Visual Neuroscience (2018), **35**, e013, 7 pages.
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doi:10.1017/S0952523817000207

SPECIAL COLLECTION

Amblyopia: Challenges and Opportunities
The Lasker/IRRF Initiative for Innovation in Vision Science

PERSPECTIVE

Early diagnosis of amblyopia

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(RECEIVED August 12, 2016; ACCEPTED September 30, 2016)

Abstract

Amblyopia can be improved or eliminated more easily when treated early in life. Because amblyopia in older children is generally less responsive to treatment (Holmes et al., 2011), there is a premium on the early identification of amblyopia and its risk factors and the subsequent treatment thereof. Clinical preference is to institute treatment in children before 7 years of age when an optimal visual outcome is typically easier to obtain.

Keywords: Vision screening, Photoscreening, Hyperopia, Risk factors, Retinal polarization scan

Considering that most amblyopia is preventable and reversible, this common cause of visual impairment could be greatly reduced with early detection of the 1–3% of affected preschool children in the United States (MEPEDS, 2008; Friedman et al., 2009; McKean-Cowdin et al., 2013). Unfortunately, young children often appear to function well despite subnormal vision in their amblyopic eye; consequently, monocular visual impairment from amblyopia often goes unrecognized until later in life when treatment is more difficult and less effective. Diagnosing amblyopia is limited by our ability to assess vision in infants and preverbal children. At present, eradication of amblyopia would require either early intervention when amblyopia is deemed likely to occur in the presence of specific risk factors or prompt initiation of treatment when amblyopia first develops. The goal of the discussion in this targeted session was to develop consensus on approaches toward optimizing the early diagnosis of amblyopia.

Early diagnosis

While it seems intuitive that the earlier the diagnosis of amblyopia is made, the better chance for optimal visual function, the existing literature does not conclusively address the optimal age for initiating treatment. A population-based study in the UK did report data supporting screening and treatment before age 3 (Williams et al., 2002). The definitive answer may depend on several factors, including the type of amblyopia (i.e., strabismic, anisometropic, combined strabismic and anisometropic, or deprivation; discussed in a separate section), the time of onset and duration, the depth of amblyopia, and associated visual deficits. A full evaluation of response to early *versus* late diagnosis and treatment will require more than the assessment of high-contrast visual acuity testing. Defining and determining the treatment response of higher-order visual functions that are disrupted in amblyopia, ranging from contrast sensitivity and binocular vision to functional measures such as reading speed and certain visuomotor tasks, would be helpful. With these unknowns in mind, we reviewed the tools and standards for making a clinical diagnosis of amblyopia with the goal of reaching a consensus on areas of investigation that might enhance early detection and diagnosis.

What is the youngest age at which a diagnosis of amblyopia can be made? The answer depends on the definition of amblyopia, which is clinically described as a decrease in best-corrected visual acuity, accompanied by one or more known amblyogenic factors (strabismus, anisometropia, high refractive error, or obstruction of the visual media) present in early childhood in an apparently healthy eye (Ciuffreda et al., 1991). The clinical definition is predicated on monocular measures of distance visual acuity with optimal refractive correction in place. Because the measurement of visual acuity is largely dependent on the ability of the patient to report what he or she can see, this means that amblyopia diagnosis is problematic when assessing preverbal and/or uncooperative younger patients. The tools used—and the training of the examiner who is employing those tools—are critical contributors. Today's gold standard visual acuity test for the diagnosis of amblyopia in young children is the use of single optotypes with crowding bars, most often the HOTV letters or LEA symbols. When visual acuity testing is performed by an eye care specialist, reliable results can be obtained with most 3-year-old and nearly all 4-year-old children with otherwise normal neurocognitive development (Vision in Preschoolers Study Group, 2004; Cotter et al., 2007); however, monocular visual acuity measures in children younger than 3 years of age are often difficult or impossible to obtain.

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https://doi.org/10.1017/S0952523817000207 Published online by Cambridge University Press

For infants, Teller acuity cards® (grating acuity with preferential looking) may be used to assess monocular visual acuity; however, measures of grating acuity can be cumbersome to administer. When amblyopia is present, grating acuity often underestimates the magnitude of difference in optotype acuity between the two eyes, particularly in patients with strabismic amblyopia (Sokol et al., 1983; Sireteanu et al., 1990). Emerging methods using electronic displays and automated tracking of infant gaze to measure resolution acuity could supplant the acuity card procedure in the future (Jones et al., 2014). Experienced eye care providers can make inferences about monocular visual function based on a child's fixation preference; however, this approach has been shown to be a poor surrogate measure of interocular difference in visual acuity (Friedman et al., 2008; Cotter et al., 2009), having particularly poor sensitivity for anisometropic amblyopia and poor positive predictive values for both anisometropic and strabismic amblyopia. Therefore, when testing is performed by an experienced eye care provider, amblyopia is most reliably diagnosed when visual acuity obtained using single-surrounded optotypes is considered together with the child's history and measures of ocular alignment, refraction, and ocular structure. For most children, this becomes possible at approximately 3 years of age.

While the diagnosis of amblyopia is predicated on reduced visual acuity (in the absence of structural anomalies and with a history of or in the presence of one or more amblyogenic risk factors), other aspects of visual function might be useful surrogates for the diagnosis of amblyopia. For example, contrast sensitivity is reduced, particularly at high spatial frequencies in amblyopia (Hess, 1979; Levi, 1988; McKee et al., 2003); however, the clinical assessment of contrast sensitivity using currently available approaches is difficult or impossible in infants and preschool children. Thus, despite the potential value of contrast sensitivity in characterizing amblyopia, it is not routinely assessed in the clinic nor is it often measured in clinical trials of amblyopia treatment.

Binocular function is impaired in all forms of amblyopia, and stereoacuity is the most sensitive measure of binocular function. When stereoacuity testing is performed by an eye care specialist, reliable results can be obtained with most 3-year-old and nearly all 4-year-old children with otherwise normal neurocognitive development (Birch et al., 1997; Tarczy-Hornoch et al., 2008). Widely instituted modes of measuring stereoacuity in young children typically rely on separate images presented through polarized filters to produce a stereoscopic image. These tests are easy to implement and thus are used routinely in clinical and research settings. While stereopsis testing used on its own has not proven to be an effective population-based screening tool for detecting amblyopia in preschool children, it is more accurate than visual acuity, autorefraction, or photorefraction in detecting strabismus (which is an amblyogenic condition) (Schmidt et al., 2004).

Amblyopia risk factors

Amblyopia risk factors—that is, ophthalmic conditions that cause amblyopia—include significant refractive error, strabismus, and conditions that interfere with clear retinal image formation. These risk factors can be diagnosed much earlier than amblyopia itself.

Refractive error can be measured in infants and is a known risk factor for both unilateral and bilateral amblyopia. Anisometropia, particularly hyperopic anisometropia, is a strong predictor of amblyopia (Weakley & Birch, 2000; Tarczy-Hornoch et al., 2011; Barrett et al., 2013). Generally, greater than 1.00 D of hyperopic anisometropia is considered potentially amblyogenic, with increasing risk as the magnitude of anisometropia increases (Tarczy-Hornoch et al., 2011). A more significant interocular difference is required for myopia to cause amblyopia; lower degrees of myopic anisometropia tend not to be associated with amblyopia (Levi et al., 2011). Thresholds for astigmatic anisometropia that can lead to amblyopia appear to be lower than the 1.50–2.00 D that was previously thought to be based on clinical samples of nonstrabismic children (Weakley, 2001); population-based studies suggest that interocular cylinder differences as small as 0.50 to 1.00 D confer an increased risk for amblyopia, although the absolute risk is low at this level (Tarczy-Hornoch et al., 2011).

In regard to bilateral amblyopia, preschool children with bilateral hyperopia of ≥4.00 D SE or astigmatism of ≥2.00 D are 11 and 17 times more likely, respectively, to have bilateral amblyopia (Tarczy-Hornoch et al., 2011). Bilateral hyperopia also places infants and young children at increased risk for esotropia, which is itself a risk factor for amblyopia. Hyperopia between 2.00 and <3.00 D poses more than a 6-fold increase in esotropia risk, with a marked rise in risk with each diopter of increasing hyperopia (Cotter et al., 2011). Data from a hyperopia-enriched clinical population have indicated that low amounts of hyperopia (2.00 to <4.00 D) that coexist with anisometropia place children at an increased risk for accommodative esotropia (Weakley & Birch, 2000).

At present, data from two large population-based cross-sectional studies clearly indicate that there is a strong dose-dependent link between refractive error and both amblyopia and esotropia; however, we cannot predict the clinical consequences of a given risk factor in any one child. Not all young children with amblyogenic risk factors are destined for eventual amblyopia—in fact, many of these children never develop amblyopia. Furthermore, the temporal relationship between these risk factors and amblyopia development remains unclear—an infant or younger child identified as being at risk at one point in time may have not yet developed impending amblyopia. Thus, longitudinal data relating early refractive error at different ages to subsequent eye alignment and vision outcomes at older ages are needed.

The majority of amblyopia is attributable entirely or partly to the refractive error (MEPEDS, 2008; Friedman et al., 2009; Groenewoud et al., 2010; McKean-Cowdin et al., 2013). However, there is a lack of consensus on when refractive error should be treated to prevent amblyopia and when it is safe to observe instead. In combined analyses of the Multi-Ethnic Pediatric Eye Study (MEPEDS) and the Baltimore Pediatric Eye Study (BPEDS), ≥2.00 D spherical equivalent anisometropia was found to be a major risk factor (odds ratio of 39.8) for unilateral decreased visual acuity in children aged 2.5 to 6 years, yet 40% of the children with this magnitude of anisometropia had <2 lines of interocular difference in visual acuity (Tarczy-Hornoch et al., 2011).

There is similar uncertainty about when uncorrected hyperopia will lead to amblyopia or strabismus. Atkinson and colleagues reported that 7- to 8-month old infants with hyperopia between +4.00 and +7.00 D in at least one meridian in one or both eyes who were prescribed a partial spectacle correction were less likely to show measureable visual acuity deficits or strabismus by 4 years of age as compared to a nontreated comparison group (Atkinson et al., 1996; Atkinson et al., 2007). In a second similar study, they found a significantly reduced rate of amblyopia but no difference in the rate of strabismus in infants with hyperopia greater than +4.00 D who were prescribed a partial refractive correction compared to those who had not been prescribed spectacle lenses (Anker et al., 2004). There is presently no single threshold level of hyperopia that is known to be an optimal criterion for the referral of children

https://doi.org/10.1017/S0952523817000207 Published online by Cambridge University Press

at risk for amblyopia or strabismus or for consideration of the prophylactic spectacle prescription (Jones-Jordan et al., 2014).

In addition to concerns about the amblyogenic consequences of hyperopia, poor performance on visual-motor (Atkinson, et al., 2002; Atkinson et al., 2005; Roch-Levecq et al., 2008; Webber, et al., 2008), visuocognitive (including attention) (Atkinson et al., 2002; Roch-Levecq et al., 2008), and spatial (Atkinson et al., 2002) measures that have been reported for young children with uncorrected moderate hyperopia as compared to emmetropic controls. Recently, the Vision in Preschoolers–Hyperopia in Preschoolers (VIP–HIP) study found significant deficits in preschool literacy among 4-and 5-year-old children with >4.00 D of hyperopia compared to emmetropic controls (Kulp et al., 2016).

Strabismus is another detectable risk factor for amblyopia; however, angles of strabismus too small to be identified by families or by primary care providers are still large enough to cause amblyopia in many cases, particularly when the strabismus is unilateral and constant. Refractive risk factors alone do not suffice for identification of strabismus because children with strabismus can have refractive errors in the normal range. Furthermore, strabismus is often not present in infancy but instead develops in the preschool years—thus strabismus screening must be ongoing. While not all patients with strabismus develop amblyopia, the duration of abnormal visual experience may be an important factor in limiting a child's potential for the recovery of binocularity (Birch, 2003). There is consensus that prompt management of strabismus is a priority in these cases and most likely to result in improved long-term visual outcomes (American Academy of Ophthalmology Preferred Practice Pattern Guidelines. Esotropia and Exotropia, 2012; American Optometric Association Clinical Practice Guideline. Care of the Patient with Strabismus, 1995); thus, ideally, screening programs for amblyopia should also include testing for strabismus.

Deprivation amblyopia, which is caused by conditions such as congenital ptosis or cataract, accounts for a small percentage of amblyopia cases (MEPEDS, 2008; Friedman et al., 2009; McKean-Cowdin et al., 2013). While in more severe cases, it is obvious that timely treatment is necessary; when milder ocular defects are present, it is not always clear whether or not the defect must be treated to prevent amblyopia. Early assessment of the visual function would help determine which children in the borderline range are at risk of developing deprivation amblyopia.

Vision screening for amblyopia detection

As with any public health screening program, the benefits of any one screening method depend on the balance of sensitivity (and the consequences of missing disease) with specificity (the cost and burden of false referrals). Systematic, ongoing cost-benefit analyses of various programs will be critical to answer this question. Key questions to consider include who will perform the screening and at what age or ages should the screening be performed. While the goal of most preschool vision screening programs is early detection of amblyopia, the possibility that early treatment of moderate hyperopia may have educational benefits raises the question of whether low or moderate hyperopia should be the target of screening. The cost of casting a wider net for referral in the context of education rather than amblyopia would need to be calculated and considered separately from the cost of a more focused program of screening for amblyopia and strabismus.

Vision screening can potentially be performed by primary care providers (physicians and physician extenders), orthoptists, school nurses, lay persons in the community, and other screening personnel in public health settings. For many screening tests, the validity of the examination is highly dependent on the training of the individual performing the screening test. Primary care providers are optimally positioned to screen for amblyopia because they have access to infants and young children at annual well-child visits. While screening in the primary care clinic keeps this activity in the medical home, it places an additional burden on already-busy providers, who must manage multiple best-practice guidelines and recommendations (and perform a complete physical examination) during a time-limited well-child visit. In addition, inaccurate screening results from nonspecialist staff members may limit the cost-effectiveness (Williams et al., 2001). If vision screening is to be conducted effectively in the primary care setting, the screening tools need to be validated by methodologically sound studies performed on the target population, be efficient and easily administered by nonmedical personnel in various environments, require minimal or no subjective interpretation by the screener, and be available at low cost (Cotter et al., 2015). In addition, any screening method should have good sensitivity as well as reasonable specificity to reduce false referrals (Kemper & Clark, 2006).

At what age and how often should vision screening for amblyopia or amblyogenic risk factors be performed? Screening for amblyogenic refractive errors in infancy can be performed using videorefractive, photorefractive, or other instrument-based screening methods (see forthcoming section "Screening Tools"); however, detection of amblyogenic refractive risk factors is likely to result in over-referrals of presumed amblyopia because not all children with amblyogenic refractive error have (Cotter et al., 2011; Tarczy-Hornoch et al., 2011) or will develop (Atkinson et al., 1996; Atkinson et al., 2007) amblyopia or strabismus. While vision screening at school age is easier because most school-aged children can read the eye chart and perform other basic testing, amblyopia is generally more difficult to treat in children of older age (Holmes et al., 2011). The age of 3 to 4 years represents a time when most amblyopia and/or associated risk factors have become manifest and allows for the detection of amblyopia at an age where there is sufficient cortical plasticity to expect acceptable results in most patients. Thus, if there were only one age at which vision screening for amblyopia and strabismus could be performed using currently available methods, it would probably be age 3 to 4 years. A single screening in childhood would represent the least expensive approach in terms of cost; however, it is unlikely to be sufficiently sensitive because there will be cases of amblyopia and accommodative esotropia not yet manifest that would be missed by early screening. Depending on the sensitivity, specificity, cost, and complexity of the screening tests used, it might be possible to perform screening at more than one age, including annually. For example, the Netherlands has a population-based child health-monitoring program, where vision screening is conducted during a series of 7 predetermined well-child visits between birth and 6 years of age. In a birth cohort study (Groenewoud et al., 2010; de Koning et al., 2013), nearly 3000 children in the city of Rotterdam were examined by orthoptists at the age of 7 years to determine the program's effectiveness in detecting amblyopia. Of the children diagnosed with amblyopia, 73% had screened positive at least once; the majority of them were identified as a result of monocular visual acuity screenings conducted at 3 to 5 years of age, as opposed to the screenings conducted prior to age 3 years. Furthermore, there was a higher amblyopia detection rate among those who had been screened 5 or 6 times *versus* those screened 4 or fewer times. The authors reported that the Dutch vision screening program had

https://doi.org/10.1017/S0952523817000207 Published online by Cambridge University Press

reduced the prevalence of undetected or insufficiently treated amblyopia at age 7 years by more than 50% (Groenewoud et al., 2010; de Koning et al., 2013). By contrast, a more conservative approach of a single vision screening at age 4–5 years is the current recommended national policy in the UK (Solebo et al., 2015).

If there were a screening approach that could identify amblyopia directly rather than detect amblyogenic risk factors, then this could allow children with only amblyogenic risk factors but without disease to be followed with annual screening so that the referral would occur only if and when amblyopia developed. This is assuming, of course, that children with risk factors known to cause amblyopia at high rates or be problematic in other ways (for example, a young child with high hyperopia deemed significant enough to interfere with visual function) would be referred to an eye care professional for appropriate management regardless of the presence of amblyopia. Whether and under what circumstances early detection and treatment of amblyogenic risk factors can benefit patients in a cost-effective manner requires further prospective study, and the answer will ultimately guide recommendations with respect to the timing of screening and conditions for referral.

Screening tools

According to a recent report by the National Expert Panel to the National Center for Children's Vision and Eye Health (Cotter et al., 2015), current U.S. best-practice vision screening recommendations for amblyopia and amblyogenic risk factors in preschool children 36 to <72 months of age are either (1) monocular visual acuity testing using single HOTV letters or LEA Symbols surrounded by crowding bars at a 5-ft (1.5 m) test distance or (2) instrument-based testing using the Suresight Vision Screener (recently discontinued by manufacturer, Welch-Allyn, Inc, Skaneateles Falls, NY) or the Retinomax (Right Mfg Co. Ltd, Tokyo, Japan) autorefractor. With specificity set at 90%, sensitivity for lay screeners was 78% and 85% for the identification of amblyopia and amblyogenic risk factors using LEA symbol visual acuity testing and the Retinomax autorefractor, respectively (Vision in Preschoolers Study Group, 2005). Because Retinomax results are provided in a prescription form, however, this technique is not always readily interpretable by non-eye care professionals and has not been widely adopted for preschool vision screening.

In addition to the aforementioned autorefractor technology, there are a variety of other automated or semi-automated instruments that have been developed in an effort to improve vision screening accuracy while reducing cost in terms of time and trained personnel. Contrary to visual acuity screening, these instruments focus almost exclusively on the assessment of refractive risk factors with an important advantage that minimal cooperation is required from the child being tested.

Many of these new instruments are photoscreeners, which are similar to autorefractors in that they provide an estimate of refractive error (cycloplegic eye drops are not administered). Unlike autorefractors, however, some photoscreeners assess both eyes simultaneously, thereby providing the opportunity to identify grossly visible strabismus. Most published studies have assessed "accuracy" in the context of detecting amblyopia risk factors rather than detecting disease (strabismus and/or amblyopia). This may give misleadingly optimistic results in terms of a positive and negative predictive value; ideally, if the goal of screening is to detect treatable conditions at a time when intervention will have maximal impact on outcomes, the gold standard for diagnosis in cost-benefit studies of refractive error screening is the presence or subsequent development of amblyopia and/or strabismus. Furthermore, the ideal refractive error criteria that should be used for vision screening cut-offs are presently debated (Nathan & Donahue, 2011). The most commonly used amblyogenic refractive error criteria are consensus based rather than evidence based (Donahue et al., 2013), and are predicated on cycloplegic-determined refractive error, whereas vision screening instruments provide an estimate of refractive error without cycloplegia. In a population-based screening study of children 8, 12, 18, 25, 31, and 37 months of age that did use clinically-confirmed amblyopia and strabismus as the outcomes, noncycloplegic photorefraction was only sufficiently specific (88%) and sensitive (97%) for detecting straight-eyed (anisometropic) amblyopia at 37 months of age; unfortunately, it only detected 35% of the strabismic cases at this age (Williams et al., 2001).

An electrophysiological assessment of visual function using square-wave grating patterns during visual evoked potential (VEP) testing has been considered as a possible vision screening instrument for amblyopia (Simon et al., 2004). Because results are analyzed for intraocular differences in the cortical response from each eye in an attempt to identify patients with amblyopia, risk factors such as strabismus and refractive error are not detected by this method. This approach has not been widely adopted, and it is unlikely that it could be a cost-effective tool for large-scale screening.

Recently approved by the FDA for the screening of amblyopia and microstrabismus associated with amblyopia, the Pediatric Vision Scanner (PVS) assesses retinal birefringence to detect foveal fixation in both eyes simultaneously (Loudon et al., 2011). This approach detects binocular alignment with high accuracy, generating a "binocularity score" that reflects the presence or absence of strabismus and of microstrabismus associated with amblyopia. Testing can be completed in 10 s in children as young as 2 years of age. Thus far, the ability of the PVS to detect amblyopia and strabismus has been promising (Loudon et al., 2011; Jost et al., 2014; Jost et al., 2015). While the device was originally designed to assess strabismus, it has been hypothesized that the PVS also detects amblyopia because, similar to strabismic patients, amblyopic patients also have inaccurate and/or unstable fixation (Loudon et al., 2011; Gonzalez et al., 2012; Jost et al., 2015).

New avenues of research

There remains considerable opportunity for innovation and discovery of new critical clinical features of and biomarkers for amblyopia. Potential avenues include identifying genetic markers that predict or contribute to the development of amblyopia. Neurophysiologic correlates such as visual evoked potentials and anatomic or structural correlates of amblyopia are potential future avenues for research in the diagnosis of amblyopia. These markers may also be helpful in predicting the response to treatment and priority for or timing of screening in individuals or groups. Discovering novel correlates of amblyopia will require advances in neurophysiologic measures and high-resolution neuro- and retinal imaging. For example, accumulating evidence that long-term chronic interocular suppression may play a key role in the development of amblyopia (Li et al., 2011; Narasimhan et al., 2012) highlights the need for further study. A better understanding of the effects of decorrelated binocular visual experience and the development of amblyopia could lead to the design of a clinical test of suppression to screen for patients with or who are at high risk for

https://doi.org/10.1017/S0952523817000207 Published online by Cambridge University Press

developing amblyopia. For any new, sophisticated assessment tool for amblyopia to have a positive impact on public health, it will need to be translated into a practical implementation that is widely available and cost effective.

At present, there is no single clinical factor that can be used to predict the presence of or development of amblyopia in very young children. This is also true in other fields of medicine, where no single clinical feature or biomarker is sufficient to predict an adverse event related to the disease. Multivariate regression analyses can help to integrate the most important contributing risk factors into a scoring system. In turn, this scoring system can be tweaked to optimize sensitivity and specificity, thereby facilitating effective identification of patients at risk for or with a disease while limiting the over referral of false-positive cases and reducing cost. Such scoring systems have been developed for several systemic diseases as well as for primary open angle glaucoma (Gordon et al., 2007). These systems use readily available clinical or laboratory values to facilitate wide implementation. Such a system for amblyopia could potentially be built from already existing datasets, enhanced by advances in amblyopia science and deployed in the context of new testing devices. Currently, our knowledge of the increased risk in relation to the magnitude of a given amblyogenic risk factor is still only fragmentary and obtained from large, population-based, cross-sectional studies (Cotter et al., 2011; Tarczy-Hornoch et al., 2011). Large, prospective clinical trials with proper randomization of study participants to two groups, with and without early treatment of the risk factor, that are heedful of treatment allocation concealment are needed to assess the risk increase in relation to the magnitude of the risk factor more accurately (Jones-Jordan et al., 2014).

Recommendations

- Untreated or insufficiently treated amblyopia may result in lifelong impairment in visual function. Early identification of patients with amblyopia is an important step toward effective treatment, but the lack of visual dysfunction evident to laypersons and primary care providers supports the need for more effective screening tools and systems. Refractive risk factors are potential targets for detection, but screening for risk factors must be weighed against the burden of over referrals since many infants and young children with risk factors will never develop amblyopia, and a program with a high false referral rate is not likely to be adopted universally. Longitudinal studies of young children with amblyogenic risk factors with and without early intervention would be ideal.
- We can improve the screening and referral process standards through the development of practical and cost-effective vision screening methods that have a strong evidence base. Ideally, vision screening instruments should undergo a robust assessment that includes the following study design characteristics: prospective, large-scale vision screening of children within the targeted age range and with a sufficient number of children with the disease of interest (e.g., amblyopia, strabismus, and refractive error); screening performed by lay screeners in the field; all children who undergo the screening also undergo a comprehensive eye examination that includes a cycloplegic refraction; and both the screeners and eye care providers are masked to the results of other testing. Any given vision screening program also should have a component to ensure that children who need treatment are indeed referred and seen by an eye care professional in a reasonable interval. Ideally an integrated data system for recording vision screening and eye care follow-up and treatment outcomes to "close the loop" should be in place (Hartmann et al., 2015).
- There is considerable opportunity for innovation and development of screening and diagnostic tools for amblyopia. Because moderate levels of hyperopic refractive error place young children at significant risk for the future development of amblyopia and strabismus and because they have been associated with impaired developmental and academic performance, we encourage ongoing work to identify clinical features that predict failure to emmetropize among infants with hyperopia. New technology that can empower lay persons and primary care providers to detect amblyopia and strabismus in preschool children with high sensitivity and specificity could improve the effectiveness of vision screening worldwide. New physiologic, anatomic, and genetic markers should not only provide valuable insights into the pathophysiology of amblyopia but should also have practical and wide-spread application if they are to be incorporated into a screening and diagnostic system for amblyopia. Existing and new clinical features could be integrated into a scoring system to predict risk for amblyopia development to guide referrals. Successful implementation of research and clinical programs that embody these principles will lead to earlier detection and treatment of amblyopia, which would have a profound positive impact on the health and well-being of future generations.

Acknowledgments

The authors would like to thank Eric Gaier,* who served as the scribe for this discussion section. We would also like to thank all discussion group participants: Jan Atkinson, Peter Bex, Eileen Birch, Dennis Levi, Sjoukje Loudon, Hugo Marx, Paul Sieving, Herb Simonsz, Earl Smith, Al Sommer, and Larry Tychsen.

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