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Can Automated Imaging for Optic Disc and Retinal Nerve Fiber Layer Analysis Aid Glaucoma Detection?

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Purpose: To compare the diagnostic performance of automated imaging for glaucoma.

Design: Prospective, direct comparison study.

Participants: Adults with suspected glaucoma or ocular hypertension referred to hospital eye services in the United Kingdom.

Methods: We evaluated 4 automated imaging test algorithms: the Heidelberg Retinal Tomography (HRT; Heidelberg Engineering, Heidelberg, Germany) glaucoma probability score (GPS), the HRT Moorfields regression analysis (MRA), scanning laser polarimetry (GDx enhanced corneal compensation; Glaucoma Diagnostics (GDx), Carl Zeiss Meditec, Dublin, CA) nerve fiber indicator (NFI), and Spectralis optical coherence tomography (OCT; Heidelberg Engineering) retinal nerve fiber layer (RNFL) classification. We defined abnormal tests as an automated classification of outside normal limits for HRT and OCT or NFI $\geq$ 56 (GDx). We conducted a sensitivity analysis, using borderline abnormal image classifications. The reference standard was clinical diagnosis by a masked glaucoma expert including standardized clinical assessment and automated perimetry. We analyzed 1 eye per patient (the one with more advanced disease). We also evaluated the performance according to severity and using a combination of 2 technologies.

Main Outcome Measures: Sensitivity and specificity, likelihood ratios, diagnostic, odds ratio, and proportion of indeterminate tests.

Results: We recruited 955 participants, and 943 were included in the analysis. The average age was 60.5 years (standard deviation, 13.8 years); 51.1% were women. Glaucoma was diagnosed in at least 1 eye in 16.8%; 32% of participants had no glaucoma-related findings. The HRT MRA had the highest sensitivity (87.0%; 95% confidence interval [CI], 80.2%–92.1%), but lowest specificity (63.9%; 95% CI, 60.2%–67.4%); GDx had the lowest sensitivity (35.1%; 95% CI, 27.0%–43.8%), but the highest specificity (97.2%; 95% CI, 95.6%–98.3%). The HRT GPS sensitivity was 81.5% (95% CI, 73.9%–87.6%), and specificity was 67.7% (95% CI, 64.2%–71.2%); OCT sensitivity was 76.9% (95% CI, 69.2%–83.4%), and specificity was 78.5% (95% CI, 75.4%–81.4%). Including only eyes with severe glaucoma, sensitivity increased: HRT MRA, HRT GPS, and OCT would miss 5% of eyes, and GDx would miss 21% of eyes. A combination of 2 different tests did not improve the accuracy substantially.

Conclusions: Automated imaging technologies can aid clinicians in diagnosing glaucoma, but may not replace current strategies because they can miss some cases of severe glaucoma. *Ophthalmology 2016;123:930-938 Crown Copyright © 2016 Published by ELSEVIER Inc. on behalf of American Academy of Ophthalmology. This is an open access article under the Open Government Licence (OGL) (http://www.nationalarchives.gov.uk/doc/open-government-licence/version/3/).*

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Diagnosis of glaucoma by an experienced ophthalmologist remains the best reference standard.[1] However, diagnosis can be challenging, especially in people with early glaucoma. Accurate clinical diagnosis of glaucoma is limited by subjectivity, reliance on the examiner's experience, and a wide variation of optic disc structure among the population.[1,2]

Automated imaging of the optic nerve head or retinal nerve fiber layer (RNFL) increasingly is being introduced into practice for diagnosis and monitoring.[3] Interpretation of some of the outputs may require expertise, but classification of results as normal or abnormal also can be generated by automatic comparison with a normative database.

Several imaging technologies that quantify the structure of the retina and optic nerve head can be used in glaucoma.[4] Confocal scanning laser ophthalmoscopy is commercially available as Heidelberg retina tomograph (HRT; Heidelberg Retina Tomograph III [Heidelberg Engineering, Heidelberg, Germany]). It includes 2 classification algorithms, the

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Moorfields regression analysis (MRA)[5] and the glaucoma probability score (GPS).[6,7] The RNFL can be assessed using either scanning laser polarimetry, currently available as the GDx-PRO (Glaucoma Diagnostics [GDx] Carl Zeiss Meditec, Dublin, CA)[8] or spectral-domain optical coherence tomography (OCT), with several commercial devices available.[9] These imaging tests are user friendly and provide automated quantitative classifications.[10]

Although many published data describe the diagnostic performance of imaging techniques in cohorts of retrospectively selected glaucoma patients or glaucoma-free normal subjects, there is no high-quality evidence of the comparative accuracy of current imaging techniques for identifying glaucoma in consecutive patients with unknown status screened for possible glaucoma.[4,11] Existing data from case-control studies may not be applicable to the clinically relevant population who undergo assessment and diagnosis.[12] We aimed to assess and compare the performance of these commercially available technologies to detect glaucoma in a prospective cohort. This work was conducted as part of a wider publicly funded study (National Institute for Health Research Health Technology Assessment [HTA], 09/22/111) that also evaluated cost-effectiveness of these imaging technologies in a triage setting in the United Kingdom.

Methods

Study Design and Participants

We conducted a pragmatic multicenter, within-patient, comparative evaluation of the diagnostic accuracy of automated imaging techniques for diagnosis of glaucoma, the Glaucoma Automated Tests Evaluation (GATE). We selected participants prospectively, and they underwent imaging with all technologies under evaluation and then had the reference standard diagnosis (clinical assessment by a glaucoma expert, including examination of the fundus by biomicroscopy and visual field testing with Humphrey 24-2 Swedish interactive threshold algorithm testing, masked to the imaging test results). The study was approved by the North of Scotland Research Ethics Committee (reference, 10/S0801/58) and was conducted according to the tenets of the Declaration of Helsinki. The full study protocol is publicly available.[13] We sought patient views on the design, conduct, and analysis of the study through representatives from the International Glaucoma Society.

The study was coordinated from a central study office in the Health Services Research Unit, University of Aberdeen, and was conducted in 5 National Health Service hospital eye services in the United Kingdom (Aberdeen, Bedford, Hinchingbrooke, Liverpool, and Moorfields). We identified eligible patients from their referral letter as being adults (age ≥18 years) who were newly referred from primary care to the department of ophthalmology of the recruiting hospital with a possible glaucoma diagnosis or glaucoma-related finding. This included high intraocular pressure; possible abnormalities in the optic disc, visual field test results, or both; and possible narrow anterior chamber angle. Patients were ineligible if they had a previous diagnosis of glaucoma or had already been seen by an ophthalmologist.

Participant Recruitment Process

We sent information about the study to potential eligible patients at each recruiting hospital, before their first hospital appointment. At their first clinic appointment, we then approached patients, and those patients who agreed to participate and signed the consent

Table 1. Possible Diagnoses by the Clinician Performing the Reference Standard Measurement, Ranked in Order of Severity

Diagnosis	Definition
Glaucoma	
Severe	Evidence of glaucomatous optic neuropathy* and a characteristic visual field loss† with MD of −12.01 dB or worse
Moderate	Evidence of glaucomatous optic neuropathy* and a characteristic visual field loss† with MD between −6.01 dB and −12 dB
Mild	Evidence of glaucomatous optic neuropathy* and a characteristic visual field loss† with MD of −6 dB or better
Glaucoma suspect	
Disc suspect	Appearance suggestive of glaucomatous optic neuropathy, but also may represent a variation of normality, with normal visual fields (with or without high IOP)
Visual field suspect	Visual field loss suggestive of glaucoma, but also may represent a variation of normality, with normal appearance of the optic disc (with or without high IOP)
Visual field and disc suspect	Both the optic disc and visual field have some features that resemble glaucoma, but also may represent a variation of normal (with or without high IOP)
Ocular hypertension	Both the visual field and optic nerve appear normal in the presence of elevated pressure >21 mmHg
Primary angle closure	Closed anterior chamber angle (appositionally or synechial) in at least 270° and at least 1 of the following 2: IOP >21 mmHg and presence of peripheral anterior synechiae; both visual field and optic nerve appear normal
Primary angle-closure suspect	Closed anterior chamber angle (appositionally without any synechiae) in at least 270°, with IOP ≤21 mmHg; both visual field and optic nerve appear normal
No glaucoma-related findings	Absence of any of the above diagnoses

IOP = intraocular pressure; MD = mean deviation.
*Any of the following: optic disc or retinal nerve fiber layer structural abnormalities; diffuse thinning, focal narrowing, or notching of the optic disc rim, especially at the inferior or superior poles; documented, progressive thinning of the neuroretinal rim with an associated increase in cupping of the optic disc; diffuse or localized abnormalities of the peripapillary retinal nerve fiber layer, especially at the inferior or superior poles; disc rim or peripapillary retinal nerve fiber layer hemorrhages; and optic disc neural rim asymmetry of the 2 eyes consistent with loss of neural tissue.
†Reliable visual field abnormality considered a valid representation of the subject's functional status. Visual field damage consistent with retinal nerve fiber layer damage (e.g., nasal step, arcuate field defect, or paracentral depression in clusters of test sites). Visual field loss in 1 hemifield that is different from the other hemifield, that is, across the horizontal midline (in early or moderate cases). Absence of other known explanations.