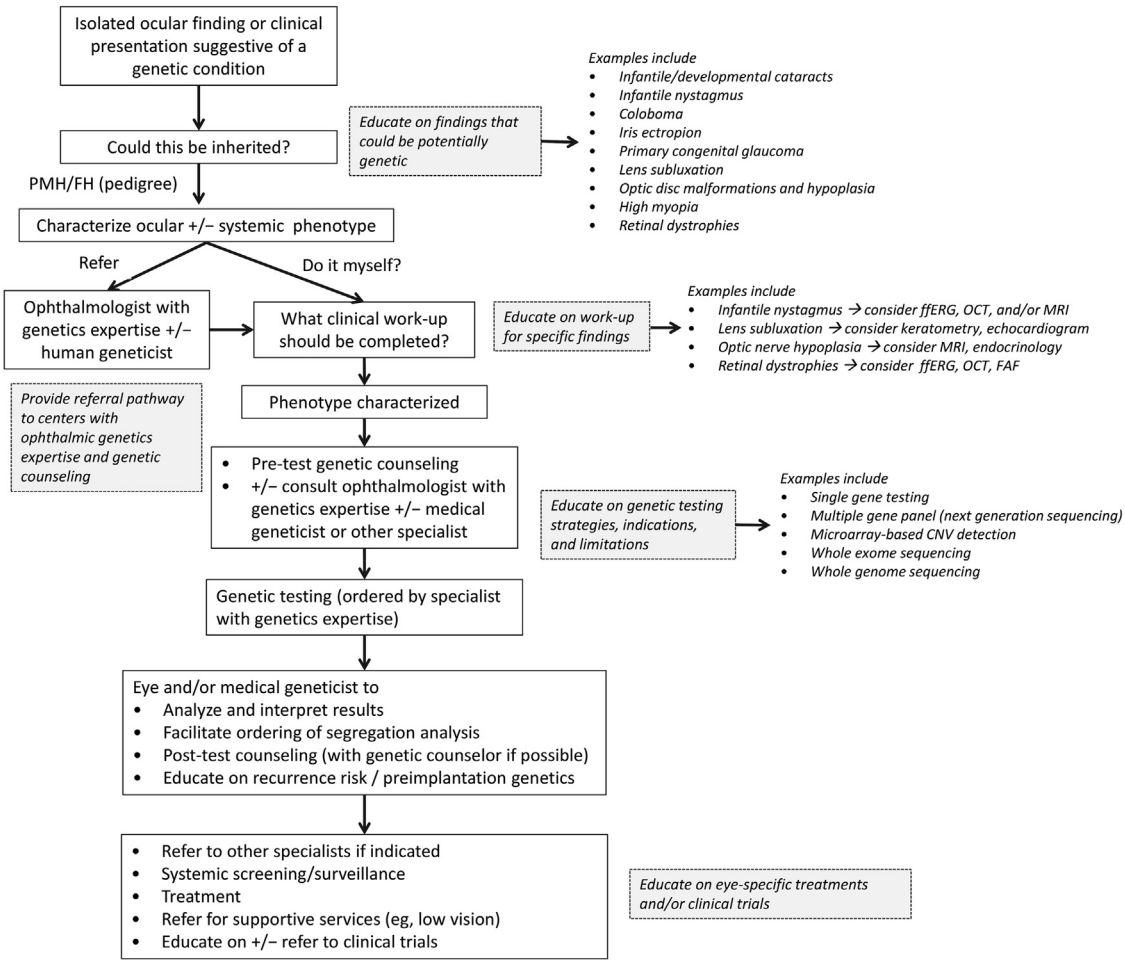

FIG 1. Proposed care process for patients with suspected inherited eye disorders. Shaded boxes represent opportunities for AAPOS Genetic Eye Disease Task Force to provide intervention/education.

those who were not, 91% expressed interest in further education on this topic. Those in a university setting were more likely to be able to identify clinical trials than those in private practice ($P = 0.0005$).

Discussion

Many early-onset ocular disorders are genetic, offering the possibility for accurate prognosis and family planning if they are diagnosed in a timely manner. Ocular findings may be the presenting clinical manifestation of a syndrome, giving pediatric ophthalmologists the unique opportunity to diagnose multisystem disorders. Pediatric ophthalmologists have a responsibility to recognize a disorder as potentially genetic and either to pursue work-up or refer to the appropriate subspecialist. Once the clinical phenotype is recognized as likely genetic, evaluation by an ophthalmologist with expertise in genetics, a genetic counselor, or medical geneticist should be considered.[1]

Many patients with congenital/juvenile cataracts,[2-4] pediatric glaucoma,[5-7] and congenital/infantile nystagmus[8,9] have a genetic basis for their disorders. For example, in 50 patients diagnosed with bilateral congenital cataracts, putative pathogenic variants were identified in 75% of cases.[3] Nine children from 6 families were diagnosed with metabolic disorders that had been missed by traditional clinical screening algorithms.[3] All children with infantile or developmental bilateral, and in select cases unilateral, cataracts should be referred to either an ophthalmic geneticist or medical geneticist for work-up. Similarly, in a cohort of 202 infantile nystagmus patients, at least 64% had a genetic cause of nystagmus.[8] In a study of 48 infantile nystagmus patients screened using a next-generation gene panel, 58.3% could be genetically diagnosed, with 21% receiving a new diagnosis.[9] An algorithmic approach that includes phenotypic characterization in concert with genetic testing is indicated for congenital nystagmus patients[8] and for all children suspected of having a genetic disorder (Figure 1). Next-generation sequencing has greatly increased the diagnostic yield for congenital/infantile cataracts and nystagmus.[2-4,8,9] Because genetic testing is most accurately interpreted with a pretest clinical diagnosis hypothesis, if referral to a medical geneticist is made, the pediatric ophthalmologist has an important role in providing a detailed clinical diagnosis that will guide genetic testing.

Pediatric ophthalmologists recognize that ocular genetic disorders are common in most practices. The majority of survey respondents identified congenital/infantile cataracts, glaucoma, and congenital nystagmus as potentially genetic. The greatest need expressed in the survey was for continuing education and resources dealing with obtaining genetic testing and identifying eligibility for clinical trials. With the FDA approval of gene therapy for *RPE65*-related retinal disease, accurate diagnosis of children with congenital nystagmus often becomes actionable. The Genetic Eye Disease Committee (formerly the Task Force) will offer educational courses and links on the AAPOS website to help address this need. Continuing education about which patients need a genetic work-up will enable AAPOS members to become active participants in the front-line of personalized medicine.

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Primary IOL implantation in children: the effect of the Infant Aphakia Treatment Study on practice patterns

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We report the long-term effects on practice patterns at a single institution before (1995-2004) and after (2009-2018) publication

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eAppendix. Survey Questions from the AAPOS Genetic Eye Disease Task Force

1. How many patients do you see per week with a suspected genetic disorder affecting the eye?
   0 <5 5-10 >11
2. Do you order genetic testing on patients with a suspected genetic disorder?
   Yes No
   Please branch based on the response to #2:
   a. If answer yes: Do you work collaboratively with a genetic counselor?
      Never Occasionally Usually Always
   b. Do you organize the genetic testing yourself?
      Yes No
   b. If answer no: Which of the following describes to whom you refer patients with a suspected genetic disorder? (Can select more than one)
   - Another pediatric specialist with ophthalmic genetics expertise
   - A retina or other specialist with ophthalmic genetics expertise
   - Collaborate with a human geneticist
   - Follow patients yourself without doing genetic testing
3. Do you categorize nystagmus as a potentially genetic disorder?
   Yes No
4. Do you have a standard complete workup for nystagmus?
   Yes No
   Please branch:
   If no, do you refer to another provider to do a workup?
   If yes, to which kind of provider do you refer?
5. Do you categorize congenital/juvenile cataracts as a potentially genetic disorder?
   Yes No
6. Do you have a standard complete workup for congenital/juvenile cataracts?
   Yes No
   Please branch:
   If no, do you refer to another provider to do a workup?
7. Do you categorize congenital glaucoma as a potentially genetic disorder?
   Yes No
8. Do you do genetic testing in patients with congenital glaucoma?
   Yes No
   Please branch:
   If no, do you refer to another provider to do a workup?
9. Do you work-up patients with malformations or syndromes yourself?
   Yes No
   If no, to which type of provider do you refer them?
10. I have a good understanding of the following types of genetic testing (check all that apply)
    - Targeted mutation (allele-specific) analysis
    - Next generation sequencing
    - Sanger sequencing
    - Microarray
    - Deletion/supplication analysis
    - Whole exome sequencing
    - Whole genome sequencing
11. How well do you understand the results of such testing and communicating the results to parents and/or patients?
    a. Not at all
    b. A little
    c. Moderately
    d. Very comfortable
    e. Completely comfortable
12. Are there any of the following types of genetic testing you would like to learn more about in relation to ophthalmic genetic disorders? (check all that apply)
    a. Targeted mutation (allele-specific) analysis
    b. Next generation sequencing
    c. Sanger sequencing
    d. Microarray
    e. Deletion/duplication analysis
    f. Whole exome sequencing
    g. Whole genome sequencing
13. I am able to identify clinical trials for genetic conditions and refer patients.
    Yes No
    Branching logic: If answer is no: Are you interested in learning more about identifying and referring patients for clinical trials for genetic conditions?
    Yes No
14. What suggestions do you have for ways in which the Genetics Task Force can educate and assist the AAPOS membership?
15. Do you practice full-time or part-time? (full-time, part-time)
16. What type of practice do you have? (university – multispecialty, university – children's hospital, private practice – pediatric ophthalmology, private practice – multispecialty group, other)