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PEDIATRICS

Validation of the 2WIN Corneal Reflexes App in children

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Abstract

Purpose To test the reliability and accuracy of the 2Win Refractometer Corneal Reflexes App (CR App) in detecting manifest strabismus in pediatric patients.

Methods Prospective study involving 167 children with suspected strabismus (mean age 7.6 years; SD = 3.0, range 2–14 years) undergoing the CR App ocular alignment assessment (Pediatric Ophthalmologist) versus the alternate cover test with prism ocular alignment assessment for distance (Orthoptist) as the gold standard. The AAPOS 2013 guidelines for the detection of manifest strabismus in primary position (> 8 PD) were used.

Results Total sensitivity, specificity, PPV, and NPV for the CR App were 79.2%, 86.2%, 86.4%, and 78.9%, respectively. The overall inconclusive rate was 17.9%, but was 36.3% in children younger than 5. Sensitivity and PPV for vertical deviations were poor (33.3% and 12.5%, respectively). The accuracy of the CR App regarding the degree (in prism diopters) of manifest deviations was tested with the Wilcoxon signed rank sum test: correlation with the gold standard was good for esodeviations (p value = 0.765, not statistically significant) and poorer for exodeviations (p value = 0.056, still not statistically significant), whereas a significant difference (p value = 0.0001) was observed for vertical deviations.

Conclusion The CR App showed good sensitivity, specificity, PPV, and NPV for manifest strabismus > 8PD in accordance with the AAPOS 2013 guidelines; sensitivity and PPV were poor for vertical deviations. The accuracy of the CR App was good for horizontal deviations, but poor for vertical deviations. The inconclusive result rate was high in younger children.

Keywords 2Win refractometer (Adaptica) · CR App (Corneal Reflexes App) · Nonrefractive amblyopia risk factors · Manifest strabismus

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Key messages

- Updated guidelines regarding the magnitude of refractive error and other nonrefractive risk factors for the development of amblyopia, which should be detected using automated preschool vision screening devices, have been published (AAPOS Vision Screening Committee Guidelines 2013).
- The validity and accuracy of the 2Win (Adaptica) and PlusoptiX A12R (PlusoptiX) refractometers were recently compared with a good correlation between the two devices in accordance with AAPOS 2013 Updated Vision Screening Pass/Fail Criteria *for refractive amblyopia risks factors*.
- Adaptica also developed an infrared transmitting occluder for the measurement of intermittent and constant strabismus (by Hirschberg analysis) using a different function: the 2Win Corneal Reflexes App (CR App).
- The purpose of this paper is to test the reliability and accuracy of the 2Win CR App in detecting manifest strabismus (*nonrefractive amblyopia risk factor*) in pediatric patients.

Introduction

Photoscreeners and autorefractors are instruments designed to detect risk factors for amblyopia rather than amblyopia itself or structural ocular abnormalities [1]; updated guidelines regarding the magnitude of refractive error and other nonrefractive risk factors for the development of amblyopia, which should be detected using automated preschool vision screening devices, have been published (AAPOS Vision Screening Committee Guidelines 2013) [2].

The American Academy of Pediatrics has issued a policy statement supporting the use of these technologies for preschool vision screening [3], and the USPSTF recommends vision screening at least once in all children aged 3 to 5 years in order to detect amblyopia or its risk factors (strabismus, refractive errors, media opacity) (B recommendation) [4].

The validity and accuracy of the 2Win (Adaptica) and PlusoptiX A12R (PlusoptiX) refractometers were recently compared [5]; good correlation between the two devices was observed in accordance with AAPOS 2013 Updated Vision Screening Pass/Fail Criteria for refractive amblyopia risks factors and using cycloplegic Retinomax (Righton) measurements as the gold standard.

Adaptica also developed an infrared transmitting occluder for the measurement of intermittent and constant strabismus using a different 2Win function: the Corneal Reflexes App (CR App). The CR App comparatively analyses the position of the first Purkinje reflex [6] on three different measurements: one binocular and two with one eye occluded to visible light. The App segments the pupils and locates the Purkinje reflex within the pupil. By comparing the binocular image with the unoccluded eye, tropias can be calculated, whereas phorias can be calculated by performing a comparison with the opposite occluded eyes.

The purpose of this paper is to test the reliability and accuracy of the 2Win CR App in detecting manifest strabismus in pediatric patients.

Subjects and methods

This study was approved by the Rovereto Hospital's Ethics Committee and was conducted in accordance with the 1975 Declaration of Helsinki. The parents or guardians of all the children gave their informed consent prior to their inclusion in the study.

We prospectively included 167 children examined (first visit) for suspected strabismus at the Pediatric Opthalmology & Strabismus Clinic, Rovereto Hospital between August 2016 and March 2019; 44 bambini were aged 5 years or under (26.3%); 16 children had a developmental delay (9.5%). All the children (mean age 7.6 years; SD = 3.0; range 2–14 years) underwent an ocular alignment assessment (in primary position, Pediatric Ophthalmologist) using the 2Win CR App (*software 5.0_171018, version 24.0 from November 2016 and software 5.3 from October 2018*; Fig. 1) and using the alternate cover test with prisms for distance (in primary position, Orthoptist).

The 2Win CR App provides complete information regarding the position of corneal reflexes under different conditions (binocular and monocular vision). A black infrared occluder is included and allows the 2Win infrared rays to pass while blocking all visible light, thereby making a reliable cover test possible. Measurements are expressed either in prism diopters or degrees (video).

When a manifest asymmetry of the corneal reflexes is detected without the cover test, the output is ET: esotropia; XT: exotropia. When an asymmetry of the corneal reflexes appears

Fig. 1 The 2Win Refractometer, the Corneal Reflexes App, and the infrared occluder

under the "infrared" cover test, only the output is EP: esophoria; XP: exophoria. When a vertical deviation appears, the output follows the same rules indicated above (HT: hypertropia; IT: hypotropia; HP: hyperphoria; IP: hypophoria) (Figs. 2, 3, and 4).

Manifest or latent strabismus (horizontal and/or vertical) was also assessed with prisms and the alternate cover test while the patient fixates on a distant target (cartoon video at 5 m).

Statistical analysis

The AAPOS 2013 guidelines for the detection of manifest strabismus in primary position (> 8 PD) were used to calculate the app reliability measurements: sensitivity, specificity, positive and negative predictive values, and inconclusive result rate (%).

Mean and standard deviation were obtained for each measurement (tropias) for the 2Win CR App and the alternate cover test with prisms, respectively. The comparison between the medians obtained for the paired tests was analyzed using the Wilcoxon signed rank sum test (significant if p value $\leq$ 0.05).

Correlations were assessed by linear regression and coefficient of determination (R^2). The regression line was entered with its equation and the R^2 value, i.e., the coefficient of determination, which summarizes in a single value to what extent the manifest deviations differ on average from the regression line. R^2 can have values between 0 (no linear relationship between the two variables) and 1 (perfectly linear relationship).

All statistical analyses were performed using SAS 9.1.3 (SAS Institute Inc., Cary, NC, USA).

Results

Data were analyzed for 137 children (mean age 7.9 years; SD = 2.9, range 2–14 years).

Thirty of the 167 children examined (mean age 6.1 years; SD = 3.1 range 2–14 years) were unable to start or to complete the 2Win CR App assessment; this group of children was younger (statistical significance = 0.003); 16 children were aged 5 years or under, and 1 had developmental delay.

The overall inconclusive rate was 17.9%, but was 36.3% in children younger than 5.

Reliability

Total sensitivity, specificity, PPV, and NPV for the 2Win CR App were 79.2%, 86.2%, 86.4%, and 78.9%, respectively (Table 1).

For the *ET* deviation subgroup, sensitivity, specificity, PPV, and NPV were 88.9%, 91.6%, 87.3%, and 92.7%, respectively; for the *XT* deviation subgroup, sensitivity, specificity, PPV, and NPV were 50.0%, 100.0%, 100.0%, and 94.6%, respectively; for the *vertical* deviations subgroup, sensitivity, specificity, PPV, and NPV were 33.3%, 89.3%, 12.5%, and 96.7%, respectively.

For the specific, limited group of subjects aged 5 years or under (28 children), reliability was: sensitivity 88.9%, specificity 80.0%, PPV 88.9%, and NPV 80.0%.

Accuracy

For *ET deviations*, we observed a good correlation between the 2Win CR App and the alternate cover test with prisms for distance: R^2 value = 0.582, p value for the Wilcoxon signed rank sum test = 0.765 (not statistically significant). For *XT deviations*, we observed poorer correlation (than the ET group) between the 2Win CR App and the alternate cover test with prisms for distance: R^2 value = 0.241, p value for the Wilcoxon signed rank sum test = 0.056 (still not statistically significant). For *vertical deviations*, a poor correlation was observed: R^2 value = 0.168, p value for the Wilcoxon signed rank sum test = 0.0001 (statistically significant) (Table 2).

Graph 1 correlates the individual patient values (tropias) measured using the 2Win CR App (x-axis, X) with those measured using the cover test with prisms (y-axis, Y).

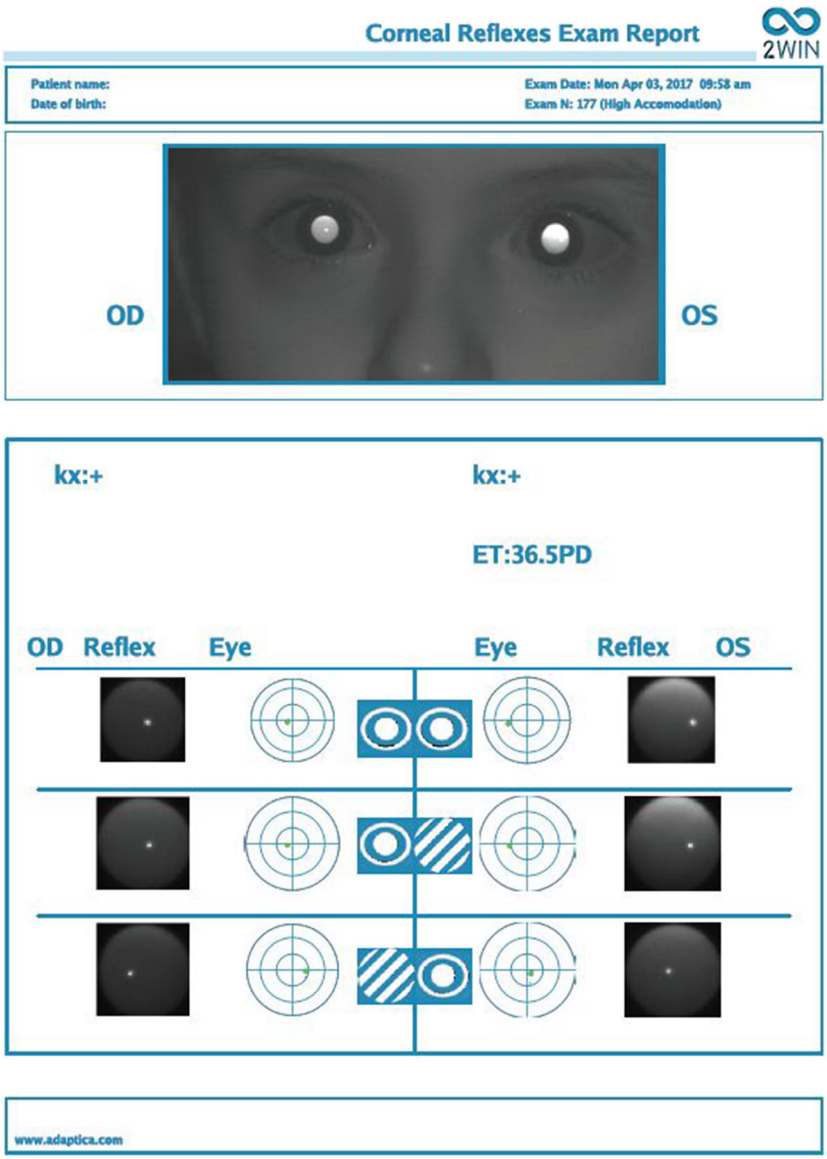


Fig. 2 The 2Win CR App printable report: left eye 36.5 PD ET

Discussion

We tested the reliability and accuracy of the 2Win (Adaptica) Corneal Reflexes App in detecting manifest strabismus in pediatric patients using the alternate cover test with prisms for distance as the gold standard.

The CR App inconclusive result rate (30 children out of 167) was 17.9% for various reasons. This group of children was younger. These children were unable to maintain stable fixation; limited eyelid opening was noted with lashes visible in the pupil field; in some cases, the pupil diameter was inadequate (Hirschberg analysis not possible); the operator experienced certain difficulties in using the black infrared occluder; excessively long acquisition times and operator problems when performing the correct image acquisition sequence were also noted; occasional software analysis abnormalities were reported.

The high number of inconclusive results in younger children (for the 5 years or under group the IR rate was 36.3%) could limit the CR App utility as a preverbal screening tool; faster image acquisition by the device and the use of a more attractive fixation target would be extremely useful. The same applies in the case of patients with developmental delays, although in our study, the IR rate for these children was 9.5%, demonstrating that age plays a more important role in correct measurement acquisition.

We observed a good correlation between the 2Win CR App measurements and those obtained with the prism cover test for distance; the application estimated large and small angle values in prism diopters.

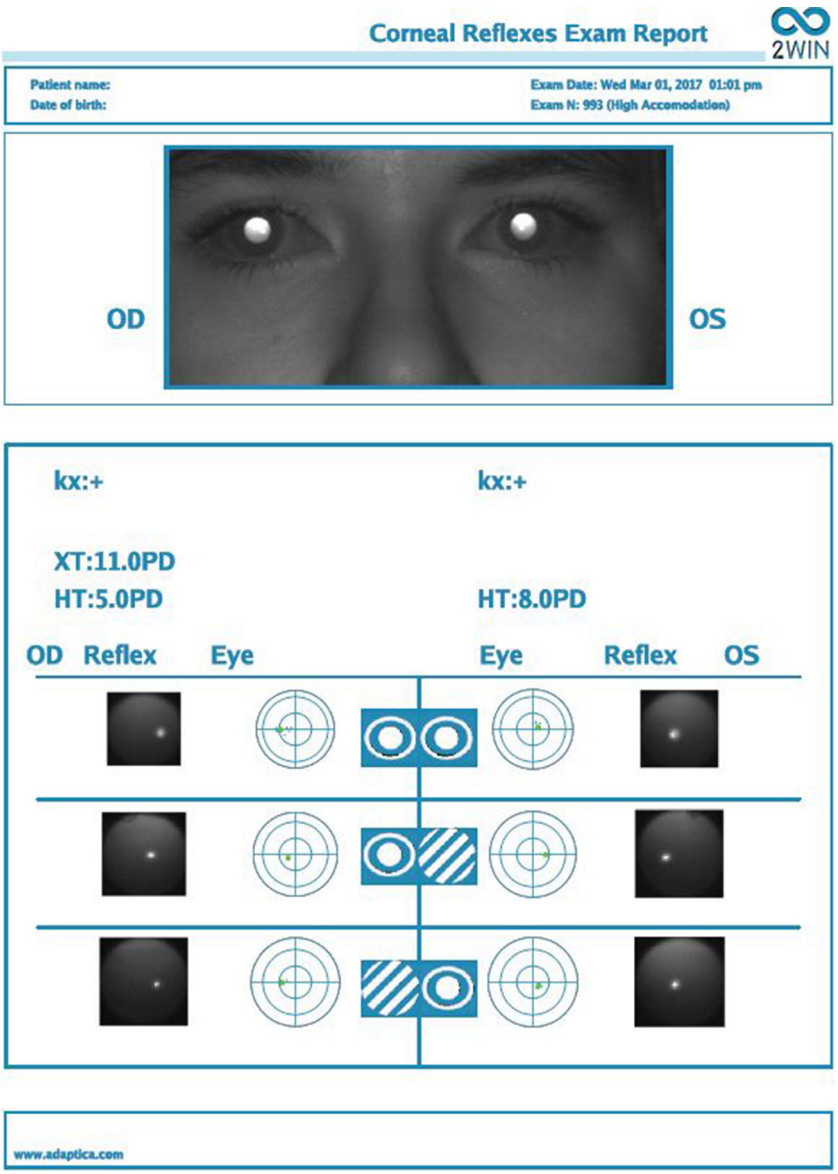


Fig. 3 The 2Win CR App printable report: right eye 11 PD XT and 5 PD HT, left eye 8 PD HT

The CR App's total sensitivity, specificity, and positive and negative predictive values were good, with ET deviations (mostly amblyogenic) having the highest rates and vertical deviations having the lowest rates. These values are in line with those reported by Peterseim et al. [7] for the Spot Vision Screener (measurement of "gaze").

The 2Win CR App was recently compared with the Rebion blinq binocular birefringent ocular alignment screener according to the 2003 AAPOS Guidelines for nonrefractive amblyopia risk factors (any manifest strabismus): the CR App's sensitivity, specificity, and PPV were 91%, 68%, and 84%, respectively, whereas the Rebion blinq's ones were 75%, 68%, and 81%, respectively [8, 9].

According to the 2013 AAPOS Updated Guidelines for nonrefractive amblyopia risk factors (manifest strabismus > 8 PD in primary position), in our study, the 2Win CR App sensitivity, specificity, PPV, and NPV are 79.2%, 86.2%, 86.4%, and 78.9%, respectively.

Although it is desirable to have tests with high sensitivity and specificity, the values for those two metrics should not be relied on when making decisions regarding individual subjects in screening situations. In this setting, use of PPVs and NPVs is more appropriate [10]. Positive predictive value (PPV) and negative predictive value (NPV), indeed, indicate the likelihood that the test can successfully identify whether people do or do not have a target condition.

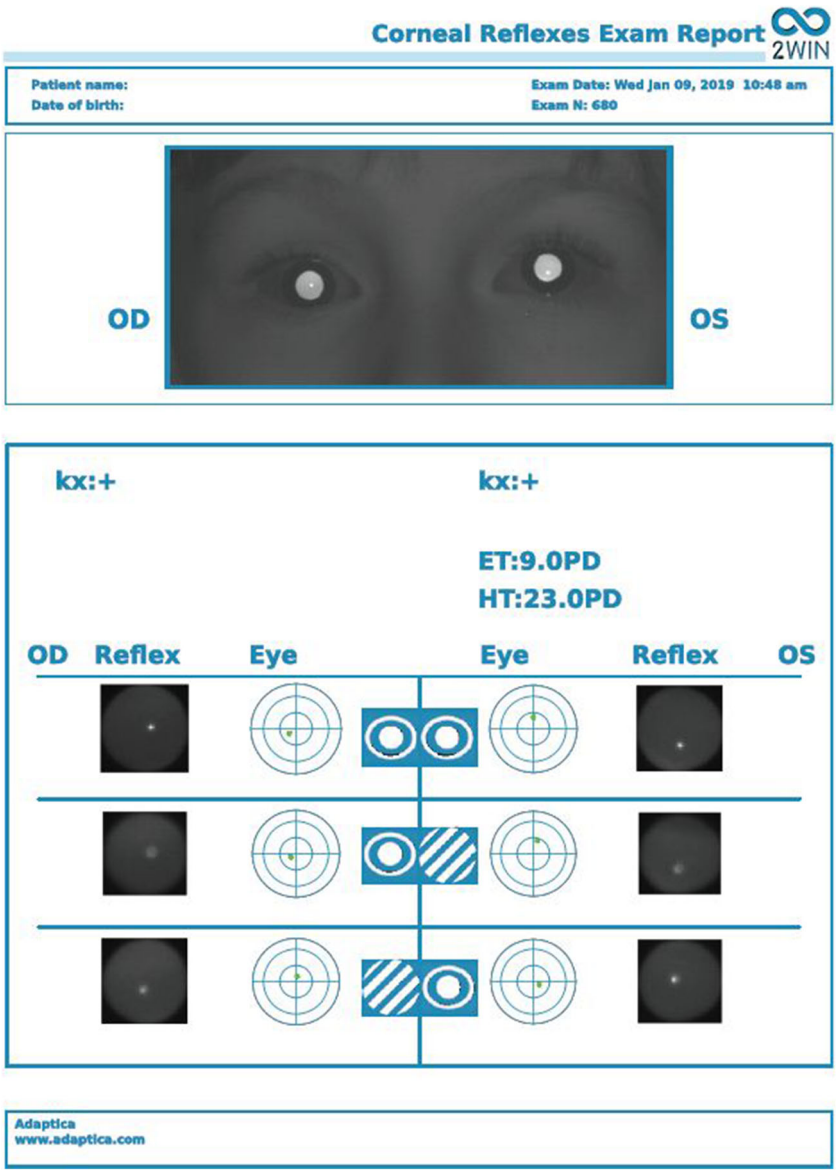


Fig. 4 The 2Win CR App printable report: left eye 9 PD ET and 23 PD HT

A PPV greater than 80% (86.2%) and a NPV of 78.9% were achieved by the CR App in an attempt to reduce false-positive referrals and restrict the number of false negatives.

The accuracy of the CR App was good for horizontal deviations, with the best correlation for ET deviations. However, for vertical deviations greater than 8 prism diopters, we observed a poor correlation with the prism cover test for

Table 1 The 2Win CR App sensitivity, specificity, positive and negative predictive values, and inconclusive results rate for manifest strabismus (> 8 PD)

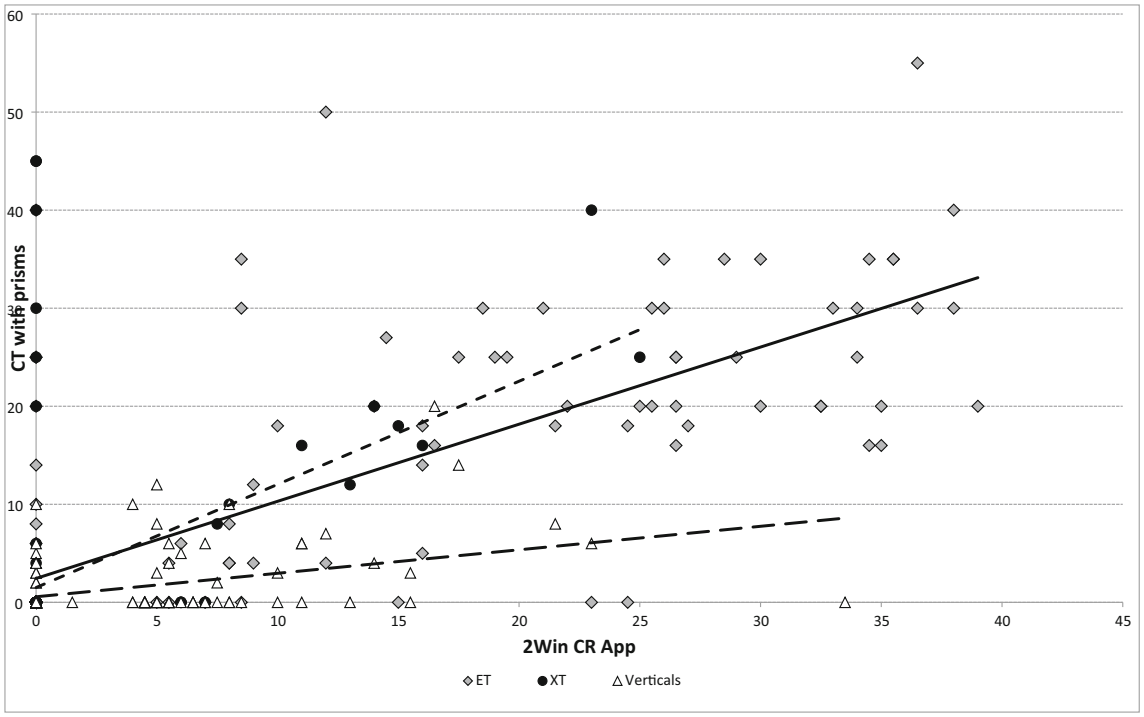
	ET	XT	Vertical deviations (IT or HT)	All deviations (total)*
Sensitivity	88.9%	50.0%	33.3%	79.2%
Specificity	91.6%	100.0%	89.3%	86.2%
PPV	87.3%	100.0%	12.5%	86.4%
NPV	92.7%	94.6%	96.7%	78.9%
Inconclusive results				17.9%

*All deviations (total) = at least one tropia > 8 PD

Table 2 Accuracy regarding the degree (in PD) of the manifest deviations

	Mean	SD	Min	Max	*p* value*
ET 2Win	10.16	13.11	0	39	0.765
ET CT	10.43	13.51	0	55	
XT 2Win	1.20	4.07	0	25	0.056
XT CT	2.77	8.72	0	45	
IT/HT 2Win	3.41	5.43	0	33.5	< 0.0001
IT/HT CT	1.39	3.18	0	20	

*Wilcoxon signed rank sum test



Graph 1 Correlation between the individual patient values (tropias) measured using the 2Win CR App (*x*-axis, X) and those measured using the cover test with prisms (*y*-axis, Y)

distance, which conflicts with the results reported in the recent article by Arnold et al. [11].

Software analysis abnormalities for vertical deviations were detected and have been corrected in the most recent version of the app. The tool now also sends the operator warnings regarding fixation, pupil diameter, and any lashes in the patient's pupil field, in order to improve measurement acquisition.

To conclude, the CR App showed good sensitivity, specificity, PPV, and NPV for manifest strabismus > 8PD in accordance with the AAPOS 2013 guidelines; sensitivity and PPV were poor for vertical deviations. The accuracy of the CR App was good for horizontal deviations, but poor for vertical deviations. The inconclusive result rate was high in younger children.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00417-020-05066-z.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were performed in accordance with the ethical standards of

the institutional review board and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from the parents (or caregivers) of all individual participants included in the study.

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