



Published in final edited form as:

JAMA Ophthalmol. 2014 July ; 132(7): 814–820. doi:10.1001/jamaophthalmol.2014.424.

Beyond Screening for Risk Factors Objective Detection of Strabismus and Amblyopia

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Abstract

IMPORTANCE—Commercially available automated vision screening devices assess refractive risk factors, not amblyopia or strabismus, underreferring affected children and overreferring healthy children. Nearly half of affected children are not identified until after age 5 years, when treatment is less effective.

OBJECTIVES—To determine the diagnostic accuracy of the Pediatric Vision Scanner (PVS), a binocular retinal birefringence scanner, to objectively identify strabismus and amblyopia, and to compare retinal birefringence screening with a widely used automated pediatric screening device.

DESIGN, SETTING, AND PARTICIPANTS—Three hundred consecutive preschool children (aged 2–6 years) were screened using the PVS and the SureSight Autorefractor at 2 pediatric ophthalmology private practices. A masked comprehensive pediatric ophthalmic examination provided the gold standard for determining sensitivity and specificity for each screening device.

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Author Contributions: Mr Jost had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Birch.

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Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Jost, Birch.

Obtained funding: Yanni, Birch.

Administrative, technical, or material support: Yanni, D. Stager, Dao.

Study supervision: Yanni, Birch.

Conflict of Interest Disclosures: None reported.

Previous Presentations: This study was presented, in part, at the annual meeting of the American Association for Pediatric Ophthalmology and Strabismus; April 6, 2013; Boston, Massachusetts, and annual meeting of the Association for Research in Vision and Ophthalmology; May 9, 2013; Seattle, Washington.

Additional Information: The US Food and Drug Administration determined that the Pediatric Vision Scanner has an Investigational Device Exemption under 21 CFR 812.2(b) for devices with a nonsignificant risk.

MAIN OUTCOMES AND MEASURES—The primary outcome was sensitivity and specificity of the PVS for detecting the targeted conditions, strabismus and amblyopia, in children aged 2 to 6 years. Secondary outcomes included the positive and negative likelihood ratios of the PVS for identifying the targeted conditions. In addition, sensitivity, specificity, and positive and negative likelihood ratios of the SureSight Autorefractor for the targeted conditions were assessed in the same cohort of children.

RESULTS—Of the 300 patients, 188 had strabismus only, amblyopia only, or both, and 112 had no strabismus or amblyopia. The sensitivity of the PVS to detect strabismus and amblyopia (0.97; 95% CI, 0.94-1.00) was significantly higher than that of the SureSight Autorefractor (0.74; 95% CI, 0.66-0.83). Specificity of the PVS for strabismus and amblyopia (0.87; 95% CI, 0.80-0.95) was significantly higher than that of the SureSight Autorefractor (0.62; 95% CI, 0.50-0.73).

CONCLUSIONS AND RELEVANCE—The PVS identified children with strabismus and/or amblyopia with high sensitivity, outperforming the SureSight Autorefractor. Accurate, early detection of these conditions could improve long-term vision outcomes of affected preschool children.

Amblyopia is the leading treatable cause of monocular vision loss in childhood, with a mean prevalence of 2.2% for amblyopia and 2.8% for strabismus.¹⁻⁴ Even children who make regular visits to their pediatricians may not be identified early, because the signs of amblyopia and strabismus can be subtle and preschool children may be uncooperative.⁵⁻¹² Commercially available automated screening devices assess refractive error because hyperopia and anisometropia are risk factors for strabismus and amblyopia.¹³ However, screening for refractive risk factors fails to identify many children with amblyopia or strabismus and overrefers healthy children.¹³⁻¹⁹ The consequences of not identifying and treating strabismus and amblyopia early include permanent visual impairment and adverse effects on school performance, fine motor skills, social interactions, and self-image.²⁰⁻²⁸

Recently, a prototype device designed to detect strabismus and amblyopia directly has been described.²⁹ Binocular retinal birefringence scans detect whether fixation of a target is foveal and steady in each eye by identifying the unique polarization signal created by the radially arranged Henle fibers (photoreceptor axons) that emanate from the fovea.²⁹⁻³¹ Specifically, when a circularly polarized spot of laser light is scanned as an annulus on both retinas, the differential polarization signal of the returning light results in a doubling of the input frequency. On the other hand, if the annulus does not surround each fovea due to strabismus, or if fixation is unsteady, as demonstrated in anisometropic amblyopia without strabismus,³²⁻³⁶ the doubled frequency is reduced in amplitude or absent from the returned signal. In a pilot study of children aged 2 to 18 years conducted by the team that developed the prototype retinal birefringence scanner, dubbed the Pediatric Vision Scanner (PVS; REBIScan, Inc), sensitivity was 97% and specificity was 98% for strabismus and amblyopia, suggesting that the PVS could accurately identify children who need ophthalmic care and minimize overreferral.²⁹ Since the pilot study, the bulky PVS was redesigned to be easily incorporated into routine pediatric care, with a reduced size and weight, an enhanced signal-to-noise ratio, the addition of a more child-friendly fixation target, and a “friendlier” look and feel.

The objective of this study was to independently evaluate the sensitivity and specificity of the redesigned PVS in the target preschool age range (ie, 2-6 years). In this initial study of the redesigned PVS, we sought to establish the accuracy of the PVS in identifying the targeted vision disorders, strabismus and amblyopia, in a clinical setting. For comparison, vision screening was also conducted with a device currently used by many for preschool vision screening, the SureSight Autorefractor (Welch Allyn). On the basis of the recent recommendations of Donahue et al¹³ on behalf of the American Association for Pediatric Ophthalmology and Strabismus (AAPOS) Vision Screening Committee, we evaluated the sensitivity and specificity of each screening device using a complete eye examination performed by a fellowship-trained pediatric ophthalmologist (C.L.B., D.R.S., D.S., or L.D.) as the gold standard.

Methods

Participants

Three hundred consecutive boys and girls aged 2 to 6 years scheduled for a comprehensive medical eye examination, including cycloplegic refraction, were recruited from the Pediatric Ophthalmology & the Center for Adult Strabismus (private practice in Dallas, Texas) and Pediatric Ophthalmology & Adult Strabismus (private practice in Plano, Texas) 1 or 2 mornings per week between November 22, 2010, and July 22, 2013. Children with developmental delay, retinal disease, cataract, or eye muscle surgery in the past 6 months were excluded. Clinical staff identified eligible children during their visit and invited the parent(s) to discuss the study with the researcher (R.M.J. or S.E.Y.). Written informed consent was obtained from the parent(s) before participation in the study. The research protocol was approved by the institutional review board of the University of Texas Southwestern Medical Center and conformed to the requirements of the Health Insurance Portability and Accountability Act of 1996.

Acquisition of Data

Children were tested with the PVS and, for comparison, with the SureSight Autorefractor. Test order was varied according to a random-number table. Total test time was less than 5 minutes. Screening tests were performed by a trained examiner (R.M.J. or S.E.Y.) who was unaware of the results of the gold standard ophthalmic examination. Likewise, the pediatric ophthalmologist who performed the gold standard examination was unaware of the results of the screening test.

PVS—Children sat on their own or were seated on a parent's lap. Trained research staff (R.M.J. or S.E.Y.) performed all measurements. The PVS was held 40 cm from the child. Room lights were dimmed to enhance interest in the illuminated smiley face fixation target and to increase pupil size. A background measurement was obtained with eyes closed and subtracted from subsequent readings to improve the signal-to-noise ratio. If the child would not close his or her eyes, the background measurement was obtained with the device aimed at his or her forehead, arm, or the parent's forehead. Data collection continued until 5 measurements were obtained (2.5 seconds). If 5 usable measurements could not be obtained, "unable" was recorded.

The PVS software performed a fast Fourier transform to analyze the power spectrum of the returning signals for each eye for each of the 5 scans. If more than 60% of the scans had predominantly 200 Hz power in both eyes (ie, simultaneous foveation), the child was categorized as “pass.” Otherwise, the outcome was “refer” (ie, either strabismus or amblyopia was present). This criterion was determined empirically in the developer’s pilot study.²⁹

SureSight Autorefractor—The SureSight Autorefractor was used according to the manufacturer’s instructions with the child calibration setting. Briefly, it was held approximately 35 cm from the child. Data collection continued until at least 5 usable measurements (ie, reliability score ≥ 5) were obtained for each eye. If 5 measurements with reliability scores of 5 or higher could not be obtained, a “no measurement possible” result was reported. The refractive error obtained with the SureSight Autorefractor was compared with the age-based 2013 AAPOS Vision Screening Committee Guidelines for Automated Preschool Vision Screening¹³ to classify the test result as “refer” or “pass.”

Gold Standard Examination—A complete eye examination was performed by 1 of 4 fellowship-trained pediatric ophthalmologists (C.L.B., D.R.S., D.S., or L.D.) on the same day as the screening. Gold standard examiners did not have access to screening results. The examination included monocular distance visual acuity assessment, cover testing, ocular motility, cycloplegic retinoscopy, evaluation of the anterior segment, and binocular indirect ophthalmoscopy. If the child was too young to provide monocular distance visual acuity, amblyopia was assessed by fixation preference. With the parents’ written consent, a copy of medical records for the gold standard examination of each child was obtained 1 to 2 weeks after the screening visit.

Sample Size

On the basis of previous studies conducted at the same clinical sites, we estimated that 60% of children enrolled would be affected by strabismus and/or amblyopia. A sample size of 300 patients was chosen because the expected enrollment of 175 children with strabismus or amblyopia who should have a “refer” outcome and 125 children with no strabismus or amblyopia who should have a “pass” outcome would provide adequate 95% CIs for estimating sensitivity and specificity of retinal birefringence scanning over a reasonable range of expected outcomes (ie, 95% CIs of approximately ± 0.04). Even if sensitivity or specificity were much lower than expected (eg, 0.90 or 0.80), the 95% CI would be only slightly larger, approximately ± 0.06 . Recruitment continued until the target enrollment of 300 was reached.

Primary Outcome

The primary outcome was sensitivity and specificity of the PVS for detecting the targeted conditions, strabismus and amblyopia, in children aged 2 to 6 years. Secondary outcomes included the positive and negative likelihood ratios of the PVS for detecting the targeted conditions. In addition, sensitivity, specificity, and positive and negative likelihood ratios of the SureSight Autorefractor for the targeted conditions were assessed in the same cohort of children.

Statistical Analysis

At the screening, eligibility characteristics, demographic information, and screening test order and results were recorded on a data form. Diagnosis of strabismus and amblyopia was extracted from the gold standard examination medical record 1 to 2 weeks after the screening visit. Children were classified as positive or negative for strabismus and/or amblyopia. Sensitivity, specificity, positive and negative likelihood ratios, and their 95% CIs were determined for each screening device. The rates of incomplete tests for the 2 screening devices were calculated as simple percentages and compared by z tests.

Results

Between November 22, 2010, and July 22, 2013, a total of 300 consecutive eligible children were enrolled in the study. The mean (SD) age was 4.1 (1.4) years; 53.0% were girls and 83.7% were white. In the cohort, 62.6% had strabismus only, amblyopia only, or both, and 37.3% had neither strabismus nor amblyopia. Details of demographics and the frequency of targeted disorders (strabismus and amblyopia) by age are summarized in Table 1. Attempts to screen were unsuccessful for 1 child with the PVS and for 17 children with the SureSight Autorefractor (Table 2). Significantly fewer screening attempts were unsuccessful with the PVS than with the SureSight Autorefractor ($z = 3.8$; $P < .001$).

Sensitivity and specificity of the PVS and SureSight Autorefractor for the targeted conditions of strabismus and amblyopia are summarized in Table 3, along with 95% CIs. Sensitivity of the PVS to detect strabismus and amblyopia (0.97) was significantly higher than that of the SureSight Autorefractor (0.74). Screening errors are summarized in Table 4. By the gold standard examination, the PVS failed to detect 1 of 131 strabismic children (0.8%) and 5 of 115 amblyopic children (4.3%). In comparison, the SureSight Autorefractor failed to detect 37 of 121 strabismic children (30.6%) and 17 of 104 amblyopic children (16.3%). Of the affected children, 37 of 44 (84.1%) who passed the SureSight Autorefractor screening were strabismic with a normal refractive error.

Specificity of the PVS for strabismus and amblyopia (0.87) was significantly higher than that of the SureSight Autorefractor (0.62). False positives (12.6%) for the PVS included 7 children who had abnormal refractive errors in 1 or both eyes and 7 who had a normal refractive error. SureSight Autorefractor false positives (38.4%) included 28 children with an abnormal refractive error and 15 with a normal refractive error.

Because the current study was based in a clinic setting with a cohort enriched with affected children, statistical inference must be used to predict the performance of the screening devices in the general population. Therefore, positive and negative likelihood ratios for each screening device are also provided in Table 3. Positive likelihood ratios describe how many more times a “refer” result is likely to be observed in children with the target disorders than in unaffected children.³⁷ The positive likelihood ratio of 7.7 for a “refer” outcome by the PVS was significantly higher than that for the Sure Sight Autorefractor and represents a moderate, but not conclusive, increase in the likelihood that the child has strabismus or amblyopia. The positive likelihood ratio of 1.9 for the SureSight Autorefractor denotes only a minimal increase in the likelihood that the child has one of these conditions. Negative

likelihood ratios describe how many fewer times a “pass” result is likely to be observed in children with the target disorders than in unaffected children.³⁷ The negative likelihood ratio of 0.03 for the PVS was significantly lower than that for the SureSight Autorefractor and represents the low probability that a child with the targeted condition of strabismus or amblyopia will receive a “pass” outcome (ie, affected children have a high probability of being correctly identified by the PVS device). The negative likelihood ratio of 0.42 for the SureSight Autorefractor reflects a moderate probability that children affected by the targeted conditions will be missed by SureSight Autorefractor screening.

Discussion

Preschool vision screening with a binocular retinal birefringence scanning device, the PVS, had high sensitivity (0.97) and specificity (0.87) for detecting the targeted conditions of strabismus and amblyopia. The PVS outperformed screening for refractive risk factors using the SureSight Autorefractor, which had 8.8 times as many false negatives and 3.1 times as many false positives as the PVS.

Overall, PVS sensitivity to the targeted conditions did not differ from the 97% reported for the prototype PVS device, but specificity was significantly lower.²⁹ This may be due to the age inclusion criterion of 2 to 6 years in the present study, while more than 50% of the participants in the prototype study were aged 7 to 18 years. Nonetheless, the PVS accurately identified 91.9% of children with anisometric amblyopia in the absence of measurable strabismus and overreferred only 3 anisometric children with orthophoria and no amblyopia. The sensitivity of the PVS to anisometric amblyopia reported here matches that reported for the prototype.²⁹ Many children with anisometric amblyopia have fixation instability, but anisometropia alone does not have this association.³²⁻³⁶ As suggested by Loudon et al,²⁹ the fixation instability that characterizes anisometric amblyopia may be sufficient to reduce or eliminate the retinal birefringence signal detected by the PVS. Moreover, anisometropia in the absence of amblyopia will not disrupt the retinal birefringence signal.²⁹

The success rate for PVS screening was more than 99%, which was significantly higher than the SureSight Autorefractor’s 94.3% success rate in the same cohort. Success rates for SureSight Autorefractor preschool screening of 76% to 89% in private practice and laboratory settings have been reported by numerous authors.³⁷⁻³⁹ On the other hand, in multisite vision preschool screening studies, much higher SureSight Autorefractor success rates (>99%) have been described.^{16,40}

One limitation of the present study is that fixation preference was used to diagnose amblyopia in some of the youngest members of the study cohort who were unable to cooperate with monocular distance visual acuity testing. Fixation preference is a less than ideal method to identify the presence or absence of amblyopia, particularly among children with orthotropia or microtropia.⁴¹⁻⁴⁷ In our cohort, 37 children (12.3%) had amblyopia diagnosed by fixation preference (5 amblyopic and 32 nonamblyopic), of whom 21 also had strabismus and, therefore, would have been categorized as affected by one of the targeted conditions regardless of the determination of visual acuity. Removing the remaining 16

children (2 amblyopic and 14 nonamblyopic) from the analysis of PVS sensitivity and specificity results in no change in sensitivity (0.97; 95% CI, 0.94-1.00) but a small improvement in specificity (0.88; 95% CI, 0.80-0.96).

A second limitation is that the present study was conducted in a clinical setting, with a cohort enriched in children affected by the targeted conditions of strabismus and amblyopia; therefore, this study cannot directly assess the performance of the PVS in a primary care screening setting. Nonetheless, calculation of the positive and negative likelihood ratios allowed us to compare the screening utility of the PVS and the SureSight Autorefractor. This analysis suggested that the use of the PVS in a screening setting would significantly change our knowledge of the probability that a child is affected by one of the targeted conditions. In comparison, use of the SureSight Autorefractor to screen children can provide only a minimal change in the probability that a child is affected by the targeted conditions. While the results of the likelihood ratio analysis are promising, the PVS needs further study in primary care settings before recommendations can be made about its regular use in that setting. Currently, we are evaluating the performance of the PVS in the setting of well-child visits at a private group pediatric practice.

One consequence of conducting this study in a clinical setting was that many of the children screened during a routine follow-up visit initially had been diagnosed with strabismus and/or amblyopia some time before. Therefore, it is possible that their strabismus and/or amblyopia had characteristics that differed from those typically seen in a screening setting or an initial office visit due to duration of the disease or to previous treatment. However, limiting the analysis to only the 56 children who were screened during their initial visit to the pediatric ophthalmologist, following a failed school or pediatric screening or due to parental concerns, provided estimates of sensitivity and specificity for both the PVS (sensitivity, 0.95 [95% CI, 0.83-1.00]; specificity, 0.86 [95% CI, 0.72-1.00]) and SureSight Autorefractor (sensitivity, 0.80 [95% CI, 0.52-1.00]; specificity, 0.64 [95% CI, 0.44-0.84]) that were similar to those derived from the entire study cohort.

The PVS does not calculate refractive error, which might be considered a disadvantage, but measurement of refractive error is not needed for the detection of amblyopia or strabismus. Devices such as the SureSight Autorefractor that do detect refractive error are more likely to generate false positives. By not detecting refractive error, false-positive referrals are reduced. No known medical harm comes from a lack of detecting nonamblyogenic refractive errors. Nonetheless, some have argued that it may be better to refer and treat all children with risk factors before amblyopia and strabismus develop.¹⁵

Because devices that screen for refractive risk factors cannot directly detect strabismus or amblyopia, children determined to be “at risk” due to a refractive error typically are referred by their primary care physician to an eye care professional for a comprehensive examination, with regularly scheduled follow-up visits, even though only 9% to 18% may eventually develop strabismus or amblyopia.^{13,14,17,48} The rationale for retinal birefringence screening with the PVS device is quite different. Namely, it is a simple, quick test that can be used to refer only affected children to eye care professionals or screen children at regular intervals in a primary care setting to provide early and accurate identification of those who

develops strabismus or amblyopia. This strategy is in keeping with the 2013 AAPOS Vision Screening Committee recommendation that vision “screening should be viewed as a continuous process that occurs throughout visual development, beginning in infancy. We anticipate that vision screening of children will take place at several times during the formative years.”^{13(p5)}

Conclusions

The failure to detect amblyopia during early childhood, when treatment may be most effective, is a serious public health problem. Amblyopia is the leading cause of monocular vision loss in children.^{49,50} Retinal birefringence scanning with the PVS is a novel approach that provides direct detection of strabismus and amblyopia, rather than the common approach of indirectly assessing refractive risk factors. The PVS is quick and simple to use, allows a long working distance (40 cm) that is comfortable for preschool children, provides an objective result of “pass” or “refer,” and is more accurate than risk factor assessment.

Acknowledgments

Funding/Support: This work was supported by grant 9491 from the Thrasher Research Fund and by grant EY022313 from the National Institutes of Health National Eye Institute.

Role of the Sponsors: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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Table 1
Demographics and Frequency Distribution of Targeted Disorders (Strabismus and Amblyopia) by Age

Characteristic	Age, y					Total, No. (%)
	2	3	4	5	6	
Female sex, No.	24	40	29	32	34	159 (53.0)
Hispanic ethnicity, No.	3	12	8	9	5	37 (12.3)
Race, No.						
White	38	53	51	59	50	251 (83.7)
African American	0	6	3	4	4	17 (5.7)
Asian	4	6	2	4	6	22 (7.3)
Pacific Islander	0	1	0	0	0	1 (0.3)
American Indian	0	0	1	2	0	3 (1.0)
1 Race	0	1	1	1	1	4 (1.3)
Unknown	0	1	0	0	1	2 (1.0)
Targeted disorder, No.						
Strabismus only ^a	14	23	13	12	11	73 (24.3)
Amblyopia only ^a	7	11	10	13	16	57 (19.0)
Both ^a	2	10	18	15	13	58 (19.3)
Neither ^a	19	24	17	30	22	112 (37.3)
Total, No. (%)	42 (14.0)	68 (22.7)	58 (19.3)	70 (23.3)	62 (20.7)	300 (100)

^aPatients with no previous treatment: strabismus only, n = 6; amblyopia only, n = 9; both, n = 5; and neither, n = 36.

Table 2
Unsuccessful Attempts to Screen With Each Device

Characteristic	Age, y					Total, No. (%)
	2	3	4	5	6	
No. of attempts	42	68	58	70	62	300 (100)
PVS, No.	1	0	0	0	0	1 (0.3) ^a
SureSight Autorefractor, No.	3	2	3	5	4	17 (5.7)

Abbreviation: PVS, Pediatric Vision Scanner.

^a $P < .001$ compared with the SureSight Autorefractor.

Table 3
Sensitivity and Specificity of the Screening Devices for Detection of Strabismus and Amblyopia

Characteristic	Result ^a
PVS Test result, positive/negative	
Strabismus, amblyopia, or both	183/5
Neither	14/97
Sensitivity	0.97 (183/188)
95% CI	0.94-1.00
Specificity	0.87 (97/111)
95% CI	0.80-0.95
Positive likelihood ratio	7.7
95% CI	4.1-14.4
Negative likelihood ratio	0.03
95% CI	0.01-0.09
SureSight Autorefractor test result, positive/negative	
Strabismus, amblyopia, or both	127/44
Neither	43/69
Sensitivity	0.74 (127/171)
95% CI	0.66-0.83
Specificity	0.62 (69/112)
95% CI	0.50-0.73
Positive likelihood ratio	1.9
95% CI	1.4-2.7
Negative likelihood ratio	0.42
95% CI	0.29-0.61

Abbreviation: PVS, Pediatric Vision Scanner.

^aData are given as number/number unless otherwise noted.

Table 4
Screening Errors by Gold Standard Examination Diagnoses and Cycloplegic Refraction^a

Characteristic	PVS	SureSight Autorefractor
False negative		
Strabismus	0 [73]	27 (40.3) [67]
Anisometropic amblyopia	3 (8.1) [37]	5 ^b (14.7) [34]
Bilateral amblyopia	1 (5.0) [20]	2 (12.5) [16]
Strabismus + amblyopia	1 (1.7) [58]	10 (18.5) [54]
Total	5 (2.7) [188]	44 (25.7) [171]
False positive		
Hyperopia	0	0
Myopia	2	1
Astigmatism	2	17
Anisometropia	2	7
Astigmatic anisometropia	1	3
Normal	7	15
Total	14 (12.6) [111]	43 (38.4) [112]

Abbreviation: PVS, Pediatric Vision Scanner.

^aValues are given as number (percentage) [number tested with each screening device in each diagnostic category].

^bOf the 2 children with fixation-defined amblyopia and no strabismus, the only error was a false-negative finding of anisometropic amblyopia with the SureSight Autorefractor.