Role of advanced technology in the detection of sight-threatening eye disease in a UK community setting

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ABSTRACT

Background/aims  To determine the performance of combinations of structural and functional screening tests in detecting sight-threatening eye disease in a cohort of elderly subjects recruited from primary care.

Methods  505 subjects aged ≥60 years underwent frequency doubling technology (FDT) perimetry, iVue optical coherence tomography ((Wellness and peripapillary retinal nerve fibre layer (RNFL) scans) and intraocular pressure with the Ocular Response Analyzer, all performed by an ophthalmic technician. The reference standard was a full ophthalmic examination by an experienced clinician who was masked to the index test results. Subjects were classified as presence or absence of sight-threatening eye disease (clinically significant cataract, primary open-angle glaucoma, intermediate or advanced age-related macular degeneration and significant diabetic retinopathy). Univariate and multivariate logistic regression analyses were used to determine the association between abnormal screening test results and the presence of sight-threatening eye disease.

Results  171 subjects (33.8%) had one or more sight-threatening eye diseases. The multivariate analysis found significant associations with any of the target conditions for visual acuity of <6/12, an abnormal FDT and peripapillary RNFL thickness outside the 99% normal limit. The sensitivity of this optimised screening panel was 61.3% (95% CI 53.5 to 68.7), with a specificity of 78.8% (95% CI 74.0 to 83.1), a positive predictive value of 59.5% (95% CI 53.5 to 68.7), with a specificity of 78.8% (95% CI 53.5 to 68.7), with an overall diagnostic accuracy of 72.9% (95% CI 68.8 to 76.8).

Conclusions  A subset of screening tests may provide an accurate and efficient means of population screening for significant eye disease in the elderly. This study provides useful preliminary data to inform the development of further larger, multicentre screening studies to validate this screening panel.

INTRODUCTION

Population ageing is leading to substantial increases in visual impairment. Sight loss from cataract, age-related macular degeneration (AMD), diabetic retinopathy and uncorrected refractive error affects approximately two million of the UK population. The burden of sight loss disproportionally affects the elderly, with one in five people aged 75 years or over, and one in two people aged 90 years and over living with sight loss. Public access to routine NHS sight testing in ‘at-risk’ populations, coupled with the absence of symptoms in the early stages of many of these diseases, can lead to delayed or late presentation. Given that a significant proportion of sight loss can be prevented through early detection and timely therapeutic interventions, it is likely that investment in prevention and screening for sight-threatening eye disease would lead to improved socioeconomic outcomes.

Previous studies have examined the predictive power of individual screening tests to detect eye disease in both clinic-based and general populations and have found that no single test has sufficient predictive power to detect sight-threatening eye disease. By contrast, the performance of combining screening tests has shown greater promise. For example, Kopplin and Mansberger evaluated a test battery performed by ophthalmic
technicians for the detection of visually significant eye disease in a population of American Indian and Alaskan Native participants. The authors identified that visual acuity worse than 6/12 (20/40), abnormal or poor-quality non-mydriatic photography, abnormal frequency doubling technology (FDT) perimetry, and abnormal or poor-quality confocal scanning laser ophthalmoscopy had the greatest predictive value.

We have previously demonstrated that combining structural and visual-function tests improves case detection of primary open-angle glaucoma (POAG) in a representative population of elderly subjects in the community. The aim of the current study was to extend this analysis to determine the performance of screening test combinations in detecting sight-threatening eye disease in the same population.

METHODS

Study population

This prospective diagnostic accuracy study was conducted in an urban community eye clinic in London, UK, between September 2012 and September 2013. Men and women aged ≥60 years were invited to participate via a written invitation sent to community groups and local optometry practices. There were no exclusion criteria, and participants with prediagnosed ocular disease were included. Participants underwent a series of technology-based index tests followed by a reference standard ophthalmic examination (detailed further), conducted on the same day, to establish ocular health status. Figure 1 shows the study flow diagram.

Index tests

The technology-based assessment comprised the measurement of intraocular pressure (IOP) using the Ocular Response Analyzer (ORA; Reichert Ophthalmic Instruments, Depew, NY, USA), assessment of visual fields with first-generation FDT perimetry (FDT; Carl Zeiss Meditec, Dublin, CA, USA) in C-20–5 suprathreshold mode and measurement of structural parameters of the macula and optic nerve head by spectral domain optical coherence tomography (SD-OCT) (iVue SD-OCT; Optovue, Fremont, CA, USA). Two optical coherence tomography (OCT) scans were performed: the proprietary iWellness protocol, which reports full retinal thickness and ganglion cell complex (GCC) thickness with normative comparisons, and a peripapillary retinal nerve fibre layer (RNFL) scan. An experienced ophthalmic technician performed all index tests with no prior knowledge of the subjects’ ocular status or findings from the reference standard ophthalmic examination. Thresholds of abnormality for the index tests were prespecified and were based on commonly used cut-offs reported in the literature or manufacturers’ suggested thresholds, based on comparisons with the instruments’ internal normative database. For the FDT, an abnormal result was defined using two thresholds: ≥1 location missed at either the p<5% or the p<1% significance level. The test was repeated once if one or more locations were missed or if the result was unreliable. For the SD-OCT, the defined cut-off for abnormality was any parameter falling outside the 99% normal limit based on the manufacturer’s integrated normal database; IOP>21 mm Hg was used as the threshold for the ORA.

Reference standard ophthalmic examination

All participants underwent a standard ophthalmological examination conducted by an experienced clinician who was trained and validated in glaucoma according to standard UK practice and also completed grader accreditation in diabetic retinopathy and AMD at the Reading Centre, Moorfield’s Eye Hospital, London, UK. The reference standard examination was conducted on the same day as the index tests, and the clinician was masked to the...
Table 1  Diagnostic criteria used for classifying the most prevalent eye diseases

| Eye condition          | Classification | Description                                                                                                                                 |
|------------------------|----------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| POAG                   | Definite       | 1. Open anterior chamber angle <br>2. Localised absence of neuroretinal rim, cup:disc ratio≥0.7, or interocular asymmetry in vertical cup:disc ratio≥0.2 in similar-sized discs <br>3. Presence of a concordant glaucomatous field defect based on criteria amended from Hodapp et al<sup>15</sup> |
|                        | Suspect        | Features of glaucomatous optic neuropathy but with normal or equivocal fields or subjects with glaucomatous visual field defects but without concordant disc damage |
| Diabetic retinopathy*  | Background retinopathy (R1) | Microaneurysms, dot and blot haemorrhages, venous loops and cotton wool spots                                                                       |
|                        | Preproliferative retinopathy (R2) | Venous beading, venous reduplication, multiple blot haemorrhages, intraretinal microvascular abnormality                                                      |
|                        | Proliferative retinopathy (R3) | Active proliferative retinopathy                                                                                                                                 |
|                        | Maculopathy (M1) | Groups of exudates, clinically significant macular oedema                                                                                     |
| AMD                    | Early AMD (AREDS category 2)<sup>34</sup> | Several small drusen or a few medium-sized drusen in one or both eyes                                                                       |
|                        | Intermediate AMD (AREDS category 3)<sup>34</sup> | Many medium-sized drusen or one or more large drusen (≥125 µm) in one or both eyes                                                                |
|                        | Advanced AMD (AREDS category 4)<sup>34</sup> | Geographical atrophy of the RPE involving the foveal centre or any features of neovascular AMD                                                   |
| Clinically significant cataract | LOCS II grading<sup>32</sup> | LOCS II score of ≥2 for cortex, posterior subcapsular, nuclear or hypermature cataract                                                       |

*The grading system for diabetic retinopathy was based on that used by the UK NHS Diabetic Eye Screening Programme (https://www.gov.uk/government/publications/diabetic-eye-screening-retinal-image-grading-criteria). AMD, age-related macular degeneration; AREDS, Age-Related Eye Disease Study; LOCS II, Lens Opacities Classification System II; POAG, primary open-angle glaucoma.

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Index test results. The reference examination consisted of LogMAR best-corrected visual acuities, full anterior segment assessment by slit-lamp biomicroscopy, assessment of limbal anterior chamber depth (with potentially occludable angles examined using gonioscopy), measurement of IOP using the Goldmann applanation tonometer, posterior segment examination through dilated pupils using indirect ophthalmoscopy and threshold visual field testing with a Humphrey field analyzer using Swedish Interactive Thresholding Algorithm (SITA) standard 24–2 pattern. The diagnostic criteria classifying the most commonly identified eye diseases are given in table 1.

**Sample size calculation**
The sample size was originally determined based on an anticipated sensitivity of 0.75 to detect POAG<sup>13</sup> with a minimal acceptable precision of ±0.25 with 0.95 probability. This would require approximately 50 cases, and based on an anticipated prevalence of POAG in an elderly population of 8%–10%,<sup>14</sup> it was therefore estimated that at least 500 participants would be needed. For this secondary analysis, we prospectively determined that a similar number of cases of intermediate and advanced AMDs would be required, based on a disease prevalence of 8% in the target population,<sup>14</sup> an anticipated index test sensitivity of 0.75 and an equivalent level of precision.<sup>14</sup>

**Statistical analysis**
Summary statistics were tabulated and standard measurements of diagnostic accuracy (sensitivity, specificity, and positive and negative predictive values) were calculated to determine the ability of each index test to detect sight-threatening eye disease. We defined sight-threatening eye disease as a clinically significant cataract, definite or suspect POAG, intermediate or advanced AMD and significant diabetic retinopathy (proliferative or preproliferative) or diabetic maculopathy.

The unit of analysis was the individual participant and a comparison was made between the most abnormal index test from either eye and the overall reference standard classification. Unreliable results from the FDT and data from repeatedly poor-quality ORA and SD-OCT acquisitions were removed from the analysis.

Binomial logistic regression was used to identify the index tests with significant univariate associations (p<0.05) with individual eye diseases. Those with significant univariate associations were included as potential covariates in a multivariate model using stepwise logistic regression. A significance level of p<0.05 was set for
entering and retaining the covariate in the final model. The impact of adding best-corrected visual acuity of <6/12 to the model was also evaluated post hoc, and the diagnostic performance of the final multivariate subset of screening tests was calculated.

All statistical analyses were performed using SPSS software V.21.0 (www.ibm.com/SPSS_Statistics) and MedCalc V.18.0 (www.medcalc.org).

Patient and public involvement
There was no patient involvement in the development of the research question or the study design; however, patient networks were used in study recruitment.

RESULTS
The study recruited a total of 505 subjects with a median age of 68 years (range 60–92). Fifty-nine per cent were female. Self-reported ethnicities were white (88%), South Asian (8%), black (2%), Chinese (1%) and ‘other’ (1%). Approximately 12% of the population had diabetes and 16% reported a family history of glaucoma.

The eye diseases most commonly identified by the reference standard ophthalmic examination were AMD, age-related macular degeneration; POAG, primary open-angle glaucoma.

| Condition                  | n (%)   |
|----------------------------|---------|
| Early                      | 155 (30.7) |
| Intermediate               | 27 (5.3)  |
| Advanced                   | 21 (4.2)  |
| Diabetic retinopathy       |         |
| Background                  | 26 (5.1)  |
| Preproliferative           | 4 (0.8)   |
| Proliferative              | 2 (0.4)   |
| Maculopathy                | 5 (1.0)   |
| POAG                       |         |
| Suspect                    | 32 (6.4)  |
| Definite                   | 26 (5.1)  |
| Cataract (clinically significant) | 54 (10.7) |

AMD, age-related macular degeneration; POAG, primary open-angle glaucoma.

The test most commonly failed was the FDT, with 193 (38%) participants missing ≥1 location(s) at the 5% level.

Logistic regression analysis
Tables 3 and 4 show the results of the univariate and multivariate logistic regression analyses for the association between abnormal screening test results and the presence of sight-threatening eye disease. An abnormal FDT (based on one or more points missed at the p<0.05 or p<0.1 levels) was significantly associated with all target diseases. Visual acuity of <6/12 similarly showed univariate associations with all diseases, with the exception of significant diabetic retinopathy/maculopathy.

An abnormal SD-OCT (one or more parameters outside the 99% normal limit) was associated with POAG, AMD and diabetic retinopathy. The strongest association was observed between peripapillary RNFL thickness and POAG. An IOP of >21 mm Hg (determined by the ORA) was uncommon (14%) and showed no significant association with any of the target conditions. The sensitivity and specificity of the individual tests can be found in the online supplementary table.

The tests that were significant (p<0.05) in the univariate analysis were used as candidate covariates in a stepwise multivariate logistic regression model (table 4). In the multivariate analysis, visual acuity of <6/12 was significantly associated with a clinically significant cataract and AMD. An abnormal FDT at either the 5% or 1% level was associated with cataract and POAG, and an abnormal SD-OCT was predictive of POAG, AMD and diabetic retinopathy. The multivariate analysis identified that visual acuity of <6/12, one or more locations missed at the 5% level on the FDT and the peripapillary RNFL thickness outside the 99% normal limit were predictive of sight-threatening eye diseases. The diagnostic performance of this optimised screening panel for any of the target conditions is summarised in table 5. The sensitivity and specificity of the panel were 61.3% and 78.8%, respectively, with a positive predictive value of 59.5% and an overall diagnostic accuracy of 72.9%. Of the subjects with a potentially sight-threatening eye disease that would not have been detected using the optimised subset of tests, the majority were classified as either having a clinically significant cataract, suspect glaucoma or intermediate AMD. Only five participants with the most severe disease, definitive glaucoma (n=1), significant diabetic retinopathy (n=1) or advanced AMD (n=5), would have been missed.

DISCUSSION
The current study evaluated the predictive value of a panel of standard screening tests in identifying sight-threatening eye disease in an elderly, predominantly white population. We established that reduced visual acuity, abnormal FDT and peripapillary RNFL thickness outside the 99% normal limit were predictive of any
Table 3  Univariate association testing of abnormal screening results with significant ocular disease using logistic regression

|                              | Clinically significant cataract | POAG (definite) | POAG (definite and suspect) | Significant diabetic retinopathy/maculopathy | Age related macular degeneration | Any sight-threatening eye disease |
|------------------------------|---------------------------------|-----------------|-----------------------------|-----------------------------------------------|---------------------------------|----------------------------------|
|                              | OR (95% CI)                     | OR (95% CI)     | OR (95% CI)                 | OR (95% CI)                                   | OR (95% CI)                      | OR (95% CI)                      |
| Visual acuity<6/12           | 6.69 (3.57 to 12.46)            | 4.54 (1.97 to 10.47) | 2.06 (1.04 to 4.06)  | NS                                            | 4.88 (2.54 to 9.40)             | 4.99 (2.90 to 8.60)              |
| Family history of glaucoma   | NS                              | 4.93 (2.19 to 11.09) | 2.92 (1.59 to 5.36)  | NS                                            | NS                              | NS                              |
| IOP>21 mm Hg                 | NS                              | NS              | NS                          | NS                                            | NS                              | NS                              |
| FDT≥1 point missed at 1%     | 3.07 (1.72 to 5.47)             | 28.69 (8.45 to 97.48) | 6.68 (3.74 to 11.92) | 5.29 (1.25 to 22.48) | 2.95 (1.60 to 5.41)             | 5.48 (3.55 to 8.46)             |
| FDT≥1 point missed at 5%     | 3.45 (1.91 to 6.23)             | 22.21 (5.19 to 95.15) | 5.20 (2.83 to 9.55)  | 5.02 (1.00 to 25.11) | 2.75 (1.50 to 5.06)             | 4.60 (3.10 to 6.83)             |
| SD-OCT (GCC thickness)       | NS                              | 28.64 (10.41 to 78.77) | 7.40 (4.10 to 13.33) | NS                                            | 3.67 (1.93 to 6.96)             | 3.77 (2.31 to 6.15)             |
| SD-OCT (full retinal thickness) | NS                              | 5.14 (2.23 to 11.81) | 3.32 (1.90 to 5.81)  | 18.06 (2.20 to 148.13) | 2.75 (1.51 to 5.03)             | 2.57 (1.72 to 3.84)             |
| SD-OCT (peripapillary RNFL thickness) | NS                              | 39.03 (15.52 to 98.12) | 19.27 (9.57 to 38.82) | NS                                            | 4.41 (2.09 to 9.29)             | 7.20 (3.54 to 14.66)             |

FDT, frequency-doubling technology; GCC, ganglion cell complex; IOP, intraocular pressure; NS, not significant; POAG, primary open-angle glaucoma; RNFL, retinal nerve fibre layer; SD-OCT, spectral domain optical coherence tomography.
also been shown to be effective for the detection other eye diseases. An abnormal FDT result showed a univariate association with all target conditions and a threshold of ≥1 point missed at the 5% level was retained in the final multivariate model. Similarly, an abnormality in one or more SD-OCT parameters showed a univariate association with POAG, AMD and diabetic retinopathy. The OCT parameters selected for the analysis and the associated pass/fail criteria (value outside the 99% CI based on the iVue SD-OCT normative database) were established a priori. Thinning of the peripapillary RNFL showed the strongest association, and this parameter was retained in the final model. Predictably, the association with POAG, AMD and diabetic retinopathy has recently been fuelled further by the application of artificial intelligence (AI) based on deep learning algorithms. Applying AI to a set of real-world OCT scans, taken from patients referred into a large tertiary referral centre, showed a diagnostic performance that was comparable and, in some cases, better than clinical experts for a range of sight-threatening retinal diseases.

**Strengths and limitations**

To our knowledge, this is the first UK study that has evaluated the performance of a combination of screening tests to detect clinically significant eye diseases in a primary care setting. The study has a number of strengths. The design, analysis and reporting complied with the principles of the Standards for Reporting of Diagnostic Accuracy statement. To reduce spectrum bias, the target population included consecutive subjects who met the inclusion criteria, and there were no exclusions. Although it is possible that higher numbers of those with a personal or family history of eye disease were more likely to agree to participate in the study, the prevalence of sight-threatening retinal disease in our population (30%) was similar to a London-based cross-sectional study that used random sampling. Therefore, we believe that the study sample is likely to be broadly representative of the
local population. The reference standard used to classify the participants’ ocular status corresponded to that used in a typical hospital eye clinic and was based on the results of a standard ophthalmic examination by a validated clinician. All index tests and the reference standard examination were undertaken on the same day, and the clinician performing the reference examination and the ophthalmic technician undertaking the index tests were masked to the results.

The study also has some limitations. Although a large sample of the population was examined, the prevalence of the individual target conditions was low, and consequently, the reported measures of index test performance were associated with wide confidence intervals. Furthermore, since the identified panel of screening tests was not tested on an independent validation sample, it is possible that the predicative value of these tests may be lower in other populations. Approximately 90% of our study population was of white European origin, and therefore, our findings may not be generalisable to other ethnic groups.

The current study did not include a formal cost-effectiveness analysis. One of the tenets of Wilson and Jungner’s widely implemented ‘Principles and Practice of Screening for Disease’ states that ‘the cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.’ An economic evaluation of any proposed screening programme is therefore essential to assess the full costs of implementing, operating and sustaining the programme. Recent studies in ophthalmology have recognised the efficiencies gained in screening for more than one eye condition. For example, AMD screening carried out simultaneously with digital screening for diabetic retinopathy is cost-effective in the context of a public healthcare system in Hong Kong.

CONCLUSIONS

Our study has demonstrated the feasibility of using a panel of standard screening tests performed by an ophthalmic technician to detect sight-threatening eye disease in a representative sample of the elderly population. The results provide useful data to inform the development of larger, multicentre population studies to evaluate the effectiveness and cost-effectiveness of screening for eye disease in the elderly.

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Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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