

Validation of the structure–function correlation report from the heidelberg edge perimeter and spectral-domain optical coherence tomography

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Received: 11 September 2017 / Accepted: 25 January 2018 / Published online: 2 February 2018
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Abstract

Purpose To compare the diagnostic assessment of glaucoma specialists with an automated structure–function correlation report combining visual field (VF) and spectral-domain optical coherence tomography (SD-OCT) imaging in subjects with glaucoma.

Methods This prospective, cross-sectional study was conducted at Wills Eye Hospital, Philadelphia, PA, USA. Subjects with glaucoma received ophthalmic examination, VF testing, and SD-OCT imaging. An automated report was generated describing structure–function correlations between the two structural elements [retinal nerve fiber layer (RNFL) and Bruch’s membrane opening–minimum rim width (MRW)] and VF sectors. Three glaucoma specialists masked to the automated report and to each other identified clinically significant structure–function correlations between the VF and SD-OCT reports. Raw agreement and chance-corrected agreement (kappa

statistics) between the automated report and the clinical assessments were compared.

Results A total of 53 eyes from 45 subjects with glaucoma were included in this study. The overall agreement between the automated report and clinical assessment comparing MRW and VF was good at 74.8% with a kappa of 0.62 (95% CI 0.55–0.69). Agreements for the six different MRW sections were moderate to good with kappa values ranging from 0.54 to 0.69. For mean RNFL thickness and VF comparisons, agreement between the automated report and clinical assessment was 75.4% with a kappa of 0.62 (95% CI 0.54–0.70). For different RNFL sectors, kappa values ranged from 0.47 (moderate agreement) to 0.80 (good agreement).

Conclusions This study suggests that the automated structure–function report combining results from the SD-OCT and the HEP may assist in the evaluation and management of glaucoma.

Keywords Structure–function correlation · Heidelberg edge perimeter · Automated perimetry · Optical coherence tomography · Glaucoma

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Introduction

Combining the diagnostic abilities of both structural and functional tests is important in the detection and management of glaucoma. In cases where localized

structural changes in the optic nerve head correlate with localized changes in the visual field (VF), the likelihood that both changes are real and related to a glaucomatous process is greatly enhanced [1–3]. Until recently, respective structural and functional findings of optic nerve head optical coherence tomography (OCT) and perimetry were not typically integrated as a comparative and comprehensive report. Previous studies often relied on statistical calculation using linear regression and logarithmic associations to demonstrate structure–function correlations in glaucoma patients [4–6].

An automated software that generates integrated structure–function reports was recently developed and launched by Heidelberg Engineering. These reports integrate VF data obtained by the Heidelberg Edge Perimeter (HEP; Heidelberg Engineering, Heidelberg, Germany) and imaging data obtained by spectral domain-OCT (SD-OCT; Spectralis; Heidelberg Engineering, Heidelberg, Germany). In this automated report, in addition to generating structure–function correlations for the traditional measurement of peripapillary retinal nerve fiber layer thickness (RNFL), the novel parameter of Bruch’s membrane opening–minimum rim width (BMO–MRW) can also be compared to VF results. The BMO is considered the true outer limit of the optic disk because retinal

ganglion cell axons do not pass through Bruch’s membrane when exiting the eye [7, 8]. As shown in Fig. 1, MRW is the minimum distance between BMO and the internal limiting membrane [9]. The benefit of using MRW as a measurement of rim width is that it measures width at an angle perpendicular to the path of the axon, which prevents overestimation of rim width when the path of the axons is parallel to the horizontal plane [9, 10]. Studies on MRW have found it to be at least comparable to, if not more sensitive than, RNFL for identifying early glaucomatous damage [11–13, 20].

This new automated structure–function report, as shown in Figs. 2 and 3, is based on the Garway–Heath map that relates VF test-points to specific regions of the optic nerve head [14–16]. Correlations are generated between VF areas and both peripapillary RNFL and MRW regions. There has been little research on the efficacy and utility of such an automated, software-generated structure–function report. The aim of this study was to evaluate the ability of an automated report to detect clinically significant structure–function correlations in comparison to the diagnostic impression of glaucoma specialists and to investigate the relationships between the two structural measures, RNFL and MRW, with VF testing results.

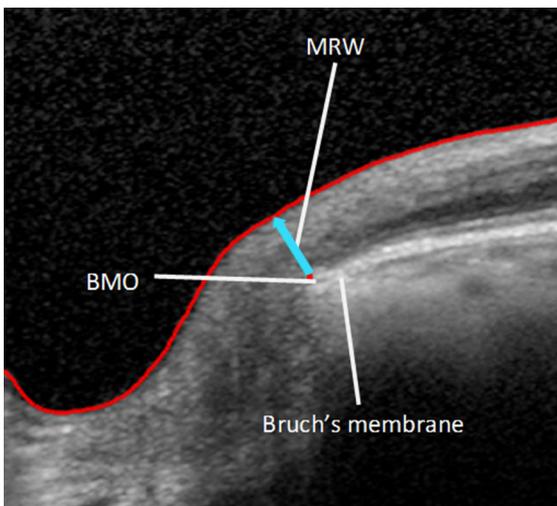


Fig. 1 Spectral-domain optical coherence tomography showing Bruch’s membrane, Bruch’s membrane opening (BMO), and Bruch’s membrane opening–minimum rim width (MRW; blue arrow), which is the shortest distance between the BMO and the internal limiting membrane (red line)

Methods

The study protocol was approved by the Wills Eye Hospital Institutional Review Board. Written informed consent was obtained from all subjects in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and the Declaration of Helsinki. This report is a sub-analysis of a study that was carried out between December 1, 2014, and June 30, 2015.

Study subjects and clinical examination

Inclusion criteria were as follows: (1) age \geq 18 years; (2) best corrected visual acuity (BCVA) of 20/40 or better in the tested eye; (3) spherical refraction within \pm 5.0 D and cylinder correction within \pm 3.0 D; and (4) a diagnosis of glaucoma of any type. Exclusion criteria were as follows: (1) any condition preventing adequate examination of the pupil or VF testing (e.g., ptosis, dense corneal

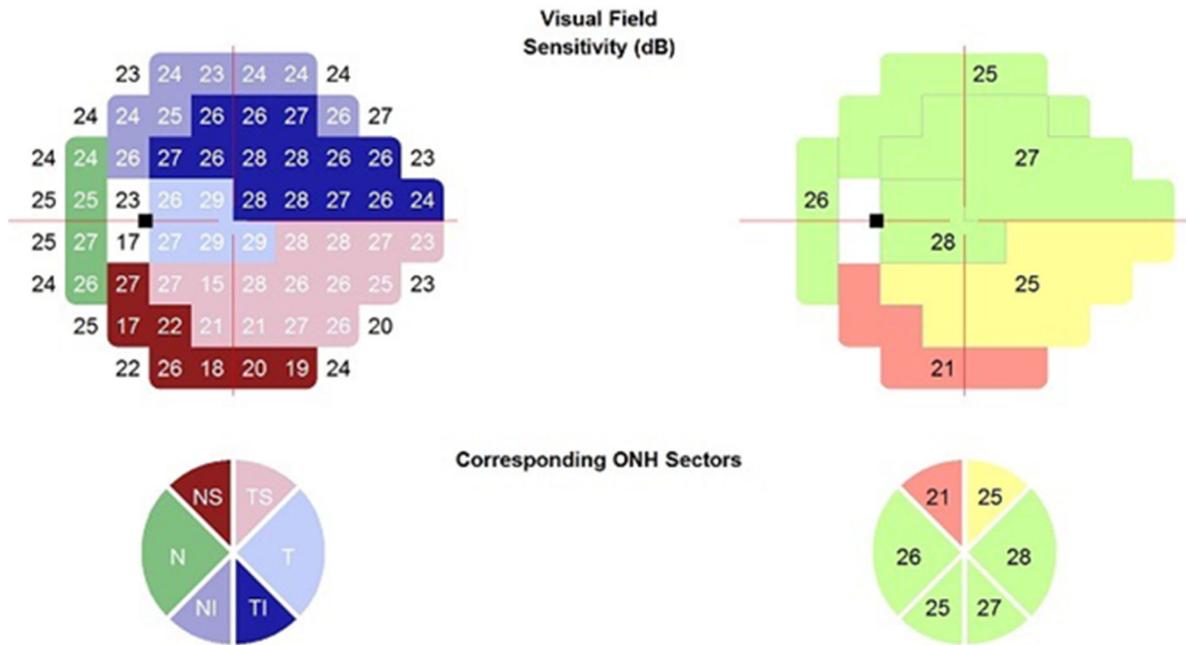


Fig. 2 A visual field (VF) report showing average sensitivities for each area of the VF and the corresponding optic nerve head (ONH) sectors based on the Garway–Heath map

opacities, lens opacities); (2) any intraocular surgical or laser procedure ≤ 4 weeks prior to enrollment; (3) use of medications known to affect VF sensitivity, and (4) diagnoses of coexisting intraocular diseases known to affect VF. For each subject, a standard ophthalmic examination by glaucoma specialists was conducted which included BCVA testing, slit-lamp biomicroscopy, Goldman applanation tonometry, and fundoscopy.

Visual field testing and optical coherence tomography

VF testing was performed using the HEP SAP III 30-2 advanced staircase thresholding algorithm (ASTA). All subjects were tested with the appropriate refraction. The mean deviation (MD) and pattern standard deviation (PSD) were recorded.

SD-OCT imaging was obtained without pupil dilation using the Glaucoma Module Premium Edition (GMPE). The RNFL and MRW measurements were recorded for the superior nasal (SN), superior temporal (ST), inferior nasal (IN), inferior temporal (IT), nasal (N), and temporal (T) sectors. An automated, integrated structure–function correlation report was generated. Figure 3 shows a sample structure–function

report for RNFL and MRW. Unreliable VF results (false positive, false negative, or fixation loss $> 30\%$) and unreliable OCT reports (Q score < 16) were excluded from analysis.

Evaluation of clinically significant structure–function correlations

Three glaucoma specialists individually evaluated the HEP VF and the SD-OCT printouts to determine structure–function correlations. The physicians did not have access to additional clinical information and were blinded to the results of the automated reports and to each other. First, each physician determined whether a clinically significant structure–function correlation exists for each set of SD-OCT and HEP VF printouts. If a correlation was present, the physician was asked to describe the location of the correlation based on the six OCT sectors: SN, ST, IN, IT, N, and T. Agreement among the three physicians with respect to both the presence and the sector location(s) of structure–function correlations was determined based on simple majority. Eyes without agreement among physicians on the presence and location(s) of correlations were excluded from analysis. The clinical structural–function correlations

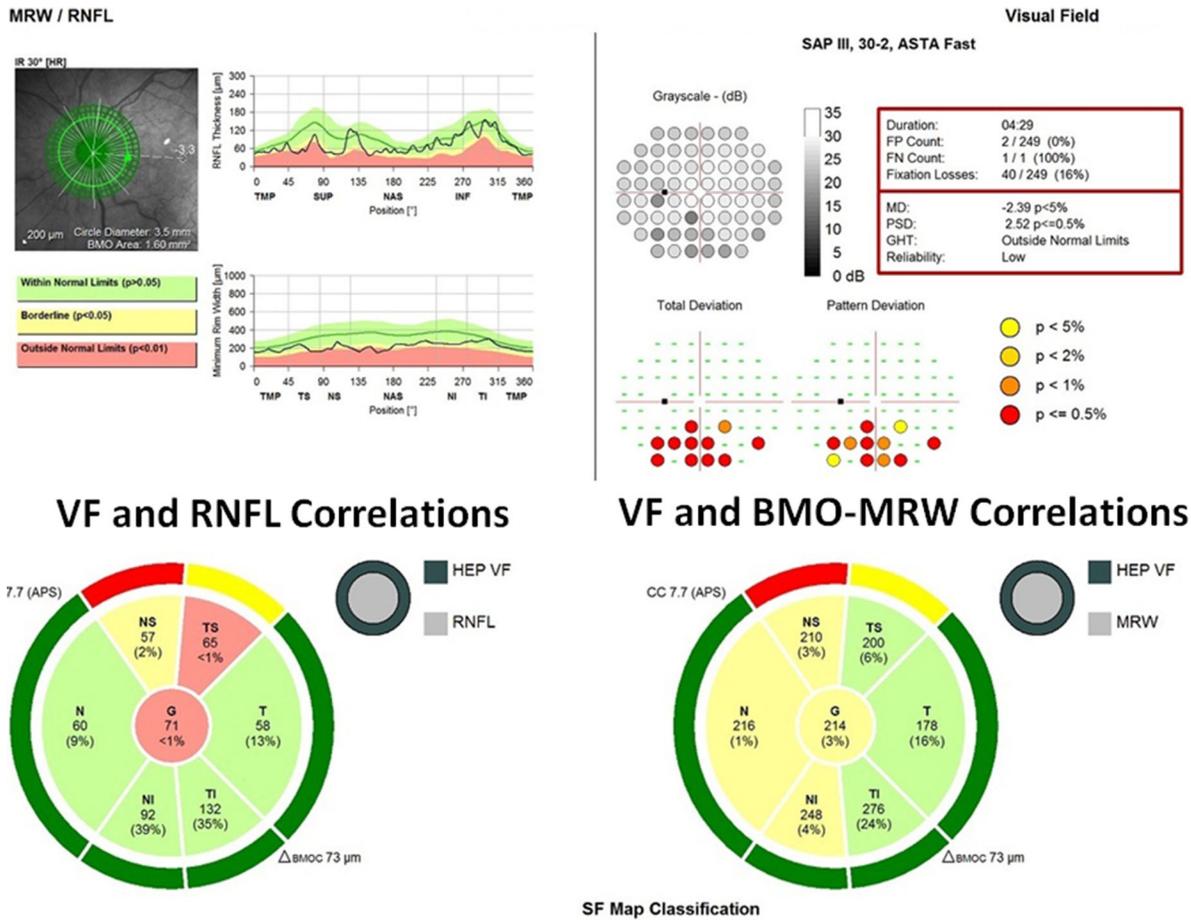


Fig. 3 A structure–function correlation report demonstrating the level of agreement between visual field (VF) and two structural parameters: retinal nerve fiber layer (RNFL, left) and Bruch’s membrane opening–minimum rim width (BMO–MRW, right). Each of the six sections in each pie chart shows the RNFL and the MRW values for that sector. The percentages in parenthesis indicate the likelihood that any particular measurement is within normal limits compared to a normative database. In each sector, green indicates “within normal limits”, yellow

indicates “borderline”, and red indicates “outside normal limits”. Letter “G” in the center of the pie chart represents the global average of the RNFL or MRW measurement. The outer encircling stripe around the pie chart represents the VF sensitivities by Garway–Heath area that corresponds to each RNFL or MRW sectors with the same green, yellow, and red color coding in each of the VF sectors. Sectors were considered “correlated” if the corresponding OCT (RNFL or MRW) and VF results had less than a 5% probability of being normal

determined in this manner were then compared with the areas of the automated structure–function report that showed correlation. In addition, for the eyes with consensus among physicians, agreements between OCT parameters (RNFL and MRW) and VF for each of the six sectors were evaluated.

Statistical analysis

All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA). To describe the demographics and clinical characteristics, continuous

variables were summarized using means, standard deviations (SDs), medians, and ranges. Categorical variables were summarized using frequencies and percentages. To assess the agreement of ratings between the VF device and the three glaucoma specialists, the percentage of agreement and chance-corrected kappa statistics were calculated. The strength of agreement was considered “Poor” with a kappa < 0.20, “Fair” with Kappa between 0.21 and 0.40, “Moderate” with kappa between 0.41 and 0.60, “Good” with kappa between 0.61 and 0.80, and “Very good” with kappa between 0.81 and 1.00 [17].

Confidence intervals (CIs) were inflated by 1.14 to account for the eight people (15%) who contributed two eyes to the study [18]. Similar analyses were performed to assess the agreement between RNFL and MRW in each sector with the corresponding VF sectors.

Results

A total of 53 eyes from 45 subjects were included in this study. Subjects consisted of 23 males (51%) and 22 females (49%) with a mean (\pm SD) age of 69.2 (\pm 7.3) years. Table 1 describes subject demographics and clinical characteristics.

Overall, inter-physician agreement on structure–function correlations between the HEP VF and the SD-OCT reports was excellent. For each of the six SD-OCT sectors, at least two physicians agreed on VF and

RNFL correlations for 94–100% of the cases, and on 96–98% of the cases for VF and MRW correlations.

Table 2 summarizes the kappa values and percent agreement between clinical assessments and structure–function reports for each SD-OCT sector compared to VF. The overall agreement between physician assessments and the structure–function reports with respect to RNFL and VF comparisons was 75.4%, with a good kappa of 0.62 (95% CI of 0.54–0.70). For MRW and VF comparisons, the overall agreement between physician assessments and the structure–function reports was 74.8%, with a good kappa value of 0.62 [95% confidence interval (CI) of 0.54–0.70]. Eyes were excluded from analysis if at least two out of three physicians did not agree. Specifically, the RNFL-VF analysis involving the “nasal inferior” sector excluded three eyes due to lack of physician consensus, while all 53 eyes were included in the RNFL-VF analysis of the “temporal superior” sector.

Table 1 Demographics and clinical characteristics of the study population

Variables	Subjects ($n = 45$)
Age (years), mean \pm SD	69.3 \pm 7.3
Gender, n (%)	
Male	23 (51.1)
Female	22 (48.9)
Race/ethnicity, n (%)	
White	32 (71.1)
African American	12 (26.7)
Asian	1 (2.2)
Diagnosis, n (%)	
Primary open-angle glaucoma	37 (70.0)
Secondary open-angle glaucoma	12 (22.5)
Primary angle-closure glaucoma	4 (7.5)
Global RNFL classification, n (%)	
Outside normal limits	36 (67.9)
Borderline	9 (17.0)
Within normal limits	8 (15.1)
Global RNFL thickness (μm), mean \pm SD	72.4 \pm 18.1
Global MRW classification, n (%)	
Outside normal limits	29 (54.7)
Borderline	12 (22.6)
Within normal limits	12 (22.6)
Global MRW (μm), mean \pm SD	202 \pm 59.6
Visual field, mean \pm SD	
MD (dB)	– 3.6 \pm 3.5
PSD (dB)	3.4 \pm 3.1

RNFL retinal nerve fiber layer, *MRW* minimum rim width, *MD* mean deviation, *PSD* pattern standard deviation

Table 2 Kappa statistics and agreement between clinical assessments and the automated structure–function reports comparing two structural parameters (retinal nerve fiber layer and Bruch’s membrane opening–minimum rim width) with visual field

Parameter	SD-OCT sector	Eyes (<i>n</i>) ^a	Agreement between clinical assessment and automated report (%)	Kappa (95% CI)
RNFL-VF	Temporal superior	53	69.8	0.54 (0.35–0.73)
	Temporal	52	63.5	0.47 (0.27–0.67)
	Temporal inferior	53	71.7	0.57 (0.38–0.76)
	Nasal inferior	50	78	0.61 (0.39–0.83)
	Nasal	51	88.2	0.80 (0.63–0.97)
	Nasal superior	51	82	0.67 (0.45–0.89)
MRW-VF	Temporal superior	52	69.2	0.54 (0.35–0.73)
	Temporal	52	69.2	0.55 (0.36–0.74)
	Temporal inferior	52	71.2	0.56 (0.36–0.76)
	Nasal inferior	51	78.4	0.64 (0.45–0.83)
	Nasal	52	80.8	0.69 (0.50–0.88)
	Nasal superior	51	80.4	0.69 (0.50–0.88)

RNFL-VF retinal nerve fiber layer thickness and visual field comparison, *MRW-VF* minimum rim width and visual field comparison, *SD-OCT* spectral-domain optical coherence tomography, *CI* confidence interval

^aA total of 53 eyes were included in this study. One to three eyes from each SD-OCT sector were excluded from analysis for lack of consensus among physicians

All other analyses involving RNFL-VF or MRW-VF excluded 1–2 eyes per sector due to lack of physician consensus (Table 2).

Table 3 summarizes the kappa values and percent agreement comparing RNFL and MRW with VF

results. Agreement between RNFL and VF ranged from poor to moderate with an overall percentage of 69.7 and a fair kappa of 0.39 (95% CI of 0.28–0.50). Agreement between MRW and VF sectors ranged

Table 3 Kappa statistics and agreement between visual field and corresponding spectral-domain optical coherence tomography sectors for the parameters of retinal nerve fiber layer and minimal rim width

SD-OCT parameter	Sector	Eyes (<i>n</i>)	Agreement between SD-OCT sector and VF (%)	Kappa (95% CI)
RNFL	Temporal superior	53	71.7	0.41 (0.13–0.70)
	Temporal	53	56.6	0.16 (– 0.11–0.43)
	Temporal inferior	53	73.6	0.41 (0.12–0.70)
	Nasal inferior	53	71.7	0.40 (0.12–0.69)
	Nasal	53	66.0	0.25 (– 0.04–0.54)
	Nasal superior	53	78.8	0.53 (0.25–0.81)
MRW	Temporal superior	53	71.7	0.44 (0.18–0.70)
	Temporal	53	66.0	0.32 (0.04–0.60)
	Temporal inferior	53	75.5	0.45 (0.16–0.74)
	Nasal inferior	53	83.0	0.66 (0.38–0.94)
	Nasal	53	58.5	0.16 (– 0.10–0.42)
	Nasal superior	53	71.2	0.43 (0.17–0.69)

RNFL retinal nerve fiber layer, *MRW* minimum rim width, *SD-OCT* spectral-domain optical coherence tomography, *VF* visual field, *CI* confidence interval

from poor to good with an overall percentage of 71.0 and a moderate kappa of 0.42 (95% CI of 0.31–0.53).

Discussion

The automated structure–function report combines structural (SD-OCT parameters of RNFL and MRW) and functional (VF) assessments and has several potential advantages in the evaluation and management of glaucoma and glaucomatous progression. It provides a one-step review of the two most commonly used tests in glaucoma, RNFL thickness and VF, by combining both results into a single report [19–21]. In addition to RNFL-VF comparisons, a second structural assessment is provided in the form of MRW, a parameter that is arguably more sensitive than RNFL in the detection of early glaucoma stages [11, 22]. The correlated report allows for ease of interpretation by generating a color-coordinated map of the different RNFL and MRW sectors in direct comparison to corresponding VF regions based on the Garway–Heath map.

The results of this study suggest moderate to good agreement between the findings of the automated report and independent assessment by experienced glaucoma specialists. Results support the utility of such reports as another tool in the assessment of glaucoma severity and monitoring of glaucomatous progression. In this study, the lowest percent agreements between clinical assessment and the automated report involved the “temporal” sectors for both RNFL and MRW measurements, and may implicate a clinical finding of unknown significance. Of note, overall agreement between the automated report and clinical assessment exists despite lower agreement between RNFL and MRW with VF results in the automated report.

The greatest proportion of the RNFL-VF and MRW-VF comparisons demonstrating disagreement between the automated report and clinical assessment consists of a finding of “no correlation” in the automated report and an interpretation of “positive agreement” from the glaucoma specialists (61 and 59% for RNFL-VF and MRW-VF, respectively). In other words, for the sectors where the automated report noted disagreement between the functional (VF) and the structural (RNFL or MRW) assessments, experienced glaucoma specialists interpreted both

assessments as corresponding and “within normal limits.” Combined with the finding that the automated report over-called “outside normal limits” compared to clinical assessment, this suggests that automated reports are most likely to falter when called upon to correlate so-called “borderline” OCT and VF results. It is in the interpretation of these borderline results, therefore, that clinical acumen becomes essential. These findings also support the validity and usefulness of the structure–function report as it suggests better than reported agreement between the automated report and clinical assessment with respect to sectors of real rim loss with corresponding VF defects. These sectors may correspond to higher glaucoma severity and are arguably areas of greater interest in the evaluation of glaucoma.

Several limitations exist for this study, one of which is the small sample size. Due to disagreement among physicians, one to three eyes were excluded from analysis for each OCT sector which could have affected final percent agreement. In addition, apart from OCT and VF results, physicians did not have access to additional clinical information or optic disk photographs which could have influenced their assessments. The almost exclusively Caucasian and African American subject population might also render it difficult to make conclusions generalizable to a more diverse population. Finally, while a 30% cut-off for indices of VF reliability is in line with those utilized in the literature, a more tolerant cut-off may translate to noisier results.

In summary, this study demonstrated good agreement between automated structure–function reports and physician evaluations, suggesting a role for these automated reports in the evaluation and treatment of glaucoma. While an integrated report does not replace clinical judgment, it could very well serve as a useful adjunct in the evaluation of glaucoma for a comprehensive eye care provider. The results presented here are those of a pilot study that provides timely data on the validity and utility of automated structure–function reports. A detailed evaluation with a larger sample size subdivided by glaucoma severity is warranted to render a definite conclusion regarding the usefulness of this novel technology.

Acknowledgements This study was made possible in part by the Wills Eye Innovation Grant No. WEF15064. Heidelberg

Engineering provided the Optical Coherence Tomography and Visual Field testing platforms used in this study.

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 in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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