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Optic Nerve Head and Retinal Nerve Fiber Layer Analysis:

A Report by the American Academy of Ophthalmology

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Abstract

Objective—To evaluate the current published literature on the use of optic nerve head (ONH) and retinal nerve fiber layer (RNFL) measurement devices in diagnosing open-angle glaucoma and detecting progression.

Methods—A search of peer-reviewed literature was conducted on February 15, 2006 in PubMed and the Cochrane Library for the period January 2003 to February 2006. The search was limited to studies of adults in English-language journals and yielded 442 citations. The panel reviewed the abstracts of these articles and selected 159 articles of possible clinical relevance for review. Of these 159 full-text articles, 82 were determined to be relevant for the first author and methodologist to review and rate according to the quality of evidence.

Results—There were no studies classified as having the highest level of evidence (level I). The ONH and RNFL imaging instruments reviewed in this assessment were determined to be highly effective in distinguishing eyes with glaucomatous visual field (VF) loss from normal eyes without VF loss, based on level II evidence. In addition, some studies demonstrated that parameters from ONH or RNFL imaging predicted the development of VF defects among glaucoma suspects. Studies on detecting glaucoma progression showed that although there was often agreement on progression between the structural and functional (VF) tests, a significant proportion of glaucoma patients progressed by either the structural or the functional test alone.

Conclusions—The ONH and RNFL imaging devices provide quantitative information for the clinician. Based on studies that have compared the various available technologies directly, there is no single imaging device that outperforms the others in distinguishing patients with glaucoma from controls. Ongoing advances in imaging and related software, as well as the impracticalities associated with obtaining and assessing optic nerve stereophotographs, have made imaging increasingly important in many practice settings. The information obtained from imaging devices is useful in clinical practice when analyzed in conjunction with other relevant parameters that define glaucoma diagnosis and progression.

Introduction

The American Academy of Ophthalmology prepares Ophthalmic Technology Assessments (OTAs) to evaluate new and existing procedures, drugs, and diagnostic and screening tests. The goal of an OTA is to review systematically the available research for the efficacy, safety, and importance of the procedure, drug, or test under review in clinical practice. After review by members of the OTA Committee, other Academy committees, relevant subspecialty societies, and legal counsel, assessments are submitted to the Academy's Board of Trustees for consideration as official Academy statements. The purpose of this assessment is to evaluate the clinical usefulness of the data obtained from optic nerve head (ONH) and retinal nerve fiber layer (RNFL) imaging devices.

An earlier assessment of these technologies and procedures was published in the July 1999 issue of this journal.[1] The American Glaucoma Society and the American Academy of

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Ophthalmology reviewed the literature on this topic (American Academy of Ophthalmology and American Glaucoma Society Work Group, unpublished data). The present OTA assesses data published since these evidence-based reviews.

Background

Glaucoma is an optic neuropathy characterized by retinal ganglion cell death and corresponding nerve fiber layer loss. Glaucomatous damage may result in characteristic visual field (VF) loss and ultimately cause blindness. Quigley et al demonstrated that there may be significant optic nerve damage before the appearance of VF loss on Goldmann perimetry.[2] More recently, in the Ocular Hypertension Treatment Study more than half of those who reached an end point (glaucoma) were diagnosed based on optic nerve progression.[3] Thus, the ability to detect preperimetric glaucoma may lead to early treatment and prevention of future field loss.

Over the past decade, imaging of the ONH and RNFL has gained widespread use for the diagnosis and follow-up of patients with and at risk for glaucoma. Traditionally, physician drawings and/or photographic documentation of the ONH have been essential aspects of the management of this disease. Serial stereophotography of the ONH has been considered the reference standard of care for patients with glaucoma. Evaluation of these photographic images has historically been recommended for assessing static optic nerve damage and for detecting glaucoma progression.[4,5]

This technology assessment provides an updated evidence-based review of OHN and RNFL analyzers used in the diagnosis and management of glaucoma. It focuses on the principal technologies—confocal scanning laser ophthalmoscopy (CSLO), optical coherence tomography (OCT), and scanning laser polarimetry (SLP). The retinal thickness analyzer (Talia Technologies, Inc., Lod, Israel), which uses the principle of slit-lamp fundus biomicroscopy to create a topographic map of the retinal thickness, was not assessed because it is no longer commercially available in the United States and peer-reviewed evidence supporting the use of this device was limited.

Brief descriptions of the 3 technologies are provided below. Table 1 lists selected specifications for the devices discussed in this assessment. For each device, normative data have been accumulated and are provided for comparison in the individual data printouts to aid in the statistical interpretation of the results.

Confocal Scanning Laser Ophthalmoscopy

Confocal scanning laser ophthalmoscopy generates up to 64 transaxial laser scans through the ONH and peripapillary retina to reconstruct a high-resolution 3-dimensional image. A 670-nm diode laser emits a beam that is focused in the x-axis and y-axis (horizontal and vertical dimensions) of the ONH, perpendicular to the z-axis (axis along the optic nerve). The reflected image from this plane is captured as a 2-dimensional scan. Successive equidistant images are obtained, up to 64 in total, depending on the cup depth. These sections are then combined to form a 3-dimensional construct of the ONH region. Surfaces of the optic cup, optic rim, and peripapillary retina are determined by a change in reflectance intensity along the z-axis at each point. This creates a topographic map for the calculation of cup-to-disc (C/D) ratio, rim area, and other optic disc parameters.

In this assessment, we focus on the CSLO devices from Heidelberg Engineering (Heidelberg, Germany): the Heidelberg Retina Tomographs I and II (HRT I and HRT II). Other CSLO devices, such as the TOP SS (Topcon, Inc., Tokyo, Japan), have not been

evaluated due to current unavailability of the device and limited published peer-reviewed evidence on the technology.

The HRT I can image at 10°, 15°, and 20° of width. The HRT II images at only 15°, with an algorithm that provides better resolution than its predecessor at that width (384 × 384 pixels, 11-μm lateral resolution). In addition, the HRT II possesses more automated features such as serial scans, averaging of the scans, and fine focus and scan depth. Both devices require user input in the form of drawing the disc margin. (The recently released HRT III has an operator-independent assessment of the disc, but evidence-based data on this function were minimal at the time of this assessment.) Optic disc parameters are then quantified as they relate to the reference plane (defined as that plane 50 μm below the neuroretinal rim as measured along the contour line at the inferior papillomacular bundle). No user input is required for progression analysis. Special algorithms in the HRT II and HRT III automatically align and normalize the entire topographic maps. Statistically significant local surface height change relative to the baseline examination is then highlighted and quantified.

Optical Coherence Tomography

Optical coherence tomography (Carl Zeiss Meditec, Inc., Dublin, CA) is the axial cross-sectional imaging of tissues based on the optical backscattering of low-coherence laser light (850 nm) as it passes through layers of differing optical density. The physical principles of OCT are similar to those of ultrasound, although OCT has much higher resolution. The backscattering of the stimulus light beam as it transitions from one layer (e.g., nerve fiber layer) to another (retinal ganglion cells) is recorded by an interferometer and amplified to construct a 2-dimensional image of the scanned area. The procedure is noncontact and requires dilation of the pupil in most cases.

Optical coherence tomography was first described in 1991 for imaging the retina and retinal pigment epithelium.[6] Subsequently, a glaucoma algorithm was developed that consisted of measuring the RNFL thickness along a 3.4-mm-diameter circle, centered on the optic disc. The OCT is also able to create a macular thickness map by performing a series of radial scans through the foveola. Recently, an additional optic disc algorithm was created that provides a 3-dimensional reconstruction of the ONH. This reconstruction is based on 3 axial scans through the center of the disc.

The currently available OCT (Stratus OCT, Carl Zeiss Meditec) is a third-generation model that delivers a resolution of approximately 7 to 8 μm. Retinal nerve fiber layer measurements for 360° are presented graphically as the double hump (in normal eyes), and averages for each quadrant and each clock hour are also displayed.

Scanning Laser Polarimetry

Scanning laser polarimetry (GDx Nerve Fiber Analyzer, Carl Zeiss Meditec) measures peripapillary RNFL thickness by sending a laser beam to the posterior retina and assessing the change in polarization (retardation) of the reflected beam. This retardation of the scanning beam results from the birefringent properties of the neurotubules contained within the ganglion cell axons. The laser scanning is also based on CSLO and has a wavelength of 780 nm. A high-resolution image of 256 by 256 pixels is created of the optic nerve and peripapillary retina. Each point is a measure of the retardation of the laser scan at its location. Three serial scans are obtained with each test. Although SLP measures RNFL thickness throughout the entire image, the RNFL thickness for the double hump is determined along a 3.2-mm-diameter 8-pixel-wide circle, centered on the disc (calculation circle). The double hump is a graphic plot of the RNFL thickness around the optic nerve that is observed in most normal individuals, with the superior and inferior poles having the

greatest RNFL thickness compared with the nasal and temporal poles. Some of the parameters presented are based on the RNFL thickness measurements within the calculation circle alone, but the nerve fiber indicator (a summary value that is intended to represent the likelihood of glaucomatous RNFL loss) is based on the entire RNFL thickness map. In addition, comparison of serial scans with normative data to help determine progression is available, and this is based on the entire image, not just the calculation circle.

Prior versions of the machine provided a fixed compensation for the corneal birefringence that contributes to the retardation of the laser signal (fixed corneal compensation [FCC]). However, the corneal effect may differ significantly among individuals, change over time, and be substantially altered after ocular surgery, particularly LASIK.[7] The updated device, GDx with variable corneal compensation (VCC), incorporates individualized compensation for the corneal component.

Food and Drug Administration Status

The HRT I, HRT II, and HRT III have been approved by the Food and Drug Administration for clinical use. The GDx, GDx VCC, OCT I, OCT II, and OCT III are also approved for clinical use. The HRT II, HRT III, GDx VCC, and OCT III are the only devices currently available for purchase in the U.S. Approval was pending for various commercial versions of the Fourier- or spectral-domain OCT during the writing of this assessment.

Resource Requirements

Although prices may vary, the list price at the time of writing (January 2007) for the HRT III (glaucoma only), Stratus OCT, and GDx VCC were $40 990, $61 950, and $47 950, respectively. In addition to the cost to purchase or lease these instruments, there is an additional expense of employing a skilled technician to obtain the imaging scans.

Questions for Assessment

The focus of this assessment is to address the following questions:

- How well does the device aid in glaucoma diagnosis, particularly as an adjunctive test to a complete ophthalmic examination including perimetric testing?
- Can glaucoma progression be detected with these devices?

Description of Evidence

A search of peer-reviewed literature was conducted on February 15, 2006 in PubMed and the Cochrane Library for the period January 1, 2003 to February 15, 2006. The search was limited to studies of adults published in English-language journals and yielded 442 citations. Abstracts of meeting presentations were not included in the analysis. The search strategy used the following terms: *confocal laser scanning tomography, laser scanning polarimetry, retinal thickness analyzer, retinal nerve fiber analysis, optical coherence tomography, optic nerve fiber analysis, optic nerve head analy* (truncated), *Heidelberg, HRT, retina* (truncated), *perimetry, static, optic nerve,* and *glaucoma.*

The panel reviewed the abstracts of these articles and selected 159 of possible clinical relevance for further review. The panel deemed 82 of these articles sufficiently clinically relevant for review by the panel methodologist and first author. They assigned one of the following ratings of level of evidence to each of the selected articles using a rating scale based on the one developed by the British Centre for Evidence-Based Medicine.[8] The OTA Committee used this system instead of the checklist for reporting diagnostic research developed by the Standards for Reporting of Diagnostic Accuracy steering committee.[9]

A level I rating was assigned to studies reporting an independent masked comparison of a cohort of consecutive patients with and without glaucoma, all of whom had undergone both the diagnostic test and the reference standard (a masked expert evaluation of stereophotographs of the ONH). A level II rating was assigned to an independent masked or objective comparison; a study performed in a set of nonconsecutive patients or confined to a narrow spectrum of study individuals (or both), all of whom had undergone both the diagnostic test and the reference standard; or an independent masked comparison of an appropriate spectrum in which the reference standard was not applied to all study patients. A level III study was applied to studies in which the reference standard was unobjective, unmasked, or not independent; studies in which positive and negative tests were verified using separate reference standards; or studies that were performed in an inappropriate spectrum of patients (comparing patients already known to have the target disorder with patients diagnosed with another condition). Of the 159 articles that were rated, none fulfilled the criteria for level I evidence. Fifty-one articles were assigned a level II evidence rating. The remaining 108 studies provided level III evidence.

The discriminate ability of the ONH and RNFL measurement devices for glaucoma is often described in the literature by the area under the receiver operator curve (ROC). The ROC is a graphical plot of the sensitivity versus (1 − specificity). The area under the ROC curve (AUC) can range from 0.5 to 1, with 1 representing the highest degree of discriminate ability.

Among the studies reviewed in this OTA, the methods used to determine glaucoma included tonometry, clinical ONH examination, stereophotography of the ONH, and automated perimetry. However, the criteria or thresholds for glaucoma varied among the studies. Similarly, the sensitivity and specificity thresholds for detecting glaucoma by an imaging device were set at differing levels in the various articles.

Published Results

How Well Does the Device Aid in Glaucoma Diagnosis, Particularly as an Adjunctive Test to a Complete Ophthalmic Examination Including Perimetric Testing?

Confocal Scanning Laser Ophthalmoscopy—Seven level II studies[10–16] addressed the correlation of CSLO output to glaucoma (Table 2). All data were acquired using the HRT I. Six of the 7 studies used a definition of glaucoma that incorporated glaucomatous VF defects (Ford et al,[11] Mardin et al,[12] Miglior I,[13] Miglior II,[14] Zangwill I[15]) or the development of VF loss (Bowd et al[10]). The definitions of glaucomatous VF defects varied among the studies. In the Ocular Hypertension Treatment Study, glaucoma was defined as a change in the optic disc consistent with glaucoma damage as determined by trained readers who were masked to the sequence of the sets of stereoscopic disc photographs they reviewed, and/or development of repeatable VF defects (Zangwill II).[16]

When an abnormal VF was used as the main criterion for glaucoma, the range of sensitivities was 51% to 97% and the range of specificities was 75% to 95% (Ford et al,[11] Mardin et al,[12] Miglior I,[13] Miglior II,[14] Zangwill I[15]). Areas under the ROC curve provided by Zangwill I[15] were between 0.75 and 0.96. Ford et al[11] compared the ability of 3 linear discriminant functions (algorithms that provide greater weight to parameters with greater importance) as well as the Moorfields Regression Analysis[17] to discriminate glaucoma from normal. Sensitivity was moderate to poor for the 3 linear discriminant functions (range, 39%–55%, with a fixed specificity of 95%) and not significantly better with the Moorfields Regression Analysis (58% sensitivity with 96% specificity when borderline outcomes were considered negative). Mardin et al[12] evaluated a nonparametric tree classifier algorithm (a detection algorithm that uses the full set of standard HRT measurements) and 2 published

linear discriminant functions and found better discrimination of glaucoma with their new system (82% sensitivity and 89% specificity). In Miglior I,[13] the authors compared the use of the Moorfields Regression Analysis with the multivariate discriminant analysis; they found better specificity with the Moorfields algorithm (94% vs. 75% by multivariate discriminant analysis) but better sensitivity using the multivariate analysis (83% vs. 74% by Moorfields Regression Analysis). In a subsequent article, Miglior II[14] compared the sensitivities and specificities of HRT I using different VF-based definitions of primary open-angle glaucoma (POAG). There was a wide range of sensitivities (51%–80%) but a narrow range of specificities (94%–95%) using 8 separate sets of VF criteria. Zangwill I[15] compared optic disc measurements—with a focus on RNFL height measurements along the rim—to parapapillary parameters on HRT I, and they reported that optic disc parameters discriminated better than parapapillary values for glaucomatous eyes. (Standard HRT printouts show global measurements of the optic disc including the rim.)

In addition to evaluating glaucoma patients with abnormal VFs, Miglior et al[13,14] studied glaucoma suspects who had intraocular pressure (IOP) > 22 mmHg. When suspect cases were included in the normal or glaucoma groups, the diagnostic accuracy (sum of true positives and true negatives divided by the total number) was reduced. This is likely due to the variable degree of disc damage, including those who did not have any significant damage, among the participants in this subgroup.

Bowd et al[10] studied the ability of HRT I classification techniques and stereophotograph evaluation to predict the development of repeatable VF defects among glaucoma suspects (ocular hypertension and/or suspicious optic nerves). The classification techniques used were standard HRT classification, Moorfields Regression Analysis, forward selection–optimized support vector machine and backward elimination–optimized support vector machine analysis of HRT data, and stereophotograph evaluation. (Support vector machine techniques are machine learning techniques applied to classification and regression problems; they are not available on standard HRT devices.) Multivariate analyses revealed that all techniques except standard HRT classification could predict the development of 2 repeatable abnormal VFs. With a criterion of 3 repeatable abnormal VF results, only support vector machine analyses and stereophotograph assessments were significant predictors.

In the Ocular Hypertension Treatment Study, a subgroup of subjects at some sites underwent HRT examination in addition to optic disc stereophotographs and VF tests. Many HRT parameters were found to be associated with the development of POAG by univariate and multivariate analyses (Zangwill II).[16] These factors included larger C/D area ratio, mean cup depth, mean height contour, cup volume, and reference plane height and smaller rim area, rim area–to–disc area ratio, and rim volume. The most predictive values were mean height contour, rim area, and mean cup depth. Outside-normal-limits classifications by the standard HRT algorithm and Moorfields algorithm were also significantly associated with glaucoma development (positive predictive value of 14% by either standard HRT or Moor-fields Regression Analysis, and 40% by Moorfields Regression Analysis temporal superior classification).

Optical Coherence Tomography—Among the studies evaluating OCT, none was rated as level I evidence, and 17 were assigned to level II (Table 3).[18–34] Ten articles used OCT III (Budenz et al,[19] Burgansky-Eliash et al,[20] Choi et al,[21] Ishikawa et al,[23] Leung I–III,[26–28] Manassakorn et al,[29] Medeiros I,[30] Wollstein I[34]), 6 used OCT II (Hougaard et al,[22] Kanamori et al,[24] Lederer et al,[25] Mok I–II,[31,32] Nouri-Mahdavi et al[33]), and 1 compared OCT II and OCT III (Bourne et al[18]). Ten studies (Budenz et al,[19] Burgansky-Eliash et al,[20] Hougaard et al,[22] Ishikawa et al,[23] Leung I,[26] Manassakorn et al,[29] Medeiros I,[30] Mok I–II,[31,32] Wollstein I[34]) compared healthy eyes with eyes that had glaucomatous VF loss, and

the other 7 (Bourne et al,[18] Choi et al,[21] Kanamori et al,[24] Lederer et al,[25] Leung II–III,[27,28] Nouri-Mahdavi et al[33]) incorporated a wider spectrum, including glaucoma suspects and/or ocular hypertensives.

Eight studies evaluated RNFL measurement and its relationship to glaucoma diagnosis or VF loss (Bourne et al,[18] Budenz et al,[19] Hougaard et al,[22] Kanamori et al,[24] Leung III,[28] Nouri-Mahdavi et al,[33] Mok I–II[31,32]). Mean RNFLs of the superior and inferior quadrants had the highest AUCs (0.79–0.952, superior; 0.863–0.971, inferior) for distinguishing eyes with glaucomatous VF loss from controls (Bourne et al, Budenz et al, Kanamori et al, Leung III, Nouri-Mahdavi et al). The 6, 7, 11, and 12 clock hours (in right eyes), representing the inferior/inferior–temporal and superior/superior–temporal areas of the optic nerve, had higher AUCs than other clock hours (Budenz et al, Kanamori et al, Nouri-Mahdavi et al). Overall, OCT III had higher AUCs than OCT II. In 3 of the studies, AUCs comparing controls and glaucoma suspects were available and were uniformly lower than for perimetric glaucoma (Kanamori et al, Leung III, Nouri-Mahdavi et al). The AUCs ranged from 0.591 to 0.840 for the superior quadrant and from 0.694 to 0.810 for the inferior quadrant.

In 3 of the 8 studies assessing the RNFL, AUCs were not available, but RNFL parameters were found to be significantly lower in perimetric glaucoma than in controls (Hougaard et al,[22] Mok I–II[31,32]). In addition, Hougaard et al found that the nerve fiber layer symmetry test, a detection algorithm comparing corresponding segments of the superior and inferior halves, had a high sensitivity (95%) and specificity (100%).

In 2 studies, macular parameters obtained from the OCT were used to distinguish glaucoma from healthy eyes (Ishikawa et al,[23] Lederer et al[25]). Using their macular segmentation algorithm and OCT III, Ishikawa et al found that the macular nerve fiber layer and inner retinal complex parameters were able to detect glaucomatous VF loss with AUCs as high as 0.97. In a study of the macular volume in normal and glaucomatous eyes using OCT II, Lederer et al reported a significant difference between controls and perimetric glaucoma but lack of significance between controls and glaucoma suspects.

Four studies compared the RNFL, ONH, and macular measurement functions of OCT III (Burgansky-Eliash et al,[20] Choi et al,[21] Medeiros I,[30] Wollstein I[34]). In 3 of the 4 studies that assessed AUCs for the structural parameters, RNFL and ONH measurements were more effective in glaucoma detection than were macular parameters (Burgansky-Eliash et al, Medeiros I, Wollstein I). Optic nerve head parameters such as C/D ratio and rim area performed very well, with AUCs similar to the best parameters of the RNFL.

Two studies evaluated both the RNFL and ONH parameters of OCT III (Leung I,[26] Manassakorn et al[29]). Leung I compared glaucoma detection using different reference plane offsets. An offset of 150 μm provided the best AUCs and correlations with VF loss for both RNFL and ONH parameters. Detection of perimetric glaucoma was similar for RNFL thickness (AUC = 0.957) as for the best ONH parameters (e.g., integrated rim volume AUC = 0.962). In comparing the fast optic disc scan and fast RNFL scan, Manassakorn et al found that both performed equivalently, with high AUCs for the 7-o'clock RNFL, inferior quadrant, and vertical C/D ratio (0.93, 0.92, and 0.90, respectively).

Finally, another study from Leung et al (Leung II[27]) compared the macular and peripapillary measurements of OCT III for detecting glaucoma among suspects and perimetric glaucoma patients. Overall, the RNFL parameters demonstrated higher AUCs than the macular parameters for both the suspect and the perimetric glaucoma groups. The inferior quadrant RNFL had the highest AUCs (0.67 for suspects, 0.91 for perimetric glaucoma).

Scanning Laser Polarimetry—There were 16 level II studies[35–50] correlating SLP measurements with glaucomatous damage (Table 4). Five of the 16 studies compared GDx VCC with GDx FCC for detecting glaucoma (Bowd II,[36] Brusini et al,[37] Da Pozzo et al,[39] Schlottmann et al,[49] Weinreb et al[50]). Five studies addressed only GDx FCC's ability to discern glaucomatous damage (Costa et al,[38] Galvao Filho et al,[41] Horn et al,[42] Mohammadi et al,[46] Munkwitz et al[47]), and the remaining 6 studies evaluated GDx VCC only (Bowd III,[35] Essock I,[40] Medeiros II–IV,[43–45] Reus and Lemij[48]). All articles except 4 (Bowd II,[36] Medeiros IV,[45] Mohammadi et al,[46] Munkwitz et al[47]) used a definition of glaucoma that required a VF defect at baseline.

The 5 studies evaluating only GDx FCC will not be discussed in detail because the device is no longer commercially available. The ability to detect glaucoma with VF defects was moderately strong at best: sensitivity and specificity were 82% and 83%, respectively, in a study by Costa et al,[38] and sensitivity was 64% at a fixed specificity of 95% in a study by Galvao Filho et al.[41]

The 6 articles on GDx VCC reported excellent correlation with glaucoma diagnosis (Bowd III,[35] Essock I,[40] Medeiros II–IV[43–45]) or VF defects (Reus and Lemij[48]). Bowd et al[35] used 2 machine learning classifiers that both had similar AUCs (0.90 and 0.91). Both Essock I and Medeiros II evaluated Fourier-based algorithms that produced high AUCs (0.938–0.978) for glaucoma detection. In another article, Medeiros III compared GDx VCC parameters with RNFL photography scores. Both techniques showed good correlations for damage in corresponding hemiretinas; however, the best GDX VCC parameter had an AUC (0.91 for nerve fiber indicator) higher than the best RNFL photography score (0.84 for global score). A subsequent article by Medeiros et al (Medeiros IV) used ONH progression by stereoscopic disc photographs as the criterion for glaucoma diagnosis. The best parameter was the nerve fiber indicator, with an AUC of 0.94 for eyes with perimetric loss at the baseline and 0.89 for preperimetric eyes. It should be noted that among standard GDx VCC parameters the nerve fiber indicator provided the highest AUCs (0.87–0.94) in the majority of studies (Bowd II, Medeiros III–IV).

Four of the 5 studies comparing GDx FCC with VCC revealed better discriminate function with VCC (Bowd II,[36] Brusini et al,[37] Schlottmann et al,[49] Weinreb et al[50]). The use of VCC significantly improved detection of glaucoma (Brusini et al, Weinreb et al) and correlation with VF loss (Boyd II, Schlottmann et al). Da Pozzo et al[39] found that all reported parameters on both GDx FCC and GDx VCC could discriminate perimetric glaucoma from healthy eyes. However, only eyes with properly compensated corneal birefringence on GDx FCC were included in this study. This was accomplished by obtaining macular retardation maps, which can indicate whether there is adequate corneal compensation.[51] As a result, comparison of results from both devices would reflect differences based on their overall technology and analytic software, independent of the corneal component. The lack of significant differences in correlation with glaucoma lends support to the concept that differences observed in the other comparative studies are directly related to the issue of accurate corneal compensation. Inadequate corneal compensation can lead to widening of the normal range, thus masking true glaucomatous defects in the RNFL.[50]

Comparison of Devices—Eight articles comparing devices in different classes were classified as level II,[52–59] and none was classified as level I (Table 5). Four studies examined OCT and GDx (Bagga et al,[52] Essock II,[53] Leung IV–V[55,56]). There was one study each on the following comparisons: HRT and GDx (Reus II[58]); HRT and OCT (Schuman et al[59]); HRT, retinal thickness analyzer, and OCT (Hoffmann et al[54]); and HRT, OCT, and GDx (Medeiros V[57]).

Two of the 4 articles that compared OCT with GDx provided AUCs for glaucoma detection (Essock II,[53] Leung IV[55]), revealing relatively equivalent abilities to discriminate. Using linear discriminant function based on Fourier analysis, Essock II found similar high AUCs for both OCT II (0.92) and GDx FCC (0.93). Leung IV compared RNFL measurement of OCT III with GDx VCC. The best regional parameters for each device were the inferior–temporal (7) clock hour of OCT III (AUC = 0.901) and the superior quadrant of GDx VCC (AUC = 0.909). Bagga et al[52] evaluated the correlation of RNFL imaging by OCT I, GDx FCC, and GDx VCC with VF loss. Using multiple regression models, several VCC parameters but no FCC parameters were correlated with VF mean deviation and OCT measurements. Leung V[56] found that, in general, OCT III values correlated with visual function better than GDx VCC in regression analyses.

The remaining comparative studies essentially found no significant differences among the compared devices. Reus II[58] showed good correlation of both the HRT I and GDx VCC sectors with VF loss as well as with each other. In the study by Schuman et al,[59] ONH measurements by the HRT I and OCT II and III showed excellent correlation with each other. There was relatively better correlation of OCT III with VF parameters as compared with OCT II. The AUCs for detecting glaucoma by clinical diagnosis or as defined by VF loss were similar in separate comparisons of the HRT I with OCT II and of the HRT I with OCT III. In their article comparing ONH measurements using the HRT II, retinal thickness analyzer, and OCT III, Hoffmann et al[54] described moderate to high correlations among the instruments. However, it was emphasized that the values were not interchangeable. Finally, Medeiros V[57] compared the 3 main devices in use today: GDx VCC (RNFL scan), HRT II (ONH scan), and OCT III (fast RNFL scan). They reported similar AUCs for the best parameters from each instrument—nerve fiber indicator for the GDx VCC (AUC = 0.91), inferior quadrant for OCT III (AUC = 0.92), and linear discriminant function of the HRT II (AUC = 0.86).

Can Glaucoma Progression Be Detected with These Devices?

There were 3 articles of level II evidence[60–62] that addressed the ability of these devices to detect progression of glaucoma (Table 6). Two of these used the HRT I (Artes and Chauhan,[60] Nicolela et al[61]) and 1 used a prototype OCT (Wollstein II[62]).

Both longitudinal prospective studies on HRT observed glaucoma patients who had already demonstrated glaucomatous VF loss at baseline. Artes and Chauhan[60] examined progression of visual function—assessed by standard automated perimetry and high-pass resolution perimetry—and optic disc changes using the HRT I. Using evidence-of-change analyses developed by their group, the authors found that although there was considerable overlap of eyes that were identified as having progressed by the 3 tests, with particularly good correlation between standard automated perimetry and high-pass resolution perimetry progressors, significant numbers of eyes were found to have progressed by only functional or structural (HRT) criteria. These findings suggest that the separate sets of tests may represent independent indicators of progression. In a study using the same test procedures for detecting progression, Nicolela et al[61] compared progression rates among different disc types and found the lowest rates of functional and structural progression among the senile sclerotic type. Across all 4 groups of different disc types (focal, myopic, senile sclerotic, and generalized), progression rates by HRT (44%–82%) were greater than those by standard automated perimetry (33%–57%), echoing their earlier reported results.[63] Furthermore, there were similarly high rates of progression by either test alone (20%–61%) across the groups.

Wollstein II[62] also reported higher rates of progression when a structural test was used (25%)—in this case, OCT—as compared with standard automated perimetry (12%), although their study population included glaucoma suspects and preperimetric glaucoma

patients in addition to patients with baseline VF defects. It is unclear if this represents greater sensitivity for progression or hypersensitivity (false positives) of the structural test.

Conclusions

Among the 159 articles reviewed in this assessment, none was rated as level I evidence, and 51 were given a level II rating. The level II studies evaluated (1) rates of detection of glaucomatous VF loss and correlation with VF loss, (2) ability to detect disease among glaucoma suspects and patients with preperimetric glaucoma, (3) relative efficacy of devices in comparative studies, and (4) rates of detection for structural changes compared with VF loss.

The AUCs and sensitivity/specificity profiles for the various instruments were highly variable depending on the definition of glaucoma, the algorithm used for detection, and the study population. Several studies examined commercially unavailable detection algorithms, such as linear discriminant functions and vector machine analyses, which often demonstrated greater sensitivity for the detection of glaucoma than standard parameters or algorithms. However, selected standard measurements and outputs have shown good detection rates. The multivariate and Moorfields algorithms of the HRT I provide good ability to distinguish between glaucomatous and normal eyes. With the OCT, RNFL and ONH scans outperform the macular scan. The RNFL thickness in the inferior and superior quadrants, as well as the inferior/inferior–temporal and superior/superior–temporal clock hours, provided the best AUCs for glaucoma detection. The C/D ratio, rim area, and integrated rim volume of the ONH scan also correlated strongly with glaucoma. With respect to the SLP technology, the GDx VCC improved the ability to detect glaucoma compared with GDx FCC, and it also had better correlation with VF defects. In most studies, the nerve fiber indicator had the highest AUCs among standard parameters.

Comparison of results between different studies cannot be made directly in this assessment. Sensitivities and specificities are highly dependent on the parameter(s) and algorithms used as well as the definition of glaucoma. As shown by Miglior et al,[14] the definition of glaucoma can vary tremendously across studies and significantly affect sensitivity (51%–80%), but less so specificity (94%–95%) of the same cohort tested with the HRT I. Furthermore, when efficacy is assessed based on user interpretation of results, the experience of the user appears to have a significant effect on sensitivity and specificity, as demonstrated by Munkwitz et al[47] with GDx FCC.

Most of the published studies have included only patients with VF loss. Although these studies are important for initial evaluation of the tests, they have limited utility in clinical practice. For the clinician, the ability to distinguish glaucoma from normal in suspect patients is of greater practical value.

In general, when glaucoma suspects with normal VFs were included in a study, the sensitivity and specificity (or the AUC) were significantly lower when compared with the patients defined as having glaucoma confirmed by VF abnormalities characteristic of the disease. Patients in the suspect groups likely included those without glaucoma. Further, those with early glaucoma who have not yet demonstrated VF abnormality or progression likely have ONH and RNFL loss that is, on average, not as advanced, as seen in the overall group of patients with documented glaucomatous VF defects. The early stage of disease is a subset of patients from this former group and may not reach the threshold for clinical classification as glaucoma. This was demonstrated by Medeiros IV,[45] who used ONH progression on stereophotographic examination as the criterion for glaucoma diagnosis. Among eyes with ONH progression, the detection rate for glaucoma using GDx VCC was

statistically significantly higher among those who had glaucomatous VF defects at baseline (AUC = 0.94 for nerve fiber indicator) than among those who had normal fields (AUC = 0.89 for nerve fiber indicator) at baseline.

Among the studies that directly compared instruments in different categories, there were no significant differences in their ability to distinguish glaucoma from controls. The comparison of GDx VCC, OCT III, and the HRT II by Medeiros V[57] showed similar AUCs for the best parameters from each device. These parameters were nerve fiber indicator for GDx VCC, inferior quadrant for OCT III, and linear discriminant functions for the HRT II.

There were few studies that addressed the detection of glaucoma progression. In all 3 level II investigations, there were significant percentages of glaucomatous eyes that progressed by either VF or structural change (as determined by HRT or OCT scanning) alone. This relative lack of concordance may reflect separate measures of progression by the functional and structural tests. In the study by Wollstein II[62] in which glaucoma suspects and preperimetric glaucoma cases were included, OCT detected progression at a substantially higher rate than the functional test, which may reflect either better sensitivity or hypersensitivity (false positives) of the structural test. Longer follow-up to observe for future VF progression as well as additional studies will help to answer the question of whether structural progression is truly an early sign of later functional loss.

Some of the reviewed studies also investigated the diagnostic effectiveness of expert evaluation of high-quality optic disc stereophotographs or red-free RNFL photographs in the diagnosis of glaucoma,[10,44,46] and they found similar or better predictive power compared with the devices that were being assessed. Such rigorous grading regimens of the disc or RNFL photographs as used in the above studies are impractical for the general clinician. Furthermore, the 2 studies[10,46] that examined optic disc photographs tested 2 older-model instruments (HRT I and GDx FCC), which had either poorer resolution (HRT I) or problems with artifact (GDx FCC) compared with their current models.

In the final analysis, the clinician needs to become familiar with the device used and incorporate his or her interpretation of the test results into the broader clinical assessment of the patient, which includes factors such as age, IOP, clinical ONH/RNFL examination, central corneal thickness, family history, and VF status. One cannot rely solely on ONH/RNFL imaging devices to diagnose and follow glaucoma with the instruments that are currently available. The positive and negative predictive values of these devices when used in conjunction with other available diagnostic modalities will vary not only by device but also by the presenting clinical scenario as well as by the skill of both operator and interpreter. However, using data from these devices can provide the practitioner with useful information in terms of quantitative structural assessment of the optic nerve, which is important in glaucoma management.

Future Research and Direction

There have been recent advances in the quality of algorithms used for detecting glaucoma and glaucoma progression with imaging devices. As newer software and hardware technologies are introduced, further refinement of the analytic software will assist in the diagnosis and follow-up of patients with glaucoma.

There is need for longer-term studies on the correlation of change in parameters assessed by such devices and glaucoma progression. Long-term follow-up is required to determine whether or not specific changes in such parameters predict later VF progression. As the use of imaging devices increases throughout the world, data sets specific to particular ethnic groups will be necessary to validate the importance of the various image parameters in such

populations. Future development of higher-resolution devices will hopefully result in greater sensitivity and specificity in diagnosing glaucoma and assessing progression. Shorter scan times will also decrease the labor costs associated with such devices.

Interpreting the relevance of the data obtained from various imaging devices will continue to be a challenge that will hopefully be diminished by better reproducibility and validity of the data that are generated.

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Table 1

Optic Nerve Head (ONH) and Retinal Nerve Fiber Layer (RNFL) Devices

Device	Resolution	Data Obtained	Acquisition Time per Scan	Dilation Required?
Heidelberg Retina Tomograph II	11 μm	ONH and rim parameters	5 sec	No
Stratus Optical Coherence Tomography	7–8 μm (axial)	RNFL thickness along 3.4-mm-diameter circle around ONH; ONH parameters; macular thickness	2 sec per structure	In most cases
GDx Nerve Fiber Analyzer VCC	13 μm	RNFL thickness along 3.2-mm-diameter circle around ONH	1 sec for corneal baseline; 1 sec for RNFL scan	No

VCC = variable corneal compensation.

Table 2

Level II Studies of Confocal Scanning Laser Ophthalmoscopy

Study	Device	Study Populations	Definition of Glaucoma	Comments
Bowd I[10]	HRT I	Glaucoma suspect	Visual field progression	Assessed HRT parameters and stereophotographs as predictors of visual field abnormalities
Ford[11]	HRT I	Healthy, glaucoma	ONH damage, abnormal visual field	Compared different analytic algorithms for glaucoma detection
Mardin[12]	HRT I	Healthy, glaucoma	Visual field defect, ONH damage on photographic examination	Evaluated new classification algorithms
Miglior I[13]	HRT I	Healthy, ocular hypertension, glaucoma	IOP > 21 mmHg, abnormal visual field loss	Compared Moorfields with multivariate discriminant analysis
Miglior II[14]	HRT I	Healthy, ocular hypertension, glaucoma	IOP > 21 mmHg, abnormal visual field	Evaluated the impact of glaucoma definition on HRT validity
Zangwill I[15]	HRT I	Healthy, glaucoma	Abnormal visual field	Compared optic disc and parapapillary retina classifiers
Zangwill II[16]	HRT I	Ocular hypertension	Optic disc, visual field progression	Evaluated predictive parameters for glaucoma development

HRT = Heidelberg Retina Tomograph; IOP = intraocular pressure; ONH = optic nerve head.

Table 3

Level II Studies of Optical Coherence Tomography (OCT)

Study	Device	Study Populations	Definition of Glaucoma	Comments
Bourne[18]	OCT II, III	Healthy, glaucoma suspect, glaucoma	Visual field defect	Comparison of RNFL measurements by OCT II versus OCT III
Budenz[19]	OCT III	Healthy, glaucoma	Visual field defect	Detection of perimetric glaucoma
Burgansky-Eliash[20]	OCT III	Healthy, glaucoma	Visual field defect, ONH damage	Analysis of machine learning classifiers in glaucoma detection
Choi[21]	OCT III	Healthy, ocular hypertension, glaucoma	Abnormal visual field, IOP > 21 mmHg, C/D ratio > 0.5	Comparison of ONH, RNFL, and macular thickness parameters
Hougaard[22]	OCT II	Healthy, glaucoma	Abnormal visual field or ONH damage	Nerve fiber layer symmetry test for glaucoma detection
Ishikawa[23]	OCT III	Healthy, glaucoma	Abnormal visual field plus ONH/RNFL damage or IOP > 32 mmHg	Macular segmentation analysis for the detection of glaucoma
Kanamori[24]	OCT II	Healthy, ocular hypertension, glaucoma suspect, glaucoma	Abnormal visual field, ONH damage	Detection of glaucoma and correlation with visual field
Lederer[25]	OCT II	Healthy, ocular hypertension, glaucoma suspect, glaucoma	Abnormal visual field, ONH/RNFL damage	Correlation of macular volume parameters with glaucoma stage
Leung I[26]	OCT III	Healthy, glaucoma	Abnormal visual field	Comparison of RNFL and ONH parameters with different reference plane offsets
Leung II[27]	OCT III	Healthy, glaucoma suspect, glaucoma	Abnormal visual field, ONH damage	Comparison of macular and RNFL measurements for the detection of glaucoma
Leung III[28]	OCT III	Healthy, ocular hypertension, glaucoma suspect, glaucoma	Visual field defect, ONH damage	Comparison of standard with fast RNFL scanning
Manassakorn[29]	OCT III	Healthy, glaucoma	Visual field defect	Comparison of RNFL and optic disc algorithms
Medeiros I[30]	OCT III	Healthy, glaucoma	Visual field defect	Comparison of RNFL, ONH, and macular parameters for glaucoma detection
Mok I[31]	OCT II	Healthy, glaucoma	Visual field defect, IOP > 22 mmHg	RNFL loss at different stages of perimetric glaucoma
Mok II[32]	OCT II	Healthy, high- and normal-tension glaucoma	Visual field defect	RNFL loss in high-tension, normal-tension glaucomas
Nouri-Mahdavi[33]	OCT II	Healthy, glaucoma suspect, early glaucoma	Abnormal visual field	Detection of preperimetric and perimetric glaucoma
Wollstein I[34]	OCT III	Healthy, glaucoma	Visual field defect	Comparison of macular, RNFL, and ONH parameters in glaucoma detection

C/D = cup-to-disc; IOP = intraocular pressure; ONH = optic nerve head; RNFL = retinal nerve fiber layer.

Table 4

Level II Studies of Scanning Laser Polarimetry

Study	Device	Study Populations	Definition of Glaucoma	Comments
Bowd II[36]	GDx FCC, GDx VCC	Glaucoma suspect, glaucoma	ONH damage and/or abnormal visual field	Correlation of FCC and VCC results to visual field
Bowd III[35]	GDx VCC	Healthy, glaucoma	Visual field loss	Comparison of 2 glaucoma detection algorithms
Brusini[37]	GDx FCC, GDx VCC	Healthy, glaucoma	Visual field loss	Comparison of FCC with VCC
Costa[38]	GDx FCC	Healthy, glaucoma	IOP > 22 mmHg, ONH damage and visual field loss	Influence of baseline factors on detection
Da Pozzo[39]	GDx FCC, GDx VCC	Healthy, glaucoma	Visual field loss	Comparison of FCC with VCC results
Essock I[40]	GDx VCC	Healthy, glaucoma	Abnormal visual field	Wavelet–Fourier analysis for glaucoma detection
Galvao Filho[41]	GDx FCC	Healthy, glaucoma	ONH damage, abnormal visual field	Detection of glaucoma and correlation with visual field
Horn[42]	GDx FCC	Healthy, ocular hypertension, preperimetric glaucoma, glaucoma	ONH damage, visual field defect	Use of frequency doubling perimetry and GDx FCC for detection of glaucoma
Medeiros II[43]	GDx VCC	Healthy, glaucoma	Visual field defect	Fourier analysis for glaucoma detection
Medeiros III[44]	GDx VCC	Healthy, glaucoma suspect, glaucoma	Visual field defect	Comparison of GDx VCC and RNFL photography
Medeiros IV[45]	GDx VCC	Healthy, glaucoma	ONH progression by photographic examination	Detection of glaucoma as defined by ONH progression
Mohammadi[46]	GDx FCC	Glaucoma suspect	Visual field progression	Parameters that predict visual field progression
Munkwitz[47]	GDx FCC	Healthy, early glaucoma, glaucoma	RNFL defects and/or visual field loss	Detection of different stages of glaucoma
Reus I[48]	GDx VCC	Healthy, glaucoma	ONH damage and visual field loss	Correlation of VCC with perimetry
Schlottmann[49]	GDx FCC and VCC with prototype compensator	Healthy, glaucoma	Visual field defect	Correlation of visual field with RNFL by FCC and VCC
Weinreb[50]	GDx FCC, GDx VCC	Healthy, glaucoma	Visual field loss	Detection of glaucoma with VCC

FCC = fixed corneal compensation; IOP = intraocular pressure; ONH = optic nerve head; RNFL = retinal nerve fiber layer; VCC = variable corneal compensation.

Table 5

Level II Studies Comparing Devices

Study	Devices	Study Populations	Definition of Glaucoma	Comments
Bagga[52]	GDx FCC, GDx VCC, OCT I	Healthy, glaucoma	ONH damage and abnormal visual field	Comparison of FCC, VCC, and OCT results
Essock II[53]	OCT II, GDx FCC	Healthy, glaucoma	Abnormal visual field	Assessment of Fourier-based analysis for glaucoma detection
Hoffman[54]	HRT II, RTA, OCT II	Healthy, glaucoma	Visual field defect	Comparison of ONH measures by 3 instruments
Leung IV[55]	OCT III, GDx VCC	Healthy, glaucoma suspect, glaucoma	Visual field defect	Detection of glaucoma, and correlation of OCT and GDx VCC measurements
Leung V[56]	OCT III, GDx VCC	Healthy, glaucoma suspect, glaucoma	Visual field defect	Correlation with visual field loss
Medeiros V[57]	HRT II, OCT III, GDx VCC	Healthy, glaucoma	Visual field defect	Comparison of devices for glaucoma detection
Reus II[58]	HRT I, GDx VCC	Healthy, glaucoma	Visual field defect, abnormal ONH	Correlation of HRT I and GDx VCC parameters with visual field
Schuman[59]	HRT I, OCT II and OCT III	Healthy, glaucoma suspect, glaucoma	ONH/RNFL defect and visual field defect or IOP > 35 mmHg	Comparison of ONH measurements

FCC = fixed corneal compensation; HRT = Heidelberg Retina Tomograph; IOP = intraocular pressure; OCT = optical coherence tomography; ONH = optic nerve head; RNFL = retinal nerve fiber layer; RTA = retinal thickness analyzer; VCC = variable corneal compensation.

Table 6

Level II Studies on Detecting Progression of Glaucoma

Study	Device	Study Populations	Definition of Glaucoma Progression	Comments
Artes[60]	HRT I	Healthy, glaucoma	Visual field progression	Correlation of visual field and HRT progression
Nicolela[61]	HRT I	Glaucoma	Visual field progression	Correlation of visual field and HRT progression with optic disc type
Wollstein II[62]	Prototype OCT	Glaucoma suspect, glaucoma	Visual field progression	Correlation of visual field and OCT progression

HRT = Heidelberg Retina Tomograph; OCT = optical coherence tomography.