



ARTICLE

Diagnostic accuracy of an iPad application for detection of visual field defects

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BACKGROUND/OBJECTIVES: Tablet-based perimetry could be used to test for glaucomatous visual field defects in settings without easy access to perimeters, although few studies have assessed diagnostic accuracy of tablet-based tests. The goal of this study was to determine the diagnostic accuracy of iPad perimetry using the visualFields Easy application.

SUBJECTS/METHODS: This was a prospective, cross-sectional study of patients undergoing their first Humphrey Field Analyser (HFA) visual field test at a glaucoma clinic in India. Participants underwent 24-2 SITA Standard HFA testing and iPad-based perimetry with the visualFields Easy application. Reference standards for both visual field loss and suspected glaucoma were determined by ophthalmologist review of HFA results and optic disc photographs. Receiver operating characteristic curves were constructed to assess diagnostic accuracy at various test thresholds.

RESULTS: 203 eyes from 115 participants were included, with 82 eyes classified as moderate or worse glaucoma. iPad perimetry had an area under the receiver operating characteristic (AUROC) curve of 0.64 (95% CI 0.57 to 0.71) for detection of any visual field defect relative to HFA and an AUROC of 0.68 (0.59 to 0.76) for detection of moderate or worse glaucoma relative to ophthalmologist examination. At a set specificity of 90%, the sensitivity of iPad perimetry for detection of moderate or worse glaucoma was 35% (22–48%).

CONCLUSIONS: iPad perimetry using the visualFields Easy application had inadequate diagnostic accuracy to be used as a screening tool for glaucoma in this South Indian population.

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INTRODUCTION

Visual field testing is essential for the diagnosis and monitoring of glaucoma [1, 2]. The Humphrey Field Analyser (HFA) visual field test is considered the gold standard perimeter but is expensive, not portable, and not always available in low-resource settings. Visual field testing that is portable and accessible could be useful for community-based glaucoma screening events as well as screening in remote populations [3, 4]. These populations are often without easy access to an ophthalmologist or HFA, particularly in low- and middle-income countries. Several portable tests are available, including the frequency doubling technology (FDT) perimeter and Moorfields motion displacement test (MDT) [5, 6]. More recently, iPad applications such as visualFields Easy and Melbourne Rapid Fields have been developed with the goal of maximizing portability and access and minimizing cost. Though such tablet-based tests are promising in terms of increasing access to visual field testing, previous studies have shown mixed results with regards to iPad perimetry as a potential screening tool for glaucoma and other visual field defects [7–11].

In this study, we tested the diagnostic accuracy of the visualFields Easy iPad application compared to an HFA and

ophthalmologist examination reference standard in a clinic-based population in India. Our objective was to determine whether an iPad application might be useful for glaucoma screening in resource-limited and community settings.

METHODS

Ethical approval for this study was obtained by the Institutional Review Boards at the University of California, San Francisco and the Narayana Nethralaya Eye Hospital in Bangalore, India. All participants provided written informed consent, and this study adhered to the tenets of the Declaration of Helsinki.

Patients presenting as part of their routine care to the glaucoma clinic at the Narayana Nethralaya Eye Hospital between October 2014 and September 2015 were offered enrollment in this study if they met the following inclusion criteria: (i) ≥ 50 years of age, (ii) no prior diagnosis of glaucoma, and (iii) no history of taking an HFA. Inclusion criteria were chosen in an attempt to mirror a population that would most likely participate in a glaucoma screening program (i.e., older age, unknown glaucoma history, no prior perimetry experience). Patients were excluded if they had undergone intraocular surgery in the 2 weeks prior to enrollment.

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Visual fields were evaluated for each eye separately with the 24-2 SITA Standard algorithm on the HFA model 720 (Carl Zeiss Meditec Inc, Dublin, CA) using a near-distance trial lens and with visualFields Easy perimetry on an iPad 4 (Apple, Cupertino, CA) without any study-provided near correction but with habitual correction if available (white-on-white algorithm, default settings, screen set to maximum brightness). Study workers positioned study participants such that the working distance for the visualFields Easy was ~33 cm, although in practice this was difficult to enforce. visualFields Easy is a free application that implements a suprathreshold testing algorithm consisting of 48 test locations per hemifield, with a field of view of 30 degrees from fixation horizontally and 24 degrees vertically [9, 10]. To the best of our knowledge this was the only iPad perimetric software available at the time of the study. Each perimetric test was performed monocularly, without mydriasis, in a dark room (illuminance was not specifically measured). The order of testing was randomized, both for the perimetric test (i.e., HFA vs. iPad) and eye (i.e., right vs. left). A single visualFields Easy test was performed. The study protocol called for 2 reliable abnormal HFA results for staging of glaucoma. Thus, unless the first HFA was reliable and without a glaucomatous defect a second HFA was performed within 90 days of the initial test. All tests were conducted by an experienced optometric technician who was masked to the results of other glaucoma diagnostics. A masked grader counted the number of points missed from each hemifield on each test, with the number of suprathreshold points counted for visualFields Easy and the number of points at the 1% and 5% levels on the pattern deviation plot counted for the HFA.

The reference standards for the study were determined by consensus of two ophthalmologists (RLS and JDK) who had access to all HFA printouts (i.e., both HFAs for those participants who had multiple tests performed) and optic nerve photographs from both eyes. Ophthalmologist consensus was used for classification of reference standard diagnoses, both for visual field defects (classified at the hemifield-level) and glaucoma (classified at the eye-level). Visual field loss in each hemifield was classified as glaucomatous, non-glaucomatous, or no visual field defect based on HFA results, using a previously reported classification system [12]. For eyes determined to have glaucomatous visual field loss, the severity of the suspected glaucoma was graded according to a previously described 5-level staging system (none, mild, moderate, advanced, severe) [13]. While glaucoma requires longitudinal follow-up for a definitive diagnosis, for the purposes of this study the provisional diagnoses of suspected glaucoma assigned by ophthalmologist consensus were used as reference standards.

Statistical analyses were restricted to eyes with visual acuity better than 20/200 that had received the intended testing algorithm (i.e., 24-2 SITA Standard) and had reliable HFA results, defined as false positives or false negatives $\leq 33\%$ and fixation losses $\leq 20\%$. Reliability for visualFields Easy was defined in the application as false positives or false negatives $< 33\%$. The diagnostic accuracy of the visualFields Easy test for visual field defects was assessed using the number of points missed per hemifield as the index test (i.e., hemifield-level data), and the diagnostic accuracy for glaucoma was assessed using the number of points missed per eye as the index test (i.e., eye-level data). Separate analyses were performed to assess the diagnostic accuracy of visualFields Easy for detecting varying severities of glaucoma; these analyses shifted the threshold for glaucoma but did not exclude any participants. Receiver operator characteristic (ROC) curves were constructed to visualize the sensitivity and specificity at varying thresholds of the index test. Sensitivity and specificity were calculated using two different thresholds for a positive test: first, with the optimal threshold according to Youden's index (i.e., the threshold that maximized the number of correctly classified eyes), and second, with the threshold that resulted in a test with 90% specificity. Bootstrapped 95% confidence intervals (1000 replications) were calculated for estimates of diagnostic accuracy, with resampling at the person level to account for non-independence of hemifields and/or eyes. All statistical analyses were performed using R version 4.1.2 (The R Foundation for Statistical Computing).

RESULTS

The study enrolled 124 patients, of which 115 met the inclusion criteria of reliable HFA results in at least one eye and visual acuity better than 20/200 (mean [±standard deviation] age 65 ± 8 years, mean logMAR visual acuity 0.12 ± 0.16 (Snellen equivalent 20/26); 48 [42%] females) (Fig. 1). A total of 203 eyes were included in the analyses, of which 91 (45%) were classified as no glaucoma, 30

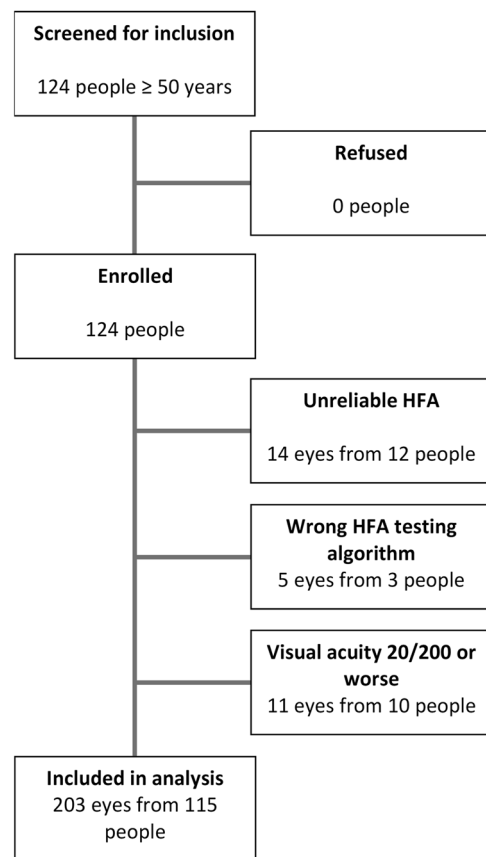


Fig. 1 Study flow. HFA Humphrey visual field analyser.

(15%) as mild glaucoma, 33 (16%) as moderate glaucoma, 25 (12%) as advanced glaucoma, and 24 (12%) as severe glaucoma. Of 406 hemifields, 180 (44%) were classified as having a glaucomatous defect, 34 (8%) a non-glaucomatous defect, and 192 (47%) no defect. Similar numbers of glaucomatous defects were found in the superior ($N = 98$) and inferior ($N = 82$) hemifields.

Of the 203 eyes tested with the visualFields Easy application, 145 (71%) had reliable results. All 203 eyes were included in the main analyses, regardless of iPad testing reliability. When assessed using hemifield-level data, the total number of points missed on the visualFields Easy test was moderately correlated with the number of points missed on HFA at the 5% level (Spearman's rho, $r_s = 0.26$, $p < 0.001$) and 1% level ($r_s = 0.31$, $p < 0.001$; Fig. 2). Similarly, when assessed using eye-level data, the number of points missed per eye on visualFields Easy was moderately correlated with the mean deviation (MD) on HFA ($r_s = 0.35$, $p < 0.001$; Fig. 2). Results were similar when restricted to the 145 eyes with a reliable visualFields Easy test (Supplementary Fig. 1).

Diagnostic accuracy was first assessed using hemifield-level data, assuming any type of visual field defect (either glaucomatous or non-glaucomatous) as the reference standard (Fig. 3). ROC curve analysis demonstrated that the visualFields Easy test provided moderate diagnostic information, with an area under the ROC curve (AUROC) of 0.64 (95% CI 0.57 to 0.71) for detection of any visual field defect. The optimal visualFields Easy test threshold according to the Youden index was ≥ 13 missed points per hemifield, providing a sensitivity of 40% (31 to 71%) and specificity of 84% (53 to 91%). If instead the threshold was defined to give 90% specificity (i.e., ≥ 19 missed points per hemifield), the resulting sensitivity declined to 22% (10 to 41%). Results were similar when the reference standard was defined as

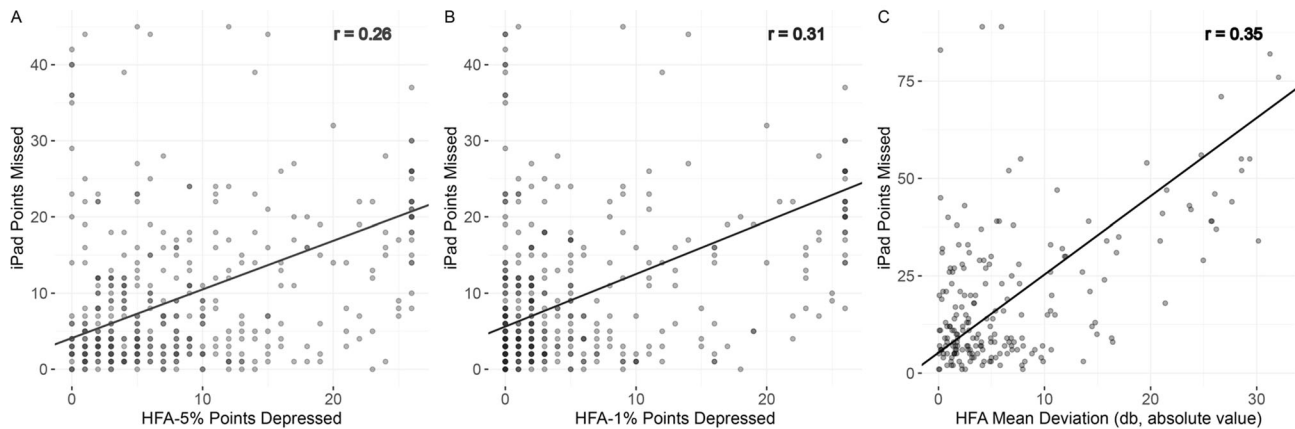


Fig. 2 Correlation between visualFields Easy and Humphrey Field Analyser (HFA). Scatter plots show the relationship between the number of points missed per hemifield on visualFields Easy with the number of points missed at the 5% (A) and 1% (B) levels per hemifield on the HFA, and the number of points missed per eye on visualFields Easy with the absolute value of the mean deviation per eye on the HFA (C). Regression lines are calculated using ranged major axis regression, which plots the geometric mean of the ordinary regression slopes for Y on X and X on Y, thus allowing for error in both axes. Spearman's rank correlation coefficient, r_s , is shown for each pairwise relationship ($p < 0.001$ in each case).

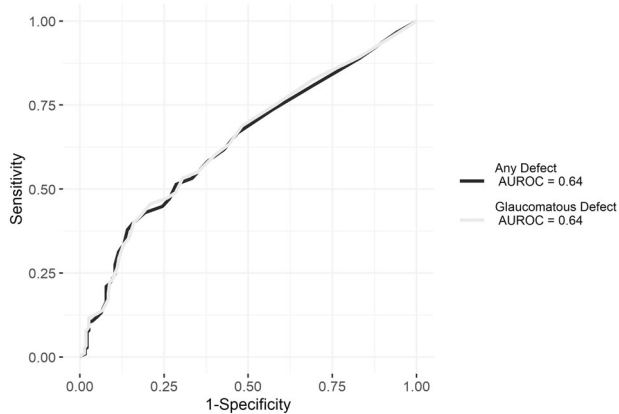


Fig. 3 Receiver operating characteristic (ROC) curves for detection of visual field defects. The ROC curve for detection of any visual field defect (purple) or glaucomatous visual field defect (gold) was plotted using the number of visualFields Easy points missed per hemifield as the index test. Ophthalmologist assessment of the relevant hemifield on the HFA printout was used as the reference standard. AUROC area under receiver operating characteristic curve.

glaucomatous defects only (Fig. 3) or when the analysis was restricted to the 290 hemifields from a reliable iPad test (Supplementary Fig. 2).

Diagnostic accuracy was also assessed at the eye level, using various levels of expert-classified glaucoma severity as the reference standard. visualFields Easy provided more diagnostic information for more advanced forms of glaucoma (Fig. 4). For example, the AUROC was 0.66 (0.58 to 0.74) for mild glaucoma, 0.68 (0.59 to 0.76) for moderate glaucoma, 0.73 (0.64 to 0.82) for advanced glaucoma, and 0.91 (0.84 to 0.96) for severe glaucoma. For detection of moderate or worse glaucoma, a threshold of ≥ 23 points missed per eye on visualFields Easy provided optimal sensitivity of 51% (95% CI 31 to 74%) and specificity of 79% (60 to 94%) according to the Youden index, and a threshold of ≥ 32 points missed per eye provided 35% sensitivity (22 to 48%) at a 90% specificity (Table 1). Accuracy was only slightly better when restricted to eyes with reliable visualFields Easy results (Supplementary Fig. 3). Diagnostic accuracy was lower for the milder forms of glaucoma when the more severe cases were excluded (Supplementary Fig. 4). Representative printouts of HFA and

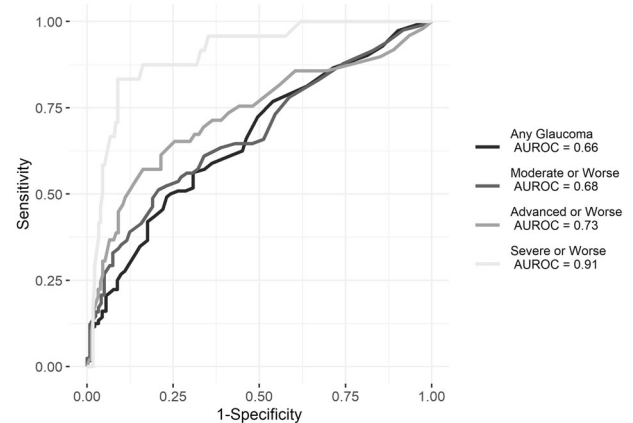


Fig. 4 Receiver operating characteristic (ROC) curves for detection of glaucoma. Glaucoma was staged using a previously reported classification system [13]. The area under the ROC curve is shown for detection of any glaucoma (purple; stages ≥ 1 vs. stage 0), moderate or worse glaucoma (blue; stages ≥ 2 vs. stages < 2), advanced or worse glaucoma (green; stages ≥ 3 vs. stages < 3), or severe or worse glaucoma (yellow; stages ≥ 4 vs. stages < 4), with the number of visualFields Easy points missed per eye. Ophthalmologist-determined glaucoma staging of the relevant eye was used as the reference standard; ophthalmologists had access to the HFA printouts and optic nerve photographs of both eyes. AUROC area under receiver operating characteristic curve.

visualFields Easy tests for eyes across the spectrum of glaucoma are shown in Supplementary Fig. 5.

DISCUSSION

As the global burden of glaucoma increases, understanding the diagnostic capabilities of inexpensive and portable perimeters is critical for earlier detection and limiting disease progression. This study explored the utility of the tablet-based perimetry application visualFields Easy to detect visual field defects and glaucoma. In this study, the number of points missed on an iPad application was moderately correlated with the number of points missed on HFA. The tablet-based perimeter had moderate accuracy for identifying visual field defects relative to HFA and moderate accuracy for identifying glaucoma relative

Table 1. Diagnostic accuracy of visualFields Easy iPad perimetry relative to the Humphrey field analyser.

Reference standard definition	Num/Total ^a	Optimal sensitivity/specificity			Constrained to 90% specificity		
		Pts ^b	Sensitivity	Specificity	Pts ^b	Sensitivity	Specificity
Hemifield-level defect							
Any defect	214/406	13	40% (31–71%)	84% (53–91%)	19	22% (10–41%)	91% (90–93%)
Glaucomatous defect	180/406	12	46% (34–75%)	79% (48–88%)	19	23% (11–39%)	90% (90–94%)
Eye-level glaucoma stage							
Mild or worse	112/203	20	49% (38–83%)	77% (41–88%)	33	27% (14–41%)	90% (90–94%)
Moderate or worse	82/203	23	51% (31–74%)	79% (60–94%)	32	35% (22–48%)	90% (90–94%)
Advanced or worse	49/203	28	57% (43–83%)	84% (61–94%)	34	45% (26–63%)	91% (90–94%)
Severe or worse	24/203	34	83% (43–100%)	91% (72–95%)	34	83% (50–96%)	91% (90–94%)

^aNumber with the reference standard classification over the total number of observations.

^bThe number of points that define the test threshold; a positive test is greater than or equal to the listed number of points.

to an ophthalmologist's assessment of the HFA results and optic nerve imaging. Ultimately, the sensitivity and specificity observed in this clinic-based setting in South India did not provide convincing evidence to support the use of visualFields Easy as a screening test for glaucoma.

Screening tests with low specificity result in a high proportion of false positive tests, which may over-burden a health care system. In this study, we set the threshold for the tablet-based visual field test based on the assumption that a screening program would be willing to accept a test with 90% specificity for detection of any visual field defect (i.e., 10% of those without disease would falsely test positive). At such a threshold, the sensitivity of visualFields Easy for detecting a visual field defect was 22%, and the sensitivity for detecting moderate or worse glaucoma was only 35%. In other words, if 1000 people were screened, of whom 2% truly had moderate or worse glaucoma, then only 7 of 105 with a positive test result would in reality have glaucoma, while 13 people who did in fact have glaucoma would be missed by the test. This level of sensitivity is probably not high enough to be considered as a meaningful screening test given that it would miss approximately two-thirds of those with moderate or worse glaucoma. Sensitivity improved when used as a test for advanced glaucoma, although even in this case over half of those with advanced glaucoma would be missed (sensitivity 45%).

Prior studies have also examined the performance of various tablet-based perimetry applications in the detection of glaucoma. The diagnostic performance of the visualFields Easy application in this study was similar to that of a clinic-based study in North India, which reported an AUROC of 0.71 (95% CI 0.63 to 0.78) for moderate glaucoma detection [10]. A clinic-based study in Nepal reported higher accuracy of visualFields Easy for detection of moderate glaucoma, with an AUROC of 0.78 (0.73 to 0.84) [9]. Both of these studies, however, compared moderate or worse glaucoma to no glaucoma, and thus are subject to spectrum bias and possible overestimation of accuracy estimates [9, 10]. Of note, when the Nepal-based study included all observations in an assessment of the accuracy of visualFields Easy for any glaucoma, the AUROC declined to 0.69 (0.64 to 0.75)—similar to our results for detection of mild or worse glaucoma [9]. Compared to tablet-based perimetry, other portable forms of perimetry such as FDT and MDT typically show higher levels of diagnostic accuracy—AUROC above 0.70 and sensitivity greater than 55% at a set specificity of 90% [14, 15].

This particular software application did not appear to have adequate diagnostic accuracy for glaucoma screening purposes. Since the implementation of this study the research group behind visualFields Easy has further developed the software, now known as Melbourne Rapid Fields (MRF), to include improved thresholding and the ability to derive mean and pattern deviation. The

mean deviation and pattern deviation indices on MRF have been found to have high correlation with those on HFA, and the test-retest reliability of MRF has been found to be comparable to that of HFA [7, 8]. The diagnostic accuracy of MRF is unclear since existing studies have used case-control designs, which tend to falsely inflate estimates of diagnostic accuracy because borderline and mild cases are left out of the study population (i.e., spectrum bias). Another emerging tablet-based perimetry software is Eyecatcher, which uses eye and head-tracking technologies to respond to visual stimuli, testing particular retinal locations based on current point of fixation [4]. This software has demonstrated strong ability to distinguish eyes with moderate or advanced field loss from those who are visually normal [4]. We anticipate even more software improvements to be developed in the future, and thus subsequent iterations of tablet-based perimetry will most likely have better diagnostic accuracy than the software tested in this study.

The visualFields Easy software has several limitations. First, inherent differences between the visualFields Easy application and HFA may limit direct comparisons of the two tests: (i) visualFields Easy tests 30 degrees from fixation horizontally and 24 vertically while 24-2 HFA tests in 24 degrees from fixation in all directions; (ii) visualFields Easy tests 96-point locations per eye, while the HFA tests 52 locations per eye; (iii) visualFields Easy is a suprathreshold test whereas HFA allows assessment of defects at various thresholds; and (iv) visualFields Easy does not have a chinrest, making precise standardization of the working distance challenging. Without stabilization by means of a chinrest or similar attachment, small head movements could shift the visual angle in a non-insignificant way. visualFields Easy also does not include a method for limiting environmental light pollution or standardization of ambient lighting, which could contribute to inconsistent diagnostic accuracy during community screening where environmental lighting would be highly variable.

The study design also had limitations. Near vision spectacle correction was not provided for the visualFields Easy but was for the HFA. We allowed participants to wear habitual distance correction for the visualFields Easy but intentionally did not provide near correction in order to mimic testing conditions in the resource-limited settings where the test would be most likely to be used. We reasoned that such a design made the assessment of diagnostic accuracy more relevant for a community-based program, although we acknowledge that this could have negatively impacted the diagnostic accuracy of the visualFields Easy software in this study. Next, though we used a standardized method for glaucoma classification and required 2 abnormal HFA tests for determination of glaucoma, it is still likely that some cases of glaucoma may have been mis-classified, especially in the absence of longer-term longitudinal testing of the visual field and

optic nerve appearance. Moreover, the HFA is not a perfect diagnostic test, and while it would be interesting to compare the diagnostic accuracy of the iPad with that of the HFA, this was not possible in the present study since the HFA results informed the reference standard diagnoses. We did not collect standardized data on test duration, ease of administration, or participant acceptability of testing methods, and thus cannot comment on these aspects of visualFields Easy. Finally, the study was conducted in a single eye clinic in South India on a study population naïve to perimetry. It is unclear if the results are generalizable to experienced test takers, a population-based glaucoma screening program, or to settings in which the test is not administered by an experienced technician.

In summary, in a population of naïve visual field test takers seen in a glaucoma clinic in South India, we found the diagnostic accuracy of visualFields Easy to be insufficient for use as a general screening tool for glaucoma. Diagnostic accuracy was greater when used as a test for more advanced forms of glaucoma, which has potential implications for monitoring patients with known glaucoma in places without sophisticated visual field equipment; however, longitudinal studies are needed to determine repeatability for this function. Better screening tests, further software improvements, and development of normative databases for perimetry tools are needed for glaucoma detection, particularly in resource-limited settings.

SUMMARY

What was known before

- Glaucoma is a sight-threatening disease with a prolonged asymptomatic phase, optimal for screening.
- Many patients delay glaucoma screening due to lack of symptoms and access to adequate eye care.
- A portable, inexpensive option for glaucoma screening could help prevent glaucoma-related vision loss. iPad perimetry, in theory, provides a highly portable, inexpensive option for glaucoma screening.
- There is mixed data about the potential of currently existing iPad perimetry software for glaucoma screening.

What this study adds

- iPad perimetry using visualFields Easy shows subpar diagnostic accuracy.
- Using a Humphrey visual field analyser reference standard, visualFields Easy demonstrated suboptimal sensitivity and specificity for both glaucoma and visual field defects.
- visualFields Easy showed moderate correlation with metrics produced via Humphrey visual field analyser perimetry. Further development and optimization of current perimeters are necessary to identify a glaucoma screening tool suitable for settings where Humphrey visual field analysers are inaccessible.

DATA AVAILABILITY

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

QRR performed statistical analysis, created figures and tables, and wrote the first draft of the paper. RSK designed the study, collected data, was responsible for implementation of the study and interpreted the results. BR, MVR, SDA, SSM, and SN collected data. CAM, DMW, and KSO helped implement the study. JTO interpreted the results. RLS procured funding, conceived of the study, designed the study, collected data, and interpreted the results. JDK designed and helped implement the study, collected data, and interpreted the results. All co-authors interpreted and critically edited the paper.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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