Compressed 3D and 2D digital images versus standard 3D slide film for the evaluation of glaucomatous optic nerve features

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ABSTRACT

Synopsis Clinicians can feel confident compressed three-dimensional digital (3DD) and two-dimensional digital (2DD) imaging evaluating important features of glaucomatous disc damage is comparable to the previous gold standard of stereoscopic slide film photography, supporting the use of digital imaging for teleglaucoma applications.

Background/aims To compare the sensitivity and specificity of 3DD and 2DD photography with stereo slide film in detecting glaucomatous optic nerve head features.

Methods This prospective, multireader validation study imaged and compressed glaucomatous, suspicious or normal optic nerves using a ratio of 16:1 into 3DD and 2DD (1024×1280 pixels) and compared both to stereo slide film. The primary outcome was vertical cup-to-disc ratio (VCDR) and secondary outcomes, including disc haemorrhage and notching, were also evaluated. Each format was graded randomly by four glaucoma specialists. A protocol was implemented for harmonising data including consensus-based interpretation as needed.

Results There were 192 eyes imaged with each format. The mean VCDR for slide, 3DD and 2DD was 0.59±0.20, 0.60±0.18 and 0.62±0.17, respectively. The agreement of VCDR for 3DD versus film was κ=0.781 and for 2DD versus film was κ=0.69. Sensitivity (95.2%), specificity (95.2%) and area under the curve (AUC; 0.953) of 3DD imaging to detect notching were better (p=0.03) than for 2DD (90.5%; 88.6%; AUC=0.895). Similarly, sensitivity (77.8%), specificity (98.9%) and AUC (0.883) of 3DD to detect disc haemorrhage were better (p=0.049) than for 2DD (44.4%; 99.5%; AUC=0.72). There was no difference between 3DD and 2DD imaging in detecting disc tilt (p=0.7), peripapillary atrophy (p=0.16), grey crescent (p=0.1) or pallor (p=0.43), although 3D detected sloping better (p=0.013).

Conclusions Both 3DD and 2DD imaging demonstrates excellent reproducibility in comparison to stereo slide film with experts evaluating VCDR, notching and disc haemorrhage. 3DD in this study was slightly more accurate than 2DD for evaluating disc haemorrhage, notching and sloping.

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INTRODUCTION

Glaucoma is a common cause of irreversible blindness worldwide.[1] Studies predict a population of 76 million individuals suffering from glaucoma by 2020 and 111.8 million by 2040.[2] Early recognition of signs of progressive optic neuropathy through direct examination and photography of the nerve can lead to prompt intervention, thereby preventing vision loss. Imaging modalities, such as optical coherence tomography, can add value but do not replace nerve assessment as key findings including haemorrhages, and pallor may be missed and there may be difficulty obtaining a high-quality scan in the presence of significant peripapillary atrophy.

Stereoscopic slide film has traditionally been the gold standard, allowing for an accurate three-dimensional examination of the optic nerve.[3 4] In the last decade, however, slide film has been displaced by digital imaging in medical practices because of accessibility, convenience, care coordination, virtual storage and improving technology. Few studies have compared digital three-dimensional (3D) or two-dimensional (2D) to stereo slide film and this validation is important for ensuring quality care whether patients are seen in person or virtually (eg, via teleglaucoma).[1 5–7]

The purpose of this study is to determine the sensitivity and specificity of 2D digital (2DD) and 3D digital (3DD) imaging in comparison to stereoscopic slide film in patients with and without glaucoma.

MATERIALS AND METHODS

This prospective, multireader validation study was approved by the University of Alberta Human Research Ethics Board. Patients from Royal Alexandra Hospital Eye Clinic in Edmonton, Alberta, Canada, were included and consented if they were over the age of 50 and were newly referred for glaucoma or diabetes, the latter of which served as the control group to provide photographs of relatively healthy optic nerves. Patients were excluded if they could not undergo fundus photography due to media opacity, nystagmus or poor mydriasis (pupil dilation <4 mm). Patients were dilated using 1.0% tropicamide and 1.0% phenylephrine and then digital photographs were taken with a 30-degree fundus camera (Zeiss ff450 plus, Carl Zeiss, Jena, Germany) followed by stereoscopic slide film photographs (Zeiss ff450i with Polaroid, Carl Zeiss). Standard stereoscopic 7-field 35 mm slide film photographs were produced and placed in film holders. Each 17.2 MB (24bits/pixel) digital image was compressed using a ratio of 16:1 to

generate a 1.1 MB (1.5bits/pixel) JPEG image using Microsoft GDI+graphics library. Image sets were viewed on a proprietary software system (www.teleophthalmology.com) (Secure Diagnostic Imaging (SDI), Edmonton, Alberta, Canada). The system uses high refresh-rate monitors (>100 Hz) as well as an emitter box and LCD (liquid crystal display) shutter glasses (NuVision 60GX, MacNaughton, OR, USA) to provide stereopsis; the SDI system has been previously validated for use in diabetic retinopathy.[8 9] Stereoscopic slide film images were viewed with Donaldson stereo viewers (5+ diopters) and a standardised lighted viewing box.

Four fellowship-trained glaucoma specialists (KFD, KV, GD, MCE) independently graded the same sample of 192 eyes from 102 patients for each format. The sample of patients was presented in random order, with the right eye viewed first, then the left eye of the same patient. A disc assessment worksheet was developed based on the Reykjavik Eye Study and included several parameters pertinent to optic nerve assessment such as image quality, disc size, tilt, vessel morphology, presence of sloping, haemorrhage, notching, peripapillary atrophy and pallor.[10] To reduce recall bias, stereoscopic slide film photographs were interpreted a minimum of 3 months after completion of digital image grading. The quality of the images was graded on a Likert scale of 1 (poor) to 5 (outstanding) independently by each glaucoma specialist.

The primary outcome was vertical cup-to-disc ratio (VCDR), which has been shown to be a more accurate predictor of glaucoma than the horizontal cup-to-disc ratio (HCDR).[11] Eyes with diabetic retinopathy that had haemorrhage adjacent to or on the disc margin were considered 'negative,' assuming they were not related to glaucoma.

Because there were four graders involved in assessing all outcomes, a protocol was implemented for harmonising the data including a consensus-based interpretation of optic nerve head features when a disparity could not be resolved using harmonisation rules (see figure 1). Other secondary characteristics of interest were notching (defined as a focal area of loss of rim tissue), disc haemorrhages, HCDR, diagnosis based on nerve assessment only (definite glaucoma, suspect, normal), sloping (any, superior, inferior, temporal), pallor, grey crescent, peripapillary atrophy and tilt.[12]

A Microsoft Excel spreadsheet was used to compile the data and SAS (V.9.3, SAS Institute) was used for all analyses. The kappa statistic was employed as a measure of reproducibility

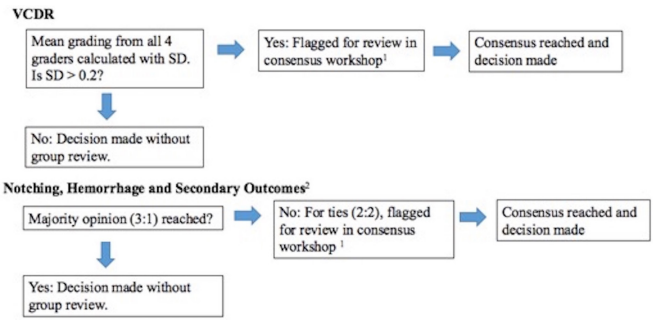

Figure 1 Harmonisation and consensus flow chart. [1]During consensus workshop, graders alternated in taking lead discussion. [2]Senior author (KFD) was used for ties relating to sloping, pallor, grey crescents, peripapillary atrophy and tilt. Note: No harmonisation for HCDR; glaucoma diagnosis(normal, suspect and definite) was based on majority assessment (3:1 or 2:1:1) with no ties. HCDR, horizontal cup-to-disc-ratio; VCDR, vertical cup-to-disc ratio.

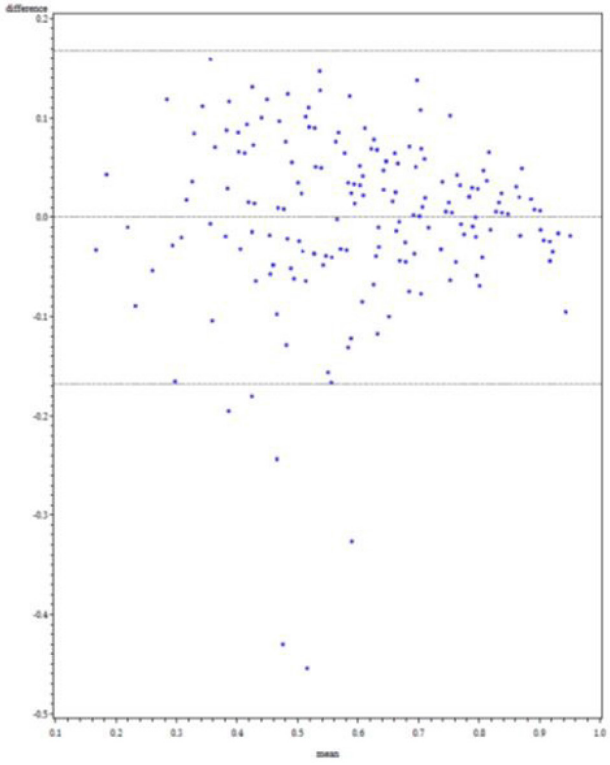

Figure 2 Bland-Altman type plot of VCDR mean 2DD and VCDR mean film. VCDR, vertical cup-to-disc ratio.

between 3DD, 2DD and stereoscopic slide film. Guidelines for evaluating the κ statistic were as follows: $\kappa>0.81$ demonstrates almost perfect agreement, $0.6<\kappa\leq0.8$ demonstrates substantial agreement, $0.4<\kappa\leq0.6$ indicates moderate agreement, $0.2<\kappa\leq0.4$ indicates fair agreement and $\kappa\leq0.2$ demonstrates only slight agreement.[13] Sensitivity, specificity and area under the receiver operating characteristic curve were calculated for the final 3DD and 2DD grading using stereoscopic slide film as the reference (gold) standard. Exact agreement was plotted for VCDR for each imaging format. Continuous variables, such as photo quality scores, were compared using simple linear regression. Statistical significance was defined as $p<0.05$. The effect of image quality was assessed through subgroup analyses that excluded eyes with mean quality image score of 2 or less.

RESULTS

A total of 192 eyes were imaged in 2DD, 3DD and stereoscopic slide film formats. Consensus review was necessary for 30 images in 2DD, 23 cases of 3DD and for 13 cases of stereoscopic slide film. Mean quality scores were significantly higher ($p<0.0001$) for stereoscopic slide film (3.62±0.68) than for 3DD (3.06±0.66) and 2DD (2.91±0.74). There were 19 images from the 3DD set, 19 images from the 2DD set and 9 images from the stereoscopic slide film set that had a mean quality score of 2 or less. Because some eyes had quality scores ≤2 for more than one image format, there were a total of 21 eyes labelled as poor quality that were excluded for the subgroup analyses of optimal image quality.

Vertical cup-to-disc ratio

The overall mean VCDR for 3DD was 0.59±0.18 and 2DD was 0.60±0.18 in comparison to 0.59±0.20 for stereoscopic slide

Table 1 Summary of agreement data for categorical variables

Feature	Kappa	AUC	Sensitivity	Specificity
Sloping (any) 3DD	0.48 (0.35–0.61)	0.77	76.64	76.36
Sloping (any) 2DD	0.34 (0.19–0.49)	0.65	89.05	41.82
Sloping (superior) 3DD	0.47 (0.33–0.61)	0.73	60.71	86.03
Sloping (superior) 2DD	0.29 (0.15–0.44)	0.65	53.57	76.47
Sloping (inferior) 3DD	0.22 (0.068–0.37)	0.61	43.18	79.73
Sloping (inferior) 2DD	0.31 (0.20–0.43)	0.72	81.82	61.69
Sloping (temporal) 3DD	0.48 (0.35–0.60)	0.74	65.12	82.08
Sloping (temporal) 2DD	0.43 (0.30–0.55)	0.72	74.42	68.87
Pallor 3DD	0.50 (0.33–0.67)	0.71	45.45	96.86
Pallor 2DD	0.53 (0.36–0.69)	0.74	45.45	94.34
Grey crescent 3DD	0.50 (0.29–0.72)	0.71	45	97.67
Grey crescent 2DD	0.49 (0.32–0.66)	0.82	75	88.95
Peripapillary atrophy 3DD	0.61 (0.48–0.75)	0.85	87.97	82.35
Peripapillary atrophy 2DD	0.48 (0.33–0.62)	0.79	83.54	73.53
Tilted discs 3DD	0.77 (0.57–0.96)	0.84	69.23	99.44
Tilted discs 2DD	0.51 (0.29–0.72)	0.82	69.23	93.85

2DD, two-dimensional digital; 3DD, three-dimensional digital; AUC, area under the curve.

film. There was substantial agreement for VCDR between 3DD and stereoscopic slide film (κ=0.781; 95% CI 0.740 to 0.823), with agreement within 0.1 for 90.6% of eyes. Similarly, κ=0.69 for 2DD (95% CI 0.63 to 0.74), which is substantial agreement with stereoscopic slide film. The VCDR was within 0.1 of the slide film value in 84.9% of cases for 2DD.

The exact agreement plot shown in figure 2 demonstrates a fairly random distribution of points above and below a mean difference of 0, although there was less variability for higher cup-to-disc ratios, suggesting better agreement when the cup-to-disc ratio is larger. Image quality did not have a significant effect on the agreement between formats; subgroup analysis excluding low-quality photographs demonstrated unchanged correlation (κ=0.790; 95% CI 0.749 to 0.832).

Secondary study outcomes

Notching

From the 3DD and the stereoscopic slide film set, there was one eye in each group that was excluded from the analysis because consensus could not be achieved during the group harmonisation process. No eyes were excluded from the 2DD set. The observation of notching correlated very well between stereoscopic slide film and 3DD, with κ=0.868 (95% CI 0.784 to 0.952; n=190). Overall, there were notches present in 22.1% of stereoscopic slide film eyes (n=42). The sensitivity and specificity (table 1) of 3DD imaging to detect notching were excellent at 95.2% and 95.3%, respectively, with an area under the curve (AUC)=0.953 (95% CI 0.916 to 0.989; figure 3).

Image quality did not affect correlation: κ=0.883 (95% CI 0.798 to 0.968) on subgroup analysis between stereoscopic slide film and 3DD. The observation of notching correlated with substantial agreement between stereoscopic slide film and 2DD, with κ=0.712 (95% CI 0.598 to 0.825; n=191). Two-dimensional digital imaging had a sensitivity of 90.5%, a specificity of 88.6% and an AUC=0.895 (95% CI 0.843, 0.947; figure 3). Image quality did not affect correlation: κ=0.731 (95% CI 0.611 to 0.8499) on subgroup analysis between stereoscopic slide film and 2DD.

Disc haemorrhage

Disc haemorrhages occurred in nine cases identified on stereoscopic slide film. The 3DD imaging had a sensitivity of 77.8% and a specificity of 98.9% to detect disc haemorrhages. The AUC was high at 0.883 (figure 4). There was substantial agreement between formats (κ=0.767; 95% CI 0.546 to 0.988), with no difference when analysing a subgroup that excluded poor image quality (κ=0.738, 95% CI 0.491, 0.984). When detecting disc haemorrhage, 2DD had a sensitivity of 44.4%, a specificity of 99.5% and an AUC value of 0.72, and there was moderate agreement (κ=0.557; 95% CI 0.241 to 0.872). Excluding poor-quality images, there was substantial agreement (κ=0.656; 95% CI 0.343 to 0.969).

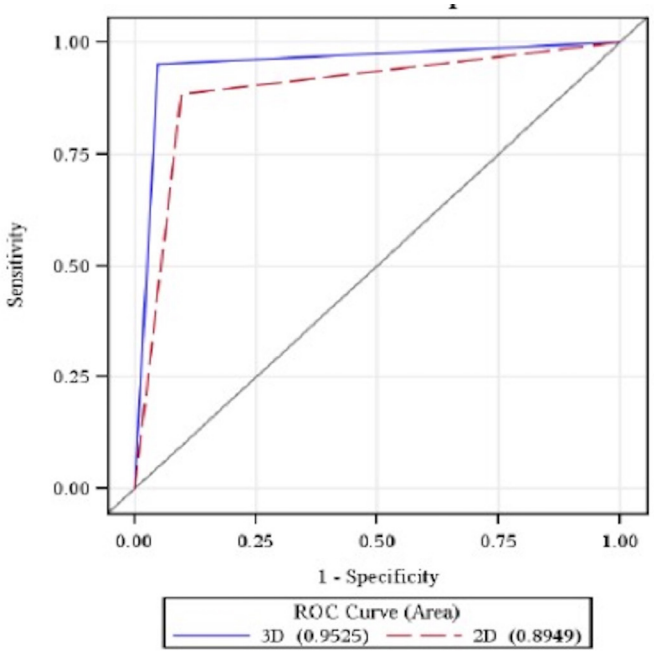

Figure 3 AUC notching ROC curves comparing 2D versus 3D digital. 2D, two-dimensional; 3D, three-dimensional; AUC, area under the curve; ROC receiver operating characteristic.

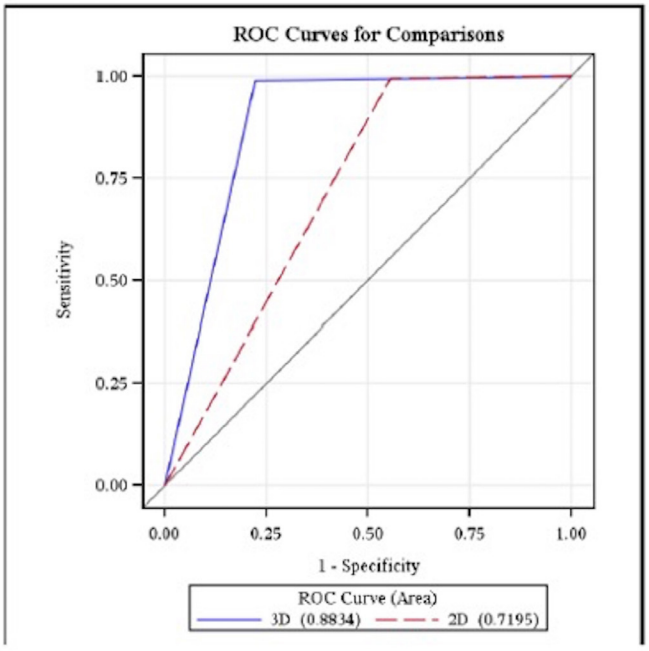

Figure 4 AUC disk haemorrhage ROC curves comparing 2D versus 3D. 2D, two-dimensional; 3D, three-dimensional; AUC, area under the curve; ROC receiver operating characteristic.

Similar data were calculated for other secondary study outcomes (table 1). The overall mean HCDR for 3DD was 0.56±0.17, for 2DD was 0.57±0.16, in comparison to 0.55±0.18 for stereoscopic slide film. Again, there was substantial agreement for HCDR between 3DD and stereoscopic slide film (κ=0.802; 95% CI 0.760 to 0.844), with agreement within 0.1 for 93.2% of eyes. There was substantial agreement between 2DD and stereoscopic slide film for HCDR 0.742 (κ=742, 95% CI 0.693 to 0.791), with agreement within 0.1 for 84.9% of eyes. The concordance for 3DD was considered moderate to substantial for most categorical disc parameters, including: sloping (any), superior sloping, temporal sloping, pallor, grey crescent, peripapillary atrophy and tilted discs. The lowest agreement occurred with inferior sloping (κ=0.22). The concordance for 2DD was considered fair to moderate for all categorical disc parameters, including: sloping (any), superior sloping, inferior sloping, temporal sloping, pallor, grey crescent, peripapillary atrophy and tilted discs.

Graders were also asked to categorically diagnose the presence of glaucoma based solely on the appearance of the optic nerve. Kappa values between graders for glaucoma diagnosis (definite glaucoma, suspect, normal) were 0.73 (95% CI 0.66 to 0.81) for 3DD and 0.65 (95% CI 0.57 to 0.73) for 2DD data.

DISCUSSION

Historically, stereoscopic slide film photography has been the gold standard for documenting disc appearance. Our results demonstrate excellent reproducibility of compressed stereo 3DD photography, when compared with stereoscopic slide film, to identify features of glaucomatous optic nerve damage including VCDR, notching and disc haemorrhage. There was also reasonable reproducibility for all other features of glaucomatous optic nerve damage such as sloping, grey crescent, pallor, peripapillary atrophy and tilt. We believe our results support the use of 3DD imaging for the diagnosis and management of glaucomatous disease.

2DD imaging also demonstrates good reproducibility compared with stereo slide film when evaluating VCDR, notching and disc haemorrhage. There was high concordance of VCDR, and many of the sensitivities and specificities were greater than 70%. When compared with 3DD, there was no difference with regard to VCDR evaluation, but 3DD was better when assessing disc haemorrhage and notching. This is intuitive, as the presence of a notch would be characterised by a change in contour that is more easily appreciated stereoscopically.

There have been few studies comparing stereoscopic digital images to conventional stereoscopic slide film, and the results vary. One small study (n=26 eyes) demonstrated perfect correlation in vertical elongation of the cup and presence of haemorrhage and 96% agreement in rim notching.[5] A study by Khouri *et al* (n=30) also demonstrated strong correlation, with a Spearman coefficient of 0.98 for VCDR and 0.95 for HCDR when comparing stereo digital to stereoscopic slide film.[6] These studies support our results for the correlation between stereoscopic digital imaging and conventional stereoscopic slide film.

Chan *et al* compared 20 pairs of monoscopic and stereoscopic images and concluded that there was good to substantial intraobserver agreement in the assessments of glaucoma likelihood (κ_w=0.56), cup shape (κ_w=0.65), nerve fibre layer loss (κ_w=0.69), VCDR (κ_w=0.58), disc shape (κ_w=0.57) and peripapillary atrophy (κ_w=0.65).[7] In our study, glaucoma diagnosis was a secondary outcome because it would be difficult for a clinician to accurately make this diagnosis without additional clinical information and functional testing.

In contrast to our study, Hasanreisoglu *et al* had three glaucoma specialists assess particular parameters of glaucoma using a majority rule (n=100).[1] For overall glaucoma diagnosis, digital imaging had a sensitivity of 61.5% and specificity of 81.3%. For the 35 mm slide film, the specificity ranged from 80% to 100% for features of glaucoma, and sensitivity ranged from 0% to 73%. With the exception of VCDR and HCDR, reproducibility between digital images of the optic nerve head and 35 mm slide film photographs was poor. For notching, Hasanreisoglu *et al* revealed low sensitivity of 54.5% when using digital imaging with 35 mm slide film serving as the gold standard, compared with 95% in our study. The three glaucoma experts failed to reach a common decision when analysing the same eye with digital imaging in 18%–46% of the eyes. Possible reasons for differences include the quality of the stereoscopic system used (Screen-Vu stereo viewer) and type of fundus camera (Zeiss 450+ and 4.5 megapixel camera), especially given that notching requires assessment of subtle differences in contour. Additionally, our study held a grading workshop prior to commencing the study to discuss and clarify definitions of notching, sloping and other parameters. As well, our images were largely of high quality, while this may have differed in the other study.

The sensitivity of the photography and the graders' ability to detect glaucomatous damage is dependent on the image quality, which is affected by the pixel resolution, storage format (lossless vs lossy compression) and camera optics quality. It is also dependent on the image viewing software, equipment and environmental variables when analysing images, such as room lighting and monitor brightness. Different methods in capturing and viewing 3D images are also available (ie, other than LCD shutter glasses) and application of these instruments needs to be assessed separately. Subjectively, the graders in this study felt that 3D slide film provided superior overall image quality after reviewing 192 images in both formats.

This study is particularly relevant because 2DD is more accessible than stereoscopic digital photos and does not require

stereo viewing devices. Our study revealed no differences in many parameters between 3DD and 2DD imaging, which suggests that it may be reasonable to use monoscopic imaging for a screening teleglaucoma programme. Innovative technologies to capture fundus photos, such as mobile phones, are increasing in popularity and may be more cost-effective compared with traditional fundus cameras. However, for staging disc damage, monitoring progression and management of patients with glaucoma, additional disc details such as disc haemorrhage, notching and sloping, which are imaged better in stereo, might be the preferred approach. Detailed comparisons of digital technology to gold standard slide film form a critical piece of the larger question of whether digital images are reliable as part of a teleglaucoma consultation, that is, whether patients with glaucoma can be safely diagnosed and managed using telehealth approaches, of which fundus photography of the optic nerve head is an integral part.[14]

There are some limitations to our study. Both eyes of a single patient were graded sequentially, although this was purposeful, in that this is how patients are evaluated in a clinical setting. A grader may have been more attune to glaucomatous features in the fellow eye if the first eye viewed demonstrated them. Graders felt the 'diagnosis' of glaucoma was artificially forced, as our study was based on nerve assessment only and did not consider the clinical exam or other ancillary testing. As such, we would not encourage readers to rely heavily on the results regarding glaucoma classification. The retinal nerve fibre layer was difficult to assess in many cases, and the study was not set up to capture this reliably, for example, with red-free photography. Disc size assessment was also not done consistently. Lastly, although this study used VCDR as the primary outcome, one could have used an alternate system for grading the nerve such as the disc damage likelihood scale.[15] Further studies are needed to investigate the reason for the low sensitivity displayed for disc haemorrhaging using 2DD.

We believe our results demonstrate that clinicians can feel confident that compressed 3DD and 2DD imaging (using specifications provided in our study) is comparable to the previous gold standard of stereoscopic slide film photography. These results support the use of digital imaging for teleglaucoma applications.

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Contributors All coauthors have read the final manuscript within their respective areas of expertise and participated sufficiently in the study to take responsibility for its conclusions. SS, CR, SA, FK: contributions to the design of the work; or interpretation of data for the work; drafting/revising of manuscript; final approval of the version to be published. The first author, SS, has had full access to all data reviewed for this manuscript and takes responsibility for the integrity of the data and affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted. GD, MCE, KV, BW: contributions to the design of the work; drafting/revising of manuscript; final approval of the version to be published. KFD: contributions to the design of the work; or interpretation of data for the work; final approval of the version to be published.

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Competing interests None declared.

Patient consent Detail has been removed from this case description/these case descriptions to ensure anonymity. The editors and reviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making.

Ethics approval University of Alberta Human Research Ethics Board.

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