Amblyopia Outcomes Through Clinical Trials and Practice Measurement: Room for Improvement: The LXXVII Edward Jackson Memorial Lecture

MICHAEL X. REPKA

• PURPOSE: To describe amblyopia prevalence and outcomes using results from randomized studies and a clinical registry.
• DESIGN: Review of published studies, analysis of data in Intelligent Research in Sight (IRIS) Registry from 2013 to 2019, personal perspective.
• METHODS: Literature review, analysis of IRIS Registry data and IRIS-50, a visual acuity quality measure.
• RESULTS: Clinical trials have reduced the treatment burden of amblyopia by reducing hours of patching and frequency of atropine eye drops with clinical success of about 83%. There is no appreciable age effect if treatment is started before 5 years of age, outcomes are stable to at least 15 years of age, and treatment can be somewhat effective until 12 years of age. The IRIS Registry identified 1,760,066 individuals with amblyopia for a prevalence of 2.47%. Refractive error alone accounted for 68.9% of childhood cases. Mean amblyopic eye visual acuity improved 1.8 lines for children 3-6 years of age and 0.8 lines for 7-12 years, but mean residual amblyopia was more than 2 lines. Among 18,841 children aged 3-7 years eligible for IRIS-50, 77.3% were successful. The odds ratios for success were significantly lower for African-American (0.67; 95% confidence interval [CI] = 0.58 to 0.78) and Hispanic or Latino (0.84; 95% CI = 0.75 to 0.94) children compared with white children.
• CONCLUSIONS: Clinical trials provided evidence of a beneficial effect from several treatments, with substantially reduced doses than previously recommended. Registry data from clinical practice found residual visual acuity impairment among all ages and races, especially among minorities. (Am J Ophthalmol 2020;219:A1–A26. © 2020 Elsevier Inc. All rights reserved.)

AJO.com Supplemental Material available at AJO.com.
Accepted for publication Jul 27, 2020.

From Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.
Inquiries to Michael X. Repka, Johns Hopkins University School of Medicine, Wilmer 273, 600 North Wolfe St, Baltimore, MD 21287-9089, USA; e-mail: mrepka@jhmi.edu

IT IS AN EXTRAORDINARY HONOR TO PRESENT THE 77TH Edward L. Jackson, MD, Memorial Lecture in 2020. Dr Edward L. Jackson was born in 1856 in West Goshen, Pennsylvania; obtained his medical degree from the University of Pennsylvania; and served as attending surgeon at the Wills Eye Hospital.[1] Dr Jackson went on to become Chair of Ophthalmology at the University of Colorado and editor of this journal, and would lead many national ophthalmology organizations. An important connection between Dr Jackson and this lecture was his popularization of the use of retinoscopy, which remains fundamental to the management of amblyopia more than a century later.

This lecture affords me the unique opportunity to highlight a common and treatable eye condition: amblyopia. Childhood eye problems have been previous subjects of this lectureship including pediatric cataract (P.A. Chandler), infantile esotropia (G. von Noorden), persistent hyperplastic primary vitreous (A.B. Reese), persistent fetal vasculature (M.F. Goldberg), and hereditary blindness (I.H. Maumenee).[2]

IMPORTANCE

IN 2017 THE NATIONAL ACADEMIES OF SCIENCE, ENGINEERing and Medicine (NASEM) noted, "Avoidable vision impairment occurs too frequently in the United States-…resulting from shortfalls in public health policy and health care delivery."[3] Among the eye problems of children that the NASEM authors highlighted in need of improvement in research and public health attention was amblyopia, which often has lifelong impact, especially among patients who are not identified and treated at a young age. The committee wrote, "The toll of correctable vision loss among children who do not receive adequate detection, follow up, and treatment is troubling."[3] Thus, amblyopia which is common, can be successfully treated with proven approaches, and has data confirming significant room for improvement in outcomes, make it a subject suitable for our attention.

My purpose is to review basic information about amblyopia, including prevalence in the United States and results of recent clinical trials, and present demographic data on

0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2020.07.053

amblyopia in current clinical practice as found in the Intelligent Research in Sight (IRIS) Registry.[4] In addition, visual acuity (VA) outcomes can be measured for the population and for individual practitioners using these "Big Data." These results could suggest new hypotheses for amblyopipa research on when and how to screen, treat, and monitor, and how to evaluate new treatments. For extensive reviews of amblyopia, I would suggest the treatises written by Simons[5] and Birch.[6]

BACKGROUND

AMBLYOPIA IS UNILATERAL (MOST OFTEN) OR BILATERAL vision loss when measured with high-contrast letter optotypes while using best refractive correction with no other identified abnormalities in the visual system (including the globe, retina, optic nerve, and brain).

Amblyopia in humans should be considered a neurologic condition. Amblyopia is caused by disruption in the visual experience of a child in the first decade of life, affecting their brain development, most often from uncorrected refractive error, strabismus, refractive-strabismus combined, or deprivation.[7–10] The impact is greatest when these risk factors affect vision development early in life,[6] leading to structural changes and functional impairment of the brain. The structural changes were demonstrated more than 50 years ago by Hubel and Wiesel in nonhuman primates.[11] For the clinician to consider a patient to have amblyopia, a plausible cause needs be present such as strabismus and anisometropia. Other diagnoses with vision impairment to be excluded include optic neuropathy, optic nerve hypoplasia, retinal dystrophy (eg, cone dystrophy, Stargardt disease), and macular hypoplasia, each of which needs a different evaluation and management.

While the most-studied functional deficit of amblyopia is high-contrast VA, most unilateral amblyopia patients have additional deficits often affecting function under binocular conditions. These include reduced binocular depth perception, visuomotor impairment,[12] slowed binocular reading speed,[13] as well as decreased motion detection[14] and vernier acuity.[15] Many affected individuals will also have subtle deficits such as microstrabismus, eccentric fixation, and fixation instability.[16] Children with amblyopia have reduced self-perception of peer acceptance and physical competence when compared with children who do not have amblyopia.[17] Even when the high-contrast VA deficit is "corrected" with conventional treatment, these problems will persist to some degree for their lifetime, with varied impact on their quality of life.

Amblyopia is the most common cause of visual impairment among children in the developed world, with an estimated prevalence of about 2.4%.[6] Recent population-based estimates in the United States found similar rates. Amblyopia in preschool children was found in 1.8% of white children, 0.8% of African-American children in Baltimore, 1.5% of African-American children in Los Angeles, and 2.6% of Hispanic/Latino children.[8,9] A population based-survey of 6-year-olds in Australia found a rate of 1.8% when they included treated children.[18] Similar rates (1.9%-3.6%) have been found in reports from Europe, the United Kingdom, and Australia.[19–21]

Amblyopia encountered in US population-based studies was largely untreated, with only 2.5% of children with unilateral decreased VA having a history of diagnosis or treatment.[22] This was despite the fact that long-standing preschool and medical home screening programs were recommended in those areas.[5] Many cases of amblyopia-associated vision loss persist into adulthood. Amblyopia has been reported to be the leading cause of monocular vision loss in the 20- to 70-year-old age group, with a prevalence of 1%-4%.[5,23–25]

Thus, there appears to be significant opportunity for improvement in detection and treatment strategies. The goal of presymptomatic identification by screening of preschool children has been widely felt to achieve better visual outcomes if prescribed treatment was available and completed in those young children. Numerous programs have been established over many years, with governmental support and philanthropic support, to detect preschool children with vision disorders and refer for treatment. In Sweden a retrospective study found the rate of deep and moderate amblyopia to have been reduced to less than 2% of the population, which in the opinion of the authors was due to early screening and treatment.[26,27]

However, despite the widespread deployment of vision screening activities, the value of such programs has been questioned because of the lack of natural history data for untreated amblyopia,[28] as well as lack of high-level evidence for effectiveness and durability of treatment. In 1997 when Snowdon and Stewart-Brown assessed this situation, data on the natural history of amblyopia and the success rates of treatment with either occlusion or penalization were largely retrospective and uncontrolled. In addition, since little was known about the course of treated amblyopia and impact on quality of life, commentators could question the value of preschool vision screening.

At about the same time the National Eye Institute became interested in real-world setting research and thus was willing and able to fund development of the Pediatric Eye Disease Investigator Group (PEDIG), a network of university-based and community-based pediatric eye care clinicians caring for children and working together with the Jaeb Center for Health Research in Tampa, Florida, to study eye diseases in children, initially amblyopia.[29] I had the privilege of becoming the first PEDIG chair and have been able to continue to work with the PEDIG network. The first amblyopia study (ATS1) developed was to provide more precise estimates of success rates of treatment, to compare widely used treatments, to identify factors that may be associated with successful and

unsuccessful treatment, and to develop some long-term outcome data. Over time the network would expand to include other common eye diseases in children, such as cataract and strabismus. PEDIG has to date successfully conducted more than 40 trials and studies, many of which have significantly influenced treatment recommendations. These studies of successful treatments directly support the value of screening for childhood eye conditions.

The level of vision loss necessary to be considered amblyopia varies widely, with 20/32 (or similar) or worse in the amblyopic eye and a 2-line intraocular VA difference the least restrictive, and worse than 20/40 with a more than 2-line interocular difference the most restrictive. Each child needs to have a known risk factor present. These fixed cut-point definitions included many younger children who were not amblyopic, as they did not account for the age effect of VA testing, where 20/40 is normal for many preschool children,[30] and for test-retest variability of VA testing in children, which means a single test could often be inaccurate. The definition of amblyopia should be considered in light of normative VA data; the most restrictive definition of abnormal vision would require an eye to be worse than 20/50 at 3 years of age, worse than 20/40 at 4 years, worse than 20/32 at 5 or 6 years, and worse than 20/25 at 7 years and older on both a test and a retest.[31,32]

The choice of amblyopia definition will vary with the intent of the survey or study. Visual acuity thresholds are required, as well as presence of a risk factor. To detect most affected children, investigators in the Baltimore Pediatric Eye Disease Survey (BPEDS) and Multi-Ethnic Pediatric Eye Disease Survey (MEPEDS) for children 30-71 months of age used low thresholds (for unilateral 20/32 and a 2-line difference; for bilateral <20/50 in children aged 30-47 months or <20/40 in children 48-71 months).[9] Alternatively, PEDIG clinical trials for unilateral amblyopia have commonly used 20/40 and a 3-line difference to allow enrollment of individuals who had sufficient room for improvement with treatment.[33]

PREVALENCE AND RISK FACTORS

IN 2 RECENT POPULATION-BASED STUDIES OF PRESCHOOL children in the United States, BPEDS and MEPEDS found the average rate of amblyopia across the studied groups to be about 2%. In MEPEDS 78% of children with amblyopia were associated with refractive error alone, 19% with strabismus, and 1.5% with deprivation.[8] In BPEDS the findings differed, with 47% associated with refractive error alone, 32% with strabismus alone, 11% with combined, and 5% with deprivation.[9] In an Australian population-based study strabismus was noted in 38% of the children with amblyopia, anisometropia in 34%, both combined in 18.8%, and isoametropia in 6.3%.[18] Similarly, the Vision in Preschoolers Study, which evaluated children enrolled in Head Start programs, found refractive error and anisometropia to be the leading cause of amblyopia, accounting for about 75% of cases; combined refractive-strabismic accounting for 10.5% of cases, and strabismus alone accounting for 3.7%.[10]

Numerous clinic-based studies have also reported data on the relative prevalence rates of common causes of amblyopia. These rates tend to vary from the population-based data with much more strabismus and less refractive error. Woodruff and associates reviewed 961 treated patients, finding the cause to be strabismus in 57%, anisometropia in 17%, and a combination of the 2 factors in 27%.[7] Shaw and associates[34] studied 1,531 amblyopic children and found that strabismus was the cause in 45%, anisometropia in 17%, a combination of the 2 in 35%, and deprivation due to cataract or corneal scarring in 3%. The relative rates of causative factors have also been examined using enrollment data from recent amblyopia treatment trials, where strabismus was the cause in 38% participants, anisometropia in 37%, and both combined in 24%.[35] Deprivation amblyopia has been excluded from PEDIG treatment trials. Refractive error is more common in population studies and strabismus is more common in treatment trials. Thus, these 2 factors, refractive error and strabismus, should remain the focus of efforts for detection and intervention. However, it is important to note that even when these risk factors are present, they usually do not cause clinically significant amblyopia.

OTHER RISK FACTORS FOR AMBLYOPIA DEVELOPMENT

LARGE POPULATION-BASED STUDIES CAN BE ANALYZED TO identify additional risk factors for development of amblyopia. These factors have included prematurity, developmental delay, maternal smoking, drugs, and alcohol.[18,19,22] In the MEPEDS/BPEDS population-based studies of eye diseases in children, an array of social and demographic factors were prospectively collected and evaluated. The risk of amblyopia was positively associated with Hispanic ethnicity, esotropia, increasing anisometropia beginning at 0.50 to <1.00 diopter (D), and increasing astigmatism more than 0.50 D, especially if oblique orientation.[22] In the analysis of bilateral decreased VA, most often amblyopia, it was associated with lack of health insurance, lower primary caregiver education, astigmatism (especially oblique), and hyperopia ≥4.00 D.

SCREENING FOR AMBLYOPIA

A KEY GOAL OF PUBLIC HEALTH POLICY IS THE PRESYMPTOMatic identification of preschool children at risk for development of amblyopia from refractive error and strabismus. Secondary goals of preschool screening are to detect

refractive errors that require correction for visual function, and to identify and refer the few other eye problems these young children have that need treatment.[36] For school-aged children, vision screening is primarily targeting children needing refractive correction for myopia and astigmatism for optimum school performance, with a substantial portion of each class needing glasses increasing with grade level.[129] Screening programs are mandated in a majority of states, although the details vary widely.

When a screening program is established it needs to be designed for the particular problems that are expected and use the best available techniques for that age group. For the most part, VA testing or automated refractive error assessment seemed efficient, although imperfect, when studied by the Vision in Preschoolers Study.[37] A study from Germany found VA testing of kindergarten-aged children compared with refractive testing to be efficient and more cost effective.[38] For school-aged children VA testing seems to be the most efficient.

For vision screening to be deemed useful, the screening program must have acceptable false-positive and false-negative rates and there needs to be an acceptable cost-effective and durable treatment. Recent data on screening of preschool children and treatment outcomes (described below) led the United States Preventive Services Task Force (USPSTF) to recommend vision screening at least once in children 3-5 years of age to detect amblyopia or its risk factors (B recommendation).[39] However, the USPSTF found the data for younger children (0-3 years of age) to be inconclusive, largely because there were no studies showing a benefit of treatment at that age. This deficiency is due to the absence of a robust quantitative clinically useful measure of VA improvement for this age range and not related to the value of the screening.

These conclusions by USPSTF generated dissent. First, some experts are of the opinion that there may be insufficient improvement for the majority of the children 3-5 years of age failing vision screening to be worth the effort at that young age.[30] This is a nuanced opinion, as children with mild VA impairment in a clinical trial did equally well if they were treated immediately or treatment delayed if still necessary, upon reaching 5 years of age for a school screening.[30] In this clinical trial children were enrolled if they had vision impairment discovered during a preschool screen, confirmed with a second screening, and had no ocular or ocular motor abnormalities. Thus, their vision impairment could be refractive error, unilateral amblyopia, or classification error (a false-positive). Randomization was to "follow up in 1 year" or to "prescribe glasses with patching if needed" with the primary outcome at 1 year. During follow-up the glasses treatment was supplemented with prescribed patching for 71% of that group. The best-corrected VA of the treated group was on average 1 line better than the no-treatment group, with a benefit of 2.03 lines with baseline acuities of 20/60 to 20/100, but a lesser benefit of 0.45 lines with baseline acuities of 20/30 to 20/40. When the untreated children had received 6-months treatment, there was no significant difference compared with the early treatment group. The authors were disappointed by the lack of a clear benefit from early detection, but inclusion in their regional screening program of children with VA of 20/30 and 20/40 at baseline (72% of the cohort), as was done, reduced the average benefit, masking the clear benefit for children with poorer initial vision. A reasonable conclusion is to not immediately refer preschool failures for 20/30 and 20/40 because the chance for benefit is limited, there is a high risk that they were misclassified (false-positive), and resources are limited. Thus, preschool vision screening programs should consider enrolling only those with poorer vision who would clearly benefit from the immediate intervention, rather than refer for 20/40, as some programs continue to do.

The second objection focused on the task force's unwillingness to extrapolate findings to ages not studied. Some commentators think it would be reasonable to generalize the recommendations of older preschool-aged children to children younger than 3 years of age, even in the absence of a measure showing benefit, rather than leave children untreated.[40] These authors necessarily recommend reliance on photo-screening evidence for referral. Complicating this decision is the knowledge that many patients with refractive error risk factors for amblyopia do not actually have amblyopia and do not require treatment. For instance, 2.00 D of anisometropia is a well-accepted strong risk factor, but only 59.5% of patients with this factor had amblyopia.[22]

With respect to treatment durability—the other important factor in making amblyopia detection and treatment quality health care—3 long-term follow-up studies provide support. In a prospective long-term outcome study of 155 children followed to 15 years of age, PEDIG found that following treatment at 3-6 years of age there was improvement during the first 2 years after study entry, but no significant improvement or deterioration in the amblyopic eye VA was identified upon completing the outcome visit 7-9 years later after treatment had been stopped for many years.[41] In a retrospective study Leiba and associates recalled 54 patients who had a mean amblyopic eye logMAR VA of 0.90 logMAR at screening (mean 5.1 years of age), 0.24 logMAR at the end of occlusion (mean 7.4 years of age), 0.35 logMAR at a mean of 13.7 years, and 0.24 logMAR at a mean of 29.0 years.[42] Although there was residual amblyopia, treatment benefit remained at each time point. Finally, Bowman and associates recalled 88 participants from a preschool vision program who had a mean amblyopic eye VA of 0.47 logMAR at time of presentation (average 4.1 years of age).[43] Their mean VA was 0.23 logMAR at end of active treatment (average 7.5 years of age) and 0.18 logMAR at a mean of 12.3 years of age, showing no loss of the benefit obtained and possible gain during long-term follow-up.

While vision screening for unilateral impairment from amblyopia may have some controversy about the VA cut

point necessary for detection and referral, screening continues to be useful for detecting and managing both unilateral and bilateral visual loss that could affect activities and school performance. There is need to update research findings to refine the ages when screening should be performed and when it should be optional, what technologies should be used for screening, and what functional improvements the children can expect to gain for the effort expended.

HISTORY OF TREATMENT OF AMBLYOPIA

TREATMENT OF AMBLYOPIA HAS BEEN DESCRIBED FOR MORE than a millennium.[44,45] Loudon and Simonsz have published a thorough history.[45] Von Noorden noted that Thabit Ibn Qurrah in Mesopotamia recommended amblyopia treatment with occlusion in the ninth century.[44] Duke-Elder credited George Louis Leclerc, Comte de Buffon, for promoting our current clinical understanding of occlusion treatment about 1743,[45] while Loudon and Simonsz suggested that Charles de Saint-Yves, who suggested treatment a few years earlier, should receive some credit.[46] Forcing the patient to use the affected eye has remained standard medical practice since that time, although the value has been challenged out of concern for adverse effects even in the early 20th century.

Complete occlusion of the fellow eye with an adhesive patch on the skin became the standard of care because it was simple, inexpensive, and easily monitored and seemed to work. More patient-friendly spectacle-mounted patches have also been used. The alternative, blurring the fellow eye with cycloplegia, is also a long-standing approach, as Claude Worth is credited with suggesting this approach in 1903.[44,46]

In recent years the importance of refractive error correction to the successful treatment of amblyopia has been re-emphasized as a prerequisite for other conventional techniques. In fact, recent research has shown that glasses alone can be successful far more often than conventionally thought. In 2002 Moseley and associates demonstrated that substantial improvement with glasses alone occurred in refractive amblyopia.[47] The authors termed this improvement refractive adaptation. Their larger subsequent study (the Monitored Occlusion Treatment of Amblyopia Study) enrolled 65 untreated children aged 3-8 years (mean age 5.1 years), with VA of 0.1 to 1.6 logMAR in their amblyopic eye (mild to severe) caused by refractive error or strabismus. The mean improvement in the initial phase with glasses alone was 0.24 logMAR (range = 0.0 to 0.6) from the eyeglasses-corrected baseline visit.[48] There was no difference in improvement when analyzed by cause of amblyopia or age. The mean time to best VA was ~14 weeks for refractive adaptation; 14 of 65 (22%) children did not need occlusion.

About the same time PEDIG conducted 2 trials of glasses-only treatment for untreated amblyopia to affirm the value of refractive error correction as initial treatment. In the first PEDIG study (ATS5) anisometropic patients (n = 84) were treated with optical correction. We found improvement of at least 2 lines in 77% of the patients and resolution of the amblyopia in 27%,[49] similar to Stewart and associates. Improvement took up to 30 weeks, far longer than most clinicians have traditionally waited to start some active intervention. As part of the project we included a pilot study of strabismic amblyopia and were surprised they responded similarly.[50] To confirm this surprising observation we conducted a full-size glasses-only observational study (ATS13) for strabismic amblyopia. In that study, 146 children with strabismic or strabismic refractive combined amblyopia were enrolled, with 75% of the participants improving at least 2 lines and 32% of children having their amblyopia resolve.[51] An intriguing observation was that the vision improved in most children, but only 24% of children regained orthotropia with eyeglasses correction. The VA improvement did not require surgical or optical realignment of the eyes. Perhaps the amblyopic eye was used for some activities despite persistence of the tropia.

ADDITIONAL TREATMENT BEYOND EYEGLASSES

AN ONGOING CONTROVERSY IN AMBLYOPIA THERAPY HAS been whether the VA improvement seen in case series and randomized trials is from the actual prescribed treatment, rather than improvement caused by continued use of eyeglasses along with age and learning effects with VA testing. Generally, experts have felt the magnitude of VA improvement of 3 or more lines from patching or atropine eye drops typical in these studies has greatly surpassed the age and learning effects observed over the short time frame of a clinical trial. Nevertheless, this question has been addressed in a several prospective randomized studies.

In the trial discussed earlier on the benefits of vision screening, Clarke and his colleagues in the United Kingdom conducted a prospective randomized trial of treating vs not treating children 3-5 years of age who failed vision screening for isolated unilateral visual impairment identified by vision screening (20/30 to 20/120 in the poorer eye).[30] Some patients had vision loss solely from refractive error. The investigators found more benefit for glasses plus patching compared with glasses alone or with no treatment for children 20/60 to 20/120. However, the institution of patching came well after randomization, so they could not be certain that the patching was additive to the glasses.

Awan and associates conducted a randomized trial of 52 children with strabismic amblyopia who had 6 weeks of spectacle correction before randomization.[52] Twelve weeks after randomization they found amblyopic eye VA improvement of 1.6 lines with glasses alone, 1.9 lines with 3 hours of prescribed daily patching, and 2.3 lines with 6 hours of prescribed daily patching. The large beneficial treatment effect seen in the no-patching group after randomization suggests that refractive adaptation was still occurring after randomization, consistent with MOTAS[48] and PEDIG[49] findings. Because of the large improvement in the glasses-only group they could not statistically conclude that there was an additional benefit to patching for the whole group. However, they did observe that when compliance with the patching was good, there was reasonable evidence that patching had an additional benefit.

In the second phase of MOTAS, 72 children underwent 16 weeks of refractive adaptation and then had patching added.[53] They improved a mean of 3.5 logMAR lines over 12 weeks, suggesting a substantial benefit to patching when needed, but the conclusion is tempered by the absence of a control group.

PEDIG also studied the benefit of adding patching to glasses with a continuing glasses-only control group. Children were placed in correct glasses and followed until the VA stopped getting better, at which time point they were randomized to continue glasses alone or continue the glasses with the addition of 2 hours of daily prescribed patching with a primary outcome at 5 weeks.[54] The patching group improved by an average of 1.1 lines, while the control group improved by 0.5 lines (mean difference in VA between groups adjusted for baseline acuity = 0.07 logMAR, 95% confidence interval [CI] = 0.02 to 0.12, $P = .006$), confirming the benefit of additional patching. With extended follow-up the patching group improved an average of 0.9 lines more than control. Best VA was achieved by most patients after 10 weeks of treatment. Similar results were found for both moderate (20/40 to 20/100) and severe (20/125 to 20/400) amblyopia. This phenomenon of slow and extended period of improvement with glasses alone has become an important consideration in both research and clinical care. Research is complicated by the control group's prolonged improvement and the clinician should have patience as improvement may continue even when it appears to have stopped.

Given the results of glasses-only treatment in the trials presented above, it has become a reasonable consensus to initially prescribe glasses and then follow the patient with this treatment until they stop improving.[55] When the vision stops improving, a treatment chosen by physician preference, family preference, and type and severity of amblyopia should be offered. Widely accepted methods studied in randomized clinical trials include occlusion with a patch, typically skin adhesive type, and pharmacologic penalization, typically with atropine. Other methods include fogging with Bangerter filters. Each method will have varied compliance rates, which affects their overall success and accounts in part for individual variability in treatment success.[52] In all cases continued use of the glasses is paramount.

PEDIG RANDOMIZED TREATMENT TRIALS

EARLY PEDIG CLINICAL TRIALS EXAMINED THE EFFECTIVEness of a variety of amblyopia treatments for anisometropic, strabismic, or combined amblyopia. Study of the treatment of deprivation amblyopia has not been conducted because it is uncommon and heterogeneous. Early PEDIG studies randomized treatments rather than compared treatment with a no-treatment control. When those initial trials were designed (late 1990s and early 2000s) the PEDIG investigators did not feel we could ethically delay standard occlusion treatment even for 4 months, for fear of causing irreparable harm to the children. Such was the prevailing thought of that period. For that reason, we required there be improvement in amblyopic-eye VA far greater than expected from the combined age and learning effect alone, as evidenced by the behavior of the fellow eyes. Subsequent analyses of PEDIG outcomes data have shown that treatment delays of a few months during a typical randomized trial are probably not important and can be managed in the study design for younger children.[56] There was a significant difference in treatment outcomes between children younger and older than 7 years of age, with less responsiveness in the older group. We found only a minor age effect among children 3 to <7 years of age, affecting only those with severe amblyopia. This evidence has allowed PEDIG in the last 10 years to design studies incorporating no-treatment or continuing glasses-only controls.

• **PATCHING COMPARED WITH ATROPINE EYE DROP CYCLOPLEGIC BLUR:** Patching is usually prescribed with an adhesive patch placed on the skin, although some children will place a patch on the glasses owing to skin irritation or unwillingness to use the adhesive patch. In the first PEDIG Amblyopia Treatment Study (ATS1) we compared patching 6 hours or more each day with 1% atropine eye drops to the fellow eye daily.[33] The chosen doses represented a compromise between the proponents of each therapy at the time the study was designed in the late 1990s. Children were 3-6 years of age because they could complete a VA test and have a good chance to show improvement. The 6-month primary outcome was also a compromise, recognizing patching was expected to be faster than atropine. Both treatment groups improved on average about 3 lines, with 77.5% improving to 20/30 or improving at least 3 lines.[33] The fellow eye improved about 0.6 lines, far less than the treated eyes, suggesting that there is a treatment benefit beyond age and learning effects. As anticipated in the design, the patching patients

did improve faster, but ended up with equivalent improvement at 6 months post randomization. Two years following randomization with investigator-determined treatment after 6 months prescribed in nearly all patients, VA in the amblyopic eye continued to improve, with an average additional 0.6 lines improvement in both groups during those 18 months.[57] The mean amblyopic eye VA was about 20/32, but that was 1.8 lines worse than the fellow eye. The main adverse effect of patching was skin irritation, reported by 41% of participants, while with atropine light sensitivity was reported by 18%. Facial flushing with atropine was noted by less than 1% and very few patients stopped the drops. Parental-reported quality of life found both treatments to be well tolerated, although atropine performed somewhat better on adverse effects, compliance, and social stigma sub-scales.[58]

• **AGE LIMIT FOR AMBLYOPIA TREATMENT:** The question of how old a child can be to consider amblyopia treatment worthwhile has long been controversial. For many years a cut point of 7 or 8 years of age was common teaching, based on our understanding of the critical period for cortical vision development. However, there were reports of successful treatment well beyond that age. In the third PEDIG amblyopia treatment study (ATS3) we randomized children 7-17 years of age to glasses alone or to glasses plus full-time occlusion for all, plus atropine penalization for the participants 7-12 years of age for 26 weeks.[59] In the 7-12 years of age group (n = 404), 53% of the full treatment group improved 2 or more lines compared with 25% of the optical correction group ($P < .001$). In the 13-17 years old age group (n = 103), rates of 2 or more lines of improvement were 25% (full treatment) and 23% (optical only). While an age effect was evident, we found that in children 13-17 years who had never been treated, the success rates were 47% (full treatment) and 20% (optical only) (adjusted $P = .03$). Of note, glasses alone helped many of the older patients, and could be at least a middle ground for treatment if the teenager had not been previously treated.

In an effort to reduce the treatment burden from the "kitchen-sink" approach of ATS3, we designed a randomized clinical trial (ATS9) comparing much lower dosages of twice-weekly atropine with 2 hours daily of prescribed patching for children 7-12 years of age for 4 months.[60] This age group has been very responsive in ATS3 described just above. Improvement of about 8 letters was found in both groups with amblyopic-eye VA improving to 20/25 or better in 17% of the atropine group and 24% of the patching group (difference = 7%; 95% CI = −3% to 17%). Although this was a less robust treatment effect than in children younger than 7 years of age, there was a measurable benefit of both treatments. Atropine was associated with better quality of life during the treatment on the social stigma subscale. Thus, there is unmistakable evidence for treating most preteens and even some teens with conventional therapy if they have not been previously treated. However, families need to understand that their child is not likely to achieve normal vision.

• **REVISED LOWER-INTENSITY PATCHING AND ATROPINE EYE DROP REGIMENS:** Following completion of the study of atropine vs patching (ATS1), we reviewed prescribed patching routines in the community and found that clinicians prescribed widely varied regimens. We also retrospectively analyzed ATS1 data and found minimal to no difference in effectiveness between 6 hours, 8 hours, and all waking hours prescribed patching.[61] This evidence, along with surveys showing clinicians prescribing less patching, led to design and launch of 2 randomized trials (ATS2) of patching dose completed in parallel, 1 addressing the patching dose for moderate amblyopia and the second for severe amblyopia. Children 3-6 years of age with amblyopia from anisometropia, strabismus, or both combined were enrolled for a 16-week trial. For moderate amblyopia (20/40 to 20/80) children were randomized to 2 hours or 6 hours of patching.[62] Mean VA improvement of 2.40 lines was observed in both groups, with a mean difference = 0.007 lines (95% CI = −0.050 to 0.036). For severe amblyopia (20/100 to 20/400) children were randomized to 6 hours or full-time patching.[63] Mean VA improvement of about 4.7 lines was observed in each group, with a mean difference = 0.02 lines (95% CI = −0.04 to 0.07). Fellow eyes improved slightly or were unchanged, suggesting a true treatment benefit. In a later pilot study of 2 hours of patching in older patients 7-12 years of age with severe amblyopia, treatment was associated with 1.8 lines (95% CI = 1.1 to 2.6 lines), suggesting merit for this low dose even among older children.[64]

These patching studies were of prescribed doses for initial treatment, monitored by parental questioning. While it was good the dosages all seemed to work, it was curious why we did not find a difference between doses. In the absence of dose monitoring it is possible that the 2 groups actually wore the patch for similar amounts of time. Alternatively, perhaps there is a maximum rate of response to patching or a maximum level of improvement possible.[53]

Analogous to the studies of reducing patching dose, it was an open question what frequency of atropine was needed. The duration of cycloplegia with even a single drop of atropine is long so maybe it was not needed daily. In addition, there were retrospective data demonstrating success with less than daily treatment.[65] The reduced atropine dosage study (ATS4) compared weekend atropine (2 consecutive days) with daily atropine. After 17 weeks of treatment the mean VA difference was 0.00 lines (95% CI = −0.04 to 0.04), with 47% of the daily group and 53% of the weekend group achieving VA of 20/25 or better or VA equal to the fellow eye.[66]

Because some amblyopic eyes are not cured with atropine administered either daily or twice weekly, some clinicians

have augmented the cycloplegic blur by reducing the hyperopic correction worn in the fellow eye, with the hope of further improvement in the amblyopic eye. This incremental step was included in the ATS1 protocol and prescribed for 60 of 204 participants. Since this action was not randomized, we could not determine its effectiveness. Kaye and associates had treated patching failures with atropine plus plano lens for the fellow eye, with VA improvement from 0.85 logMAR (20/113) to 0.28 (20/37), with no adverse impact.[67] Using these pilot data PEDIG launched ATS8, which compared atropine-only with atropine plus plano lens treatment. Amblyopic-eye VA improved 2.4 lines in the atropine-only group and 2.8 lines in the atropine + plano lens group; amblyopic-eye VA improved to 20/25 or better in 29% of the atropine-only group and 40% of the atropine + plano lens group ($P = .03$).[68] However, more patients in the atropine + plano lens group experienced a temporary decline in fellow-eye vision, which recovered when the treatment was stopped. If this approach is prescribed, these patients need more frequent monitoring than typically used with atropine treatment.

Initial PEDIG studies used atropine eye drops only for children with moderate amblyopia owing to the belief it was not likely effective for severe amblyopia.[69] Once effectiveness of atropine was established for moderate amblyopia, the network gathered pilot data using weekend atropine for severe amblyopia (20/125 to 20/400) over 4 months.[64] Among children 3-6 years of age, VA improved an average of 4.5 lines in the weekend atropine-only group and 5.1 lines in the atropine + plano group. In children 7-12 years of age improvement averaged 1.5 lines with weekend atropine. These improvements would be in excess of what is expected from age or learning effects in 4 months. These findings would allow the patient who could not tolerate more intensive occlusion to try a less difficult alternative for a period of time to obtain some improvement, thereby making other, perhaps more intensive, treatment feasible.

Nearly all of the PEDIG amblyopia trials have enrolled patients who were just beginning treatment. One of the difficult clinical questions is what to do when the patient stops getting better with treatment, yet their VA has not reached normal levels. To address that question, PEDIG conducted a randomized trial (ATS15) that compared continuing the current occlusion dose of 2 hours per day with an increase to 6 hours per day for children 3-7 years of age for 10 weeks.[70] The amblyopic-eye VA improved an average 0.5 line in the 2-hour group and 1.2 lines in the 6-hour group (difference adjusted for acuity at randomization = 0.6 line; 95% CI = 0.3-1.0; $P = .002$). A similar trial design (ATS16) was used for patients treated with atropine, randomizing to continued atropine-alone or continued atropine with addition of a plano lens for the fellow eye.[68] At the 10-week primary outcome visit, amblyopic-eye VA improved an average 0.6 lines with atropine only and 1.1 lines with the plano lens addition (difference adjusted for acuity at randomization = 0.5 line; 95% CI = −0.1 to 1.2). This trial was stopped due to insufficient recruitment. In both trials enhanced therapy had some benefit, although the outcome was statistically superior only for the patching incremental approach. In addition, even though the children who enrolled in these 2 studies appeared to not be getting better with their current therapy, in fact there was slow improvement with the lower dose as seen in the comparison group. Thus, the clinician may want to continue current treatment longer than they might have typically recommended.

• **OPTICAL TREATMENT:** Optical methods of amblyopia treatment include Bangerter foils (Ryser Optik AG, St. Gallen, Switzerland) and increased plus power of the lens used by the fellow eye. Bangerter foils, which are translucent filters of varied density placed on the lens of the fellow eye, are typically recommended for mild and moderate amblyopia. PEDIG compared full-time Bangerter fogging (0.2 and 0.3 density foils) to patching for a 24-week treatment period in children 3-9 years of age (ATS10). Improvement averaged 1.9 lines for foils and 2.3 lines for patching, respectively.[71] Similar percentages in each group had 20/25 amblyopic-eye acuity (36% vs 31%, respectively). Since the foil treatment is less burdensome than patching, it may be considered a reasonable alternative for children willing to wear the foils full time.

Optical fogging is done by adding 1-3 D of plus to the fellow-eye lens, blurring the eye at distance, forcing the patient to use the amblyopic eye. Case series have shown benefit, but there have been no randomized comparison trials with patching or optical only to verify a benefit.[69,72]

• **SYSTEMIC MEDICATIONS:** For years clinicians have hoped to discover a systemic medication that might act in the brain to allow successful amblyopia treatment for older children or children not responsive to conventional treatment. One of these is levodopa, converted to dopamine in the central nervous system, which has important activity in the retina and the visual cortex. One hypothesis for treatment benefit is that levodopa temporarily improves vision in the amblyopic eye, making conventional treatment effective. A meta-analysis of 4 randomized placebo-controlled studies (110 subjects) found oral levodopa treatment to be associated with a mean improvement of 1.1 logMAR lines (95% CI = 0.2 to 1.9).[73]

To address this uncertainly PEDIG studied levodopa treatment for residual amblyopia. Residual amblyopia was chosen as we felt parents would not use an oral medication if their child would respond to conventional treatment. Children 7-12 years of age with residual amblyopia were enrolled, continued patching 2 hours per day, and were randomized to 3-times-per-day use of oral levodopa 0.76 mg/kg with carbidopa 0.17 mg/kg or oral placebo (ATS17).[74] At 18 weeks, amblyopic-eye VA improved a mean of 5.2 letters in the levodopa group and 3.8 letters in the placebo

group (difference adjusted for baseline VA = +1.4 letters, 2-sided 95% CI = −0.4 to +3.3). Although not clinically significant, the medication was well tolerated, with no serious adverse effects. Despite this negative result, use of medication to affect molecular and cellular processes in the brain to reopen the critical period remains an important research area.[75]

• **VISION THERAPY:** Vision therapy is offered by some clinicians to treat amblyopic children, using a sequence of visual activities prescribed to facilitate the effects of eyeglasses and patching by targeting accommodation, eye movements, and suppression.[76–78] PEDIG designed and conducted a randomized study (ATS12) from 2008 to 2011 to address the clinical value of a standardized vision therapy program (16 weeks; once-weekly in-office and daily home computer-based training) compared with 2 hours per day patching. Unfortunately, PEDIG was unable to recruit a sufficient sample of participants to draw meaningful conclusions. However, we did identify considerations for future study designs, including learning that 16 weeks of therapy was feasible, but home compliance monitoring was difficult and eligibility criteria need be less restrictive to recruit a sufficient cohort.[79]

• **BINOCULAR THERAPY:** Much recent amblyopia research has centered on use of binocular therapy. This approach is designed to reduce interocular suppression and thereby allow improvement in the vision of the amblyopic eye while using both eyes. The most common approach has been dichoptic stimulus presentation, in which a green image is shown to the amblyopic eye and a red image with greatly reduced contrast to the fellow eye.[80,81] Both the distinct image seen by each eye and the reduction in contrast in the fellow eye image are felt crucial to the treatment effect. For this approach to work the patient needs to be orthotropic, have only a microstrabismus, or have an imaging system that can compensate for strabismus. Case series have reported treatment to be effective in children as well as for some older patients resistant to conventional therapy or felt too old for success.[82–85] Given the novelty of the treatment, a tablet computer platform, and the use of video content, this approach is highly attractive to children and their parents.

A small randomized trial found a benefit of a falling-blocks design game which incorporated reduced contrast and the dichoptic presentation compared with patching after 2 weeks of play.[86] PEDIG conducted 2 adequately powered randomized trials of this game design, comparing game play with patching 2 hours per day for 16 weeks in children 5-12 years of age[87] and 13-17 years of age (ATS18).[88] There was no significant benefit of game play for either age group compared with patching. In both studies compliance with game play was poor. An international randomized study found no benefit in a randomized trial comparing falling-blocks game play with placebo game play, also noting difficulty with compliance.[89]

A more engaging game design, Dig Rush (Amblyotech, Inc, Boston, Massachusetts, USA), uses animated characters moving about in a gold mine. In a randomized trial of binocular game play compared with continued glasses alone of 138 children 5-12 years of age, mean amblyopic-eye VA letter score improved by 1.3 letters with binocular treatment and by 1.7 letters with continued spectacle correction alone (ATS20).[90] There was no benefit to stereoacuity and no significant adverse events. A randomized trial in children 3-5 years of age has been completed, with results expected in late 2020.

The most recent approaches being described are using widely available movie and video content. Dichoptic viewing using polarized images and contrast reduction in a case series of 27 children has shown a possible benefit, especially in young children.[85] Other approaches with video content are being studied using partial masking of the images in the fellow eye with or without contrast reduction delivered dichoptically through a head-mounted display.[130] A consensus statement from the American Academy of Ophthalmology noted that binocular therapy cannot yet be recommended as a replacement for standard amblyopia therapy.[91] However, the authors allowed that ongoing research could alter this conclusion.

STABILITY OF THE AMBLYOPIA TREATMENT RESULT—WHEN TO STOP TREATMENT?

IT IS WELL KNOWN THAT AMONG YOUNGER CHILDREN there can be a recurrence of amblyopia when active therapy is stopped, especially in the short term. One retrospective study found recurrence to occur in about 27% of children.[92] In a prospective study of recurrence, PEDIG found a rate of 24%, more often following 6 or more hours patching than with 2 hours of patching (ATS2C).[93] Most of the recurrences were detected within 6 months of cessation of treatment, with only a few occuring beyond a year after stopping treatment. Recurrence was more common with better VA outcomes at the end of treatment and even in the presence of good stereoacuity.[94] Conclusions were that careful monitoring when any amblyopia therapy is discontinued is required for up to a year and it is better to wean patients if they had been treated with intense patching. When recurrence occurs, the amblyopia treatment needs to be restarted and in most cases will be successful.

There are limited prospective data available about long-term recurrence of amblyopia. PEDIG included a prospective study of the long-term outcomes and recurrence rates in the ATS1 design. The protocol specified annual visits until age 10 years and a final visit at age 15 years, a time point at which we felt the chance of recurrence was low. The care provided during follow-up was the clinical care determined by the investigator and managed by the family.

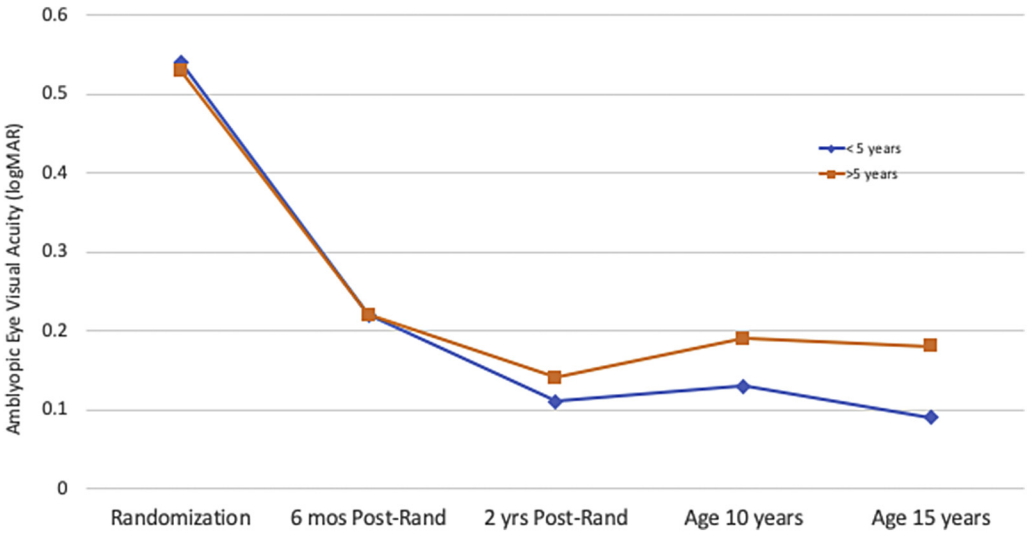

FIGURE 1. Amblyopia eye visual acuity: randomization to age 15 years. Amblyopic eyes in Amblyopia Treatment Study 1 showed improvement over the first 2 years of the study, the first 6 months in the randomized trial with subsequent care at investigator discretion. Two years after randomization, children younger than 5 years of age at enrollment continued to improve, whereas children 5 years of age and older did not show improvement beyond the 2-year postrandomization visit.

At 15 years the mean amblyopic eye acuity was 0.14 logMAR (approximately 20/25); 78% of amblyopic eyes had acuity of 20/32 or better, 58% 20/25 or better, and 34% 20/20 or better.[41] Mean fellow-eye acuity was −0.07 logMAR (approximately 20/16), with 96% of participants 20/20 or better. The mean interocular difference (IOD) was 10.5 letters (2.1 logMAR lines), with 57% having an IOD of 10 or more letters (2 or more lines) and 85% 5 or more letters (1 or more lines). Stereoacuity was reduced, with 42.5% of children achieving 800 arcseconds or better and just 13.7% achieving normal levels of 60 arcseconds or better. There was no tendency for the group to lose their treatment benefit.

Evaluating VA over each study segment, there was improvement for the first 2 years after enrollment (Figure 1). Nearly all children were treated during this time, even after completing the initial 6-month randomized treatment phase. After the 2-year postrandomization time point there was essentially no change in VA for the overall cohort up to 15 years of age. However, for a subgroup of children younger than 5 years of age at randomization, they did continue to improve after the 2-year time point so that at the final outcome their mean VA was better than children who were 5-6 years of age at initial treatment.

QUALITY OF LIFE WITH AMBLYOPIA

QUALITY OF LIFE (QOL) RELATED TO AMBLYOPIA MAY BE divided into short-term effects associated with treatment and the life-long impact of the disease on the individual. It is important to recognize that for patients with strabismic amblyopia, there is difficulty in separating the effects of amblyopia and strabismus. Strabismus has been associated with decreased QOL associated with poor self-image and problems with interpersonal relationships.[95] In addition, glasses are used for first-line therapy for both conditions and likely play a role in social interactions at all ages.

Atropine, patching, and binocular dichoptic treatments are generally well tolerated, although atropine had a slightly higher degree of acceptability on the parental questionnaire when compared with patching in children 3-6 years of age.[33] With atropine eye drop treatment, there was no social concern expressed by the parents or their children. With patching the social issues of interaction with other children and adults was of mild concern. However, concern with patching increases with age. In a study from the UK, patching was associated with a 36% increase of "physical or verbal bullying."[96] The lower-dose treatments introduced in later PEDIG studies may be reducing this concern. One year after patching treatment of children with refractive amblyopia, there were no reported negative psychosocial effects when compared with glasses-only treatment.[97]

With respect to long-term impacts of amblyopia on QOL outcomes and economic consequences in school and in the workforce, there are limited data. Birch and associates found that among preschool and young school-aged children with amblyopia from anisometropia, strabismus, or both combined, there was reduced self-perception of peer acceptance and physical competence, slower reading speed, and reduced motor skills.[17,98] The authors noted that these effects were apparent even in the absence of strabismus with refractive amblyopia.

Beyond childhood impacts, there are 2 population-based studies that have evaluated longer-term outcomes. The Blue Mountains Eye Study from Australia assessed

occupational and educational outcomes of individuals with amblyopia at a mean age of 67.0 years.[99] While the distribution of occupations did not differ between individuals with and without amblyopia ($P = .5$), fewer amblyopic individuals were found to have completed higher university degrees ($P = .05$).

A report from the UK evaluated the consequences of amblyopia through 41 years of age in a country-wide birth cohort (n = 8,861) born in 1958.[100] The authors found no impact on childhood behavior of QOL, bullying, or playing sport; fairly equal education attainment and jobs performed; no predisposition for workplace injury; and no adverse impact on general health. Nonetheless, concern about fellow-eye injury among amblyopic patients has long supported treatment in children as good public policy. Using UK-wide surveillance data Rahi and associates projected a lifetime risk of bilateral vision loss for an individual with unilateral amblyopia to be in the range of 1.2% to 3.3%.[101] If vision loss occurred in the fellow eye, only 36 of 102 people (35%) previously in paid employment were able to continue.

In the study from Australia, there also was a significant increased relative risk (2.7; 95% CI = 1.6 to 4.6) over 5 years of visual impairment in the better-seeing eye of an adult with amblyopia compared with adults without amblyopia.[99] Similarly, the Rotterdam Eye Study investigators reported the risk of binocular vision impairment nearly doubled in the presence of amblyopia.[102]

Amblyopia has also been recently associated with other bodily injuries. Among Medicare-aged beneficiaries there was a 27% higher risk of musculoskeletal injury, fracture, or fall in patients with a disorder of binocular vision including amblyopia and strabismus, when compared with individuals without such history.[103] When the analysis was limited to beneficiaries with amblyopia alone, the risk was 12% higher, suggesting amblyopia alone has a significant role.

Although it is reasonable that improvement in the VA of amblyopia eyes is important, more studies of qualitative and quantitative QOL outcomes beyond high contrast VA improvement for individuals with amblyopia are needed to fully characterize the benefit of therapy and provide support for early interventions targeting timely detection and treatment.

MEASURING TREATMENT SUCCESS IN CLINICAL PRACTICE AND RESEARCH

THE METHOD CHOSEN FOR MEASUREMENT OFTEN VARIES for research, for patient education, or for clinical performance assessment. Clinicians have long considered fixed cut points a simple way to measure their patient's success and explain the goal to the child's parents. For example, some clinicians might use 20/30 or better to represent success of amblyopia treatment, while others use attainment of equal vision or additional VA cut points. Using a single cut point for success can be a problem. A fixed cut point for VA success allows misclassification of an individual patient outcome (a shift of a letter or 2 changes the acuity level and the outcome), reduces the study efficiency (need larger sample sizes), and has the potential for a ceiling effect for those with minimal room for improvement.[104] For these reasons PEDIG research studies have used VA as a continuous outcome for primary analyses. Commonly, the design is to reject a null hypothesis of no difference when the true change in mean VA is greater than 0.1 logMAR. For ATS1 the mean difference in treatments was 0.034 logMAR (one-third of a line), which we concluded was not clinically meaningful.[33] But the outcome "difference in mean VA change" between the treatment and controls groups is not easy to understand or explain to a parent, so a cut-point outcome is often reported as a secondary outcome. One such definition is VA of 20/32 or better OR 3 lines improvement to allow the magnitude of improvement to be considered. The secondary success rates using this definition at 6 months for occlusion and atropine in a clinical trial (ATS1) were 79% and 74%, respectively.[33] Composite definitions of success were developed for the IRIS Registry to analyze clinical outcomes because they could be easily understood (Supplemental Table [Supplemental Material available at AJO.com] and Methods, below).

VA outcomes achieved in clinical trials such as those conducted by PEDIG may provide the most favorable estimate of the outcome for the recruited population, considering the strict inclusion criteria, as the trials recruit participants most likely to benefit from the treatment, the families are typically motivated, and investigators are likely engaged in the research. In addition, study coordinators are employed to provide additional support and information to the families, much more than could be managed in clinical practice. Such education improves amblyopia treatment outcomes.[105]

Clinical outcomes from review of practice data can also be used to benchmark success, as in 2 studies by Flynn and associates. In the first Flynn and his colleagues pooled data on 689 patients from 23 amblyopia treatment studies with patching.[106] They relied on the cut point of 20/40 or better for success achieved in 74.3% of cases (512 of 689). The rates were 77.6% (312 of 402) in strabismic amblyopia, 58.7% (44 of 75) in combined strabismic-anisometropic amblyopia, and 66.7% (72 of 108) in anisometropic amblyopia. In a separate analysis of treatment success in an English cohort, Flynn and associates found an overall success rate of 59.9%(353 of 589).[107] It is difficult to fully understand what differences in age distribution, actual treatment, access to health care, loss to and duration of follow-up and treatment compliance may have existed in these samples, but it is reasonable to expect success to be somewhat poorer than in a clinical trial, but better than in clinical practice because of exclusion in the research data set.

TABLE 1. International Classification of Diseases Diagnostic Codes for Amblyopia

Brief ICD Descriptor	ICD9-CM	ICD10-CM
Unspecified	368.00	H53.00x
Strabismic amblyopia	368.01	H53.03x
Refractive amblyopia[a]	368.03	H53.02x
Combined strabismus and refractive amblyopia[b]	368.01 + 368.03	H53.02x + H53.03x
	OR 368.0 + 378	OR H53.02x + (H49 or H50)
Deprivation amblyopia	368.02	

ICD9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; ICD10-CM = International Classification of Diseases, Tenth Revision, Clinical Modification.

Lowercase "x" is a placeholder for laterality, when reported in ICD10: 1 is right eye, 2 is left eye, 3 is both eyes, and 9 is unspecified eye. Laterality was not specified in ICD9.

[a]Includes anisometropia.

[b]Categorized as combined amblyopia if a strabismic amblyopia code and a refractive amblyopia code were each reported at least once at any visit in IRIS Registry.

AMBLYOPIA IN THE UNITED STATES: DEMOGRAPHICS, MANAGEMENT, AND OUTCOMES FROM IRIS REGISTRY

• **INTRODUCTION:** The collection of "big data" in health care has provided the opportunity to study common and uncommon diseases in new ways. Clinical data registries are used to study patient care and quality improvement, and explore outcomes at individual doctor and health care system levels.[108] These analyses are helpful in identifying gaps in care, value of care provided, and whether a treatment should be covered by insurance. The opportunity to evaluate and monitor a large community's health care without an administrative burden on the provider was made possible by the deployment of electronic health care records, from which data can be automatically uploaded to registries. Such data, when drawn from a large group, can allow overall assessment of outcomes of clinical care, but also descriptive data from subgroups by age, sex, and race/ethnicity that might never have been evaluated with clinical trials data or retrospective studies, and to generate hypotheses for new research.

In ophthalmology, the American Academy of Ophthalmology developed the IRIS Registry in the early 2010s. The IRIS Registry is a centralized data repository from real-world ophthalmology practice retrieved from electronic health records and practice management software of ophthalmology practices across the United States, including sociodemographic and some ophthalmologic data, which began data collection on January 1, 2013. The IRIS Registry currently receives data from more than 60% of ophthalmologists in the United States.

The IRIS Registry was developed as a means for ophthalmologists to succeed in value-based payment programs for Fee-for-Service Medicare. During recent years the Centers for Medicare and Medicaid Services (CMS) have shifted from process measures to outcome measures to evaluate a provider or a practice. In response, the IRIS Registry developed disease-specific outcome measures relevant to ophthalmology including amblyopia that can be reported to this program. In addition, these measures can be used to assess quality and monitor outcomes over time, with comparisons to benchmarks. Such data can also be aggregated for research.

The first measure developed for amblyopia was IRIS-7, which evaluated the proportion of children 3 to <7 years of age with 3 lines or more of amblyopia from strabismus, anisometropia, or both combined. The measure outcome for success was improvement in VA to an interocular difference of 2 or fewer lines after 1 year of management. IRIS-7 was applied retrospectively in a chart review with a success rate of 47%.[109] A subsequent record review found a success rate of 71%.[110]

Owing to technical limitations imposed by CMS and concern that the outcome in IRIS-7 did not adjust for baseline VA, IRIS-50 was developed.[111] Success in IRIS-50 requires meeting 1 of 3 criteria for vision improvement over 3-12 months. (Methods and the Supplemental Table describe the measure specifications.) In a retrospective chart review a success rate of 81% was found.[110] Only 167 of 1,817 (9.2%) patients were eligible owing to the specifications.

What would the outcome for IRIS-50 be for children enrolled in clinical trials? Applying the IRIS-50 measure to ATS1 outcomes at 6 months we found the success rates for occlusion and atropine to be 85% and 82%, respectively (personal communication: Kraker R, Jaeb Center for Health Research, Inc; unpublished data) These clinical trial outcomes could be considered the gold standard or upper limit of what is achievable with conventional therapies for children 3-6 years of age no worse than 20/100 at baseline. The measure includes 7-year-old children and worse initial acuity, so outcomes including 7-year-old children might be worse.

TABLE 2. Prevalence of Amblyopia by Age in IRIS Registry

Age at First IRIS Registry Diagnosis (years)	Number of Patients With Amblyopia	Number of Patients Evaluated	Prevalence	Rate per 100,000
Overall	1,760,666	71,186,048	2.47%	2,473
<1	9,428	198,226	4.76%	4,756
1-2	54,570	453,145	12.04%	12,042
3-6	250,347	134,1263	18.67%	18,668
7-12	260,700	2,655,828	9.82%	9,816
13-17	107,667	2,230,251	4.83%	4,827
≥18	1,077,007	64,251,410	1.68%	1,676
Unknown	947	55,925	1.69%	1,693

Prevalence in children from birth to 17 years of age was 9.92%.

The purpose of the following sections of this Jackson Lecture is to provide initial analyses of new IRIS registry data concerning amblyopia including descriptive data and success rates for IRIS-50 in clinical practice.

• **METHODS FOR IRIS REGISTRY DATA:** This study was conducted to characterize amblyopia in current clinical practice in the United States. Data from the American Academy of Ophthalmology's IRIS Registry, the nation's first comprehensive clinical registry of eye disease, were used.[4] The IRIS Registry is a centralized data repository of real-world practice patterns from electronic health records of ophthalmology practices across the US.[112] Sociodemographic data (age, sex, race/ethnicity) were collected from patient encounters between January 1, 2013, and December 31, 2019. As of January 1, 2020, there were 11,574 ophthalmologists in 3,096 electronic health record–integrated practices participating in the IRIS Registry; 427 physicians were self-designated pediatric ophthalmology specialists.

Data in the IRIS Registry are de-identified for research and thus these analyses did not require patient or parental consent. Providers reported every encounter on every patient in their practices. All diagnoses attributed to a patient in the electronic health records were included. Some patients may have been seen by multiple providers in different practices with differing electronic health records. Analytics in the IRIS Registry merge records of unique patients using probabilistic matching based on age, sex, and other sociodemographic characteristics.

Patient data (age, sex, diagnoses, insurance, VA, number of visits) were extracted from the IRIS Registry for unique patients with amblyopia diagnoses reported using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) or International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10) code, 368.00, 368.01, 368.02, 368.03, H35.00, H35.01X, H35.02X, and H35.03X (Table 1). The switch to ICD-10 occurred on October 1, 2015. Laterality is only available with ICD-10. Among those patients with only refractive amblyopia coded, we reviewed their diagnoses for any strabismus diagnosis (378, H50, and H49) at any registry visit. If these strabismus codes had been used, the patient diagnosis was reclassified as combined refractive strabismic amblyopia.

For descriptive and demographic statistics of the population, 1 visit in the patient record was required for inclusion. For VA longitudinal analysis, we selected those patients 3 years of age and older with unilateral amblyopia with a visit at which amblyopia was first reported to the IRIS Registry and a subsequent visit. Corrected VA was used when available; otherwise, uncorrected acuity was used for the visit. VA data were pooled for refractive, strabismic, and refractive-strabismic amblyopia. Unilateral deprivation amblyopia was considered separately. Amblyopia treatments are not currently reported to the IRIS Registry in claims or other data fields, so treatment use or duration cannot be identified.

Success was assessed using IRIS-50 for eligible children 3-7 years of age with a baseline visit and a second visit 3-12 months later, using the latest visit in window (Supplemental Table). IRIS-50 excludes unspecified, bilateral, and deprivation amblyopia. Success on IRIS-50 is determined by meeting at least 1 of the following criteria:

- Corrected interocular (or if not reported, uncorrected) VA difference <0.23 logMAR 3-12 months after first diagnosis of amblyopia;
- Improvement in the corrected VA of the amblyopic eye of 3 or more Snellen lines (≥0.30 logMAR) 3-12 months after first diagnosis of amblyopia;
- Final VA in the amblyopic eye equal to 20/30 or better (≤0.18 logMAR) 3-12 months after first diagnosis of amblyopia

Although the measure was designed for children 3-7 years of age, a secondary analysis was performed applying the measure to children 8-12 years of age.

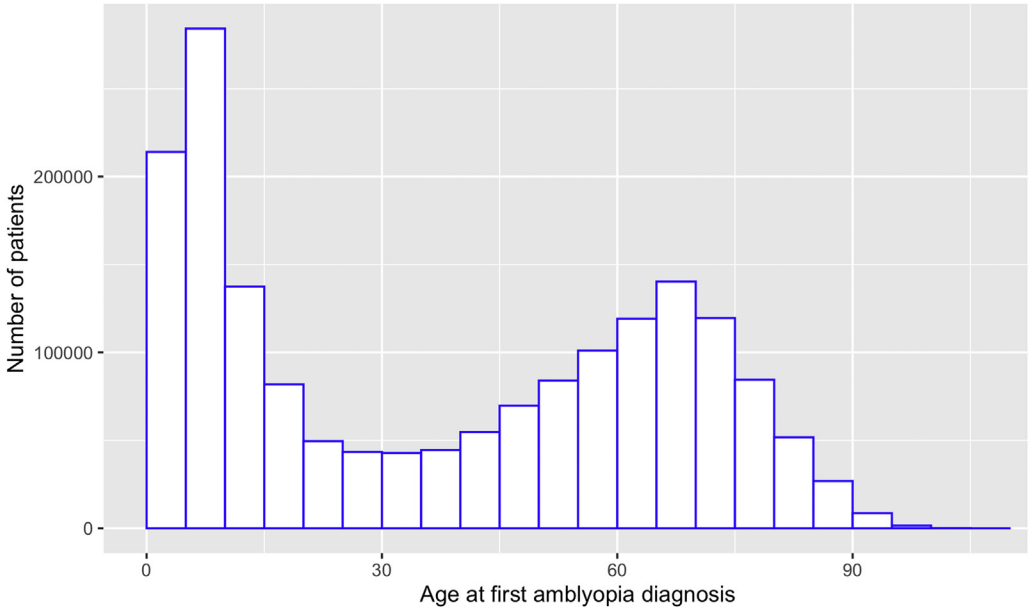

FIGURE 2. Distribution of patients with amblyopia by age at first IRIS Registry visit.

• **STATISTICAL ANALYSES:** Descriptive statistics were used. Statistical tests were 2-sided, with a P value $< .001$ used for statistical significance. P values smaller than .001 are shown as <.001 owing to the large data set. Tests of single proportion used a z-test and comparisons of proportions were analyzed with a χ^2 test (MedCalc Software, Ltd, Ostend, Belgium). Univariate logistic regression models were used to calculate odds ratios (R Project for Statistical Computing, Vienna, Austria; https://www.R-project.org).

• **RESULTS:** *Demographics of amblyopia in IRIS registry.* For the period January 1, 2013, to December 31, 2019, the IRIS Registry collected data from 71,186,048 unique patients. Of those, 1,760,666 had the diagnosis of amblyopia coded at least at 1 visit, for an overall prevalence of 2.47%: 9.92% in children and 1.68% among adults (Table 2, Figure 2). There were 675,554 amblyopic children with a mean age of 7.9 years (median 7.0 years) at diagnosis. The prevalence for children in participating practices was 4.76% in the first year of life, increasing to 18.7% among children 3-6 years of age, and then declining to 4.83% among teenagers (Table 2). The median number of office visits reported during the year after first IRIS Registry diagnosis was 3 for children from birth to 6 years of age, 2 for children 7-12 years of age, and 1 for children 13-17 years of age (Table 3). There were a mean of 4.53 in-office visits for children under age 1 year during the first year of follow-up. Additional visit frequency data by age are listed in Table 3.

Boys and girls were equally affected (Tables 3 and 4). However, women accounted for 56.9% of adults with amblyopia (95% CI = 56.8% to 57.0%; $P < .001$ from a test of 1 proportion) compared with men at 42.9%. Race/ethnicity data were available for 77.2% of patients. For amblyopic children with race/ethnicity specified, 64.6% were white, 19.7% Hispanic or Latino, 10.6% black/African-American, and 3.9% Asian. For adults, whites accounted for 81.9% of amblyopic patients, while 8.3% of patients were Hispanic or Latino and 7.0% black/African-American.

Amblyopia cause was frequently unspecified (43.6%) (Tables 3 and 4). Of those individuals with a specified cause, refractive amblyopia alone was reported for 65.5% of children and 53.3% of adults. Combined strabismic refractive amblyopia was infrequently reported, in just 4.7% of children. Deprivation amblyopia was reported in about 6% of children and adults.

Although unilateral amblyopia was more common than bilateral amblyopia, bilateral amblyopia was reported for 39.9% of children and 10.3% of adults (Tables 3 and 4). Left eyes were significantly more often amblyopic than right eyes for all age groups and all races/ethnicities. Among children with unilateral amblyopia, the left eye was affected in 54.5% (95% CI = 54.3% to 54.7%; $P < .001$ from a test of 1 proportion). Among adults with unilateral amblyopia it was reported in the left eye in 54.9% (95% CI = 54.8% to 55.0%, $P < .001$ from a test of 1 proportion). In logistic regression models including laterality, the odds ratio for amblyopic left eyes in female compared with male patients was 1.08 (95% CI, 1.07 to 1.09, $P < .001$), and in African Americans compared with whites the odds ratio for left eyes was 0.88 (95% CI = 0.87 to 0.90, $P < .001$). There was no clinically significant difference in laterality between white and Asian or Hispanic/Latino groups.

Insurance coverage, when known, was most commonly commercial, with Medicaid second most common for children and Medicare second for adults. It was not possible to separate uninsured from unknown.

TABLE 3. Characteristics of Amblyopic Patients by Age Group

	Age at Diagnosis (Years)							
	<1	1 to 2	3 to 6	7 to 12	13 to 17	≥18	Unknown	Overall
Unique patients	4,476	42,919	244,135	270,430	113,594	1,084,197	915	1,760,666
Sex								
Female	2,204	21,357	120,839	133,276	56,923	616,803	452	951,854
Male	2,261	21,512	122,620	136,313	56,335	465,223	427	804,691
Unknown	11	50	676	841	336	2,171	36	4,121
Race/ethnicity								
Asian	119	1,137	8,388	7,766	2,612	18,077	13	38,112
Black/African American	381	3,303	19,365	22,242	8,834	59,304	58	113,487
White	2,225	22,256	117,268	128,407	58,416	696,197	508	1,025,277
Hispanic or Latino	417	3,897	35,960	44,717	15,388	70,324	102	170,805
Other	36	320	1,930	2,200	854	5,657	24	11,021
Unknown	1,298	12,006	61,224	65,098	27,490	234,638	210	401,964
Affected eye laterality[a]								
Right	944	9,746	52,251	61,231	29,874	366,152	221	520,419
Left	1,300	12,853	60,281	73,239	36,776	446,433	267	631,149
Both	1,509	13,499	98,028	86,220	25,167	92,863	104	317,390
Not specified/unknown	723	6,821	33,575	49,740	21,777	178,749	323	291,708
Amblyopia cause								
Strabismus	1,333	16,785	61,640	52,476	20,074	192,943	223	345,474
Refractive	830	9,854	103,625	122,927	49,007	269,915	235	556,393
Combined (strabismus + refractive)	121	1,660	8,909	7,382	2,321	12,513	18	32,924
Deprivation	903	3,360	10,371	9,009	3,401	31,086	22	58,152
Unspecified	1,289	11,260	59,590	78,636	38,791	577,740	417	767,723
Number of office visits in first year after diagnosis								
Mean	4.53	3.87	3.23	2.43	2.00	3.44	4.57	3.18
SD	4.14	3.21	2.45	2.01	1.83	3.78	5.02	3.32
95% CI	4.41 - 4.66	3.84 - 3.90	3.22 - 3.24	2.42 - 2.44	1.99 - 2.02	3.43 - 3.45	4.24 - 4.89	3.17 - 3.18
Median	3.00	3.00	3.00	2.00	1.00	2.00	3.00	2.00
Health insurance at first IRIS Registry visit								
Commercial	1,671	16,909	94,679	103,799	46,728	366,910	252	630,948
Medicaid	1,209	11,128	65,813	77,854	28,698	59,424	111	244,237
Medicare	39	558	2,563	3,136	1,360	355,185	275	363,116
Other government including military	176	1,799	8,312	8,543	3,359	64,919	80	87,188
Unknown	1,381	12,525	72,768	77,098	33,449	237,759	197	435,177
Number of patients by year of first amblyopia diagnosis in IRIS Registry								
2013	522	4,847	36,031	55,475	19,654	152,154	110	268,793
2014	609	5,238	31,710	39,463	17,047	152,489	73	246,629
2015	695	6,353	34,814	38,502	16,703	165,525	111	262,703
2016	740	6,817	36,804	36,834	16,086	159,983	202	257,466
2017	626	6,307	34,957	33,464	14,692	155,528	171	245,745
2018	663	6,584	35,160	33,746	14,794	152,024	68	243,039
2019	621	6,773	34,659	32,946	14,618	146,494	180	236,291

CI = confidence interval; SD = standard deviation.

[a]Laterality was not specified while International Classification of Diseases, Ninth Revision was in use prior to October 2015.

TABLE 4. Summary Characteristics of Amblyopia by Child and Adult Groups

Patient Characteristics	Child		Adult	
Age at diagnosis, y	<1 to 17		≥18	
Unique patients	675,554		1,084,197	
Mean age, y (median)	7.9 (7.0)		38.4 (39)	
Sex, n (%)				
Female	334,599	49.5%	616,803	56.9%
Male	339,041	50.2%	465,223	42.9%
Unknown	1,914	0.3%	2,171	0.2%
Race/ethnicity,[a] n (%)				
Asian	20,022	3.9%	18,077	2.1%
Black/African American	54,125	10.6%	59,304	7.0%
White	328,572	64.6%	696,197	81.9%
Hispanic or Latino	100,379	19.7%	70,324	8.3%
Other	5,340	1.1%	5,657	0.7%
Unknown	167,116		234,638	
Affected eye laterality,[a] n (%)				
Right	154,046	27.4%	366,152	40.4%
Left	184,449	32.8%	446,433	49.3%
Both	224,423	39.9%	92,863	10.3%
Not specified/unknown	112,636		178,749	
Amblyopia cause,[a] n (%)				
Strabismus	103,432	23.7%	192,943	38.1%
Refractive	286,243	65.5%	269,915	53.3%
Combined (strabismus + refractive)	20,393	4.7%	12,513	2.5%
Deprivation	27,044	6.2%	31,086	6.1%
Unspecified	189,566		577,740	
Health insurance at first IRIS Registry visit,[a] n (%)				
Commercial	263,786	55.1%	366,910	43.3%
Medicaid	184,702	38.6%	59,424	7.0%
Medicare	7,656	1.6%	355,185	42.0%
Other government including military	22,189	4.6%	64,919	7.7%
Unknown	197,210		237,759	

[a]Proportions of those patients with a specified factor, excluding those not specified or unknown.

Visual acuity. For this analysis VA data for patients with unilateral amblyopia not including deprivation were included if the patient had at least 2 visits with VA reported in the IRIS Registry (Table 5, age group values). The mean logMAR VA of the amblyopic eyes in 45,079 children 3-6 years of age at presentation was 0.41 (95% CI = 0.41 to 0.41; median = 0.30) compared with the fellow eye of 0.15 (95% CI = 0.15 to 0.15; median = 0.10). With ongoing clinical care for a median of 2.3 years, until the most recent registry visit, the amblyopic eye logMAR VA of the children aged 3-6 years improved to mean of 0.23 (95% CI = 0.23 to 0.23; median = 0.18), or about 2 lines of improvement, while the fellow eye improved from a mean logMAR VA of 0.15 to 0.08. Children 7-12 years of age improved an average of 0.8 lines in their amblyopic eyes over a median of 2.6 years, while children 13 to <17 years improved 0.4 lines over a median of 2.5 years.

Granular VA data for each year of age from 3 to 17 years of age at baseline and most recent follow-up in the amblyopic and fellow eyes are shown in Figures 3 and 4. The VA of amblyopic eyes improved for all ages other than for 11- and 12-year-old children. The VA of the fellow eye for children 3-6 years of age had mild improvement, while for those 7 years of age and older their VA did not appreciably change. A VA deficit compared with fellow eyes remained for all ages, as presented in Figure 5.

The mean logMAR VA of the unilateral amblyopic eye in adults not due to deprivation was 0.61 (95% CI = 0.61 to 0.62; median = 0.49) compared with the fellow eye of 0.15 (95% CI = 0.15 to 0.15; median = 0.10) (n = 312,435) (Table 5). There was 0.4 line improvement (2 letters) in the amblyopic eye VA, while the fellow eye VA improved 0.1 lines (0.5 letter) during median follow-up of 2.6 years.

Similar data for 14,073 patients with unilateral deprivation are shown in Table 6. In 1,743 children 3-6 years of age there were 1.5 lines of improvement over a mean of 2.6 years. Less than 1 line of improvement was found among the children 12-17 years of age and adults.

TABLE 5. Visual Acuity at Baseline and Most Recent IRIS Registry Follow-up for Unique Patients With At Least Two Visits and Unilateral Amblyopia Excluding Deprivation

	Age (Years)[a]			
	3 to 6	7 to 12	13 to 17	≥18
Unique patients (n = 442,854)	45,079	58,323	24,173	315,279
VA at first visit with diagnosis				
LogMAR VA for amblyopic eye				
Mean	0.41	0.33	0.35	0.61
SD	0.31	0.31	0.34	0.49
95% CI	0.41-0.41	0.33-0.33	0.34-0.35	0.61-0.62
Median	0.30	0.30	0.30	0.48
Interquartile range	0.18-0.54	0.10-0.48	0.10-0.48	0.30-0.90
LogMAR VA for fellow eye				
Mean	0.15	0.08	0.07	0.16
SD	0.16	0.14	0.14	0.21
95% CI	0.15-0.15	0.08-0.08	0.07-0.07	0.16-0.16
Median	0.10	0.00	0.00	0.10
Interquartile range	0.00-0.18	0.00-0.10	0.00-0.10	0.00-0.18
Median time from baseline to most recent visit (years)	2.3	2.6	2.5	2.6
Visual acuity at most recent visit				
LogMAR VA for amblyopic eye				
Mean	0.23	0.25	0.31	0.57
SD	0.26	0.29	0.34	0.50
95% CI	0.23-0.23	0.25-0.26	0.31-0.32	0.56-0.57
Median	0.18	0.18	0.18	0.40
Interquartile range	0.10-0.30	0.10-0.35	0.10-0.40	0.18-0.90
LogMAR VA for fellow eye				
Mean	0.08	0.06	0.06	0.15
SD	0.13	0.13	0.13	0.22
95% CI	0.08-0.08	0.06-0.06	0.05-0.06	0.15-0.15
Median	0.00	0.00	0.00	0.10
Interquartile range	0.00-0.10	0.00-0.10	0.00-0.10	0.00-0.18

CI = confidence interval; SD = standard deviation; VA = visual acuity.
[a]Age at first IRIS Registry visit with diagnosis of amblyopia.

IRIS registry outcome measure—IRIS-50. This clinical care performance measure was applied to the children who met the eligibility criteria in 2 age groups, 3-7 years of age and 8-12 years of age (Table 7, Supplemental Table for specifications) Accounting for numerator and denominator exclusions and the required 3- to 12-month follow-up period produced sample sizes of 18,841 for the younger group and 9,762 for the older group. Overall success on the measure was 77.3% for younger children and 55.5% for older children. The performance criterion of reducing the interocular VA difference to <0.23 logMAR was the most often achieved, with success rates of 65.6% and 44.8%, respectively. The hardest criterion to achieve was improvement to 20/30 or better.

The odds ratio (OR) for success on IRIS-50 (3-7 years) for girls compared with boys was 1.00 (95% CI = 0.93 to 1.07). Black/African-American and Hispanic/Latino children had significantly reduced chances for success compared with whites, OR = 0.67 (95% CI = 0.58 to 0.78) and OR = 0.84 (95% CI = 0.75 to 0.94), respectively. The lower success rate for black/African-American children compared with white children was also true for children 8-12 years of age (OR = 0.78; 95% CI= 0.66 to 0.92), but the success rate was higher for Hispanic or Latino children 8-12 years of age (OR = 1.12; 95% CI 1.00 to 1.26).

CONCLUSIONS ABOUT AMBLYOPIA FROM THE IRIS REGISTRY

RESEARCH USING MEDICAL RECORDS AND CLAIMS DATA collected in a clinical data registry describes the characteristics and outcomes of a large clinical population but should not be generalized to the population. However, the IRIS Registry is estimated to include data from more than two-thirds of practicing ophthalmologists, so the findings could

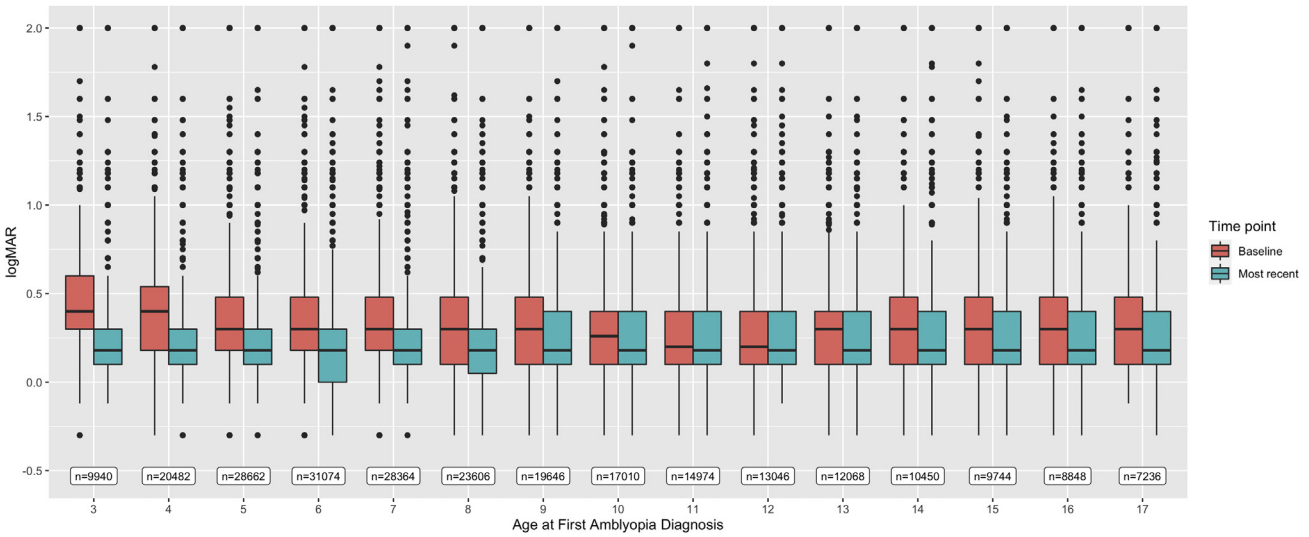

FIGURE 3. Visual acuity of amblyopic eyes of children with unilateral amblyopia excluding deprivation by age in IRIS Registry at baseline and most recent follow-up. The horizontal line inside the box is the median, the box represents the interquartile range (IQR), and lines represent 1.5× the IQR with outliers plotted beyond. Amblyopic eyes showed improvement in visual acuity for most ages, but especially among the younger patients.

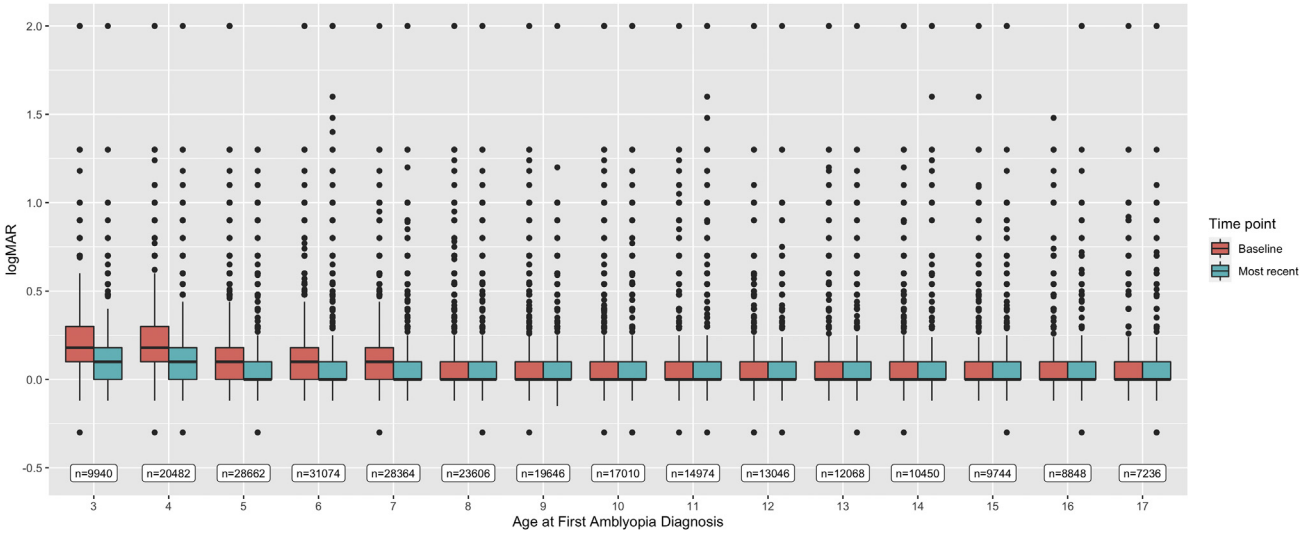

FIGURE 4. Visual acuity of fellows eyes of children with unilateral amblyopia excluding deprivation by age in IRIS Registry at baseline and most recent follow-up. The horizontal line inside the box is the median, the box represents the interquartile range (IQR), and lines represent 1.5× the IQR with outliers plotted beyond. Fellow eyes showed some improvement in visual acuity among children 3-7 years of age, whereas there was no change in older children.

be a good estimate of the population able to access eye care in the United States. Amblyopia prevalence was 2.48% among all patients in the IRIS Registry. The IRIS Registry rate of 9.92% in children was higher than population estimates because children with vision loss from all causes were more likely to be in clinical care and thus included than those with no known problem. A composite value of 2.4% for amblyopia in children has been suggested by Birch from population-based studies of children.[6,8,9] The adult rate of 1.68% in the IRIS Registry was in the 1% to 4% range cited for adult amblyopia prevalence.[113,114] Refractive causes of amblyopia accounted for nearly 70% of cases in children, far more often than strabismus. This high proportion of refractive error causation is similar to reports from population-based and preschool studies,[8–10] as compared with clinical samples in which strabismus or

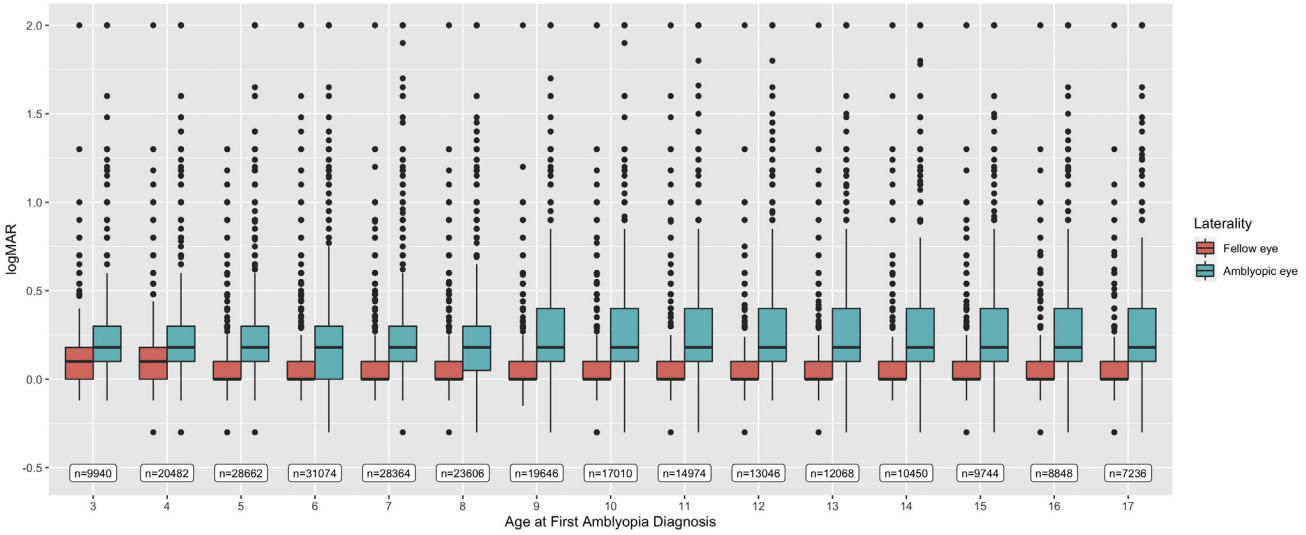

FIGURE 5. Visual acuity of amblyopic and fellow eyes of children with unilateral amblyopia excluding deprivation by age in IRIS Registry at most recent follow-up. The horizontal line inside the box is the median, the box represents the interquartile range (IQR), and lines represent 1.5× the IQR with outliers plotted beyond. The visual acuity of amblyopic eyes was poorer than the fellow eyes for all ages.

strabismus refractive combined account for about two-thirds.[115] Combined cases typically constitute one-third of amblyopia cases in clinical cohort studies, yet they were less than 5% in the registry. This could be related to a bias of patients with strabismus being seen in specialty practices not participating in IRIS Registry or perhaps the failure of practices to submit more than 1 amblyopia diagnosis required for billing purposes.

We found bilateral amblyopia to account for nearly 39.9% of childhood diagnoses. A similar high level of 37.7% of cases was noted by the Vision in Preschoolers group.[10] This high rate of bilateral refractive amblyopia is important, as it often responds well to glasses alone if the child receives timely eyeglasses.[116] It is possible this rate may be overestimated if a medical diagnosis of amblyopia was used for symmetric mild refractive error for billing purposes.

Left eyes were more often affected than right eyes in unilateral amblyopia, an observation previously noted for anisometropic and combined anisometropic-strabismic amblyopia.[117] Found in all age groups and races, this left-eye predominance was slightly more prominent for female and white subjects. The reason for this left-eye predilection is not known, although it has been speculated it could "be related to microtropia, sighting dominance, or other forms of ocular dominance; developmental or neurological factors; laterality in the development of refractive error; or a combination thereof."[117]

VA did improve in children 3-6 years of age by about 2 lines over the mean of 2.3 years they were followed in the registry, but residual amblyopia was common, with a mean VA at outcome of 0.23 (20/34). Children 7-12 years of age improved by about a line, but still had significant residual VA deficit at 0.25 (20/36). The nature of the nonstandardized VA measurement and uncertainty about the quality and use of refractive correction at first visit could mean some of this treatment effect was related to optical correction, age, and learning for the children 3-6 years of age where the fellow eye improved about three-quarters of a line. The data confirm a substantial financial and treatment burden by the family during the first year after diagnosis, with a median of 3 visits for children up to 6 years of age. Adults did not show any significant change in VA during a mean of 2.6 years of follow-up.

Overall performance on the IRIS-50 VA outcome measure was 77.3%. This was slightly poorer than the 83% achieved in an amblyopia treatment clinical trial and 81% in a retrospective chart review,[110] but the IRIS Registry included more severe cases than included in the clinical trial and some patients were not being actively treated. The relatively high success rate seen with the 3 criteria in the IRIS Registry may reassure clinicians they are doing well, but this outcome also means there is little room to improve compared with the 83% success achieved in the gold-standard clinical trial. Thus, measure developers may wish to consider use of only a single criterion, such as achieving an interocular acuity difference of <0.23 logMAR, for which there is room to improve, or develop new measures in which there is a larger gap in current outcomes of care. Measures that extend beyond the calendar year of diagnosis are not possible in current Medicare performance systems, but could be developed for more general use in IRIS Registry.

There was a large difference in success rates when evaluated by race/ethnicity, with black/African-American and

TABLE 6. Visual Acuity at Baseline and Most Recent IRIS Registry Follow-up for Unique Patients with at least Two Visits and Unilateral Deprivation Amblyopia

	Age (Years)[a]			
	3 to 6	7 to 12	13 to 17	≥ 18
Unique patients (n = 14,073)	1,743	2,027	755	9,548
VA at first visit with diagnosis				
LogMAR VA for amblyopic eye				
Mean	0.56	0.55	0.60	0.76
SD	0.43	0.48	0.53	0.56
95% CI	0.54-0.58	0.53-0.57	0.56-0.63	0.75-0.78
Median	0.48	0.40	0.48	0.60
Interquartile range	0.30-0.70	0.18-0.70	0.18-0.88	0.30-1.00
LogMAR VA for fellow eye				
Mean	0.15	0.09	0.07	0.16
SD	0.16	0.16	0.16	0.22
95% CI	0.15-0.16	0.09-0.10	0.06-0.08	0.16-0.17
Median	0.10	0.00	0.00	0.10
Interquartile range	0.00-0.18	0.00-0.15	0.00-0.10	0.00-0.18
Median time from baseline to most recent visit (years)	2.6	2.9	2.9	2.9
Visual acuity at most recent visit				
LogMAR VA for amblyopic eye				
Mean	0.41	0.48	0.57	0.72
SD	0.45	0.50	0.55	0.59
95% CI	0.39-0.43	0.46-0.49	0.18-0.80	0.71-0.74
Median	0.30	0.30	0.40	0.54
Interquartile range	0.10-0.54	0.10-0.67	0.18-0.80	0.30-1.00
LogMAR VA for fellow eye				
Mean	0.08	0.07	0.06	0.15
SD	0.13	0.16	0.13	0.21
95% CI	0.07-0.09	0.06-0.08	0.05-0.07	0.15-0.16
Median	0.00	0.00	0.00	0.10
Interquartile range	0.00-0.10	0.00-0.10	0.00-0.10	0.00-0.18

CI = confidence interval; SD = standard deviation; VA = visual acuity.
[a]Age at first IRIS Registry visit with diagnosis of amblyopia.

Hispanic/Latino children 3-7 years of age doing significantly less well than white children. This disparity in outcome was also seen for older African-American children. Future research in amblyopia needs to probe the racial/ethnicity disparity in treatment outcome found in these data. Additional analyses of IRIS Registry data regarding outcomes by cause of amblyopia, treatment, sex, race/ethnicity, and magnitude of strabismus and refractive error, as well as change in outcomes over time, will be pursued.

Limitations of the IRIS Registry include missing data, loss to follow-up, incomplete visit documentation, incomplete diagnostic coding, uncertainly about refractive correction used for VA testing in some patients, the fact that refractive amblyopia coding does not include more specific causes or severity, and the potential for unrecognized coding errors. Reporting of amblyopia cause was not at the highest level of specificity for more than 40% of patients and combined diagnoses with strabismus were reported uncommonly. Laterality reporting was incomplete, available only for patients seen after the switch to ICD-10. Racial/ethnicity data were missing for about 20% of the sample. Initial visual acuities were with best-corrected VA when available, but there could have been some immediate VA improvement from glasses alone for the overall VA improvement if new glasses were prescribed. In addition, the IRIS Registry does not yet include treatment information, since treatments do not generate specifically indentifiable claims. The ability in the future to extract these data elements with natural language processing from the health records could ease retrieval of prescribed treatments and better define outcomes. IRIS-50 outcomes were for clinical care and not limited to 1 or more active treatments. We did not risk-adjust for comorbidities (other than not include deprivation amblyopia) that make amblyopia treatment more difficult or unlikely

TABLE 7. IRIS Registry Outcome Measure (IRIS-50)

	Age 3 to 7 Years		Age 8 to 12 Years	
Total patients with IRIS data meeting measure eligibility (denominator)	18,841		9,762	
	Patients Meeting Success			
Criterion 1: A corrected interocular (or if not reported, uncorrected) visual acuity difference <0.23 logMAR 3-12 months after first diagnosis of amblyopia	12,352	65.6%	4,364	44.8%
Criterion 2: Improvement in the corrected visual acuity of the amblyopic eye of 3 or more Snellen lines (≥0.30 logMAR) 3-12 months after first diagnosis of amblyopia	10,387	55.1%	3,170	32.7%
Criterion 3: A visual acuity in the amblyopic eye equal to 20/30 or better (≤0.18 logMAR) 3-12 months after first diagnosis of amblyopia	7,578	40.2%	3,161	32.8%
Overall Measure Performance: Patients satisfying at least 1 of the 3 criteria listed above	14,570	77.3%	5,390	55.5%

IRIS-50 was developed for children 3-7 years of age. Measure was also applied to children 8-12 years of age to explore their outcomes.

to succeed, although such cases would be relatively uncommon and would not be expected to affect overall outcomes appreciably. Lastly, participation by academic medical centers has lagged, thus possibly excluding some patients with more complicated causes of amblyopia and possibly worse outcomes. Despite these limitations, registry findings can be used to identify future areas for research.

ADVOCACY FOR AMBLYOPIA DETECTION AND TREATMENT

WHILE PHYSICIANS HAVE TRADITIONALLY FOCUSED ON improving their individual patients' outcome from a disease, there is consensus that there is a need to improve our society's vision care and eye health.[3] Amblyopia remains the most common treatable ocular condition in children, with residual disease in about 2% of adults. However, health care needs are exquisitely vulnerable to shifting priorities of funding and public interest. There is little doubt that amblyopia, once identified, along with any associated strabismus and refractive error, are important medical problems with life-long consequences. Further, amblyopia affects a large number of individuals who can benefit from treatment. However, with finite medical resources, attention to when and how to detect these important eye conditions such as amblyopia and at what societal cost has been and continues to be debated.[3,118,119]

The availability of cost-effective treatments demonstrated through clinical trials over the last 2 decades serves to elevate the early identification and treatment of amblyopia from opinion to evidence-based must-do efforts.[55,111] Continued updating of the evidence of a benefit for current and new interventions is required to maintain the effort. In addition, ongoing performance measurement of the clinical application of practice guidelines to a large group of children, as in this review of IRIS Registry data for amblyopia, could be used to show value of an intervention and encourage improvement. In addition, when performance improves, this serves to support the investment of time, personnel, and financial resources for all or some subgroups of children with amblyopia.

There are numerous organizations, internationally, nationally, and regionally, that have worked collectively with health care providers, advocates, and families to promote eye health, eye protection, and early detection of childhood eye diseases including amblyopia. These include Prevent Blindness (Chicago, Illinois, USA) (with whom I have worked) and its state-based affiliates in the United States who have supported research, developed consensus guidelines for preventive eye care,[120] and have long advocated along with medical specialty societies and patient advocacy groups for more attention and funding for eye care for children and adults. Such organizations advocate locally and help ensure policies to protect vision and need ophthalmologist input and assistance.

The federal government has multiple agencies that work with all stakeholders to improve vision for our society. The National Eye Institute of the National Institutes of Health was established in 1968 and has had the preeminent position, providing funding, promoting eye research, and educating the public. The National Eye Institute has funded the PEDIG network since 1997, along with other important clinical trials in eye care.

Of importance for vision screening and amblyopia care are 2 additional government agencies, USPSTF and HRSA (Health Resources Service Administration). These agencies consider the value of medical services to prevent disease and make recommendations about their use which strongly influence public health efforts and insurance coverage. Each accepts informed input about their recommendations. USPSTF currently recommends preschool vision screening to detect amblyopia and other eye diseases at least once between the ages of 3 and 5 years.[121] The recommendation was termed "moderate" because

"untreated amblyopia results in permanent, uncorrectable vision loss, and the benefits of screening and treatment potentially can be experienced over a child's lifetime." Vision and eye screening is also part of the recommended pediatric evaluation from infancy through the teenage years in Bright Futures, a collaboration between the American Academy of Pediatrics and the Maternal and Child Health Bureau of the Department of Health and Human Services.[122] A similar approach exists in the UK for the 3-to-5-year-old age group, where screening has been found slightly more effective than no screening.[123] Population-based preschool vision screen programs, promoted by non-governmental and governmental entities, are credited in some countries with reducing the number of amblyopic children.[27,124]

Preschool screening programs are designed to detect amblyopia or amblyopia risk factors. These are often run by non-profit local organizations which beenfit from local physician involvement. Expert opinion and evidence-based recommendations about the best method for screening vary depending on patient age, but should include periodicity, methods, and referral protocol.[120,125] One systematic approach would include these actions: (1) screening should occur annually (best practice) or at least once (acceptable minimum standard) between 3 and 6 years of age, and periodically throughout the school years for children who do not receive comprehensive eye examinations; (2) personnel should be trained and certified; and (3) results should be recorded and communicated to the child's parents, primary care provider, and school with referral for examination and treatment if needed.[126]

School-based vision screening programs are required in the majority of states, but there is marked variation in the laws and regulations around these screenings.[127] These programs, while concerned with amblyopia detection, are focused primarily on detecting significant refractive error in 1 or both eyes that would harm school performance. Fortunately, the same failure criteria should be sufficient to accomplish these goals.

FUTURE DIRECTIONS FOR AMBLYOPIA THERAPY

ALTHOUGH CURRENT AMBLYOPIA THERAPY HAS BEEN associated with improvement in most patients, about 20% have a residual high-contrast VA deficit worse than 20/32.[41] IRIS Registry analysis confirms significant residual vision impairment in many adults. Many more patients will have deficiencies in low-contrast VA, binocular vision, and reading speed. Treatments that eliminate or reduce these deficits would hopefully provide an improved quality of life, and should be the aim of future study. In many cases variations of spectacle correction, conventional occlusion, binocular therapy, and blurring of the fellow eye will be studied.

To gain insight into future amblyopia research breakthroughs, an expert panel was convened by the Albert and Mary Lasker Foundation and the International Retinal Research Foundation in 2017-2018.[75] The panel on future treatment was led by Michael P. Stryker and Siegrid Löwel. A key strategy continues to be finding a method to unlock a brain's plasticity well after the normal critical period for development of neurologic functions has normally closed. This approach has been used as the rationale for past treatments using dopamine and cytidine-5′-diphosphocholine (citicoline) to alter central nervous system neurotransmitter balance. Despite the rationale and some early success in case series, these medications have yet to convincingly prove more effective than conventional treatment or successfully treat residual amblyopia in older patients.[74,128] Nonetheless, study of systemic medications, which can alter the levels of neurotransmitters and neuromodulators in the brain or by other mechanisms which adjust the balance of excitatory and inhibitory synaptic elements, is intriguing.

Another approach is direct treatment of neuronal DNA at the cellular level to alter its activity. It is known that vision and life experiences affect neuronal DNA through methylation and histone modifications during childhood. These changes affect gene transcription. If these epigenetic regions of DNA could be altered by treatment to revert to the childhood state, that could allow reopening the window of plasticity for vision development.

Neuroscientists are also testing nonpharmacologic methods for adjusting brain plasticity using transcranial stimulation, with direct current or magnetic fields. These approaches could alter neuronal excitability, thereby opening a window in which to introduce additional treatment to stimulate vision development, perhaps some form of behavioral vision training or experience. Even with the recent disappointments in this field surrounding conventional vision therapy and binocular therapy, novel and well-targeted treatments may be a route to improved outcomes.

SUMMARY

AMBLYOPIA REMAINS A COMMON PEDIATRIC EYE CARE problem in need of timely detection and effective treatment. It is most often associated with uncorrected refractive error in medical records data. A substantial number of patients of all ages with amblyopia receive care, with acceptable outcomes for about 75% of patients in terms of high-contrast VA in clinical trials and clinical practice. However, residual deficits remain in most patients, affecting vision-related activities throughout their lifetimes. The success rate found in the IRIS Registry differed significantly by race/ethnicity, an association that deserves research to understand why and how to mitigate.

FUNDING/SUPPORT: THIS RESEARCH DID NOT RECEIVE ANY SPECIFIC GRANT FROM FUNDING AGENCIES IN THE PUBLIC, commercial, or not-for-profit sectors. IRIS data and analytics were provided by the American Academy of Ophthalmology for purposes of this lectureship. Financial Disclosures: Michael X. Repka discloses the following: consultant for American Academy of Ophthalmology; salary support from National Eye Institute; medical monitor for Luminopia, Inc Clinical Trial of Luminopia One. The author attests to meeting the current ICMJE criteria for authorship.

Data and statistical support for IRIS Registry data: Charles Li, Danielle Fujino, and Flora Lum.

REFERENCES

1. Newell FW. Edward Jackson, MD–a historical perspective of his contributions to refraction and to ophthalmology. *Ophthalmology* 1988;95(4):555–558.
2. Liesegang TJ, Hoskins HD, Jensen AD. The significance of the Edward Jackson Lecture. *Am J Ophthalmol* 2005; 139(3):530–532.
3. National Academies of Sciences, Engineering, and Medicine, Health and Medicine Division, Board on Population Health and Public Health Practice, Committee on Public Health Approaches to Reduce Vision Impairment and Promote Eye Health. Making eye health a population health imperative: vision for tomorrow. Washington, DC: The National Academies Press; 2016.
4. Parke DW II, Rich WL, Sommer A, Lum F. The American Academy of Ophthalmology's IRIS (Intelligent Research in Sight Clinical Data); A look back and a look to the future. *Ophthalmology* 2017;124(11):1572–1574.
5. Simons K. Amblyopia characterization, treatment, and prophylaxis. *Surv Ophthalmol* 2005;50(2):123–166.
6. Birch EE. Amblyopia and binocular vision. *Prog Retin Eye Res* 2013;33:67–84.
7. Woodruff G, Hiscox F, Thompson JR, Smith LK. Factors affecting the outcome of children treated for amblyopia. *Eye* 1994;8:627–631.
8. Multi-Ethnic Pediatric Eye Disease Study Group. Prevalence of amblyopia and strabismus in African American and Hispanic children ages 6 to 72 months the multi-ethnic pediatric eye disease study. *Ophthalmology* 2008;115:1229–1236.
9. Friedman DA, Repka MX, Katz J, et al. Prevalence of amblyopia and strabismus in white and African-American children aged 6 through 71 months: The Baltimore Pediatric Eye Disease Study. *Ophthalmology* 2009;116:2128–2134.
10. Pascual M, Huang J, Maguire MG, et al. Risk factors for amblyopia in the Vision in Preschoolers Study. *Ophthalmology* 2014;121(3):622–629.e621.
11. Hubel D, Wiesel T. Receptive fields, binocular interaction and functional architecture in the cat's visual cortex. *J Physiol* 1962;160(1):106–154.
12. Grant S, Moseley MJ. Amblyopia and real-world visuomotor tasks. *Strabismus* 2011;19(3):119–128.
13. Kelly KR, Jost RM, De La Cruz A, et al. Slow reading in children with anisometropic amblyopia is associated with fixation instability and increased saccades. *J AAPOS* 2017; 21(6):447–451.
14. Simmers AJ, Ledgeway T, Hutchinson CV, Knox PJ. Visual deficits in amblyopia constrain normal models of second-order motion processing. *Vision Res* 2011;51(18): 2008–2020.
15. McKee S, Levi DM, Movshon JA. The pattern of visual deficits in amblyopia. *J Vis* 2003;3:380–405.
16. González EG, Wong AM, Niechwiej-Szwedo E, Tarita-Nistor L, Steinbach MJ. Eye position stability in amblyopia and in normal binocular vision. *Invest Ophthalmol Vis Sci* 2012;53:5386–5394.
17. Birch EE, Castañeda YS, Cheng-Patel CS, et al. Self-perception in children aged 3 to 7 years with amblyopia and its association with deficits in vision and fine motor skills. *JAMA Ophthalmol* 2019;137(5):499–506.
18. Robaei D, Rose KA, Ojaimi E, et al. Causes and associations of amblyopia in a population-based sample of 6-year-old Australian children. *Arch Ophthalmol* 2006;124:878–884.
19. Williams C, Northstone K, Howard M, Harvey I, Harrad RA, Sparrow JM. Prevalence and risk factors for common vision problems in children: data from the ALSPAC study. *Br J Ophthalmol* 2008;92:959–964.
20. Groenewoud JH, Tjiam AM, Lantau VK, et al. Rotterdam AMblyopia screening effectiveness study: detection and causes of amblyopia in a large birth cohort. *Invest Ophthalmol Vis Sci* 2010;51(7):3476–3484.
21. Pai AS, Rose KA, Leone JF, et al. Amblyopia prevalence and risk factors in Australian preschool children. *Ophthalmology* 2012;119:138–144.
22. Tarczy-Hornoch K, Varma R, Cotter SA, et al. Risk factors for decreased visual acuity in preschool children: The Multi-Ethnic Pediatric Eye Disease and Baltimore Pediatric Eye Disease Studies. *Ophthalmology* 2011;118:2262–2273.
23. National Eye Institute Office of Biometry and Epidemiology. Report on the national eye institute's visual acuity impairment survey pilot study. Washington, DC: Department of Health and Human Services; 1984.
24. Lennerstrand G, Jakobsson P, Kvarnstrom G. Screening for ocular dysfunction in children: approaching a common program. *Acta Ophthalmol* 1995;26–38.
25. Attebo K, Mitchell P, Cumming R, et al. Prevalence and causes of amblyopia in an adult population. *Ophthalmology* 1998;105:154–159.
26. Kvarnstrom S, Jakobsson P, Lennerstrand G. Screening for visual and ocular disorders in children, evaluation of the system in Sweden. *Acta Pediatr* 1998;87:1173–1179.
27. Kvarnström G, Jakobsson P, Lennerstrand G. Visual screening of Swedish children: an ophthalmological evaluation. *Acta Ophthalmol Scand* 2001;79(3):240–244.
28. Snowdon S, Stewart-Brown SL. Preschool vision screening. *Health Technol Assess* 1997;1(i-iv):1–83.
29. Beck RW. The Pediatric Eye Disease Investigator Group. *J AAPOS* 1998;2(5):255–256.
30. Clarke MP, Wright CM, Hrisos S, Anderson JD, Henderson J, Richardson SR. Randomised controlled trial of treatment of unilateral visual impairment detected at preschool vision screening. *BMJ* 2003;327(7426):1251–1255.
31. Drover JR, Felius J, Cheng CS, Morale SE, Wyatt L, Birch EE. Normative pediatric visual acuity using single

surrounded HOTV optotypes on the Electronic Visual Acuity Tester following the Amblyopia Treatment Study protocol. *J AAPOS* 2008;12(2):145–149.
32. Pan Y, Tarczy-Hornoch K, Cotter SA, et al. Visual acuity norms in pre-school children: the Multi-Ethnic Pediatric Eye Disease Study. *Optom Vis Sci* 2009;86(6):607–612.
33. Pediatric Eye Disease Investigator Group. A randomized trial of atropine vs patching for treatment of moderate amblyopia in children. *Arch Ophthalmol* 2002;120(3):268–278.
34. Shaw DE, Fielder AR, Minshull C, Rosenthal AR. Amblyopia - factors influencing age of presentation. *Lancet* 1988;2:207–209.
35. Pediatric Eye Disease Investigator Group. The clinical profile of moderate amblyopia in children younger than 7 years. *Arch Ophthalmol* 2002;120(3):281–287.
36. Repka MX, Friedman DS, Katz J, Ibironke J, Giordano L, Tielsch JM. The prevalence of ocular structural disorders and nystagmus among preschool-aged children. *J AAPOS* 2012;16(2):182–184.
37. Schmidt P, Maguire M, Dobson V, et al. Comparison of preschool vision screening tests as administered by licensed eye care professionals in the Vision In Preschoolers Study. *Ophthalmology* 2004;111(4):637–650.
38. Konig H, Barry JC. Economic evaluation of different methods of screening for amblyopia in kindergarten. *Pediatrics* 2002;109:e59.
39. US Preventive Services Task Force. Vision screening in children aged 6 months to 5 years: US Preventive Services Task Force Recommendation Statement. *JAMA* 2017;318(9):836–844.
40. Silverstein E, Donahue SP. Preschool vision screening: where we have been and where we are going. *Am J Ophthalmol* 2018;194:xviii–xxiii.
41. Pediatric Eye Disease Investigator Group. Atropine vs patching for treatment of moderate amblyopia: follow-up at 15 years of age of a randomized clinical trial. *JAMA Ophthalmol* 2014;132(7):799–805.
42. Leiba H, Shimshoni M, Oliver M, et al. Long-term follow-up of occlusion therapy in amblyopia. *Ophthalmology* 2001;108:1552–1555.
43. Bowman RJC, Williamson TH, Andrews RGL, Aitchison TC, Dutton GN. An inner city preschool visual screening programme: long term visual results. *Br J Ophthalmol* 1998;82:543–548.
44. Von Noorden GK, Campos E. Binocular vision and ocular motility: theory and management of strabismus. 6th ed. St. Louis: Mosby; 2002.
45. Duke-Elder S. Anomalies of ocular motility. In: Ocular motility and strabismus. St. Louis: Mosby; 1973:292–294.
46. Loudon SE, Simonsz HJ. The history of the treatment of amblyopia. *Strabismus* 2005;13(2):93–106.
47. Moseley MJ, Neufeld M, McCarry B, et al. Remediation of refractive amblyopia by optical correction alone. *Ophthalmic Physiol Opt* 2002;22:296–299.
48. Stewart CE, Moseley MJ, Fielder AR, Stephens DA. Refractive adaptation in amblyopia: quantification of effect and implications for practice. *Br J Ophthalmol* 2004;88(12):1552–1556.
49. Pediatric Eye Disease Investigator Group. Treatment of anisometropic amblyopia in children with refractive correction. *Ophthalmology* 2006;113(6):895–903.
50. Cotter SA, Edwards AE, Arnold RW, et al. Treatment of strabismic amblyopia with refractive correction. *Am J Ophthalmol* 2007;143(6):1060–1063.
51. Pediatric Eye Disease Investigator Group, Cotter SA, Foster NC, Holmes JM, et al. Optical treatment of strabismic and combined strabismic-anisometropic amblyopia. *Ophthalmology* 2012;119(1):150–158.
52. Awan M, Proudlock FA, Gottlob I. A randomized controlled trial of unilateral strabismic and mixed amblyopia using occlusion dose monitors to record compliance. *Invest Ophthalmol Vis Sci* 2005;46(4):1435–1439.
53. Stewart CE, Moseley MJ, Stephens DA, Fielder AR. Treatment dose-response in amblyopia therapy: the Monitored Occlusion Treatment of Amblyopia Study (MOTAS). *Invest Ophthalmol Vis Sci* 2004;45(9):3048–3054.
54. Pediatric Eye Disease Investigator Group. A randomized trial to evaluate two hours of daily patching for amblyopia in children. *Ophthalmology* 2006;113(6):904–912.
55. Wallace DK, Repka MX, Lee KA, et al. Amblyopia preferred practice pattern(R). *Ophthalmology* 2018;125(1):P105–P142.
56. Holmes JM, Lazar EL, Melia BM, et al. Effect of age on response to amblyopia treatment in children. *Arch Ophthalmol* 2011;129(11):1451–1457.
57. Pediatric Eye Disease Investigator Group. Two-year follow-up of a 6-month randomized trial of atropine vs patching for treatment of moderate amblyopia in children. *Arch Ophthalmol* 2005;123(2):149–157.
58. Holmes JM, Beck RW, Kraker RT, et al. Impact of patching and atropine treatment on the child and family in the amblyopia treatment study. *Arch Ophthalmol* 2003;121(11):1625–1632.
59. Pediatric Eye Disease Investigator Group. Randomized trial of treatment of amblyopia in children aged 7 to 17 years. *Arch Ophthalmol* 2005;123(4):437–447.
60. Pediatric Eye Disease Investigator Group. Patching vs atropine to treat amblyopia in children aged 7 to 12 years: a randomized trial. *Arch Ophthalmol* 2008;126(12):1634–1642.
61. Pediatric Eye Disease Investigator Group. The course of moderate amblyopia treated with patching in children: experience of the Amblyopia Treatment Study. *Am J Ophthalmol* 2003;136(4):620–629.
62. Pediatric Eye Disease Investigator Group. A randomized trial of patching regimens for treatment of moderate amblyopia in children. *Arch Ophthalmol* 2003;121(5):603–611.
63. Pediatric Eye Disease Investigator Group. A randomized trial of prescribed patching regimens for treatment of severe amblyopia in children. *Ophthalmology* 2003;110(11):2075–2087.
64. Repka MX, Kraker RT, Beck RW, et al. Treatment of severe amblyopia with weekend atropine: results from 2 randomized clinical trials. *J AAPOS* 2009;13(3):258–263.
65. Simons K, Stein L, Sener EC, Vitale S, Guyton DL. Full-time atropine, intermittent atropine, and optical penalization and binocular outcome in treatment of strabismic amblyopia. *Ophthalmology* 1997;104(12):2143–2155.

66. Pediatric Eye Disease Investigator Group. A randomized trial of atropine regimens for treatment of moderate amblyopia in children. *Ophthalmology* 2004;111(11):2076–2085.
67. Kaye SB, Chen SI, Price G, et al. Combined optical and atropine penalization for the treatment of strabismic and anisometropic amblyopia. *J AAPOS* 2002; 6(5):289–293.
68. Pediatric Eye Disease Investigator Group. A randomized trial of adding a plano lens to atropine for amblyopia. *J AAPOS* 2015;19(1):42–48.
69. Repka MX, Ray JM. The efficacy of optical and pharmacological penalization. *Ophthalmology* 1993;100:769–775.
70. Pediatric Eye Disease Investigator Group, Wallace DK, Lazar EL, et al. A randomized trial of increasing patching for amblyopia. *Ophthalmology* 2013;120(11):2270–2277.
71. Pediatric Eye Disease Investigator Group. A randomized trial comparing Bangerter filters and patching for the treatment of moderate amblyopia in children. *Ophthalmology* 2010;117(5):998–1004.
72. France TD, France LW. Optical penalization can improve vision after occlusion treatment. *J AAPOS* 1999;3(6): 341–343.
73. Yang X, Luo D, Liao M, Chen B, Liu L. Efficacy and tolerance of levodopa to treat amblyopia: a systematic review and meta-analysis. *Eur J Ophthalmol* 2013;23(1):19–26.
74. Pediatric Eye Disease Investigator Group, Repka MX, Kraker RT, et al. A randomized trial of levodopa as treatment for residual amblyopia in older children. *Ophthalmology* 2015;122(5):874–881.
75. Stryker MP, Löwel S. Amblyopia: new molecular/pharmacological and environmental approaches, Amblyopia: challenges and opportunities. Albert and Mary Lasker Foundation. International Retinal Research Foundation; 2017.
76. Garzia R. Efficacy of vision therapy in amblyopia: a literature review. *Am J Optom Physiol Opt* 1987;64:399–404.
77. Frantz K. Rationale for refractive correction, occlusion and active vision therapy for amblyopia treatment. *J Bev Optom* 1995;6(1):18–19.
78. Suttle CM. Active treatments for amblyopia: a review of the methods and evidence base. *Clin Exp Optom* 2010;93(5): 287–299.
79. Lyon DW, Hopkins K, Chu RH, et al. Feasibility of a clinical trial of vision therapy for treatment of amblyopia. *Optom Vis Sci* 2013;90(5):475–481.
80. Hess RF, Thompson B. Amblyopia and the binocular approach to its therapy. *Vision Res* 2015;114:4–16.
81. Li SL, Reynaud A, Hess RF, et al. Dichoptic movie viewing treats childhood amblyopia. *J AAPOS* 2015;19(5):401–405.
82. Hess RF, Mansouri B, Thompson B. A new binocular approach to the treatment of amblyopia in adults well beyond the critical period of visual development. *Restor Neurol Neurosci* 2010;28(6):793–802.
83. Hess RF, Babu RJ, Clavagnier S, Black J, Bobier W, Thompson B. The iPod binocular home-based treatment for amblyopia in adults: efficacy and compliance. *Clin Exp Optom* 2014;97(5):389–398.
84. Birch EE, Li SL, Jost RM, et al. Binocular iPad treatment for amblyopia in preschool children. *J AAPOS* 2015;19(1): 6–11.
85. Birch EE, Jost RM, De La Cruz A, et al. Binocular amblyopia treatment with contrast-rebalanced movies. *J AAPOS* 2019; 23(3):160.e161–160.e165.
86. Kelly KR, Jost RM, Dao L, Beauchamp CL, Leffler JN, Birch EE. Binocular iPad game vs patching for treatment of amblyopia in children: a randomized clinical trial. *JAMA Ophthalmol* 2016;134(12):1402–1408.
87. Holmes JM, Manh VM, Lazar EL, et al. Effect of a binocular iPad game vs part-time patching in children aged 5 to 12 years with amblyopia: a randomized clinical trial. *JAMA Ophthalmol* 2016;134(12):1391–1400.
88. Manh VM, Holmes JM, Lazar EL, et al. A randomized trial of a binocular iPad game versus part-time patching in children aged 13 to 16 years with amblyopia. *Am J Ophthalmol* 2018; 186:104–115.
89. Gao TY, Guo CX, Babu RJ, et al. Effectiveness of a binocular video game vs placebo video game for improving visual functions in older children, teenagers, and adults with amblyopia: a randomized clinical trial. *JAMA Ophthalmol* 2018; 136(2):172–181.
90. Pediatric Eye Disease Investigator Group, Holmes JM, Manny RE, et al. A randomized trial of binocular dig rush game treatment for amblyopia in children aged 7 to 12 years. *Ophthalmology* 2019;126(3):456–466.
91. Pineles SL, Repka MX, Yu F, Lum F, Coleman AL. Risk of musculoskeletal injuries, fractures, and falls in medicare beneficiaries with disorders of binocular vision. *JAMA Ophthalmol* 2015;133(1):60–65.
92. Bhola R, Keech RV, Kutschke P, Pfeifer W, Scott WE. Recurrence of amblyopia after occlusion therapy. *Ophthalmology* 2006;113:2097–2100.
93. Holmes JM, Beck RW, Kraker RT, et al. Risk of amblyopia recurrence after cessation of treatment. *J AAPOS* 2004;8(5): 420–428.
94. Holmes JM, Melia M, Bradfield YS, et al. Factors associated with recurrence of amblyopia on cessation of patching. *Ophthalmology* 2007;114(8):1427–1432.
95. Satterfield D, Keltner JL, Morrison TL. Psychosocial aspects of strabismus study. *Arch Ophthalmol* 1993;111(8): 1100–1105.
96. Horwood J, Waylen A, Herrick D, Williams C, Wolke D. Common visual defects and peer victimization in children. *Invest Ophthalmol Vis Sci* 2005;46:1177–1181.
97. Guimarães S, Carção AA, Carvalho MR, Vieira MJ, Freitas C, Morgado P. Quality of life and mental health in amblyopic children treated with and without occlusion therapy. *J AAPOS* 2019;23(6):339.e331–339.e335.
98. Birch EE, Castañeda YS, Cheng-Patel CS, et al. Self-perception of school-aged children with amblyopia and it association with reading speed and motor skills. *JAMA Ophthalmol* 2019;137(2):167–173.
99. Chua B, Mitchell P. Consequences of amblyopia on education, occupation, and long term vision loss. *Br J Ophthalmol* 2004;88(9):1119–1121.
100. Rahi JS, Cumberland PM, Peckham CS. Does amblyopia affect educational, health, and social outcomes? Findings from 1958 British birth cohort. *BMJ* 2006;332(7545): 820–825.
101. Rahi J, Logan S, Timms C, Russell-Eggitt I, Taylor D. Risk, causes, and outcomes of visual impairment after loss of

vision in the non-amblyopic eye: a population-based study. *Lancet* 2002;360(9333):597–602.
102. van Leeuwen R, Eijkemans MJ, Vingerling JR, Hofman A, de Jong PT, Simonsz HJ. Risk of bilateral visual impairment in individuals with amblyopia: the Rotterdam Study. *Br J Ophthalmol* 2007;91(11):1450–1451.
103. Pineles SL, Repka MX, Yu F, Lum F, Coleman AL. Evaluating the impact of strabismus surgery on the association of musculoskeletal injuries, fractures, and falls with disorders of binocular vision in medicare beneficiaries. *J AAPOS* 2017;21(3):239–241.
104. Beck RW, Maguire MG, Bressler NM, Glassman AR, Lindblad AS, Ferris FL. Visual acuity as an outcome measure in clinical trials of retinal diseases. *Ophthalmology* 2007; 114(10):1804–1809.
105. Newsham D. A randomised controlled trial of written information: the effect on parental non-concordance with occlusion therapy. *Br J Ophthalmol* 2002;86:787–791.
106. Flynn J, Schiffman J, Feuer W, Corona A. The therapy of amblyopia: An analysis of the results of amblyopia therapy utilizing the pooled data of published studies. *Trans Am Ophthalmol Soc* 1998;96:431–453.
107. Flynn JT, Woodruff G, Thompson JR, et al. The therapy of amblyopia: an analysis comparing the results of amblyopia therapy utilizing two pooled data sets. *Trans Am Ophthalmol Soc* 1999;97:373–390.
108. McNeil JJ, Evans SM, Johnson NP, Cameron PA. Clinical-quality registries: their role in quality improvement. *Med J Aust* 2010;192(5):244–245.
109. West C, Cobb M, White D. Amblyopia treatment outcome assessment usiung the AAO's IRIS-7 measure [abstract]. *J AAPOS* 2015;20:e10.
110. Shoshany T, Michalak S, Chinn B, Staffa S, Hunter DG. Evaluating amblyopia treatment success using the American Academy of Ophthalmology's IRIS7 and IRIS50 measures. *Ophthalmology* 2020;127(6):836–838.
111. American Academy of Ophthalmology. IRIS50: Amblyopia: Interocular visual acuity. Available at https://www.aao.org/medicare/quality-reporting-measure/iris50-amblyopia-interocular-visual-acuity-copy. Accessed June 15, 2020.
112. Chiang MF, Sommer A, Rich WL, Lum F, Parke DW 2nd. The 2016 American Academy of Ophthalmology IRIS®Registry (Intelligent Research in Sight) Database Characteristics and Methods. *Ophthalmology* 2018;125(8): 1143–1148.
113. National Eye Institute Office of Biometry and Epidemiology. Report on the National Eye Institute's visual acuity impairment survey pilot study. Washington, DC: Department of Health and Human Services; 1984.
114. Attebo K, Mitchell P, Cumming R, Smith W, Jolly N, Sparkes R. Prevalence and causes of amblyopia in an adult population. *Ophthalmology* 1998;105(1):154–159.
115. Woodruff G, Hiscox F, Thompson JR, Smith LK. The presentation of children with amblyopia. *Eye* 1994;8:623–626.
116. Pediatric Eye Disease Investigator Group. Treatment of bilateral refractive amblyopia in children three to less than 10 years of age. *Am J Ophthalmol* 2007;144(4):487–496.
117. Repka M, Simons K, Kraker R. Laterality of amblyopia. *Am J Ophthalmol* 2010;150(2):270–274.
118. Stewart-Brown SL, Snowdon SK. Evidence-based dilemmas in pre-school vision screening. *Arch Dis Child* 1998;78(5): 406–407.
119. Carlton J, Karnon J, Czoski-Murray C, Smith KJ, Marr J. The clinical effectiveness and cost-effectiveness of screening programmes for amblyopia and strabismus in children up to the age of 4-5 years: a systematic review and economic evaluation. *Health Technol Assess* 2008;12(25):iii. xi-194.
120. Cotter SA, Cyert LA, Miller JM, Quinn GE, National Expert Panel to the National Center for Children's Vision and Eye Health. Vision screening for children 36 to <72 months: recommended practices. *Optom Vis Sci* 2015; 92(1):6–16.
121. US Preventive Services Task Force, Grossman DC, Curry SJ, et al. Vision screening in children aged 6 months to 5 years: US Preventive Services Task Force Recommendation Statement. *JAMA* 2017;318(9):836–844.
122. Hagan JF, Shaw JS, Duncan PM, eds. Bright Futures. Guidelines for Health Supervision of Infants, Children, and Adolescents [pocket guide]. 4th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2017.
123. Williams C, Northstone K, Harrad R, et al. Amblyopia treatment outcomes after preschool screening vs. school entry screening: observational data from a prospective cohort study. *Br J Ophthalmol* 2003;87(8):988–993.
124. Thorisdottir RL, Faxén T, Blohmé J, Sheikh R, Malmsjö M. The impact of vision screening in preschool children on visual function in the Swedish adult population. *Acta Ophthalmol* 2019;97(8):793–797.
125. Kulp MT, Vision in Preschoolers Study Group. Findings from the Vision in Preschoolers (VIP) study. *Optom Vis Sci* 2009;86:619–623.
126. Marsh-Tootle WL, Russ SA, Repka MX, for the National Expert Panel to the National Center for Children's Vision and Eye Health. Vision and eye health in children 36 to <72 months: proposed tracking definitions. *Optom Vis Sci* 2015;92(1):17–23.
127. Naser NT, Hartmann EE. Comparison of state guidelines and policies for vision screening and eye exams; preschool through early childhood. *Invest Ophthalmol Vis Sci* 2008; 49(13):3131.
128. Fresina M, Dickmann A, Salerni A, De Gregorio F, Campos EC. Effect of oral CDP-choline on visual function in young amblyopic patients. *Graefes Arch Clin Exp Ophthalmol* 2008;246(1):143–150.
129. Nguyen Angeline, Guo Xinxing, Inns Amanda, Kretz Alyssa, et al. Refractive error prevalence among inner-city students receiving school-based vision screenings and eye exams. *J AAPOS*. 2019; 23(4):e47. *J AAPOS* 2019;23(4):e47.
130. Xiao Scott, Gaier Eric, Mazow Malcolm, et al. Improved adherence and treatment outcomes with an engaging, personalized digital therapeutic in amblyopia. *Sci Rep* 2020;10:8328. https://doi.org/10.1038/s41598-020-65234-3.