NCT Number: NCT02536963

Study Title: Improving Quality Vision Outcomes in Managed Care Setting While Reducing Cost by Use of Accurate, Automated Screening

Document: Study Protocol

Date Created: August 2015

Objectives and Purpose

2.1 The purpose of this study is to assess the performance of the Pediatric Vision Scanner at identifying amblyopia/strabismus on children older or equal to 2 years of age, and less than 6 years of age in a busy pediatric clinic setting and to compare it to an examination comprised of visual acuity testing, stereopsis, eye alignment, and cycloplegic refraction.

2.2 The hypothesis is that the false positive rate of REBIScan is 10% or less. The proportion of patients without amblyopia or strabismus will be less than 10% of patients screened positive by the device.

- Amblyopia will be defined as a two or more line difference between the eyes or a clear fixation preference in either eye, in the presence of a known amblyogenic factor.
    - 2-3 year old: vision >20/50
    - 4 year old - vision > 20/40
    - 5 year old - vision > 20/30
- Strabismus is defined as misalignment of the eyes.

3.0 Study Design

Cohort study of children tested with the REBIScan device followed by a vision examination.

The data will be collected using one PVS device during the child's regularly scheduled examination or on a single examination on another day at a pediatric center within the KP system. The additional examination following PVS will consist of an eye examination by a pediatric ophthalmologist. Parents and patients will be given the opportunity to complete all of the study testing during their initial visit.

4.0 Device Information

4.1 Description of Device

The Pediatric Vision Scanner is a binocular scanner, which detects fixation in both eyes simultaneously. It detects fixation of the human eye remotely by scanning the eye with an annulus of low-intensity, polarized laser light. Previous studies have shown that it is capable of detecting strabismus in children as young as 2 years of age. Additional studies showed it could detect amblyopia in apparently straight-eyed subjects due to the high accuracy of fixation detection. REBIScan has built hand-held prototypes for clinical testing.

To allow easy operation, the PVS was equipped with a simple two-button interface and binary red-light/green light output. The device displays a binocularity score to indicate the accuracy of fixation on an internal target. A binocularity score of 60% and above (with 2 green lights) gives a "pass" recommendation; lower binocularity (with one or two red lights) results in a "refer" recommendation.

For PVS data collection, the child will be seated approximately 40 cm from the instrument fixation target. Room lights will be dimmed to enhance interest in the illuminated target and to increase pupil size. A background measurement will be obtained with eyes closed, and subtracted from subsequent readings to improve the signal to noise ratio. Data collection will last between 2.5 and 5 seconds of attention to the fixation target. Results will be recorded on the data form, but the patient, parents, and ophthalmologists will not be informed of the results.

The PVS can be operated by lay users, but some training is required, and it is possible that some individuals may have difficulty following the protocol. The Contact PI has extensive experience training users of all backgrounds in use of the device. Regular site visits by REBIScan study personnel will ensure that testing is being performed according to instruction and allow for correction of any observed problems.

In the event that meaning of the results is conveyed to a participant, caregivers, or providers, the participant will be excluded from the study and recruitment will continue until at least 300 participants who are eligible for analysis have been tested.

4.2 IND/IDE Number

The FDA has determined that the Pediatric Vision Scanner is a non-significant risk (NSR) device because it does not meet the definition of a significant risk (SR) device under § 812.3(m) of the investigational device exemptions (IDE) regulation (21 CFR 812). As a result, an IDE application is not required to be submitted to, or approved by, the FDA for a NSR study.

4.3 Device Supplier Information

During Phase II, REBIScan will provide one unit upon study commencement, and will have a second device available for use, if necessary and mutually agreed upon, by study personnel.

5.0 Selection and withdrawal of subjects

5.1 Inclusion Criteria

Children who present to the pediatric clinic will be invited to participate in the study if they are aged older or equal to 2 years of age, and less than 6 years of age.

5.2 Exclusion Criteria

- Developmental delay or cognitive deficit
- Visually obvious ocular conditions that would warrant specialist referral

- The PVS is designed to identify patients requiring referral to a specialist for evaluation of amblyopia or strabismus. Patients with these conditions often have no external signs of an abnormality, and thus will not be referred if they are not tested. In contrast, children with, for example, ptosis, periocular masses, ocular discharge, active conjunctivitis, corneal scarring, abnormal pupils, anterior polar or total cataracts, orbital cellulitis, ocular trauma, or large-angle strabismus will need to be referred to a specialist regardless of the results of the PVS scan. For this reason there is no benefit to enrolling such patients in a study of how effective the PVS is at referring children with amblyopia and strabismus (including microstrabismus.) Each of these excludable conditions would be easily recognized by a pediatrician.

5.3 Withdrawal Criteria

If a participant is unable to complete the PVS scan due to lack of cooperation, such as refusing to open one's eyes or take further direction, then the inability to participate will be recorded, and the participant will be excluded from the study, post-hoc, and not considered a part of the 300-participant cohort.

A participant may also be excluded from the study post-hoc if study personnel vocally share results of the PVS with the participant, parent, or provider prior to the Ophthalmic Examination. General observation of device indicator lights by the participant, parent, or provider is not justification for exclusion.

Finally, a participant can be excluded post-hoc if unable to complete the ophthalmic examination.

All excluded participants will be documented in the final analysis to compare how many participants were unable to perform the screening. Post-hoc exclusions at this stage will be determined by the study coordinator prior to review of the PVS screening results.

6.0 Stratification / Descriptive Factors / Randomization Scheme

KP staff will manage all recruitment efforts for participation, as well as completing consent and data forms for all enrollees. Children who present to the pediatric clinic and meet the inclusion criteria will be invited to participate in the study until 300 participants have been enrolled and are eligible for analysis. The researcher will describe the study to their parents and obtain informed consent. The consent form will be written at a level simple enough for parents to read meaningfully and for older children to understand.

7.0 Study Agent administration or intervention and toxicity management plan

Not applicable

8.0 Assessment of efficacy and safety

The primary efficacy outcome is amblyopia, defined as as a two or more line difference between the eyes or a clear fixation preference in either eye:

- 2-3 year old: vision >20/50
- 4 year old - vision > 20/40
- 5 year old - vision > 20/30

; and/or the presence of strabismus, defined as the misalignment of the eyes.

The device is considered a non-significant risk device. As such, no risk is expected with its use.

9.0 Clinical and laboratory evaluations and study calendar

See Appendix IV, Study Workflow.

The Informed Consent, Pediatric Vision Screener (PVS) exam and Ophthalmic Exam are to be performed on the same day unless otherwise desired by the patient and/or parent/legal guardian.

	Responsibility				
	MD	MD	Tech	Tech	MD – independent
Informed Consent Discussion	X	X	X	X	
Perform Physical Examination	X	X			
Inclusion/Exclusion Criteria Review	X	X	X	X	
CRF Completion & Correction	X	X	X	X	
CRF Review & Signature	X	X			
Obtain Medical History	X	X	X	X	
Ophthalmic Exam	X	X			
PVS Exam			X		
Oversight					X

Study Calendar

Month	Task
1	Work out clinical logistics and test patient flow
2	Commence subject enrollment, 1-2 days per week
6	Submit AAPOS abstract on preliminary data
20	Complete subject enrollment
20-22	Data analysis
22-24	Report to device maker and draft JAMA manuscript

10.0 Criteria for evaluation and endpoint definitions

The following results will be obtained when performing the PVS scan: Test length in seconds (time required to obtain a reliable scan), Yield, Tries and Binocular Score. Timing will begin once the study subject is in the chair and ready, and will conclude upon placing instrument down after all steps to acquire measurement have been completed.

At age 2-5, visual acuity testing is not always reliable or possible, and so the gold standard for this group for detection of amblyopia will be imperfect. However the goal of the study is to implement this screening tool in a pediatric practice in an effort to identify cases of strabismus and amblyopia at an early age, and therefore it is important to attempt screening at this age. Where possible, visual acuity testing will be used. In the absence of this, clinical judgement will be used to determine whether a patient has amblyopia, including fixation preference (if present), stereopsis testing, and cycloplegic refraction. It may be necessary to analyze the group in which visual acuity could be obtained separately from the group in which visual acuity could not be obtained, leaving the gold standard diagnosis uncertain. Future studies will be able to follow up on these patients later to determine whether they developed amblyopia or strabismus after referral. To standardize the way in which vision is tested all patients whose acuity is checked will be assessed using HOTV with crowding bar. Regarding logMAR testing, the problem is that the clinic is not currently set up with the acuity charts in logMAR mode, but all methods (LEA, HOTV, and Snellen) use the same standard sequence of 20/100, 20/80, 20/70, 20/50, 20/40, 20/30, 20/25, and 20/20.

The ophthalmic exam consisting of visual acuity, sensorimotor status (including stereopsis), color vision, and cycloplegic refraction will be performed by a pediatric ophthalmologist. The individual performing the ophthalmic exam will be masked to the PVS results. Stereopsis will be measured using the Preschool Random Dot Stereogram test (Stereo Optical), with the published norms to be used as the definition of reduced stereo:

Ages 2-3	≥400 arcsec
Ages 4-5	≥200 arcsec

The test consists of a book wth 3 pairs of pages. Each pair contains two sets of four random dot shapes (one is blank, the other three contain shapes) that can be named or matched to the easily visible black-and-white shapes on the other side of the book. Page 1 is presented first to test 200 arcsec and 100 arcsec levels of disparity. If the child is able to correctly identify two of three shapes at both of these disparity levels, Page 2 is presented next to test 60 arcsec and 40 arcsec disparity. If the child is unable to identify two of the three shapes at 200 arcsec disparity, Book 3 is presented instead to test 800 arcsec and 400 arcsec disparity. Stereoacuity is defined as the smallest disparity at which the child is able to correctly identify at least two of three shapes. Visual acuity will be measured monocularly using a standard eye chart at standard testing distance. An adhesive patch will cover one eye during acuity testing. Cover-uncover and alternate cover testing will be performed at distance and at 40 cm (the testing distance of the PVS device) by asking the subject to focus on a letter target or sticker while alternately covering

the two eyes; the observer watches for movement of the eyes as cover alternates. A cycloplegic refraction will be performed on all children.

KP study personnel will compile all data forms and KP biostatisticians will perform the statistical analysis.

Feasibility acceptance is for non-ophthalmic personnel to perform PVS testing in less than 2 minutes, and with fewer than 3 attempts, on 90% of the enrolled cohort.

11.0 Data collection and monitoring

Name, date of birth, and medical record number will be recorded on an enrollment form (see appendix), which will also include a numeric study identification code. Subject confidentiality will be maintained by utilizing this code in lieu of identifiable subject information. A study identification log will be utilized as the only link between a subject's study identification code and their identifiable information such as name and medical record number. The study identification log will be kept in a locked file accessible only to study staff for the purposes of enrolling subjects.

Data forms will be completed for each PVS screen. Key data collected include PVS binocularity score and total time spent testing. Timing will begin once the study subject is in the chair and ready, and will conclude upon placing instrument down after all steps to acquire measurement have been completed. Data acquisition procedures and collection updates will be reviewed during site visits.

Data collected on case report forms will be entered into a database periodically. The data capture screens will be designed to capture the information from the data collection case report forms. System security will be maintained by requiring user authentication to gain access to the file on the site's private secure network. Only authorized users will be permitted access to the data files. Only de-identified information will be transferred to REBIScan. All study data that was agreed to be shared with REBIScan will be given only to authorized study personnel in compliance with IRB and HIPAA requirements.

Subject Safety and Data Monitoring

Study patients will be monitored for the occurrence of events defined as any undesirable experience. Adverse events will be classified and handled according to Kaiser Permanente Standard Operating Procedures (document attached). Patients will be monitored during the day of enrollment. All adverse events will be recorded on an adverse event case report form and will include a description of all undesirable experiences, required interventions, patient's condition after the event, an estimate of the extent of injury and potential strategies to prevent future occurrences. The principal investigator will classify the relationship of the study protocol to the event. The principal investigator is responsible for reporting serious adverse events (death, life threatening, new, serious or permanent disability) to the Kaiser Permanente IRB.

12.0 Statistical considerations

This study is the second of a two-phased study. The first phase was a pilot and feasibility study to understand the utility of using the PVS device within Kaiser Permanente. This second phase is to determine the sensitivity and specificity of the device and its feasibility for widespread deployment in a primary care setting.

The collected data will generate patient demographic and clinical descriptives to describe the study population.

The outputs that will be calculated are sensitivity and specificity for detecting amblyopia or strabismus. The current published data on PVS sensitivity and specificity is 97% and 87% respectively.[Error! Bookmark not defined.] It is anticipated that sensitivity will be within 5% of the published results; that is, 92% sensitivity and 82% specificity (contained within the calculated 95% confidence intervals.) Assuming a 5% prevalence rate of the conditions, in a sample size of 300 children we anticipate 15-20 children presenting with amblyopia or strabismus; therefore we expect to identify 14-18 cases, while having no more than 45 false referrals.

13.0 Registration guideline

14.1 Recruitment

Patients will be recruited at the time of their visit. Patients may be contacted at the request of the patient or parent.

14.2 Forms and Records for Recruitment: Source Document, Informed Consent, Case Report Form

At the time of registration, two copies of a signed and dated patient Informed Consent form with Bill of Rights must be available (an original for patient's medical chart; one copy for the patient; and the other for the PI's file).

The forms and records needed for registration are:

- Source Document
- Informed Consent (1 original, 2 copies): original for patient's medical chart, one copy for the patient, one copy for the PI's file
- Case Report Form

14.0 Ethical and regulatory considerations

All institutional and Federal regulations concerning the Informed Consent form will be fulfilled. The study will be conducted in adherence to ICH Good Clinical Practice.

15.0 References

1. Hunter DG, Patel SN, Guyton DL. Automated detection of foveal fixation using retinal birefringence scanning. Applied Optics 1999;38:1273-7.
2. Hunter DG, Sandruck JC, Sau S, Patel SN, Guyton DL. Mathematical modeling of retinal birefringence scanning. J Opt Soc Am A Opt Image Sci Vis 1999;16:2103-11.
3. Guyton DL, Hunter DG, Sandruck JC, Patel SN, Fry RL, inventors; The Johns Hopkins University School of Medicine, assignee. “Eye fixation monitor and tracker”, US patent #6,027,216. 2000 22 February.
4. Loudon SJ, Rook CA, Nassif DS, Piskun NV, Hunter DG. Rapid, High-Accuracy Detection of Strabismus and Amblyopia Using the Pediatric Vision Scanner. Invest Ophthalmol Vis Sci 2011;52:5043-8.
5. Hunter DG, Shah AS, Sau S, Nassif DS, Guyton DL. Automated detection of ocular alignment using binocular retinal birefringence scanning. Applied Optics 2003;42:3047- 53.
6. Hunter DG, Nassif DS, Piskun NV, Winsor R, Gramatikov BI, Guyton DL. The Pediatric Vision Screener 1: Instrument design and operation. Journal of Biomedical Optics 2004;6:1363-8.
7. Nassif DS, Piskun NV, Gramatikov BI, Guyton DL, Hunter DG. The Pediatric Vision Screener 2: A pilot study in adults. Journal of Biomedical Optics 2004;6:1369-74.
8. Nassif DS, Piskun NV, Hunter DG. The Pediatric Vision Screener III. Detection of Strabismus in Children. Arch Ophthalmol 2006;124:509-13.
9. Jost RM, Yanni SE, Beauchamp CL, Stager DR, Stager D, Dao L, Birch EE. Beyond Screening for Risk Factors: Objective Detection of Strabismus and Amblyopia. JAMA Ophthalmology 2014; 132:814-820.
10. Jost RM, Stager Jr D, Dao L, Katz S, McDonald R, Birch E. High specificity of the Pediatric Vision Scanner in a private pediatric primary care setting. J AAPOS 2015; 19: 521-525.
11. Stewart J, Gross K, Hare F, Murphy C. Enlisting the eccentric photoscreener in a public hospital eye department. Aust N Z J Ophthalmol. 1991;19:283–290.
12. Salcido AA, Bradley J, Donahue SP. Predictive value of photoscreening and traditional screening of preschool children. J AAPOS 2005;9:114-20.
13. Arnold RW. Amblyopia Risk Factor Prevalence. J Pediatr Ophthalmol Strabismus 2013;50:213-217.
14. Tarczy-Hornoch K, Varma R, Cotter SA, et al. Risk factors for decreased visual acuity in preschool children: The multi-ethnic pediatric eye disease and Baltimore pediatric eye disease studies. Ophthalmology 2011;118:2262-73.
15. Cotter SA, Varma R, Tarczy-Hornoch K, et al. Risk factors associated with childhood strabismus: The multi-ethnic pediatric eye disease and Baltimore pediatric eye disease studies. Ophthalmology 2011;118: 2251-61.
16. Garry GA, Donahue SP. Validation of Spot screening device for amblyopia risk factors. Journal of AAPOS (2014).