The Boston Amblyopia Project:

Analyzing real-world outcomes in amblyopia treatment, identifying major challenges in management, and characterizing unique patient subgroups through a large retrospective database

by

Talia N. Shoshany

Submitted in Partial Fulfillment of the Requirements for the M.D. Degree with Honors in a Special Field at Harvard Medical School

February 10, 2020

ABSTRACT

Objective: Amblyopia is a major cause of vision loss, and questions remain regarding optimal treatment and outcomes. The objective of this study was to develop and query a large retrospective database of amblyopia patients treated at Boston Children's Hospital to assess specific aspects of follow-up and treatment and to characterize one particularly rare subtype.

Methods: A comprehensive database was created of 2037 patients diagnosed with amblyopia at Boston Children's Hospital from 2010-2014 to conduct three distinct but interrelated analyses. *IRIS analysis:* Amblyopia treatment success was measured using the AAO IRIS7 and IRIS50 criteria, and multiple demographic and baseline measures were evaluated as independent predictors of success. *Lost-to-follow-up analysis:* Rate of LTFU was calculated, and multivariate logistic regression was used to create a risk score for predicting LTFU status. *Asymmetric, bilateral amblyopia analysis:* Patients meeting criteria for asymmetric, bilateral amblyopia were divided into primary and secondary occlusion groups based on timing of patching prescription. Improvement in VA was measured at first, 12-18mo, and last visits and compared between groups.

Results: *IRIS analysis:* 71% were successful by IRIS7 and 81% by IRIS50 ($p=0.006$). Initial IOD and insurance status correlated with IRIS7 success, while no variables correlated with IRIS50 success. *LTFU analysis:* A large proportion of patients (23%) were LTFU after first visit. Older age, non-white race, lack of insurance, previous glasses or atropine treatment, and longer requested follow-up intervals were independent predictors of LTFU status. A multivariable risk score was created to predict probability of LTFU (AUC 0.68). *Asymmetric, bilateral amblyopia analysis:* Of all patients in the database, 7.6% had asymmetric, bilateral amblyopia. The 98 patients meeting inclusion criteria for analysis were divided equally between primary (n=50) and secondary (n=48) occlusion groups. VA in both eyes, IOD, and stereopsis improved similarly between groups, even after stratifying by amblyopia subtype ($p\geq0.48$).

Conclusions: Our comprehensive amblyopia database allows us to evaluate the AAO's new IRIS criteria as a concrete measure for defining amblyopia treatment success, predict which patients are more likely to be LTFU after baseline visit, and develop strategies to mitigate these effects. Finally, we identified a sub-population of patients with asymmetric, bilateral amblyopia, concluding that in this cohort, primary patching or atropine therapy provides no benefit to spectacle correction alone. These findings may help with practice efficiency and improve patient outcomes in the future by transitioning these analyses to an electronic medical record that could be programmed to provide continually updated decision support for individual patients based on large datasets.

TABLE OF CONTENTS

GLOSSARY

AAO – American Academy of Ophthalmology

AUC – Area under the curve

BCH – Boston Children's Hospital

BCVA – Best corrected visual acuity

ICD – International Classification of Diseases

IOD – Interocular difference

IQR – Interquartile range

IRIS – Intelligent Research in Sight

LogMAR – Logarithm of the minimum angle of resolution (a measure of visual acuity that is calculated by taking the negative logarithm of the Snellen fraction, i.e., Snellen 20/20 = 0 logMAR, Snellen 20/200 = 1 logMAR)

LTFU – Lost to follow-up

OR – Odds ratio

PEDIG – Pediatric Eye Disease Investigator Group

ROC – Receiver operating characteristic

VA – Visual acuity

INTRODUCTION

A. The Boston Amblyopia Project

Amblyopia, commonly referred to as 'lazy-eye,' is the leading cause of reduced visual acuity (VA) in children in North America, with a prevalence of 4%.[1,2] It is defined as having sub-optimal best-corrected visual acuity (BCVA) despite an obvious organic or structural cause, and results from lack of normal stimulation and subsequent under-development of the visual pathways between the retina and the brain in one or both eyes. This may be due to strabismus (eye-misalignment), refractive error or anisometropia (differences in refractive error between eyes), or less commonly, deprivation (i.e., cataracts, ptosis, optic nerve or retinal disease). Each of these conditions deprives the eye of a focused image on the retina, and thus under-stimulates the optic nerve and visual pathway on one or both sides.[1-3]

Treatment for amblyopia has not changed drastically since its inception and consists of refractive correction, strabismus surgery to restore ocular misalignment, and occlusion of the better-seeing eye to encourage development of the neural pathways in the weaker eye.[3,4] Although there have been many randomized control trials conducted by the Pediatric Eye Disease Investigator Group (PEDIG) evaluating the nuances of amblyopia treatment, there are relatively few studies reporting amblyopia treatment success in a real-world setting. This is important as it allows us to establish a benchmark for successful amblyopia treatment based on the current gold standard and assess new treatment strategies as they emerge. It also facilitates the identification of major challenges in amblyopia management and characterization of different patient populations within the larger cohort who may be managed more effectively.

The goal of this study was to develop a comprehensive database of all patients diagnosed with amblyopia at Boston Children's Hospital (BCH) over a 5- year period and track patient demographics, baseline characteristics, management, and treatment outcomes, which we term the Boston Amblyopia Project. This thesis will explore three individual analyses that emerged from the Boston Amblyopia Project database: (1) Real-world treatment success using the American Academy of Ophthalmology (AAO) IRIS7 and IRIS50 measures,[5,6] (2) Identifying characteristics predictive of lost-to-follow-up (LTFU) status in amblyopia, and (3) Identification and evaluation of treatment strategies for individual subgroups of amblyopia patients (i.e., asymmetric, bilateral amblyopia).

B. Real-world treatment success using the AAO IRIS7 and IRIS50 measures

Despite the prevalence and impact of amblyopia, there are few consensus measures of treatment success. Most published studies measure relative improvement in visual acuity without establishing concrete criteria for success. Furthermore, there is inconsistency in outcome measures and reporting timelines among investigators.[7] Establishing definitive measures of success may better inform individual practitioners of their own performance while allowing for assessment of new treatment strategies. To address this issue, the AAO developed criteria for measuring amblyopia treatment success in 2015. In patients aged 3-7 years with starting interocular difference (IOD) >0.29 logMAR, success was defined as having final IOD <0.23 at 12-18 months (IRIS7, © AAO, 2015).[5] Only one group to date has reported their real-world outcomes based on IRIS7, finding a 46% success rate.[8] In January of 2019, the AAO modified these success criteria with the new IRIS50 measure (© AAO, 2019). Specifically, the follow-up time was shortened to 3-12 months to fit within the yearly reporting period required by the

Centers for Medicare & Medicaid Services. In addition, 2 new measures of success were added, including final VA of 20/30 or better (≤0.18 logMAR) or VA improvement of 2 lines or more (≥0.18 logMAR) in the affected eye.[6] In this analysis, we utilize the Boston Amblyopia Project database to evaluate amblyopia treatment outcomes based on both the IRIS7 and IRIS50 measures. We also evaluate multiple demographic and baseline visual acuity measures in predicting success status.

C. Identifying characteristics predictive of lost-to-follow-up status in amblyopia

A major predictor of amblyopia treatment success is timely diagnosis and treatment adherence, before the end of the 'critical period' of brain plasticity.[9] Although current studies are finding that improvement is still possible at older ages, especially if previous treatment has not been attempted, the most pronounced effects occur before the age of 7 years.[10,11] This is the basis for school-based vision screening programs aimed to identify children with risk factors for amblyopia at an early age and refer them for timely treatment.[12] Persistent challenges in amblyopia treatment include barriers to attending referral appointments after failed vision screening, failure to follow up after the initial referral appointment, and poor adherence to treatment.[4] There have been many published studies on the socioeconomic factors correlating with poor follow-up after failed vision screening and reasons for suboptimal adherence.[13,14] However, there are few studies measuring characteristics predictive of LTFU status after initial referral.

The challenge of appropriate follow-up pervades many chronic diseases within ophthalmology. A retrospective review by Davis and colleagues out of Moorfields Eye Hospital

analyzed the total number of LTFU episodes and calculated the % LTFU by subspecialty, accounting for patient volume within each specialty. They found a relatively high prevalence of LTFU in comprehensive, vitreoretinal, medical retina, pediatrics, and strabismus clinics, while % LTFU in glaucoma clinics was lower than expected.[15]

Despite the significant burden of LTFU in the subspecialties of pediatrics and strabismus, most published studies focus on LTFU in the management of glaucoma and retinal diseases which, like amblyopia, have a critical treatment window to prevent irreversible disease progression. For example, Kim and colleagues reported that lack of understanding of treatment importance, unawareness of appointment schedule, older age, male gender, and lower baseline intraocular pressure were predictors of LTFU status among 123 glaucoma patients in South Korea.[16] To our knowledge, there is no similar study within amblyopia treatment. In this analysis, we utilize the Boston Amblyopia Project database to determine the frequency of LTFU status among amblyopia patients and characterize independent predictors of LTFU. The hope is to identify patients most at risk for being LTFU at their baseline visit and employ strategies to promote return to care.

D. Effect of primary occlusion therapy in asymmetric, bilateral amblyopia

Bilateral amblyopia, defined as BCVA of 20/40 (0.3 logMAR) or worse in both eyes, is most often a result of strabismus or refractive error in each eye, causing abnormal development of the visual cortex bilaterally.[17-19] Bilateral amblyopia is much less common than unilateral amblyopia, with an estimated prevalence of 0.5% in school-aged children[20] compared to the overall prevalence of amblyopia of 4%.[2] It is often treated as a single form of amblyopia in the

literature with regard to epidemiology and management, however it may be further subdivided into symmetric and asymmetric types. Although most children with bilateral amblyopia have similar VA in both eyes, there is a subgroup of children with 'asymmetric, bilateral amblyopia' who have an IOD of 2 lines (0.18 logMAR) or more.

Historically, bilateral amblyopia has been treated with spectacle correction. Most amblyopia research has been focused on treatment protocols for unilateral amblyopia. There have been few retrospective studies and only one prospective PEDIG study of treatment outcomes in bilateral amblyopia,[21] with no studies to-date focusing on asymmetric, bilateral amblyopia.

Given the disproportionate VA difference between eyes in asymmetric, bilateral amblyopia, there is concern that occluding the stronger - yet still amblyopic - eye could hinder its improvement. Although patching is sometimes initiated at an individual provider's discretion,[21] outcomes of glasses plus additional treatment have not been compared to outcomes of glasses alone. In our Boston Amblyopia Study database, we have found that physicians have differing approaches to managing this group of patients (i.e., 'primary occlusion' where patching commences at the time of diagnosis vs. 'secondary occlusion' where patching is initiated only after spectacle treatment has led to an improvement in the less amblyopic eye). This creates an opportunity to evaluate outcomes resulting from two different philosophies for managing the same condition. To our knowledge there has been no review of the effectiveness of these varying therapeutic methodologies.

The goal of this analysis is to utilize the Boston Amblyopia Project database to characterize the prevalence and characteristics of asymmetric, bilateral amblyopia presenting to a pediatric ophthalmology clinic and to analyze the VA outcomes of differing treatment strategies. We hope to help inform a more standardized treatment protocol in this population.

METHODS

A. Database creation

This single-center, retrospective review of amblyopia outcomes was approved by the BCH Institutional Review Board (IRB) and adhered to the tenets of the Declaration of Helsinki. Need for informed consent was waived by the IRB. We created a database of all patients diagnosed with amblyopia in our large pediatric ophthalmology practice from 2010 through 2014. Patient records were identified using ICD billing codes for amblyopia (ICD 9-368.XX). Manual review of scanned medical records was performed for these patients. Data collected from each visit included patient demographics, family history, ocular history, past amblyopia treatment, visual acuity, sensorimotor evaluation, stereopsis measurement, cycloplegic refraction, and treatment recommendation and adherence.

Best corrected visual acuity was measured by one of 16 BCH-trained orthoptists in the 2010-2014 period. Snellen, HOTV, or LEA optotypes (linear, crowding bars, or single letters) were used based on the patient's age and literacy, starting with the right eye at the first visit and the more amblyopic eye at all subsequent visits. Optotype acuity was recorded for each of the visits and the method used was adjusted over the course of the study period with the patients' educational development. If VA was tested with multiple optotypes, only the best visual acuity

was recorded. For patients with refractive error, acuity was generally re-checked after retinoscopy to ensure that the best corrected VA was recorded at first visit, though in some cases the baseline acuity may not have been recorded until the follow-up visit. Stereopsis was measured at near by Titmus fly, Randot animals and circles, the Frisby Near Stereo Test or the Lang I Stereo card, based on the patient's age and ability. The highest grade of stereopsis achieved was recorded, regardless of the test performed.

For all analyses, type of amblyopia was defined as follows: anisometropic, at least 0.5 D difference in spherical equivalent between eyes; strabismic, any degree of tropia (phorias were excluded); mixed, met definition for both anisometropic and strabismic; deprivation, diagnosis of cataract, corneal opacity, ptosis, or other pathology obstructing the visual axis; criteria not met, patients with refractive error below anisometropic threshold and no tropia.[22] These definitions overruled any ICD diagnosis coding for amblyopia subtypes. Amblyopia severity was defined as 'sub-threshold,' BCVA 20/25; mild, BCVA 20/30-20/40; moderate, BCVA 20/50-20/100; severe, BCVA >20/100.

B. IRIS7 and IRIS50 analysis

Inclusion criteria were (1) ICD 9 billing codes 368.01 (refractive amblyopia), 368.03 (strabismic amblyopia), and 368.00 (amblyopia not otherwise specified). [Deprivation amblyopia (368.02), cataract (366.XX), aphakia (379.31), pseudophakia (V41.1), amblyopia ex anopsia (368.0), and toxic optic neuropathy were excluded.]; (2) age 3-7 years; (2) newly diagnosed amblyopia (no prior treatment); (3) starting IOD <0.29 logMAR; (4) no deprivation amblyopia.[5,6]

Success by IRIS7 was defined as having IOD of <0.23 at 12-18 months, while success by IRIS50 was defined as either (1) IOD <0.23, (2) VA ≤0.18 in the affected eye, or (3) improvement in VA ≥0.18 in the amblyopic eye, all at 3-12 months.[5,6] Multiple variables were evaluated for correlation with success by both IRIS measures, including age at first visit, race, public vs. private insurance, type of amblyopia (anisometropic vs. strabismic vs. mixed), family history of amblyopia, starting VA, IOD, stereopsis, and treatment type.

P values were calculated using the Mann-Whitney U test, the Chi-square test or Fisher's exact test, as appropriate. For variables that initially emerged as correlating with success, multivariable logistic regression analysis was performed to determine independent associations between predictor variables and success. Comparison of success rate between the two IRIS measures was performed using McNemar's test for paired data. Spearman rank correlation was used to calculate how stereopsis improvement correlated with VA and IRIS success.

C. Lost-to-follow-up analysis

Inclusion criteria for LTFU analysis was all patients 2-12 years of age with amblyopia codes 368.00-368.03 (including deprivation amblyopia). Patients with and without previous treatment were included in the analysis. Those who had come for second opinion only were excluded. Patients were divided into 'LTFU' or 'return-to-care' groups. 'LTFU' was defined as any patient who did not return after the first visit, excluding those who came for second opinion only. 'Return-to-care' was defined as anyone who returned after the first visit, regardless of how many subsequent visits they attended or their adherence with treatment.

As with the IRIS analysis, multiple variables were evaluated for correlation with LTFU status, including age at first visit, race and ethnicity, public vs. private insurance, type of amblyopia (anisometropic vs. strabismic vs. mixed), family history of amblyopia, amblyopia severity, previous treatment, recommended treatment, and requested follow-up time. Continuous variables were presented using medians and interquartile ranges (IQR) while categorical data were presented as frequencies and percentages. Univariate P values were calculated using the Mann-Whitney U test, the Chi-square test or Fisher's exact test, as appropriate.

For variables that initially emerged as being associated with LTFU status, multivariable logistic regression analysis was performed to determine risk factors associated with increased odds of LTFU. Results from regression modeling were presented as adjusted odds ratios (OR) with corresponding 95% confidence intervals and P values. Receiver operating characteristic (ROC) curve analyses were performed for significant continuous predictors (age and requested follow-up time) and Youden's J Index was examined in order to determine the best cut-off value for dichotomization. The final dichotomized variables were included in a logistic regression model to calculate a multivariable risk score. Points were assigned for each variable by rounding two times the log-odds ratio (the regression coefficient) to the nearest integer. The multivariable risk score was examined for predictive performance regarding LTFU status using the area under the ROC curve (AUC). Predicted probabilities of LTFU status were determined with 95% confidence intervals using logistic regression.

D. Asymmetric, bilateral amblyopia analysis

Asymmetric, bilateral amblyopia was defined as VA ≥0.3 logMAR bilaterally, with IOD ≥0.18 logMAR. Inclusion criteria for analysis were: (1) a diagnosis of asymmetric, bilateral amblyopia, (2) age 2-12 years, and (3) objective optotype-measurement of visual acuity across all visits (including LEA 'matching'). Patients measured by Preferential Looking Test or those unable to perform objective VA measurements (too young, developmentally-delayed) were excluded. Those who were LTFU or who came for second opinion only (i.e., had only 1 visit) and those who had surgical treatment during the study period were excluded from this analysis. Additionally, patients with any other eye disease (including optic nerve disease, retinal disease, eyelid or corneal pathology causing deprivation amblyopia) as well as neurological associations were excluded.

Patients meeting inclusion criteria were divided into two groups: (1) 'primary occlusion' (patching or atropine prescribed while both eyes are amblyopic; most often initiated at first visit) and (2) 'secondary occlusion' (i.e., initiated to correct residual IOD (if applicable), only after the better eye achieved the 20/30 threshold). The primary endpoints were VA improvement in each eye, IOD and stereopsis improvement, and percentage of patients reaching IOD ≤0.18 and VA ≤0.18 in the stronger and weaker eyes. Improvement was measured between the first and last visits as well as between the first and 12-18 month visits, the latter designated as a standard follow-up interval by the AAO IRIS7 amblyopia measures.[5]

Comparisons between primary and secondary occlusion groups were performed using the Chi-square test, Fisher's exact test, or the Wilcoxon rank sum test, as appropriate. Visual acuity

data were assessed for normality using the Shapiro-Wilk test, which revealed significant skewness and departure from a Gaussian distribution for all continuous visual acuity variables within each group. Therefore, visual acuity outcomes are presented as median and interquartile range and analyzed using the non-parametric methods. The Wilcoxon rank sum test was used to analyze visual acuity data at specific measurement time points between the primary and secondary occlusion groups. Longitudinal visual acuity data were analyzed non-parametrically using the Wilcoxon signed rank test to compare first visit, 12-18-month visit, and last visit in order to take into account repeated measurements within patients. Stratified analyses were performed within type of amblyopia subgroups (anisometropic, strabismic and mixed).

For all analyses, zero stereopsis was designated as 10,000 arcsec for the purposes of logarithmic transformation.[23] All statistical analyses were performed using Stata (version 15.0, StataCorp LLC, College Station, Texas). A two-tailed alpha level of 0.05 was used to determine statistical significance, and P values were adjusted to account for multiple comparisons.

RESULTS

A. General

A total of 2037 patients aged 0-18 years were included in the database (51% male). Median age was 5.6 years (IQR 4.1 to 7.6 years). Fifty-two percent of patients reported being white, 7% African American, 4% Asian, 14% were listed as 'other,' and 23% declined to answer. Fifty-four percent of patients had private insurance, 41% had public insurance, and 5% had no insurance/self-pay. One quarter of patients reported a family history of amblyopia or strabismus. Forty percent had some previous treatment, most often glasses (88%) or patching (56%).

Regarding amblyopia subtype, 46% had pure anisometropic amblyopia, 8% had pure strabismic amblyopia, 12% were mixed (anisometropic and strabismic), 3% had deprivation amblyopia, and 22% were 'other' (did not fit any criteria). Nine percent had some other ocular comorbid condition that did not cause deprivation amblyopia. Regarding amblyopia severity, 22.5% had 'sub-threshold amblyopia' (0.1 logMAR), 38% had mild amblyopia (0.18-0.3 logMAR), 30% had moderate amblyopia (0.4-0.7 logMAR), and 9.5% had severe amblyopia (>0.7 logMAR). Median IOD among the entire cohort was 0.18 logMAR (IQR 0.08 to 0.4), and median log stereoacuity was 4.94 (IQR 4.38 to 8.01).

B. IRIS7 and IRIS50 analysis

The database for the IRIS studies included 1817 patients with the ICD 9 diagnosis codes 368.01, 368.03, and 368.00. Of these, 1226 were between the ages of 3-7 years as specified by the IRIS criteria. Nineteen percent (238/1226) met the additional IOD criteria to be analyzed by IRIS7 or IRIS50. Table 1 outlines demographics, amblyopia subtypes, baseline visual acuity measures, and treatment provided for those patients meeting IRIS inclusion criteria. Treatment was offered at the discretion of the individual provider and was generally concordant with PEDIG guidelines. At first visit, glasses were prescribed to 217 patients (91%), patching was offered to 88 (37%), and atropine to 2 (0.8%). For those who received only glasses at first visit, patching was usually prescribed at subsequent visits (81 patients at visit 2 and 12 at visit 3). For almost all patients, patching was attempted before using atropine.

Of the 238 patients meeting inclusion criteria, 168 (70.6%) had a visit recorded within 12-18 months to be analyzed for success by IRIS7, while 167 (70%) of those had a visit recorded

within 3-12 months to be analyzed for success by IRIS50. The remaining patients were either LTFU, came for second opinion, or did not return for follow-up within the required reporting timeline.

Using IRIS7 criteria, 71% of qualifying patients (119/168) had successful outcomes. Presenting age, amblyopia type, family history, and initial VA did not correlate with success, while private insurance status and better IOD and stereopsis at baseline were predictive (all $p \leq 0.01$). Prescription of atropine was negatively associated with success by IRIS7 ($p=0.013$). Multivariable logistic regression analysis identified private insurance and better IOD at baseline as the only significant independent predictors of success ($p \leq 0.023$), where the odds ratio for successful treatment based on private vs. public insurance was 4.47 (Tables 2, 3).

Using IRIS50 criteria, 81% of qualifying patients (135/167) had successful outcomes. Within this group, 66% achieved success by final IOD <0.23, 53% by final VA ≤0.18, and 65% by improvement in VA of ≥0.18 in the affected eye. (Percentages add up to >100% as many patients achieved success by multiple criteria). The same variables were analyzed to determine predictors of success by IRIS50, and none emerged as correlating with success status (Table 4).

We also evaluated how measured stereopsis correlated with VA and IOD over the treatment period. In the entire cohort of 238 patients (regardless of success status), we found moderate correlations between less IOD and better stereopsis ($r=0.4$; $p<0.0001$) and between better VA in the affected eye and better stereopsis ($r=0.5$; $p<0.0001$) for both pre- and post-treatment measurements. There was a weak correlation of less IOD and better VA with stereopsis

improvement (r=0.2; p<0.0001). After stratifying by amblyopia subtype, correlation between both IOD and VA with stereopsis was stronger for anisometropic patients (r=0.5 and 0.57, respectively, all p<0.0001). These correlations were weaker for strabismic patients (r=0.2 for both IOD and VA with stereopsis, all p=0.01) and remained the same for mixed patients (r=0.4 for IOD with stereopsis, r=0.5 for VA with stereopsis, all p<0.0001). Success status was predictive of better final stereopsis both by IRIS7 (p<0.001) and IRIS50 (p=0.005).

There was a large cohort of patients (n=147) who met all the IRIS criteria for inclusion except for having had previous treatment. These patients tended to have poorer outcomes than treatment-naïve patients, both by IRIS7 (65% success) and IRIS50 (73% success); (p=0.14). On average, previously treated patients were older than treatment-naïve patients (4.9 vs. 5.4 years, p=0.002) and had similar baseline VA and IOD (p≥0.7).

C. Lost-to-follow-up analysis

A total of 324 patients aged 2-12 years met criteria for LTFU status (failed to return after first visit), while 1072 patients returned to care, yielding a LTFU rate of 23% in this cohort. Univariate analysis demonstrated that older age at presentation, longer requested follow-up time, African American race, lack of insurance, and diagnosis of sub-threshold amblyopia were all predictive of LTFU status (all p≤0.04). Previous amblyopia treatment (glasses, patching, or atropine) was also associated with loss to follow-up. White race (vs. other) race and private (vs. public) insurance predicted return to care (Table 5).

The significant variables from univariate analysis were then analyzed in a multivariable logistic regression model to determine which were independently associated with increased odds of LTFU (Table 6). For the continuous variables, age > 6 years and follow-up time ≥ 3 months were determined to be the most significant cut-off values for predicting LTFU status. Lack of insurance was the strongest predictor of LTFU status (OR 4.26, p<0.001), followed by previous atropine treatment (OR 2.48, p=0.035), previous glasses treatment (OR 2.23, p<0.001), follow-up time ≥ 3 months (OR 1.82, p=0.001), and age > 6 years (OR 1.51, p=0.007). The final 6 independent predictors of LTFU were utilized to calculate a risk score for each patient (Table 7 and Figure 1.) A cumulative risk score of 0 conferred an 8.2% probability of LTFU, while a risk score of ≥ 5 conferred a 57.5% probability. These risk scores were examined for predictive performance regarding LTFU status; the area under the ROC curve was 0.68 (Figure 2).

D. Asymmetric, bilateral amblyopia analysis

Of all patients included in the Boston Amblyopia Study database, 167 (7.6%) met criteria for asymmetric, bilateral amblyopia. Eighteen were excluded due to age, 24 for surgical management, and 27 for loss to follow-up or second opinion only. A total of 98 patients were thus included in the analysis. Median age of presentation was 4.2 years, and median length of follow-up was 4 years. Median VA in the stronger and weaker eyes were 0.3 and 0.7 logMAR, respectively, IOD was 0.22 logMAR, and the majority of patients were stereo-blind (median log of stereopsis was 9.21). In the overall cohort, 31% had strabismic amblyopia, 22% had anisometropic amblyopia, and 35% had mixed-type amblyopia. Those who did not meet the above criteria were classified as ‘other,’ and had sub-threshold refractive error or some degree of phoria or intermittent tropia.

Treatment consisted of spectacle correction for all patients, with some providers initiating primary occlusion therapy (consisting of patching averaging 2 hours daily or atropine twice weekly to the "stronger" – yet still amblyopic – eye). Patients were equally divided between primary (n=50) and secondary (n=48) occlusion groups. In the secondary occlusion group, occlusion was initiated to correct any residual IOD (if applicable) after an initial improvement in the better eye to 20/30. Not all patients in this group eventually required patching or atropine. Patient demographics, amblyopia characteristics, and baseline VA measurements are compared between the two groups in Tables 8 and 9. There were no significant differences between groups in presenting age, race or ethnicity, insurance status, family history of amblyopia, previous amblyopia treatment, baseline VA in stronger or weaker eyes, or initial IOD (all $p \geq 0.22$). The primary occlusion group did have a higher percentage of strabismic amblyopia ($p=0.007$), while the secondary occlusion group had a higher percentage of anisometropic amblyopia ($p=0.008$). The primary occlusion group had worse stereopsis at first visit ($p<0.001$), likely due to the higher incidence of strabismic amblyopia.

Regarding optotype-based VA measurements, 33% of patients were measured using Snellen, 52% using LEA symbols, and 11% using HOTV optotypes at the initial visit, with 59% single letters, 20% crowding bars, and 21% linear. This reflects the younger age of patients at the beginning of the study period. By the last visit, 78% of patients were measured using Snellen, 15% using LEA, and 7% using HOTV, with 19% single letters, 11% crowding bars, and 70% linear. All patients who were measured by Snellen at first visit were subsequently measured only

by Snellen. This progression based on the patient's age and literacy is our standard practice for measuring VA.

Both cohorts had significant improvement in VA in each eye, IOD, and stereopsis at the 12-18 month (all $p \leq 0.001$) and last visit (all $p \leq 0.002$). There was no difference in VA, IOD, or stereopsis improvement between groups (all $p \geq 0.48$) at both time intervals; both groups achieved median VA improvement of 0.4 logMAR in weaker eye and 0.2 logMAR in stronger eye at 12-18 month and last visits, and IOD improvement of 0.18 logMAR at 12-18 month and 0.13 logMAR at last visits. At 12-18 months, the percentage of patients achieving final VA of 20/30 or better in both eyes and IOD of 1 or fewer lines was significantly higher in the secondary occlusion group (all $p \leq 0.04$) but was similar between groups at the last visit ($p \geq 0.08$). Results are reported in Tables 9 and 10. Patients self-reported strong adherence with treatment in both groups (all $p \geq 0.5$). Median adherence across all visits was 100% for glasses in both groups, 50-75% for atropine in both groups (when applicable), and 75-100% for patching in the primary occlusion group compared to 50-75% for patching in the secondary occlusion group (when applicable).

Given the significant difference in the proportion of strabismic and anisometropic amblyopes between groups, we repeated the analysis stratifying by strabismic, anisometropic, and mixed subtypes to avoid any confounding variables. The results were similar to our analysis of the entire cohort; baseline VA in both eyes and IOD were similar between groups. Differences in baseline stereopsis largely disappeared in the stratified analysis, although in anisometropic amblyopes, stereopsis in the secondary occlusion group was still slightly better than the primary

occlusion group (p=0.01). Regarding treatment outcomes, there were no significant differences in the change or absolute measurements of VA, IOD, or stereopsis between groups after stratifying by anisometropic (all p≥0.06), strabismic (all p≥0.5), or mixed amblyopia subtypes (all p≥0.08). The results are reported in Tables 11-13.

DISCUSSION

The Boston Amblyopia Project database has facilitated the assessment of amblyopia treatment outcomes in a real-world setting and has helped identify potential improvements in amblyopia management within the realm of our current treatment guidelines. This includes identifying those with risk factors for lost-to-follow-up status and classifying subgroups of patients that may be managed more effectively, such as those with asymmetric, bilateral amblyopia.

This is, to our knowledge, the first study to evaluate amblyopia treatment success based on the AAO's newly published IRIS50 criteria, and one of two based on IRIS7. West and colleagues report their IRIS7 outcomes in a cohort of 199 patients at Cincinnati Children's Hospital, finding an overall success rate of 48%. Similar to our study, investigators at Cincinnati Children's reported that baseline IOD and atropine prescription were predictive of outcomes, while age and race were not. They found no association of outcomes with insurance payer.[8] Their success rate was significantly lower as they counted those lost to follow-up as failures; when accounting for those lost to follow-up, our success rate dropped to 50% (IRIS7) and 57% (IRIS50), in line with West and colleagues.

In another recent study, Buckle et al retrospectively reviewed amblyopia outcomes of 877 patients cared for in the Gloucestershire Eye Unit, UK. They included children aged <7 years with initial VA of ≥0.3 logMAR in the affected eye; however, they did not utilize IRIS criteria in their outcome assessment. They found that at 48 weeks, 147/288 (51%) patients with severe amblyopia achieved final VA of <0.4. At 32 weeks, 386/589 (66%) patients with moderate amblyopia achieved final VA of <0.3. This takes into account those who were lost to follow-up (16% in the severe amblyopia group and 13% in the moderate amblyopia group).[24]

Our study compared both IRIS measures and found a significantly higher success rate using IRIS50. This is not unexpected, given that IRIS50 encompasses additional measures of success apart from final IOD. Specifically, IRIS50 takes into account *change* in VA, which may include patients who had denser amblyopia at baseline but nevertheless improved. The trend toward a slightly lower success rate with IRIS50 when considering only IOD criteria, if validated statistically with a larger sample size, may be explained by the longer length of follow-up for IRIS7 (12-18 months vs. 3-12 months). The lower success in the atropine group using IRIS7 criteria may have been influenced by the propensity of many of our practitioners to prescribe atropine only after patching therapy had failed due to poor adherence; thus, patients in this group may have been refractory to treatment or had lower adherence to treatment overall. A similar trend was observed in the Cincinnati study.[8] In IRIS50, insurance status and initial IOD were no longer independent predictors of success. This may be due to the shorter reporting timeline of IRIS50; an association of insurance coverage with likelihood of follow-up[25] could also be a factor. We believe that IRIS50 is a more realistic reporting measure for amblyopia outcomes than IRIS7 as it is inclusive of patients with worse VA at baseline and eliminates all independent

predictors of success. This creates a level playing field for patients and practices with different demographics and baseline visual acuities.

Overall, changes in VA and IOD correlated moderately with stereopsis, regardless of treatment success; however, as expected, patients achieving successful amblyopia treatment by either IRIS measure had better stereopsis outcomes than those not meeting success criteria. Final log of stereopsis in those successful by IRIS7 was better than in those successful by IRIS50, with lower values indicating enhanced performance (4.25 vs 4.61, $p=0.04$). This may be a result of the longer follow-up required for inclusion in IRIS7; another possibility is that final IOD, rather than VA in the affected eye, is more predictive of stereopsis. The latter hypothesis underlies current efforts to explore the efficacy of binocular treatments for amblyopia. Additional studies are warranted to more systematically assess predictors of stereopsis success in amblyopia treatment.

A major limitation of both IRIS measures is the exclusion of a large proportion of patients treated for amblyopia. Only 19% of patients in the Boston Amblyopia Project database met criteria to be included in the analysis, even after accounting for age. Groups who made up a large percentage of our database that could not be assessed by IRIS measures were those with previous treatment (147, 12%), those with bilateral amblyopia (228, 19%), and those with sub-threshold IOD (452, 37%). We believe that additional criteria should be established to allow practices to evaluate outcomes in an expanded but defined cohort of amblyopia patients.

Furthermore, the exclusion of 25% of our qualified patients who did not return within the reporting timeline, as well as the lower success rates reported by the West and Buckle studies

when accounting for LTFU status indicates that more efforts should be tailored toward improving treatment follow-up rather than improving therapy for those who do return to care. This led us to analyze the cohort of LTFU patients within our database and identify the major demographic and clinical risk factors for not returning to care, with the hope of implementing new strategies within practice to mitigate these effects.

In our LTFU analysis, a significant proportion of patients (23%) did not return to care after first visit. We found that older age at presentation, longer requested follow-up time, non-white race, lack of insurance, and previous glasses or atropine treatment were all independently predictive of loss to follow-up. Of those, lack of insurance and previous atropine prescription were the strongest predictors, conferring risk scores of 3 and 2 respectively. The presence of older age (> 6 years) as a risk factor for LTFU may be due to the perceived lack of benefit of amblyopia treatment by the provider and family at an older age. Nonetheless, this age group requires perhaps the *strongest* level follow-up and treatment adherence in order to improve vision, especially in those who were not previously treated. It is surprising that previous treatment with glasses and atropine correlated negatively with follow-up, as those seeking additional treatment from another provider would presumably be more adherent to care. However, this may also relate to the perceived lack of benefit of further treatment. Additionally, as in our IRIS analysis, poorer outcomes in those who were prescribed atropine may relate to its use as a last resort in patients who are non-adherent to other forms of occlusion therapy.

The emergence of socioeconomic characteristics as significant LTFU risk factors is unfortunately not unexpected; these factors have been identified as barriers to follow-up for

ophthalmic care in several other studies. Kemper and colleagues investigated the barriers to follow-up eye care after failed preschool vision screening, and found that those who identified as Hispanic or non-white, those with public insurance, and those with family income ≤ 200% of federal poverty level were less likely to follow up with an eye care provider.[13] Conversely, our analysis found that type of insurance (public vs. private) did not affect probability of LTFU; only *lack* of insurance was identified as an independent predictor. This may be because of the relatively generous public insurance coverage available in the state of Massachusetts, where lack of any coverage is highly unusual, as compared to in Michigan and North Carolina where the other study was conducted. Because of the retrospective nature of our database, we were unable to evaluate other related variables such as parental education level and occupation or family income for correlation with LTFU status.

Another common risk factor for LTFU status in ophthalmic treatment is lack of education about the disease process. For example, Kim and colleagues found that lack of understanding of treatment importance was predictive of LTFU status among glaucoma patients in South Korea.[16] Although we were not able to measure parental education about the importance of amblyopia treatment in our study, family history of the disease may partially serve as a proxy for this. Those who have witnessed the effects of amblyopia on the social, educational, and occupational opportunities in their family members may have a better understanding of the disease process and the importance of timely treatment. Nonetheless, family history of amblyopia did not correlate with probability of follow-up in our analysis.

We found that the only modifiable risk factor for LTFU status was requested follow-up time by provider; patients who were asked to schedule an appointment in ≥ 3 months were less likely to return to care. Although 2-3-month follow-up intervals are recommended by PEDIG preferred practice guidelines,[26] providers may consider shortening this interval for those who have other LTFU risk factors.

Based on our analysis, we have created a risk score calculator for predicting probability of LTFU in new patients presenting to an academic pediatric ophthalmology practice. Although the AUC for this model (0.68) is below the pre-designated target of 0.7 for distinguishing between LTFU and return-to-care patients, this risk score may serve as a useful preliminary tool for providers seeking to identify patients most at risk for loss to follow-up. Additional efforts may be made at the first visit to help engage patients and families with amblyopia treatment, such as improved education about the disease process, consultation with a social worker or case manager, decreased follow-up time intervals, and use of appointment reminders.

In addition to describing our real-world outcomes in the most common cohort of amblyopia patients (as specified by the IRIS inclusion criteria) and identifying characteristics predictive of loss to follow-up, our database has allowed us to identify additional sub-populations that are not prioritized in the literature, such as those with asymmetric, bilateral amblyopia. Although this is a relatively rare form of the disease, we have found that many of our patients do fit into this category. Using the Boston Amblyopia Project database, we found that approximately 7.6% of amblyopes have asymmetric, bilateral amblyopia, resulting in a prevalence of 0.3% in the population (using a total amblyopia frequency of 4%).[2] This is slightly

higher than the prevalence reported in one PEDIG study, where among 113 patients with bilateral amblyopia (frequency of 0.5%), 23 had an IOD of 2 lines or more, giving a prevalence of 0.1%.[21] We believe our larger sample size provides a more accurate estimate of the disease prevalence.

Given the paucity of literature on the asymmetric, bilateral subgroup, no previous attempts have been made to propose a standardized treatment protocol. The few reviews of bilateral amblyopia treatment do not differentiate between symmetric and asymmetric types. A prospective study of bilateral amblyopia by Wallace et al found that binocular VA improved by 0.4 logMAR units after 1 year of spectacle correction. The authors did describe a subset of patients with IOD of 2 lines or more, of which about 1/4 were treated with patching or atropine (vs. spectacles alone).[21] However, the investigators did not comment on timing of occlusion therapy and comparison of VA outcomes between those with and without occlusion. Additionally, VA in that study was measured binocularly rather than with each eye separately, which makes it difficult to assess how occlusion therapy affected the stronger and weaker eyes.

In our study, we found that both primary and secondary occlusion groups improved similarly with respect to VA of both eyes as well as IOD. Overall, patients improved by about 4 lines in the stronger eye, 2 in the weaker eye, and 2 in IOD, regardless of treatment group. These results were maintained after stratifying by amblyopia subtype. The primary occlusion group had significantly worse median stereopsis at baseline (stereo-blind vs. 400 arcsec), concordant with the larger percentage of strabismic amblyopes in that cohort. Stereopsis is known to be impacted more by strabismic than anisometropic amblyopia and requires more active treatment to recover

in strabismic amblyopes.[27,28] Differences in baseline stereopsis largely disappeared with stratification by amblyopia subtype, as expected. In anisometropic amblyopia, the primary occlusion group still tended to have worse stereopsis at baseline (3000 vs 100 arcsec), but improved more and caught up to the secondary occlusion group by the final visit (70 arcsec). In strabismic amblyopes, both groups were stereo-blind at baseline and did not recover stereopsis by the final visit. The fact that we excluded those managed surgically from our analysis may have contributed to the poor stereopsis outcomes in strabismic amblyopes. Lastly, in mixed amblyopes, there was no significant difference in stereopsis at baseline or at final visit, although the secondary occlusion group tended to improve more (3000 vs 100 arcsec).

These trends in stereopsis improvement are consistent with previous reports concluding that measurable stereopsis at baseline is a positive predictor for treatment success and further stereopsis development.[27,29] Of our asymmetric, bilateral cohort, only the patients with anisometropic amblyopia in both groups and with mixed amblyopia in the secondary occlusion group recovered functional depth perception (defined as 100 arcsec or less). This is consistent with our cohort's overall poor stereopsis at baseline. The reason for the slightly enhanced improvement in the secondary occlusion group must be explored further, but may be related to increased time of binocular experience for the period when no occlusion was prescribed.

Outcomes were compared both between the first and last visits and the first and 12-18 month visits, as visit numbers and length of follow-up varied between patients. Consistent with this, we found that most improvement occurred by the 12-18-month visit. For both primary and secondary occlusion groups, 100% of the VA improvement in the weaker eye and 100% of the

IOD improvement occurred in the first 12-18 months. However, only about 50% of the total improvement in the stronger eye occurred during the first 12-18 months. This did not differ between the primary and secondary occlusion groups, and thus occlusion is not likely responsible for prolonging improvement in the stronger eye. However, the fact that the proportion of patients achieving 20/30 or better in both eyes and IOD of 1 or fewer lines was higher in the secondary occlusion group at 12-18 months (but equalized at the last visit) may indicate overall slower improvement in the initial occlusion group, even though they ultimately improved equally.

Our results indicate that for asymmetric, bilateral amblyopia, primary occlusion therapy provides no further benefit to spectacle alone, nor does it hinder final VA improvement in the stronger eye. This may be because in the immature visual cortex in this population, the brain may not have developed a preference for one eye over another, thus extending the window of plasticity for VA improvement. This has possible implications for informing standardized treatment guidelines in asymmetric, bilateral amblyopia. Our results suggest that this population may be initially treated with glasses alone, with the addition of patching or atropine to correct any residual IOD after VA reaches 20/30 or better in at least one eye. This change in practice would save time and energy for families and providers in enforcing patching or atropine for young children. Additionally, similar to unilateral amblyopia, most of the improvement in asymmetric, bilateral amblyopia occurs in the first 18 months (assuming treatment adherence). Lastly, stereopsis improvement depends more on amblyopia subtype and measurable baseline stereopsis than treatment type.

For all analyses, results are limited by the study's retrospective nature. Visual acuity and other objective measures were entered into the database as recorded in patients' charts. Although all BCH providers are trained to follow PEDIG guidelines for VA measurement and amblyopia treatment based on patient age and ability, inherent inter-provider variability may still exist. In particular, although only patients with objective optotype-based measurements were included, the exact optotype used was subject to change over the course of the study period as patients grew older (i.e., Snellen vs. LEA). Additionally, for newly-diagnosed amblyopia patients with refractive error, the post-cycloplegic corrected visual acuity was used to establish baseline visual acuity. In cases where post-cycloplegic acuity was not measured at the first visit, the baseline acuity was that obtained at the first visit where corrected visual acuity was available, which may have underestimated the severity of amblyopia at diagnosis. We also recognize the lack of an objective measure of adherence with glasses or occlusion; adherence to glasses and occlusion therapy was reported by family members at each visit based on estimated hours per day.

In the analysis of patients with asymmetric, bilateral amblyopia, the rationale for initiating patching therapy was not known, and thus there is potential for a confounding bias in the choice of primary vs. secondary occlusion therapy. We tried to account for this by ensuring that there were no major differences in age, prior treatment, and initial VA or IOD between the groups that may have compelled a physician to initiate one approach over another. Stratification by amblyopia type was also performed for this reason. There was a larger percentage of patients whose previous treatment consisted of something other than spectacles in the primary occlusion group; although not a significant difference, we cannot rule it out as a confounding factor. Finally, stratification by amblyopia subtype resulted in small number of patients with primary

and secondary occlusion within each category. In addition to the nonparametric statistical methods used in order to analyze the non-normally distributed data, the small sample sizes limit the statistical power for detecting differences when performing statistical tests for these stratified analyses.

CONCLUSIONS AND FUTURE DIRECTIONS

Our comprehensive database of over 2000 patients with amblyopia serves as a reference for evaluating real-world amblyopia outcomes in a pediatric ophthalmology department and identifying ways to improve management in practice. Analysis of treatment success using the AAO's newly published IRIS measures found a relatively high success rate, yet accounted for only a small percentage of patients treated for amblyopia at our practice. Nonetheless, these criteria provide the first concrete measure for defining amblyopia treatment success and may lend to more efficient reporting of quality metrics for individual practices and large groups alike. It will also allow for assessment of the effectiveness of new amblyopia treatments as they emerge, such as binocular therapies. Importantly, our analysis was conducted by manual review of patient charts and largely avoided errors of mis-transciption of data and mis-categorization of diagnosis codes; thus, we believe that this study sets the benchmark out of one institution for future comparisons on a larger scale where the variables are automatically generated from electronic medical records.

The analysis of independent predictive factors of lost-to-follow-up status and creation of a risk score calculator may help establish strategies or protocols to mitigate their effects, such as reducing follow-up time intervals and providing increased education to patients and families. As

concluded in our IRIS analysis, efforts may be better focused on improving treatment follow-up rather than improving therapy for those who do return to care. Future studies that prospectively evaluate the predictive value of our LTFU risk calculator and assess the effectiveness of mitigating strategies are warranted.

Finally, unlike in many retrospective reviews that evaluate amblyopia patients possessing a defined set of criteria, the Boston Amblyopia Project database encompasses *all* amblyopia patients seen over a 5- year period in our practice. This has allowed us to survey our entire patient population and identify subgroups that are largely unrecognized within the literature. Stemming from this, we are the first to describe the nuances in management for asymmetric, bilateral amblyopia. Our retrospective study supports the treatment of asymmetric, bilateral amblyopia with spectacles alone; however, a randomized, controlled trial may be warranted to inform standardized guidelines for these patients.

We believe the findings from our comprehensive database may help augment practice efficiency and improve outcomes by providing continually updated decision support through the electronic medical record, such as identifying patients at risk for amblyopia treatment failure and loss to follow-up, as well as suggesting the most effective therapeutic option based on a patient's particular diagnosis and baseline characteristics.

DISCLOSURES: None.

FUNDING: Financial support was provided by the Children's Hospital Ophthalmology Foundation, Inc., Boston, MA.

ACKNOWLEDGEMENTS: I would like to acknowledge Suzanne Michalak, MD for help with database development and data entry, Ryan N. Chinn, BS for help with data entry and lost-to-follow-up analysis, Kaila Bishop, Ms(C) for help with data entry, and Steven J. Staffa, Ms(C) for help with all statistical analyses and models. I acknowledge David G. Hunter, MD, PhD for his role in overseeing the project.

REFERENCES

1. DeSantis D. Amblyopia. Pediatr Clin N Am. 2014;61: 505–518.
2. Wu C, Hunter DG. Amblyopia: Diagnostic and therapeutic options. Am J Ophthalmol. 2006 Jan;141(1):175-184.
3. Gopal SKS, Kelkar J, Kelkar A, Pandit A. Simplified updates on the pathophysiology and recent developments in the treatment of amblyopia: A review. Indian J Ophthalmol. 2019;67(9):1392–1399.
4. Papageorgiou E, Asproudis I, Maconachie G, Tsironi EE, Gottlob I. The treatment of amblyopia: Current practice and emerging trends. Graefes Arch Clin Exp Ophthalmol. 2019;257:1061-1078.
5. IRIS7: Amblyopia: Interocular visual acuity. AAO. 2015.
6. IRIS50: Amblyopia: Interocular visual acuity. AAO. 2019.
7. Al Jabri S, Kirkham J, Rowe FJ. Development of a core outcome set for amblyopia, strabismus and ocular motility disorders: A review to identify outcome measures. BMC Ophthalmol. 2019 Feb;19(1):47.
8. West CE, Cobb MS, White DL. Amblyopia treatment outcome assessment using AAO's IRIS-7 measure. [Abstract] J AAPOS. 2015;20:e10.
9. Epelbaum M, Milleret C, Buisseret P, Dufier JL. The sensitive period for strabismic amblyopia in humans. Ophthalmology. 1993;100:323–327.
10. 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;45:3048–3054.

11. Fronius M, Cirina L, Ackermann H, Kohnen T, Diehl CM. Efficiency of electronically monitored amblyopia treatment between 5 and 16 years of age: New insight into declining susceptibility of the visual system. Vis Res. 2014;103:11–19.
12. Zimmerman DR, Ben-Eli H, Moore B, Toledano M, Stein-Zamir C, Gordon-Shaag A. Evidence-based preschool-age vision screening: Health policy considerations. Isr J Health Policy Res. 2019 Sep 12;8(1):70.
13. Kemper AR, Uren RL, Clark SJ. Barriers to follow-up eye care after preschool vision screening in the primary care setting: Findings from a pilot study. J AAPOS. Oct 2006;10(5):476-478.
14. Dixon-Woods M, Awan M, Gottlob I. Why is compliance with occlusion therapy for amblyopia so hard? A qualitative study. Arch Dis Child. 2006;91:491–494.
15. Davis A, Baldwin A, Hingorani A, Dwyer A, Flanagan D. A review of 145,234 ophthalmic patient episodes lo to follow-up. Eye. 2017;31:422-429.
16. Kim YK, Jeoung JW, Park KH. Understanding the reasons for loss to follow-up in patients with glaucoma at a tertiary referral teaching hospital in Korea. Br J Ophthalmol. 2017;101:1059-1065.
17. Pascual M, Huang J, Maguire MG, et al. Risk Factors for Amblyopia in the Vision in Preschoolers Study. Ophthalmology. 2014 Mar;121(3):622-9.
18. Klimek DL, Cruz OA, Scott WE, Davitt BV. Isoametropic amblyopia due to high hyperopia in children. J AAPOS. 2004 August;8(4):310-3.
19. Ziylan S, Yabas O, Zorlutuna N, Serin D. Isoametropic amblyopia in highly hyperopic children. Acta Ophthalmol Scand. 2007 Feb;85(1):111-3.

20. Haase W, Muhlig HP. The incidence of squinting in school beginners in Hamburg [author's translation]. Klin Monatsbl Augenheikd. 1979;174:232–235.
21. Wallace, D, Chandler DL, Beck RW, et al. Treatment of bilateral refractive amblyopia in children three to less than 10 years of age. Am J Ophthalmol. 2007 October;144(4):487-96.
22. Tarczy-Hornoch K, Varma R, Cotter SA, et al. Risk factors for decreased visual acuity in preschool aged children. Ophthalmology. 2011 Nov;118(11):2262-2273.
23. Whitman MC, MacNeill K, Hunter DG. Bifocals fail to improve stereopsis outcomes in high AC/A accommodative esotropia. Ophthalmology. 2016 April;123(4):690-696.
24. Buckle M, Billlington C, Shah P, Ferris JD. Treatment outcomes for amblyopia using PEDIG amblyopia protocols: a retrospective study of 877 cases. J AAPOS. 2019 Apr;23(2):98.e1-98.e.
25. Cousineau MR, Kim SE, Hamilton AS, et al. Insurance coverage, and having a regular provider, and utilization of cancer follow-up and noncancer health care among childhood cancer survivors. Inquire. 2019;56:1-8.
26. Amblyopia Preferred Practice Patterns. AAO. 2017.
27. Levi DM, Knill DC, Bavelier D. Stereopsis and amblyopia: A mini-review. Vision Res. 2015;114:17-30.
28. Birch EE, Wang J. Stereoacuity outcomes after treatment of infantile and accommodative esotropia. Optom Vis Sci. 2009;86(6):647–652.
29. Birch, E. E. Amblyopia and binocular vision. Prog Retin Eye Res. 2013:67–84.

FIGURES AND TABLES

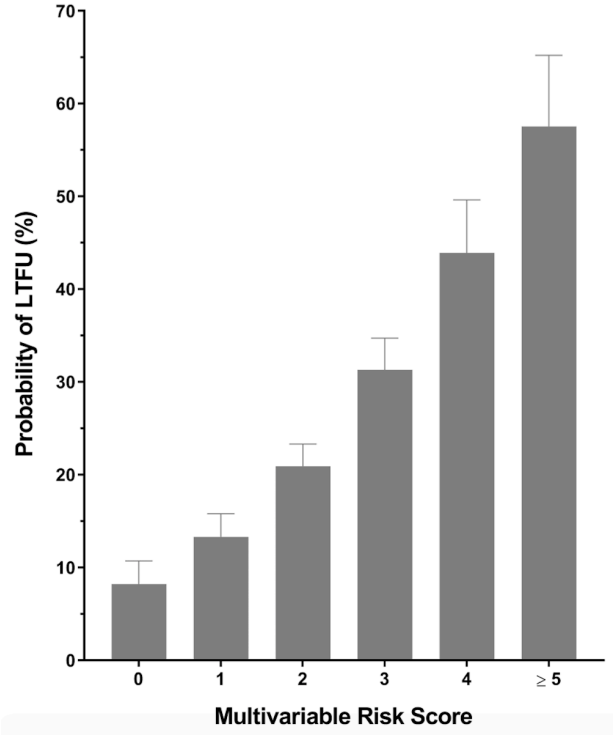

Figure 1. Probability of lost-to-follow-up status in amblyopia therapy based on multivariable risk score. The final 6 dichotomized variables that emerged as independent predictors of LTFU status were included in a logistic regression model to calculate a multivariable risk score. Points were assigned for each variable by rounding two times the log-odds ratio (the regression coefficient) to the nearest integer. See Table 7 for breakdown of risk score variables.

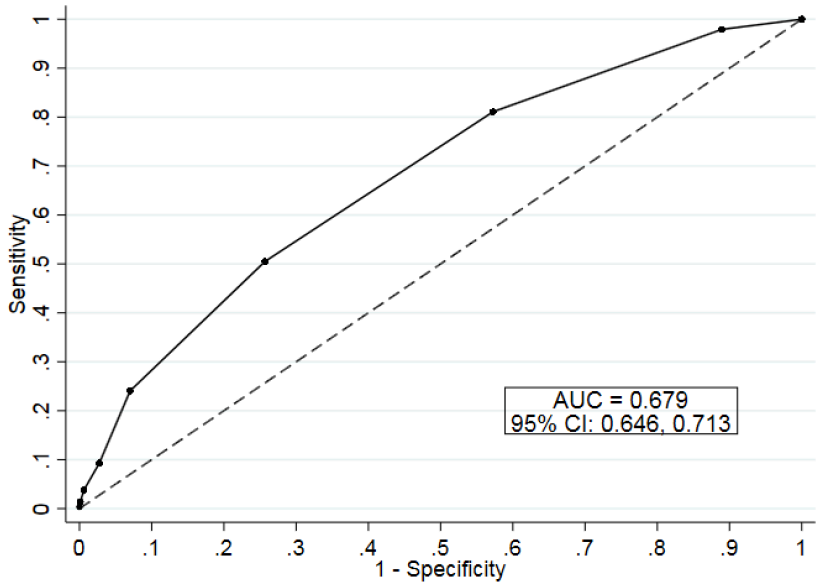

Figure 2. ROC curve for risk calculator predicting lost-to-follow-up status in amblyopia therapy. A risk score was created using the 6 variables that emerged as independent predictors of LTFU status from the multivariable logistic regression model (see Figure 1 and Table 7). The risk score was then examined for predictive performance regarding LTFU status, with an AUC of 0.68 (95% CI: 0.65-0.71). ROC=receiver operating characteristic; AUC=area under the curve.

Table 1. Demographics and visual acuity description of the entire cohort, *IRIS analysis*

Variable	n (%) or median (IQR)
N	238
Age at first visit	4.9 (4.1, 5.6)
Race	
Asian	7 (3%)
Black or African American	13 (5%)
White	144 (61%)
Other	26 (11%)
Unknown	6 (3%)
Unable/Declined to Answer	42 (18%)
Insurance Payer	
Public	71 (30%)
Private	164 (69%)
None/Self Pay	3 (1%)
Type of amblyopia	
Anisometropic	133 (56%)
Strabismic	31 (13%)
Mixed	47 (20%)
None	27 (11%)
Family history of amblyopia	73 (31%)
Starting VA in worse eye	0.6 (0.4, 0.8)
Starting IOD	0.5 (0.3, 0.7)
Starting log stereoacuity	5.99 (4.61, 9.21)
Surgery	10 (4%)
Amblyopia treatment type[a]	
Glasses	217 (91%)
Patching	90 (38%)
Atropine	5 (2%)

IQR= interquartile range

[a]Treatment refers to therapy recommended at any visit until the reporting period and was offered in concordance with PEDIG guidelines. Patching and atropine percentages are low as this cohort includes both patients who were followed until the reporting period and those who were lost to follow-up who may not have been recommended these treatments at the first visit.

Table 2. Comparison of patients with and without final success based on IRIS7

Variable	Success (n=119)	No Success (n=49)	P value
Age at first visit	4.7 (4.1, 5.5)	5.1 (4.2, 5.5)	0.16
Race			0.30
Asian	4 (3%)	3 (6%)	
Black or African American	5 (4%)	3 (6%)	
White	81 (68%)	26 (53%)	
Other	12 (10%)	4 (8%)	
Unknown	2 (2%)	2 (4%)	
Unable/Declined to Answer	15 (13%)	11 (22%)	
Insurance Payer			**<0.01***
Public	25 (21%)	24 (49%)	
Private	92 (77%)	25 (51%)	
None/Self Pay	2 (2%)	0 (0%)	
Type of amblyopia			
Anisometropic	73 (61%)	26 (53%)	0.32
Strabismic	14 (12%)	4 (8%)	0.59
Mixed	21 (18%)	13 (27%)	0.19
None	11 (9%)	6 (12%)	0.58
Family history of amblyopia	37 (31%)	15 (31%)	1.00
Starting VA in worse eye	0.5 (0.4, 0.7)	0.8 (0.5, 1)	**<0.01***
Starting IOD	0.5 (0.3, 0.6)	0.6 (0.4, 0.9)	**<0.01***
Starting log stereoacuity	5.99 (4.61, 9.21)	8.01 (5.3, 9.21)	**0.01***
Surgery	8 (7%)	4 (8%)	0.75
Amblyopia treatment type			
Glasses	110 (92%)	47 (96%)	0.51
Patching	99 (83%)	38 (78%)	0.39
Atropine	11 (9%)	12 (24%)	**0.013***
Final Log of Stereoacuity	4.25 (3.91, 5.3)	8.01 (4.61, 9.21)	**<0.01***
Change in Stereoacuity (reduction)	0.92 (0.23, 3.4)	0 (0, 1.2)	**<0.01***

Data are presented as median (interquartile range) for continuous variables and n (%) for categorical variables. P values were calculated using the Mann-Whitney U test, the Chi-square test or Fisher's exact test, as appropriate. *Statistically significant at $P < 0.05$.

Table 3. Multivariable logistic regression analysis of success based on IRIS7

Variable	Odds Ratio for Success	95% CI	P value
Insurance Payer			
Public	Reference	.	.
Private	4.47	(1.79, 11.18)	**<0.01***
None/Self Pay	Omitted – no patients without success		
Starting VA in worse eye	5.69	(0.12, 265.3)	0.37
Starting IOD	0.01	(0.001, 0.52)	**0.02***
Starting log stereoacuity	0.93	(0.75, 1.16)	0.53
Atropine treatment	0.83	(0.23, 3.02)	0.78

Variables with P < 0.05 upon univariate analysis were included in the multivariable model. CI: confidence interval. *Statistically significant at P <0.05.

Table 4. Comparison of patients with and without final success based on IRIS50

Variable	Success (n=135)	No Success (n=32)	P value
Age at first visit	4.6 (4, 5.5)	5.1 (4.2, 5.9)	0.11
Race			0.88
Asian	4 (3%)	2 (6%)	
Black or African American	9 (7%)	2 (6%)	
White	84 (62%)	18 (56%)	
Other	12 (9%)	3 (9%)	
Unknown	3 (2%)	1 (3%)	
Unable/Declined to Answer	23 (17%)	6 (19%)	
Insurance Payer			0.78
Public	35 (26%)	7 (22%)	
Private	98 (73%)	25 (78%)	
None/Self Pay	2 (1%)	0 (0%)	
Type of amblyopia			
Anisometropic	78 (58%)	20 (63%)	0.63
Strabismic	15 (11%)	2 (6%)	0.53
Mixed	25 (18%)	6 (19%)	1.00
None	17 (13%)	4 (12%)	1.00
Family history of amblyopia	37 (28%)	13 (42%)	0.13
Starting VA in worse eye	0.6 (0.4, 0.9)	0.5 (0.4, 0.7)	0.15
Starting IOD	0.5 (0.4, 0.7)	0.5 (0.4, 0.6)	0.63
Starting log stereoacuity	5.99 (4.61, 9.21)	8.01 (5.3, 9.21)	0.22
Surgery	9 (7%)	1 (3%)	0.69
Amblyopia treatment type			
Glasses	125 (93%)	30 (94%)	1.00
Patching	53 (39%)	13 (41%)	1.00
Atropine	3 (2%)	0 (0%)	1.00
Final Log Stereoacuity	4.61 (3.91, 5.99)	5.99 (4.61, 9.21)	**<0.01***
Change in Stereoacuity (reduction)	0.69 (0.22, 2.08)	0.35 (0, 1.38)	0.23

Data are presented as median (interquartile range) for continuous variables and n (%) for categorical variables. P values were calculated using the Mann-Whitney U test, the Chi-square test or Fisher's exact test, as appropriate. *Statistically significant at $P < 0.05$.

Table 5. Univariate comparison of patients with and without lost-to-follow-up status

Variable	Lost-to-follow-up (n=324)	Returned to care (n=1072)	P value
Age (years) (n=1396)	6.2 (4.5, 8.1)	5.3 (4.1, 6.5)	**<0.001***
Requested follow-up time (days) (n=1276)	90 (90, 180)	90 (60, 120)	**<0.001***
Race (n=1396)			
White	132 (41%)	565 (53%)	**<0.001***
Black/African American	36 (11%)	81 (8%)	**0.043***
Asian	15 (5%)	61 (6%)	0.576
Other	55 (17%)	157 (15%)	0.306
Declined to Answer/Unable/Unknown	86 (27%)	208 (19%)	**0.006***
Ethnicity (n=1392)			
Hispanic or Latino	45 (14%)	149 (14%)	0.999
Not Hispanic or Latino	202 (63%)	690 (65%)	0.51
Unknown	48 (15%)	154 (14%)	0.839
Declined to Answer	28 (9%)	76 (7%)	0.35
Insurance (n=1396)			
No Insurance	33 (10%)	24 (2%)	**<0.001***
Public	145 (45%)	468 (44%)	0.727
Private	146 (45%)	580 (54%)	**0.004***
Family History (n=1385)			
No	239 (74%)	749 (70%)	0.191
Yes	73 (23%)	287 (27%)	0.121
Adopted/Unknown	10 (3%)	27 (3%)	0.581
Severity of amblyopia (n=1316)			
Sub threshold	60 (20%)	105 (10%)	**<0.001***
Mild Amblyopia	71 (23%)	191 (19%)	0.1
Moderate Amblyopia	34 (11%)	154 (15%)	0.07
Severe Amblyopia	13 (4%)	58 (6%)	0.311
Does not fit criteria/likely binocular amblyopia	128 (42%)	502 (50%)	**0.016***
Type of Amblyopia (n=1396)			
Depravation Amblyopia	8 (2%)	28 (3%)	0.999
Anisometropic Amblyopia	162 (50%)	518 (48%)	0.596
Strabismic Amblyopia	23 (7%)	78 (7%)	0.914
Mixed Amblyopia	27 (8%)	109 (10%)	0.329
None	82 (25%)	247 (23%)	0.399
Has a comorbid ocular condition	22 (7%)	92 (9%)	0.302
Past Amblyopia Treatment (n=1396)			

Glasses	121 (37%)	234 (22%)	**<0.001***
Atropine/Pharmacological	15 (5%)	18 (2%)	**0.005***
Patching/Occlusion	65 (20%)	152 (14%)	**0.010***
Surgery	7 (2%)	15 (2%)	0.317
Current Amblyopia Treatment Prescribed (n=1396)			
Glasses	290 (90%)	934 (87%)	0.254
Atropine/Pharmacological	14 (4%)	41 (4%)	0.687
Patching/Occlusion	83 (26%)	310 (29%)	0.247
Surgery	4 (1%)	31 (3%)	0.107

Data are presented as median (IQR) for continuous variables and n (%) for categorical variables.
P values were calculated using the Wilcoxon rank sum test, Chi-square test, or Fisher's exact test, as appropriate.
*Statistically significant at $P < 0.05$.
Sample sizes are shown in order to depict missing data for certain variables.

Table 6. Multivariable logistic regression analysis of loss to follow-up

Variable	Odds Ratio	95% CI	P value
Age > 6 years	1.51	(1.11, 2.05)	**0.007***
Requested follow-up time ≥ 3 months	1.82	(1.26, 2.63)	**0.001***
Race			
White	0.67	(0.46, 0.98)	**0.039***
Black/African American	1.52	(0.89, 2.59)	0.128
Declined to Answer/Unable/Unknown	1.33	(0.86, 2.05)	0.197
Insurance			
No Insurance	4.26	(2.19, 8.24)	**<0.001***
Private	0.79	(0.59, 1.08)	0.147
Severity of amblyopia			
Sub threshold	1.39	(0.83, 2.31)	0.211
Does not fit criteria/likely binocular amblyopia	0.88	(0.63, 1.24)	0.471
Past Amblyopia Treatment			
Glasses	2.23	(1.53, 3.25)	**<0.001***
Atropine/Pharmacological	2.48	(1.07, 5.78)	**0.035***
Patching/Occlusion	0.6	(0.38, 0.97)	0.037

Variables that were statistically significant upon univariate analysis (Table 5) were included in the multivariable model. *Statistically significant increased odds of loss-to-follow-up at $P < 0.05$. These variables were subsequently included in the multivariable risk score. Patching/occlusion is not included as it is associated with *decreased* odds.

Table 7. Multivariable risk score for lost-to-follow-up status

Variable	Points
Age > 6 years	**+1**
Requested follow-up time ≥ 3 months	**+1**
Non-white race	**+1**
No insurance	**+3**
Past amblyopia treatment - glasses	**+1**
Past amblyopia treatment - atropine/pharmacological	**+2**

Probability of Loss-to-follow-up by risk score

Risk Score	Probability	95% CI
0	8.2%	(6.2%, 10.7%)
1	13.3%	(11.1%, 15.8%)
2	20.9%	(18.6%, 23.3%)
3	31.3%	(28.1%, 34.7%)
4	43.9%	(38.5%, 49.6%)
≥ 5	57.5%	(49.5%, 65.2%)

The 6 dichotomized variables that were statistically significant in multivariate analysis (Table 6) were included in a LTFU risk score calculator.

Table 8. Primary vs. secondary occlusion: Demographics and patient characteristics,
Asymmetric, bilateral amblyopia analysis

Variable	Primary Occlusion (n=50)	Secondary Occlusion (n=48)	P value
Age (years)	3.89 (3.12, 5.22)	4.37 (3.29, 5.67)	0.172
Sex			0.317
Female	29 (58%)	23 (48%)	
Male	21 (42%)	25 (52%)	
Race			0.373
Asian	2 (4%)	3 (6%)	
Black or African American	1 (2%)	3 (6%)	
White	31 (62%)	27 (56%)	
Other	7 (14%)	11 (23%)	
Unknown or Declined/Unable to Answer	9 (18%)	4 (8%)	
Ethnicity			0.955
Hispanic or Latino	8 (16%)	7 (15%)	
Not Hispanic or Latino	34 (68%)	34 (71%)	
Unknown or Declined to Answer	8 (16%)	7 (15%)	
Insurance Payor			0.581
Private	32 (64%)	29 (62%)	
Public	17 (34%)	18 (38%)	
International Self Payor	1 (2%)	0 (0%)	
Family History of Amblyopia	16 (33%)	17 (35%)	0.830
Prior Treatment	17 (34%)	11 (23%)	0.225
Glasses	15 (30%)	9 (18%)	0.243
Occlusion	11 (22%)	4 (8%)	0.091
Pharmacological	2 (4%)	0 (0%)	0.495
Surgical	2 (4%)	3 (6%)	0.674
Type of Amblyopia			
Deprivation Amblyopia	0 (0%)	0 (0%)	0.999
Anisometropic	9 (18%)	21 (44%)	**0.008***
Strabismic	17 (34%)	5 (10%)	**0.007***
Mixed	21 (42%)	13 (27%)	0.121
Other	3 (6%)	9 (19%)	0.068
Length of Follow-up (years)	3.37 (1.84, 5.58)	4.32 (2.04, 5.55)	0.459
Longer than 12-18 months of follow-up	40 (80%)	38 (79%)	0.918
Glasses Compliance (median across all visits)[a]	1 (1, 2)	1 (1, 1)	0.504
Patching Compliance (median across all visits)[a]	2 (1, 5)	3 (2, 4)	0.497
Atropine Compliance (median across all visits)[a]	3 (1, 5)	3 (1, 6)	0.696

Data are presented as frequency (percentage) for categorical data and median (interquartile range) for continuous data. P values are obtained using the Chi-square test, Fisher's exact test or the Wilcoxon rank sum test, as appropriate. *Statistically significant at P <0.05.

[a]Compliance is coded as 1=100%, 2=75%=100%, 3=50%-75%, 4=25%-50%, 5=1%-25%, 6=0%.

Table 9. Primary vs. secondary occlusion: Visual acuity measures at baseline, 12-18 month, and last visit, *Asymmetric, bilateral amblyopia analysis*

Variable	Primary Occlusion (n=50)	Secondary Occlusion (n=48)	P
Baseline Comparison			
Visual Acuity in Worse Eye	0.7 (0.48, 0.88)	0.6 (0.54, 0.75)	0.335
Visual Acuity in Better Eye	0.3 (0.3, 0.4)	0.4 (0.3, 0.44)	0.153
Interocular Difference	0.23 (0.18, 0.5)	0.22 (0.18, 0.3)	0.159
Log Stereopsis	9.21 (8.01, 9.21)	5.99 (4.61, 9.21)	**<0.001***
Analysis of Improvement from first to 12-18 month visit			
Change in Visual Acuity in Worse Eye	-0.38 (-0.58, -0.16)	-0.4 (-0.5, -0.3)	0.486
Change in Visual Acuity in Better Eye	-0.2 (-0.3, -0.12)	-0.22 (-0.3, -0.1)	0.756
Change in Interocular Difference	-0.18 (-0.28, 0)	-0.18 (-0.2, -0.08)	0.814
Percent achieving logMAR 0.18 or less in both eyes	12 (24%)	21 (44%)	**0.039***
Percent achieving logMAR 0.18 or less in worse eye	13 (26%)	22 (46%)	**0.041***
Percent achieving logMAR 0.18 or less in better eye	31 (62%)	27 (56%)	0.563
Percent achieving IOD 0.18 or less	21 (42%)	30 (63%)	**0.042***
Analysis of Improvement from first to last visit			
Change in Visual Acuity in Worse Eye	-0.38 (-0.6, -0.2)	-0.44 (-0.6, -0.25)	0.407
Change in Visual Acuity in Better Eye	-0.3 (-0.3, -0.12)	-0.3 (-0.35, -0.12)	0.553
Change in Interocular Difference	-0.13 (-0.2, -0.02)	-0.14 (-0.22, -0.06)	0.685
Percent achieving logMAR 0.18 or less in both eyes	22 (44%)	29 (60%)	0.104
Percent achieving logMAR 0.18 or less in worse eye	22 (44%)	29 (60%)	0.104
Percent achieving logMAR 0.18 or less in better eye	43 (86%)	36 (75%)	0.169
Percent achieving IOD 0.18 or less	29 (58%)	36 (75%)	0.075
Change in Log Stereopsis	-0.18 (-3.91, 0)	-0.92 (-1.96, 0)	0.869

Data are presented as frequency (percentage) for categorical data and median change (interquartile range) for continuous data. P values are obtained using Fisher's exact test or the Wilcoxon rank sum test, as appropriate. *Statistically significant at $P < 0.05$.

Table 10. Visual acuity improvement at 12-18 month and last visit: Entire cohort, *Asymmetric, bilateral amblyopia analysis*

Variable	First Visit	12-18 month Visit	Last Visit	P value 1[a]	P value 2[a]	P value 3[a]
Primary Occlusion (n=50)						
Visual Acuity in Worse Eye	0.7 (0.48, 0.88)	0.3 (0.18, 0.48)	0.3 (0.18, 0.48)	**<0.001***	**0.003***	**<0.001***
Visual Acuity in Better Eye	0.3 (0.3, 0.4)	0.18 (0.1, 0.18)	0.1 (0, 0.18)	**<0.001***	**<0.001***	**<0.001***
Interocular Difference	0.23 (0.18, 0.5)	0.12 (0, 0.36)	0.13 (0, 0.3)	**0.001***	0.617	**<0.001***
Log Stereopsis	9.21 (8.01, 9.21)	.	7.46 (4.61, 9.21)	**.**	**.**	**0.002***
Secondary Occlusion (n=48)						
Visual Acuity in Worse Eye	0.6 (0.54, 0.75)	0.18 (0.18, 0.3)	0.18 (0, 0.39)	**<0.001***	**0.001***	**<0.001***
Visual Acuity in Better Eye	0.4 (0.3, 0.44)	0.18 (0, 0.3)	0 (0, 0.24)	**<0.001***	**<0.001***	**<0.001***
Interocular Difference	0.22 (0.18, 0.3)	0.1 (0, 0.18)	0.1 (0, 0.19)	**<0.001***	0.674	**<0.001***
Log Stereopsis	5.99 (4.61, 9.21)	.	4.49 (3.69, 8.01)	**.**	**.**	**<0.001***

Data are presented as median (interquartile range). P values are obtained using the Wilcoxon signed rank test for paired data. *Statistically significant at $P < 0.05$.

[a]P value 1 is first vs 12-18 month visit, P value 2 is 12-18 month vs last visit, P value 3 is first visit vs last visit.

Table 11. Anisometropic amblyopes: Comparison of primary vs. secondary occlusion,
Asymmetric, bilateral amblyopia analysis

Variable	Primary Occlusion (n=9)	Secondary Occlusion (n=21)	P value
Baseline Comparison			
Visual Acuity in Worse Eye	0.7 (0.6, 0.88)	0.6 (0.54, 0.7)	0.492
Visual Acuity in Better Eye	0.4 (0.3, 0.54)	0.3 (0.3, 0.4)	0.209
Interocular Difference	0.2 (0.2, 0.24)	0.24 (0.2, 0.3)	0.553
Log Stereopsis	8.01 (8.01, 9.21)	4.61 (4.61, 6.4)	**0.010***
Last Visit Comparison			
Visual Acuity in Worse Eye	0.18 (0, 0.48)	0.1 (0, 0.3)	0.256
Visual Acuity in Better Eye	0.18 (0, 0.18)	0 (0, 0.1)	0.083
Interocular Difference	0.1 (0, 0.22)	0.08 (0, 0.1)	0.471
Log Stereopsis	4.25 (3.91, 5.29)	4.25 (3.69, 4.94)	0.682
Analysis of Improvement in Visual Acuity from First Visit to Last Visit			
Change in Visual Acuity in Worse Eye	-0.36 (-0.6, -0.3)	-0.54 (-0.7, -0.32)	0.339
Change in Visual Acuity in Better Eye	-0.36 (-0.4, -0.12)	-0.3 (-0.4, -0.3)	0.727
Change in Interocular Difference	-0.18 (-0.2, -0.04)	-0.2 (-0.3, -0.1)	0.259
Percent achieving logMAR 0.18 or less in both eyes	5 (56%)	15 (71%)	0.431
Percent achieving logMAR 0.18 or less in worse eye	5 (56%)	15 (71%)	0.431
Percent achieving logMAR 0.18 or less in better eye	7 (78%)	19 (90%)	0.563
Percent achieving IOD 0.18 or less	6 (67%)	19 (86%)	0.329
Change in Log Stereopsis	-4.10 (-4.60, -1.05)	-0.92 (-1.61, -0.36)	0.063

Data are presented as frequency (percentage) for categorical data and median change (interquartile range) for continuous data. P values are obtained using Fisher's exact test or the Wilcoxon rank sum test, as appropriate. *Statistically significant at $P < 0.05$.

Table 12. Strabismic amblyopes: Comparison of primary vs. secondary occlusion,
Asymmetric, bilateral amblyopia analysis

Variable	Primary Occlusion (n=17)	Secondary Occlusion (n=5)	P value
Baseline Comparison			
Visual Acuity in Worse Eye	0.6 (0.48, 0.7)	0.7 (0.54, 1.3)	0.356
Visual Acuity in Better Eye	0.3 (0.3, 0.3)	0.54 (0.4, 0.54)	**0.023***
Interocular Difference	0.2 (0.18, 0.4)	0.18 (0.16, 0.3)	0.603
Log Stereopsis	9.21 (9.21, 9.21)	9.21 (8.01, 9.21)	0.145
Last Visit Comparison			
Visual Acuity in Worse Eye	0.3 (0.18, 0.48)	0.48 (0.1, 0.7)	0.663
Visual Acuity in Better Eye	0.1 (0.1, 0.3)	0.4 (0, 0.48)	0.522
Interocular Difference	0.1 (0, 0.22)	0.1 (0, 0.3)	0.936
Log Stereopsis	9.21 (6.91, 9.21)	9.21 (4.61, 9.21)	0.327
Analysis of Improvement in Visual Acuity from First Visit to Last Visit			
Change in Visual Acuity in Worse Eye	-0.3 (-0.4, -0.2)	-0.38 (-0.54, -0.22)	0.666
Change in Visual Acuity in Better Eye	-0.2 (-0.3, -0.12)	-0.2 (-0.3, -0.14)	0.603
Change in Interocular Difference	-0.1 (-0.18, -0.02)	-0.14 (-0.16, -0.08)	0.999
Percent achieving logMAR 0.18 or less in both eyes	8 (47%)	2 (40%)	0.999
Percent achieving logMAR 0.18 or less in worse eye	8 (47%)	2 (40%)	0.999
Percent achieving logMAR 0.18 or less in better eye	12 (71%)	2 (40%)	0.309
Percent achieving IOD 0.18 or less	11 (65%)	3 (60%)	0.999
Change in Log Stereopsis	0 (-1.38, 0)	0 (-0.36, 0)	0.628

Data are presented as frequency (percentage) for categorical data and median change (interquartile range) for continuous data. P values are obtained using Fisher's exact test or the Wilcoxon rank sum test, as appropriate. *Statistically significant at $P < 0.05$.

Table 13. Mixed amblyopes: Comparison of primary vs. secondary occlusion,
Asymmetric, bilateral amblyopia

Variable	Primary Occlusion (n=21)	Secondary Occlusion (n=13)	P value
Baseline Comparison			
Visual Acuity in Worse Eye	0.8 (0.7, 1)	0.6 (0.54, 0.7)	0.081
Visual Acuity in Better Eye	0.3 (0.3, 0.4)	0.3 (0.3, 0.4)	0.984
Interocular Difference	0.48 (0.18, 0.6)	0.24 (0.18, 0.4)	0.112
Log Stereopsis	9.21 (8.01, 9.21)	8.01 (5.3, 9.21)	0.196
Last Visit Comparison			
Visual Acuity in Worse Eye	0.3 (0.18, 0.48)	0.18 (0.1, 0.48)	0.231
Visual Acuity in Better Eye	0 (0, 0.18)	0 (0, 0.18)	0.953
Interocular Difference	0.22 (0.1, 0.4)	0.19 (0.1, 0.2)	0.193
Log Stereopsis	8.01 (4.61, 9.21)	4.61 (3.69, 8.01)	0.084
Analysis of Improvement in Visual Acuity from First Visit to Last Visit			
Change in Visual Acuity in Worse Eye	-0.4 (-0.7, -0.2)	-0.44 (-0.52, -0.26)	0.656
Change in Visual Acuity in Better Eye	-0.3 (-0.3, -0.22)	-0.3 (-0.3, -0.12)	0.926
Change in Interocular Difference	-0.16 (-0.32, -0.04)	-0.12 (-0.18, -0.04)	0.595
Percent achieving logMAR 0.18 or less in both eyes	7 (33%)	8 (62%)	0.160
Percent achieving logMAR 0.18 or less in worse eye	7 (33%)	8 (62%)	0.160
Percent achieving logMAR 0.18 or less in better eye	21 (100%)	10 (77%)	**0.048***
Percent achieving IOD 0.18 or less	10 (48%)	9 (69%)	0.296
Change in Log Stereopsis	0 (-2.71, 0)	-1.25 (-2.08, -0.69)	0.402

Data are presented as frequency (percentage) for categorical data and median change (interquartile range) for continuous data. P values are obtained using Fisher's exact test or the Wilcoxon rank sum test, as appropriate. *Statistically significant at $P < 0.05$.