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Diagnostic accuracy of frequency doubling technology and Moorfields motion displacement test for glaucoma

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Abstract

Purpose: Portable perimetric testing could be useful for community-based glaucoma screening programs. Frequency doubling technology (FDT) and the Moorfields motion displacement test (MDT) are portable perimeters which have shown promise as potential screening tools for glaucoma. This study's goal was to determine the diagnostic accuracy of FDT and MDT for visual field defects and glaucoma.

Design: Prospective, cross-sectional, diagnostic accuracy study.

Participants: A consecutive series of patients aged ≥50 years who presented to a glaucoma clinic in South India and had never undergone Humphrey field analyzer (HFA) visual field testing in the past.

Methods: Participants underwent 24–2 SITA Standard HFA perimetry, FDT perimetry, MDT perimetry, and iPad perimetry using visualFields Easy in random order. Ophthalmologist grades of HFA and optic nerve head photographs were used as the reference standards for glaucoma and field defect presence. Receiver operating characteristic curves were constructed to assess diagnostic accuracy of various parameters for each test.

Main outcome measures: Sensitivity, specificity, area under the receiver operating characteristic curve (AUROC)

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Results: 292 eyes from 173 participants were included, with 112 eyes classified as moderate or worse glaucoma. For moderate or worse glaucoma detection, the best parameter on FDT was mean deviation (MD) (AUROC 0.84, 95% CI 0.79 to 0.89), and the best parameter on MDT was global probability of true damage (GPTD) (AUROC 0.87, 95% CI 0.82 to 0.91). When specificity was set to 90%, the sensitivity for detection of moderate or worse glaucoma was 55% (95% CI 39 to 68%) for FDT MD and 62% (95% CI 52 to 71%) for MDT GPTD.

Conclusions: FDT and MDT perimetry had fair diagnostic accuracy for glaucoma detection when administered to naïve test-takers in this South Indian population. Although not appropriate for use as a sole glaucoma screening test, these perimetric tests may be useful as ancillary tests.

Keywords

glaucoma; frequency doubling technology; Moorfields motion displacement test; visual fields

Glaucoma is the leading cause of irreversible blindness worldwide.[1] Portable perimetry devices are attractive as screening tools since they can be easily transported to community-based settings. Portable devices could play a larger role in remote or resource-limited settings, since a portable device could be shared by multiple clinics and thus be more cost-efficient. Previous diagnostic accuracy studies of portable devices such as the frequency doubling technology (FDT) or Moorfields motion displacement test (MDT) perimeters have found variable results, perhaps due to differences in sample sizes, testing parameters, and perimetry experience among participants.[2–7] Additional study on this topic is warranted, especially in populations of naïve test-takers who would comprise the vast majority of patients screened in a community-based setting.

We administered FDT and MDT perimetry as part of a diagnostic accuracy study of several glaucoma tests set at an eye hospital in Bangalore, India to patients who were naïve to standard automated perimetry.[8] We previously published the main pre-specified analyses of the study, which used thresholds for an abnormal test based on the published literature.[6,7] However, we acknowledge that different test thresholds or a different test parameter than what we pre-specified might have had higher diagnostic accuracy. The objective of the present study was to assess the diagnostic accuracy of each of the FDT and MDT parameters at different test thresholds to find the parameters and thresholds that optimally classified glaucoma in the study population.

Methods

Overview.

This is an ancillary analysis from a prospective cross-sectional study that assessed the diagnostic accuracy of several tests for glaucoma.[8] Participants in the study underwent FDT, MDT, and Humphrey field analyzer (HFA) testing in random order to minimize learning effects of prior visual field testing experience. In the present study, we re-analyzed the data with receiver operating characteristic (ROC) curves to assess the test parameters with the best diagnostic performance for detecting (i) a visual field defect relative to an ophthalmologist-interpreted HFA test and (ii) glaucoma relative to ophthalmologists' interpretation of an HFA printout and stereoscopic optic nerve photograph. This study was

approved by the University of California, San Francisco, and Narayana Nethralaya Eye Hospital in Bangalore Institutional Review Boards. Written, informed consent was provided by all participants. The study abided by the Tenets of the Declaration of Helsinki.

Eligibility.

Patients seen at the Narayana Nethralaya Eye Hospital glaucoma clinic between October 2014 and September 2015 for routine care who were 50 years of age or older, had no prior glaucoma diagnosis, and had never undergone HFA were approached for enrollment in this study. Patients who had received intraocular surgery in the three months prior to enrollment were excluded.

Index tests.

Participants were tested with the 24–2 threshold algorithm of the Humphrey Matrix FDT (Carl Zeiss Meditec AG, Jena, Germany) and with the enhanced suprathreshold algorithm 99.5% MDT (Moorfields Eye Hospital), with each device and each eye tested in random order. An iPad perimetry software application, visualFields Easy, became available after starting the study and was subsequently added to the protocol (white-on-white algorithm, default settings, screen set to maximum brightness).[9] All tests were performed while wearing habitual refractive correction in a dark room without windows according to the manufacturer's recommendations. MDT was performed at a distance of 30 cm, implemented by using a custom-made chinrest. iPad perimetry was performed at a targeted distance of 33 cm, although in practice the distance was difficult to enforce. An experienced optometry technician, masked to results of other glaucoma tests, conducted all tests. FDTs were considered reliable if false positives, false negatives, and fixation errors were each less than 33%. MDTs were considered reliable if the false positive response rate was <15%.

Reference standard.

Participants underwent the 24–2 SITA Standard algorithm on an HFA model 720 (Carl Zeiss Meditec AG, Jena, Germany) using a near-distance trial lens, and had stereoscopic optic nerve photographs taken with a nonmyd 7 camera (Kowa Company, Nagoya, Japan). If the HFA had any abnormalities or was deemed unreliable, the test was repeated until two reliable HFAs were available. The HFAs and optic nerve photographs of both eyes were presented to two ophthalmologists (RLS and JDK), who independently classified each eye hemifield for the presence or absence of a visual field defect and each eye for the presence or absence of glaucoma. Hemifield defects were further classified as glaucomatous vs. non-glaucomatous using a previously described classification system, and glaucoma severity was assessed according to a previously described 5-level staging system (Figure S1).[10,11] The ophthalmologist panel trained by reviewing the relevant publications and improved standardization of grading by discussing before grading and reviewing the results after grading 25 participants. Agreement between the two ophthalmologists was high (quadratic weighted Cohen's kappa of 0.89 for glaucoma severity and 0.79 and 0.68 for superior visual field defects of the right and left eyes, respectively and 0.68 and 0.74 for inferior visual field defects of the right and left eyes, respectively); discrepancies were adjudicated by reviewing together all available data until consensus could be reached.

Statistical analysis.

Eyes were excluded from the analysis if HFA showed false positives greater than 15% or false negatives or fixation losses greater than 33%; if the 24–2 HFA was not available; or if visual acuity was worse than 20/400. Five test parameters were considered for the FDT: number of points missed per hemifield (i.e., superior or inferior hemifield) on the pattern deviation plot at the 5% level, number of points missed per hemifield on the pattern deviation plot at the 1% level, mean deviation (MD) in decibels, pattern standard deviation (PSD) in decibels, and glaucoma hemifield test (GHT). FDT GHT outputs were converted to numerical values for use in ROC analysis as follows: “Within normal limits” = 1, “Borderline” = 2, and “Outside normal limits” = 3. Two parameters were considered for the MDT: number of points missed per hemifield (i.e., superior or inferior hemifield) on the pass/fail plot and MDT global probability of true damage (GPTD).[12] One parameter was considered for the visualFields Easy: number of points missed per hemifield. The diagnostic accuracy of detecting a visual field defect was determined using the number of points missed per hemifield as the index test and ophthalmologist-assigned hemifield grade (any defect [either glaucomatous or non-glaucomatous] vs. no defect) as the reference standard. The diagnostic accuracy of detecting glaucoma was assessed using the number of points missed per eye or one of the other eye-level test parameters (e.g., MD, GHT, GPTD) as the index test and the eye-level ophthalmologist-assigned glaucoma grade as the reference standard. The diagnostic accuracy of each index test was explored for various thresholds of glaucoma severity; such analyses included all cases above and below the threshold to guard against spectrum bias. Visualization of sensitivity and specificity at varying thresholds was achieved by constructing ROC curves for each index test parameter. Sensitivity and specificity were calculated using two thresholds: 1) the optimal threshold calculated from the Youden index and 2) the threshold resulting in a 90% specificity constraint, with the rationale being that a screening program would not want a test with more than 10% false positives in order to limit unnecessary referrals. Non-independence of eyes and/or hemifields was addressed by using cluster-bootstrapped 95% confidence intervals (1000 replications) with resampling at the person level to account for the intra-cluster correlation between two eyes of the same person.[13] DeLong’s test for correlated ROC curves was used to identify statistically significant differences in area under the receiver operating characteristic curve (AUROC) for pairs of index test parameters using a technique that accounted for person-level clustering (i.e., eyes from the same person).[14] Classification and Regression Tree (CART) analysis was used to explore the diagnostic accuracy of combinations of index test parameters, limiting the depth of the tree to 3 nodes to limit overfitting and enhance clinical usability of any generated decision trees. All analyses were performed using *R* version 4.1.2 (The R Foundation for Statistical Computing).

Results

A total of 217 patients were enrolled, of which 173 met inclusion criteria (mean age 65.1 years, standard deviation [SD] ± 8.2 years; 86 [50%] participants were females; the mean logMAR visual acuity was 0.20 ± 0.27 [Snellen equivalent 20/32]); Figure 2. The study included 292 eyes, of which 99 (34%) were classified by the ophthalmologist reference standard as not glaucomatous, 81 (28%) as mild glaucoma, 44 (15%) as moderate glaucoma,

33 (11%) as advanced glaucoma, and 35 (12%) as severe glaucoma or worse. Among 584 total hemifields, a glaucomatous defect was detected in 267 (46%), a non-glaucomatous defect in 58 (10%), no defect in 243 (42%), and indeterminate defect in 16 (3%). All 292 eyes had available FDT and MDT results. Duration and reliability metrics for HFA, FDT, and MDT are found in Table 1. Ultimately, 228 of 292 (78%) eyes achieved a reliable FDT and 290 of 292 (99%) eyes achieved a reliable MDT.

The correlation between three HFA parameters (i.e., points missed at the 1% threshold on the pattern deviation plot, points missed at the 5% threshold on the pattern deviation plot, and MD) with each of the index test parameters was explored in scatter plots (Figures S3, S4). When analyzing hemifield-level data, the number of HFA points missed per hemifield at the 1% threshold was most strongly correlated with the number of MDT points missed (Spearman's rho, $r_s = 0.57$). The most correlated FDT parameter was points missed at the 5% level ($r_s = 0.32$). When analyzing eye-level data, the HFA MD was most strongly correlated to the MDT GPTD ($r_s = 0.76$) and slightly less correlated with the FDT MD ($r_s = 0.70$).

ROC analysis was first used to assess diagnostic accuracy using hemifield-level data with the reference standard defined as any visual field defect (i.e., either glaucomatous or non-glaucomatous); Figure 5. Points missed on MDT provided the most diagnostic information for detecting a visual field defect with an AUROC of 0.78 (95% CI 0.73 to 0.82). The optimal threshold determined from the Youden index was ≥2 MDT hemifield points missed, which provided a sensitivity of 75% (95% CI 50 to 80%) and specificity of 70% (95% CI 64 to 94%). A threshold of ≥8 MDT missed points per hemifield constrained the specificity to 90% while providing a sensitivity of 49% (95% CI 41 to 61%).

Diagnostic accuracy was then assessed for each test parameter at the eye-level, with various thresholds of glaucoma severity used as the reference standard (Table 2; Figure 6). MDT GPTD provided the most diagnostic information for detection of moderate or worse glaucoma, with an AUROC of 0.87 (95% CI 0.82 to 0.91)—although this was not significantly different than the best FDT parameter, MD (AUROC for moderate or worse glaucoma: 0.84, 95% CI 0.79 to 0.89); p = 0.21. Using the Youden index, the optimal diagnostic accuracy for detecting moderate or worse glaucoma with the MDT GPTD was reached at a threshold of ≥9.8 units, which provided a sensitivity of 83% (95% CI 60 to 93%) and specificity of 74% (95% CI 65 to 96%). A threshold of ≥17.9 GPTD units constrained the specificity to 90% while giving a sensitivity of 62% (95% CI 52 to 71%). Sensitivities for the other index test parameters when held to a 90% specificity constraint were lower (Table 2). Diagnostic accuracy was better for detecting more severe forms of glaucoma (Table 2). For example, the AUROC for detecting severe or worse glaucoma was 0.93 (95% CI 0.88 to 0.97) for FDT MD and 0.92 (95% CI 0.88 to 0.96) for MDT GPTD (Figure 7). ROC curves constructed for isolated glaucoma severities can be found in Figure S8 with FDT MD, MDT points missed, and MDT GPTD demonstrating superior diagnostic accuracy for increasing disease severity compared to the other test parameters. Combining multiple index test parameters from the FDT or MDT printout offered minimal improvement in diagnostic accuracy when assessed with CART analysis but at the cost of a much more complicated threshold rule (Figure S9). Restricting the analysis to only the subset of eyes

with reliable results resulted in higher estimates of diagnostic accuracy for FDT parameters but similar results for the MDT (Table S3).

A subset of 81 eyes from 48 participants had results from the visualFields Easy iPad application in addition to FDT and MDT. visualFields Easy had an AUROC of 0.78 (95% CI 0.64 to 0.89) for detection of moderate or worse glaucoma, which was non-significantly lower than that of the best performing FDT (AUROC 0.88 [95% CI 0.79 to 0.96]; p = 0.14) and MDT parameters (AUROC 0.83 [95% CI 0.72 to 0.92]; p = 0.43) within this subset. Sensitivity of visualFields Easy for moderate or worse glaucoma detection was 55% (95% CI 35 to 74%) when specificity was constrained to 90% (Figure S10).

Discussion

Investigation of the diagnostic ability of currently available portable technologies for glaucoma is needed to better establish the role of screening tools in resource-limited areas. This study focused on the diagnostic accuracy of FDT and MDT for detection of visual field defects and glaucoma. In this South Indian population, with a reported open-angle glaucoma prevalence of 3.5% among those 40 years and older,[15] the best-performing diagnostic parameter for glaucoma diagnosis when using the FDT was the MD and when using the MDT was the GPTD. Each of these parameters had about 60% sensitivity for detection of moderate or worse glaucoma when the specificity was constrained to 90% (i.e., an arbitrary specificity estimate chosen to limit the number of false positive referrals). Sensitivity was greater for more advanced forms of glaucoma, with a maximum of 83% sensitivity for detection of severe glaucoma by the FDT MD when the specificity was constrained to 90%. The MDT and FDT were each more accurate than the visualFields Easy iPad application for diagnosis of glaucoma, though the difference was not statistically significant.

At the hemifield-level, the number of points missed on MDT had a stronger correlation with HFA than did the points missed on FDT, and the points missed on MDT also conveyed more diagnostic information (i.e., a greater AUROC) for detection of a visual field defect. At the eye-level, MDT points missed, MDT GPTD, and FDT MD showed fairly strong positive relationships with HFA MD (i.e., Spearman’s rho 0.70 or above) and demonstrated relatively high AUROCs for various stages of glaucoma, with greater AUROCs for the more advanced stages. For example, at a 90% specificity constraint, the sensitivity of each of three parameters (i.e., MDT points missed, MDT GPTD, and FDT MD) for detection of severe glaucoma was 80% or higher. However, sensitivity estimates were lower for mild and moderate glaucoma, limiting their utility as glaucoma screening tools. MDT GPTD was the best diagnostic test for moderate or worse glaucoma, but even this parameter only had a sensitivity of 62% (95% CI 52 to 71%) when specificity was constrained to 90%, and its diagnostic accuracy was not significantly different than FDT MD.

While both are portable perimeters, FDT and MDT have fundamental differences which may explain result discrepancies in our study. First, Humphrey Matrix FDT uses a series of white and black band targets, each representing a 5 degree square, cumulatively providing a 54-point platform with test result output similar to 24–2 SITA Standard HFA.[16] In contrast, MDT uses vertical white line stimuli and assesses 31 test locations, spatially corresponding

to 24–2 HFA.[12] MDT is a suprathreshold test that takes approximately 5 minutes to administer to both eyes. While the FDT offers a suprathreshold function, for this study we used the full threshold test, which requires around 5 minutes per eye.[4]

Prior studies have investigated the diagnostic capacity of portable perimeters. Our study is consistent with a study of the Humphrey Matrix FDT that reported an AUROC of 0.73 for pattern deviation points at the 5% level, 0.76 for pattern deviation points at the 1% level, and 0.76 for MD, with a sensitivity of 47% using a 90% specificity constraint for the most accurate parameter (i.e., pattern deviation points missed at the 1% level) for glaucoma detection.[2] FDT performance in the present study was at the lower end of reported estimates, as evidenced by a meta-analysis that found a sensitivity of 92% (95% CI 65 to 99%) and specificity of 94% (95% CI 73 to 99%) for the FDT using a hierarchical summary receiver operating characteristic model—although that meta-analysis included both suprathreshold and full threshold FDT algorithms.[17] The diagnostic accuracy we observed for MDT was also somewhat lower than that found in a previous study, which reported a sensitivity of 88.5% for GPTD at a set specificity of 85% relative to clinical examination.[7] The reasons for the relatively lower diagnostic accuracy in the present study are not clear, although it is worth pointing out that, unlike some previous studies, we did not exclude any unreliable index tests. Our secondary analysis using only reliable test results found modestly higher accuracy estimates for the FDT, though still lower than many previous reports.

This study has limitations. This study did not exclude eyes with unreliable index test results as determined by false positives, false negatives, or fixation errors, since our goal was to assess the index tests as potential screening tools. A subgroup analysis found that diagnostic accuracy was better in the more reliable FDT tests. Though we tried to limit referral bias by only recruiting patients who had no known diagnosis of glaucoma or HFA exposure, patients were likely referred to the glaucoma clinic based on some suspicion of glaucoma, so our findings may not be representative of naïve test-takers in the general population. HFA was used for determination of the reference standard, but the HFA may also produce false positives and negatives. We did not address the test-retest reliability of the index and reference test procedures. Lastly, this study was performed at a single eye-care center in Southern India, so the results may not be generalizable to settings without an available experienced technician such as during home or community screening.

In summary, we found that HFA results were more correlated with MDT than FDT. The best-performing parameters of each test, the MDT GPTD and the FDT MD, had a similar sensitivity for moderate or worse glaucoma: approximately 60% when the specificity was constrained to 90%. Such sensitivity is not adequate for use as a single test in a glaucoma screening program since many patients with glaucoma would not be identified. The diagnostic accuracy of each device was higher for increasing levels of glaucoma severity, suggesting that the devices could be considered as ancillary tests for confirming a glaucoma diagnosis or for monitoring patients with known glaucoma over time. Further assessment of portable perimetric tests in a diversity of clinical settings is important for full characterization of their diagnostic accuracy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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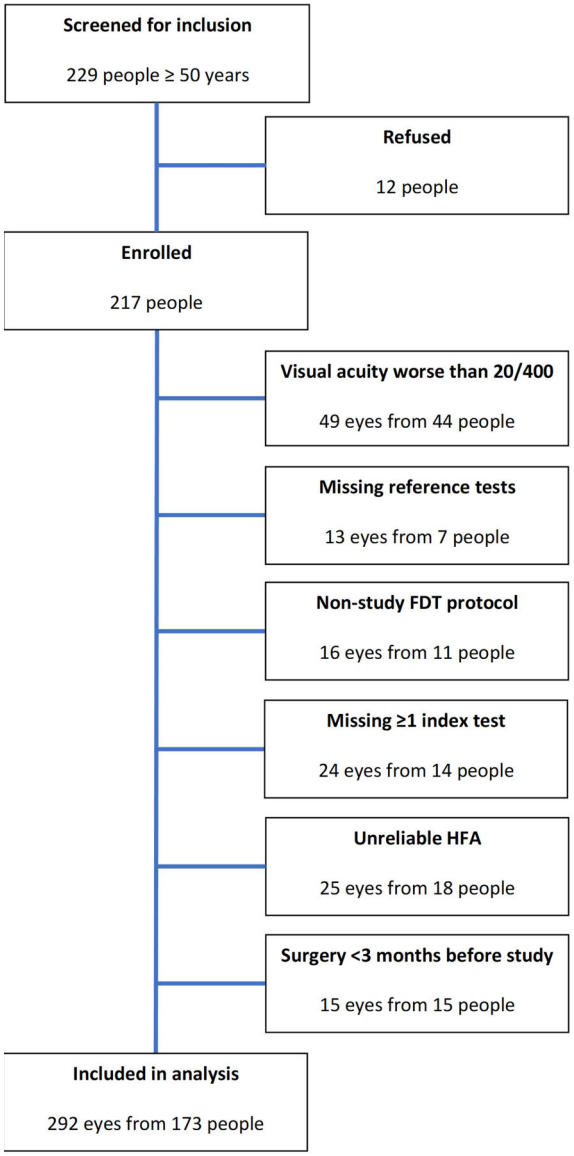

Figure 2. Study flow.

FDT = frequency doubling technology, HFA = Humphrey visual field analyzer

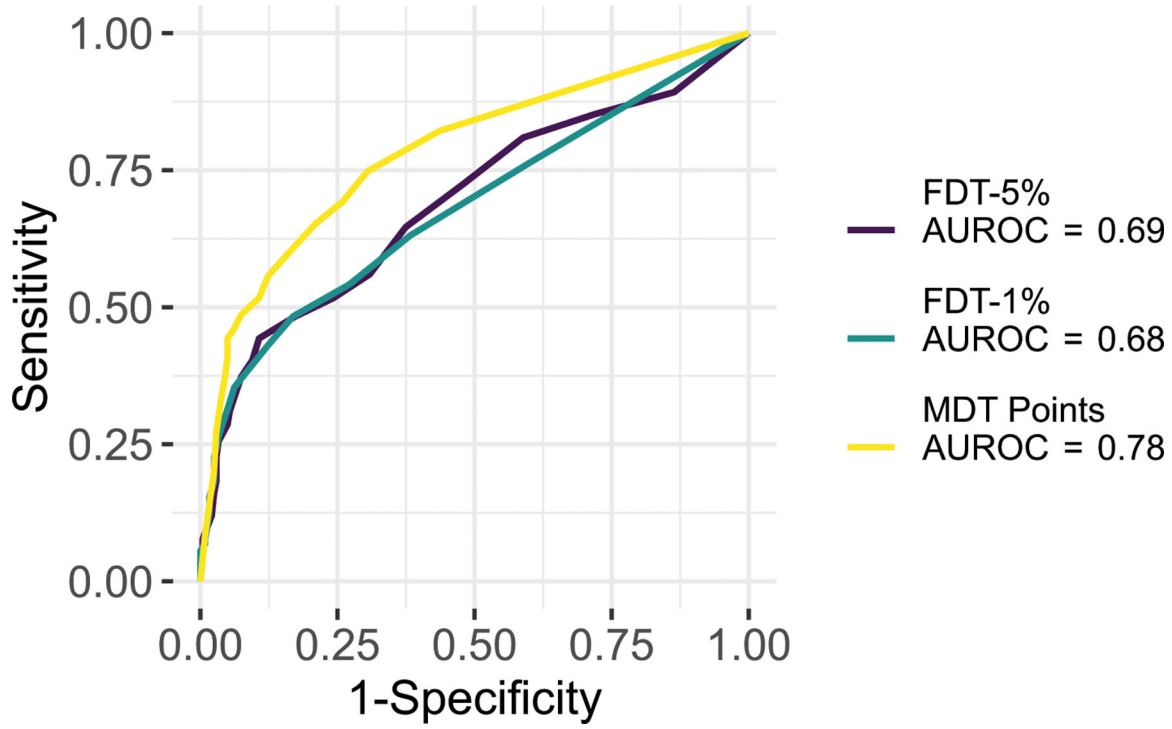

Figure 5. Receiver operating characteristic (ROC) curves for detection of hemifield-level visual field defects by frequency doubling technology (FDT) and Moorfields motion displacement test (MDT).

The area under the ROC curve (AUROC) is listed for detection of any visual field defect for the following index tests: points missed per hemifield on the FDT pattern deviation plot at the 5% level (purple) and 1% level (green) and points missed on the MDT pass/fail plot (yellow), with ophthalmologist assessment of the relevant hemifield on the Humphrey field analyzer printout as the reference standard.

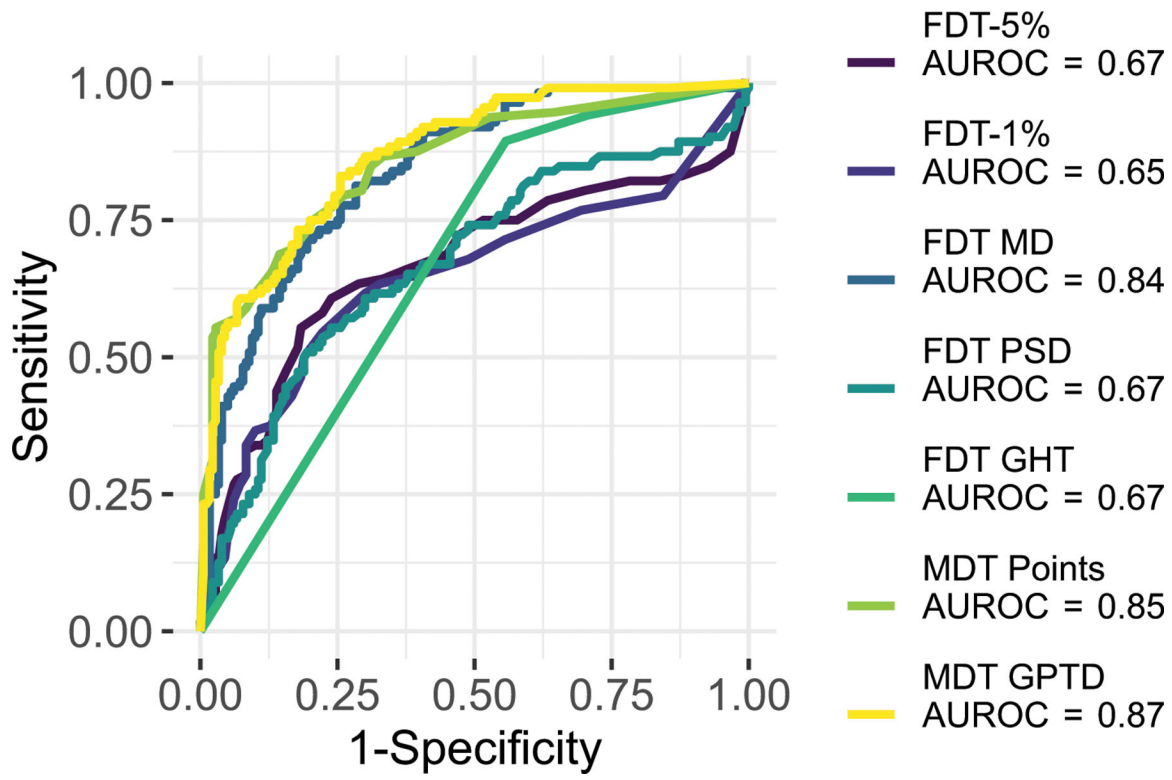

Figure 6. Receiver operating characteristic (ROC) curves for detection of glaucoma using frequency doubling technology (FDT) and Moorfields motion displacement test (MDT).

The area under the ROC curve (AUROC) is shown for detection of moderate or worse glaucoma for several index test metrics: FDT points missed on pattern deviation plot at the 5% level (purple) and 1% level (indigo), FDT mean deviation (FDT MD; blue), FDT pattern standard deviation (FDT PSD; blue-green), FDT glaucoma hemifield test (FDT GHT; green), MDT points missed on the pass/fail plot (lime), and MDT global probability of true damage (MDT GPTD; yellow).

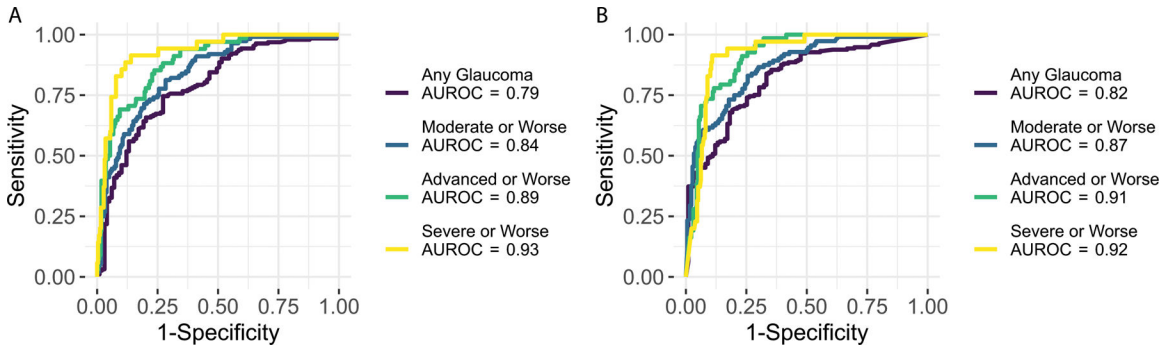

Figure 7. Receiver operating characteristic (ROC) curves for detection of various glaucoma severities using frequency doubling technology mean deviation (FDT MD) and Moorfields motion displacement test global probability of true damage (MDT GPTD).

A) Diagnostic accuracy of FDT MD for various glaucoma thresholds (any glaucoma: purple, moderate or worse glaucoma: blue, advanced or worse glaucoma: green, severe or worse glaucoma: yellow). B) Diagnostic accuracy of MDT GPTD for various glaucoma thresholds (any glaucoma: purple, moderate or worse glaucoma: blue, advanced or worse glaucoma: green, severe or worse glaucoma: yellow). Ophthalmologist-determined glaucoma staging of the relevant eye served as the reference standard. Glaucoma was staged using a previously reported classification system.[11] Ophthalmologists had access to the Humphrey field analyzer printouts and optic nerve photographs of both eyes.

AUROC = area under the receiver operating characteristic curve

Table 1.

Average index test duration and reliability metrics for Humphrey field analyzer (HFA), frequency doubling technology (FDT), and Moorfields motion displacement test (MDT) with 95% confidence intervals. Late response rate is unique to MDT. False negative rate is not calculated by the MDT software.

	HFA	FDT	MDT
Test duration (minutes)	8.9 (8.6–9.3)	7.5 (7.1–7.9)	4.0 (3.7–4.3)
False positive rate (%)	3.4 (2.9–3.9)	4.4 (3.4–5.3)	2.4 (1.9–2.9)
False negative rate (%)	6.1 (5.3–6.9)	13.0 (10.2–15.7)	–
Late response rate (%)	–	–	8.6 (7.2–10.0)

Table 2.

Diagnostic accuracy of frequency doubling technology (FDT) and Moorfields motion displacement test (MDT) relative to the Humphrey field analyzer.

The listed sensitivities were calculated at a set specificity of 90% for each index test. 95% confidence intervals are given in parentheses. FDT mean deviation, FDT pattern standard deviation, and MDT global probability of true damage are eye-level metrics, so hemifield-level analyses were not included.

Reference standard definition	Num/ Total[a]	FDT-5% Level		FDT-1% Level		MDT Points		FDT MD		FDT PSD		MDT GPTD	
		Pts[b]	Sensitivity	Pts[b]	Sensitivity	Pts[b]	Sensitivity	Pts[b]	Sensitivity	Pts[b]	Sensitivity	Pts[b]	Sensitivity
Hemifield-level defect													
Any defect	325/568	10	40% (29–49)	6	40% (29–47)	8	49% (41–61)						
Glaucomatous defect	267/568	12	32% (29–49)	8	33% (29–47)	8	55% (41–61)						
Eye-level glaucoma stage													
Any glaucoma	193/292	17	45% (22–58)	11	39% (17–53)	15	46% (35–67)	14.2	43% (26–62)	5.3	36% (16–51)	14.7	49% (39–67)
Moderate or worse	112/292	24	34% (20–50)	15	37% (18–47)	17	62% (50–72)	15.3	55% (39–68)	6.3	26% (15–48)	17.9	62% (52–71)
Advanced or worse	68/292	25	47% (28–59)	16	47% (25–61)	20	72% (58–84)	16.2	69% (53–79)	6.4	34% (21–49)	21	74% (62–86)
Severe or worse	35/292	29.5	37% (19–55)	21	29% (14–50)	26	80% (42–93)	19.2	83% (68–96)	7.1	23% (07–37)	25.4	83% (47–98)

[a]Number with the reference standard classification over the total number of observations.

[b]The number of points that define the test threshold; a positive test is greater than or equal to the listed number of points.

FDT = frequency doubling technology, MDT = Moorfields motion displacement test, MD = mean deviation, PSD = pattern standard deviation, GPTD = global probability of true damage