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Abstract

Automated imaging technologies for the diagnosis of glaucoma: a comparative diagnostic study for the evaluation of the diagnostic accuracy, performance as triage tests and cost-effectiveness (GATE study)

Augusto Azuara-Blanco,[1*] Katie Banister,[2] Charles Boachie,[3] Peter McMeekin,[4] Joanne Gray,[5] Jennifer Burr,[6] Rupert Bourne,[7] David Garway-Heath,[8,9] Mark Batterbury,[10] Rodolfo Hernández,[11] Gladys McPherson,[2] Craig Ramsay[2] and Jonathan Cook[12]

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Background: Many glaucoma referrals from the community to hospital eye services are unnecessary. Imaging technologies can potentially be useful to triage this population.

Objectives: To assess the diagnostic performance and cost-effectiveness of imaging technologies as triage tests for identifying people with glaucoma.

Design: Within-patient comparative diagnostic accuracy study. Markov economic model comparing the cost-effectiveness of a triage test with usual care.

Setting: Secondary care.

Participants: Adults referred from the community to hospital eye services for possible glaucoma.

Interventions: Heidelberg Retinal Tomography (HRT), including two diagnostic algorithms, glaucoma probability score (HRT-GPS) and Moorfields regression analysis (HRT-MRA); scanning laser polarimetry [glaucoma diagnostics (GDx)]; and optical coherence tomography (OCT). The reference standard was clinical examination by a consultant ophthalmologist with glaucoma expertise including visual field testing and intraocular pressure (IOP) measurement.

Main outcome measures: (1) Diagnostic performance of imaging, using data from the eye with most severe disease. (2) Composite triage test performance (imaging test, IOP measurement and visual acuity measurement), using data from both eyes, in correctly identifying clinical management decisions, that is 'discharge' or 'do not discharge'. Outcome measures were sensitivity, specificity and incremental cost per quality-adjusted life-year (QALY).

Results: Data from 943 of 955 participants were included in the analysis. The average age was 60.5 years (standard deviation 13.8 years) and 51.1% were females. Glaucoma was diagnosed by the clinician in at least one eye in 16.8% of participants; 37.9% of participants were discharged after the first visit. Regarding diagnosing glaucoma, HRT-MRA had the highest sensitivity [87.0%, 95% confidence interval (CI) 80.2% to 92.1%] but the lowest specificity (63.9%, 95% CI 60.2% to 67.4%) and GDx had the lowest sensitivity (35.1%, 95% CI 27.0% to 43.8%) but the highest specificity (97.2%, 95% CI 95.6% to 98.3%). HRT-GPS had sensitivity of 81.5% (95% CI 73.9% to 87.6%) and specificity of 67.7% (95% CI 64.2% to 71.2%) and OCT had sensitivity of 76.9% (95% CI 69.2% to 83.4%) and specificity of 78.5% (95% CI 75.4% to 81.4%). Regarding triage accuracy, triage using HRT-GPS had the highest sensitivity (86.0%, 95% CI 82.8% to 88.7%) but the lowest specificity (39.1%, 95% CI 34.0% to 44.5%), GDx had the lowest sensitivity (64.7%, 95% CI 60.7% to 68.7%) but the highest specificity (53.6%, 95% CI 48.2% to 58.9%). Introducing a composite triage station into the referral pathway to identify appropriate referrals was cost-effective. All triage strategies resulted in a cost reduction compared with standard care (consultant-led diagnosis) but with an associated reduction in effectiveness. GDx was the least costly and least effective strategy. OCT and HRT-GPS were not cost-effective. Compared with GDx, the cost per QALY gained for HRT-MRA is £22,904. The cost per QALY gained with current practice is £156,985 compared with HRT-MRA. Large savings could be made by implementing HRT-MRA but some benefit to patients will be forgone. The results were sensitive to the triage costs.

Conclusions: Automated imaging can be effective to aid glaucoma diagnosis among individuals referred from the community to hospital eye services. A model of care using a triage composite test appears to be cost-effective.

Future work: There are uncertainties about glaucoma progression under routine care and the cost of providing health care. The acceptability of implementing a triage test needs to be explored.

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AUC	area under the curve
CI	confidence interval
DOR	diagnostic odds ratio
ECC	Enhanced Corneal Compensation
EQ-5D	European Quality of Life-5 Dimensions
GAT	Goldmann applanation tonometry
GATE	Glaucoma Automated Tests Evaluation
GDx	glaucoma diagnostics
GPS	glaucoma probability score
HRT	Heidelberg Retinal Tomography
HRT-GPS	Heidelberg Retinal Tomography glaucoma probability score
HRT-MRA	Heidelberg Retinal Tomography Moorfields regression analysis
ICER	incremental cost-effectiveness ratio
IOP	intraocular pressure
MD	mean deviation
MRA	Moorfields regression analysis
NFI	nerve fibre indicator
NICE	National Institute for Health and Care Excellence
OAG	open-angle glaucoma
OCT	optical coherence tomography
OHT	ocular hypertension
PAC	primary angle closure
PSD	pattern standard deviation
QALY	quality-adjusted life-year
RNFL	retinal nerve fibre layer
ROC	receiver operating characteristic
SD	standard deviation
SD-OCT	spectral domain optical coherence tomography
STARD	standards for the reporting of diagnostic accuracy studies
TSC	Trial Steering Committee
TSNIT	temporal, superior, nasal, inferior, temporal
VA	visual acuity
VFI	visual field index

Plain English summary

Glaucoma is a lifelong eye disease. Treatment is usually effective to slow the progression of glaucoma. About 4000 people are registered with sight impairment each year because of glaucoma. Many healthy subjects are unnecessarily referred from the community to hospital eye services to rule out glaucoma.

New imaging tests that investigate the back of the eye can aid in the diagnosis of glaucoma and are safe and easy to perform. These technologies measure with high accuracy the tissues in the back of the eye that are typically thinned in glaucoma. This study was designed to evaluate the performance of four imaging tests at identifying, among patients referred to hospital, those who have glaucoma or are at risk and those who do not have any eye disease. We compared the imaging test results with an experienced eye doctor's diagnosis. We also evaluated how well a possible care pathway would perform using imaging results combined with measurements of the eye pressure and vision, to identify whether or not the individual needed to see an eye doctor.

In total, 955 individuals were recruited. The best-performing test correctly diagnosed glaucoma in 87 out of every 100 patients tested. If imaging tests with an eye pressure test and a visual acuity test were used to screen out people without eye disease, there would be substantial savings to the health service, but not all patients with disease would be picked up. A relatively small proportion of patients with glaucoma and at risk of glaucoma would be missed (approximately one in seven).

Scientific summary

Background

Glaucoma describes a group of chronic age-related eye diseases in which there is progressive damage of the optic disc and characteristic visual field loss. Glaucoma is a significant public health problem, as it is the second leading cause of blindness in the UK.

Glaucoma care constitutes a major proportion of the workload of the hospital eye service. In England there are over 1 million glaucoma-related outpatient visits to the acute sector annually. Considerable NHS resources are required to assess referrals to hospital eye services for possible glaucoma, which are typically initiated by community optometrists. However, fewer than one-quarter of referrals are found to have glaucoma, and nearly half of the referred individuals are discharged after their first visit. If referrals could be triaged in a clinically effective and cost-effective manner, resources could be better utilised for other needs.

Glaucoma is diagnosed by clinicians detecting structural changes of the optic nerve head, also known as the optic disc, and corresponding visual field defects. New imaging techniques for assessment of the structural changes have emerged: scanning laser ophthalmoscopy, commercially available as the Heidelberg Retinal Tomograph [HRT; including two diagnostic algorithms, Moorfields regression analysis (HRT-MRA; Heidelberg Engineering, Heidelberg, Germany) and glaucoma probability score (HRT-GPS; Heidelberg Engineering, Heidelberg, Germany)] and scanning laser polarimetry, commercially available as glaucoma diagnostics (GDx; Carl Zeiss Meditec, Dublin, CA, USA) and spectral domain optical coherence tomography (SD-OCT; Heidelberg Engineering, Heildelberg, Germany), with several commercial devices available.

Imaging technologies are being introduced into glaucoma services but their role in the diagnostic pathway is unclear. Imaging tests are user-friendly and safe, provide automated classifications and potentially could reduce the need for an examination by a clinician.

Aim

To assess the relative performance and cost-effectiveness of diagnostic imaging technologies as triage tests in secondary care for identifying people with glaucoma.

Objectives

Primary objective

To compare the diagnostic performance (in terms of sensitivity and specificity) in a cohort of patients referred to hospital eye services with possible glaucoma, of:

- four imaging tests [HRT-MRA, HRT-GPS, GDx and optical coherence tomography (OCT)] for diagnosis of glaucoma
- a composite triage test [combining imaging tests, visual acuity (VA) and intraocular pressure (IOP) measurements] in correctly identifying patients to be discharged from secondary care.

Secondary objectives

- To explore alternative thresholds for determining abnormal tests.
- To evaluate the diagnostic performance of combinations of imaging tests.
- To evaluate the performance of the tests across the spectrum of glaucoma (mild, moderate and severe).
- To evaluate the cost-effectiveness of incorporating imaging in a triage test in hospital eye services compared with current practice of diagnostic examination by a clinician.
- To evaluate patient preferences related to different imaging technologies.

Methods

We designed a pragmatic within-patient comparative diagnostic and triage evaluation of imaging techniques for glaucoma. Participants were adult patients referred from community optometrists or general practitioners with any possible glaucoma-related findings. Five UK NHS centres participated: three academic centres and two district general hospitals.

Participants received all imaging tests: HRT-GPS, HRT-MRA, GDx and OCT. Possible tests results were within normal limits, borderline or outside normal limits.

The HRT uses confocal laser scanning to allow quantitative structural measurement of the optic disc anatomy. There are two main classification tools to relate measurements to normative data: (1) HRT-MRA, which requires user definition of the optic disc boundary, and (2) HRT-GPS, which is fully automated.

The GDx scanning laser polarimeter measures the retinal nerve fibre layer (RNFL) thickness surrounding the optic disc utilising the birefringent properties of the RNFL. The software provides a discriminating classifier termed the nerve fibre indicator, which is fully automated.

Spectral domain OCT is an optical imaging technique providing high-resolution, cross-sectional imaging of the retina analogous to B-scan ultrasonography but using light instead of sound. The Spectralis® optical coherence tomograph (Heidelberg Engineering, Heidelberg, Germany) was used in this study.

The reference standard was a full clinical examination, including visual field testing, by a consultant ophthalmologist with glaucoma expertise to determine (1) a diagnosis of glaucoma (mild, moderate or severe) according to well-defined criteria (diagnosis analysis) and (2) whether or not the patient would be discharged or should be monitored/treated within hospital eye services (triage analysis).

Statistical analysis

Sample size calculations were based on standard diagnostic accuracy study methods. A 5% significance level based on a two-sided test was used, which required a study of 897 individuals to have 90% power to detect an accuracy difference of 9% for the primary outcome of glaucoma diagnosis. Including a 6% indeterminacy rate increased the sample size to 954.

Two diagnostic performance analyses were undertaken: a diagnosis and a triage analysis. For the diagnosis analysis (classification of glaucoma), one eye per patient was used: the eye with more severe disease except for in one sensitivity analysis. The test 'abnormal' definition was an imaging test result of 'outside normal limits', with 'borderline' cases classified as 'normal'. This was compared with a reference standard diagnosis of 'glaucoma'.

For the triage analysis, a composite test (including three components: imaging, IOP measurement and VA) was compared with a reference standard of clinical decision 'do not discharge'. The test categorised a patient as needing evaluation by a clinician if any elements of the composite triage test were themselves 'abnormal' in either eye: imaging classification 'outside normal limits' or IOP > 21 mmHg or VA of 6/12 or poorer.

Primary diagnostic performance outcomes were the sensitivity and specificity of tests. Secondary diagnostic performance outcomes were likelihood ratio and diagnostic odds ratio (DOR). The proportions of indeterminate test results, low-quality imaging and need for pupil dilatation were measured and patient preference for the tests was ranked. The test performance was assessed with respect to the glaucoma spectrum (mild, moderate and severe), when including glaucoma suspects in the reference standard diagnosis, and when including 'borderline' results as abnormal. The diagnostic performance of combinations of tests was also evaluated.

Economic analysis

A current practice pathway model was developed whereby patients referred to hospital eye services were seen by a nurse for VA assessment, a technician for visual field measurement and by a clinician.

In an alternative triage care pathway model, individuals were seen by a nurse for VA examination and IOP measurement and a technician for imaging assessment. The triage test results classified patients as needing referral for clinician diagnosis or as discharged. Those referred were seen by a technician for visual field measurement and examined by a clinician.

The cost-effectiveness of four triage pathways, each using IOP, VA and one of the four imaging technologies (which varied by their diagnostic ability and capital cost), and their subsequent care management pathways was assessed using a multistate Markov model compared with current practice.

The cohort started in one of six health states: normal; at risk of glaucoma; mild glaucoma; moderate glaucoma; severe glaucoma; or sight-impaired. The sensitivity and specificity of each triage strategy determined if diagnosis was correct and, depending on this, the health state that patients would move to and the associated progression of any underlying glaucoma.

Modelled care pathways were developed in consultation with the study team and the independent steering committee and used our previous models in this area and reviewed guidelines, study data and expert opinion.

Consequences were considered in terms of monetary costs (of testing and subsequent management of the patient's condition) to the NHS and in terms of the effects on quality of life (by assigning utility weights). Combining these data with the probabilities of events occurring over time enabled costs, patient outcomes and quality-adjusted life-years (QALYs) to be estimated for a hypothetical cohort of patients undergoing each modelled strategy.

Model results were analysed as incremental cost per QALY and incorporated (1) costs (of testing) and triage diagnostic outcomes, (2) costs (of testing and subsequent management) and (3) QALYs. The base-case analysis used a cohort of 40-year-old males using prevalence data from the Glaucoma Automated Tests Evaluation (GATE) study and for a 50-year time horizon. Cycle length was 1 year. The results were presented in incremental cost-effectiveness ratios (ICERs).

Several deterministic sensitivity analyses were explored, which varied: the annual probability of discharged patients having a sight test; the cost of triage tests; the start age of the cohort; the performance of the diagnosing clinician; the diagnostic performance of imaging technologies; the prevalence of glaucoma in the referred population; and utility weights for those 'at risk of glaucoma'. The possibility of a hypothetical pathway, in which patients diagnosed as 'at risk of glaucoma' were discharged from the service, was explored to investigate the impact in terms of costs and QALYs.

Results

Between April 2011 and July 2013, 2088 participants were identified as potentially eligible: 2013 were invited to take part. Of those invited, 966 (48%) agreed to take part. Following consent, 11 participants were found to be ineligible and did not participate and 12 were excluded as they did not receive all four imaging tests. Therefore, 943 participants were available for the comparisons of tests.

The average age of participants was 60.5 years [standard deviation (SD) 13.8 years] and 51.1% were female. Non-participants had similar age and sex balance. Most participants (89.2%) were of 'white British' ethnicity. The average IOP at referral was 20 mmHg. The most common diagnosis was 'no glaucoma-related findings' (31.7% of participants). Comorbidities were uncommon, except for cataract, which was reported in 8.3% of right eyes and 7.4% of left eyes. Glaucoma was diagnosed in at least one eye in 16.8% of the GATE cohort and 6.5% had glaucoma in both eyes at referral. Overall, 37.9% of GATE participants were discharged after the first visit.

Performance of the imaging tests in diagnosing glaucoma differed. HRT-MRA had the highest sensitivity [87.0%, 95% confidence interval (CI) 80.2% to 92.1%] but the lowest specificity (63.9%, 95% CI 60.2% to 67.4%), GDx had the lowest sensitivity (35.1%, 95% CI 27.0% to 43.8%) but the highest specificity (97.2%, 95% CI 95.6% to 98.3%) and the other two tests provided intermediate results (HRT-GPS sensitivity 81.5%, 95% CI 73.9% to 87.6% and specificity 67.7%, 95% CI 64.2% to 71.2%; OCT sensitivity 76.9%, 95% CI 69.2% to 83.4% and specificity 78.5%, 95% CI 75.4% to 81.4%).

Likelihood ratios showed evidence of being able to both rule in and rule out the presence of glaucoma for all four imaging tests (95% CIs did not contain 1.0). DORs ranged from 9.24 for HRT-GPS to 18.48 for GDx.

When including borderline imaging results as an abnormal test, the sensitivity increased but with a corresponding decrease in specificity. In this sensitivity analysis, HRT-MRA had the highest sensitivity (94.9%, 95% CI 89.8% to 97.9%) but the second lowest specificity (43.9%, 95% CI 40.2% to 47.6%), GDx had the lowest sensitivity (60.4%, 95% CI 51.6% to 68.8%) but the highest specificity (82.8%, 95% CI 79.8% to 85.5%) and the other two tests provided intermediate results.

The impact of combining two imaging tests was improved detection of glaucoma but the effect was marginal and smaller than the loss of specificity.

When considering participants with severe glaucoma, according to our definition of disease stage, OCT had the highest sensitivity (95.2%, 95% CI 76.2% to 99.9%) and the second highest specificity (70.9%, 95% CI 67.7% to 73.9%), GDx had the lowest sensitivity (78.9%, 95% CI 54.4% to 93.9%) but the highest specificity (93.7%, 95% CI 91.8% to 95.2%) and the other two tests provided intermediate results.

The performance of triage tests (a composite assessment comprising imaging test, IOP and VA assessments) in correctly identifying patients to be discharged from secondary care showed that triage including HRT-GPS had the highest sensitivity (86.0%, 95% CI 82.8% to 88.7%) but the lowest specificity (39.1%, 95% CI 34.0% to 44.3%) and GDx had the lowest sensitivity (64.7%, 95% CI 60.7% to 68.7%) but the highest specificity (53.6%, 95% CI 48.2% to 58.9%), the other two tests providing intermediate results [HRT-MRA values were very similar to the HRT-GPS results in sensitivity (86.0%, 95% CI 82.8% to 88.7%) and specificity (53.6%, 95% CI 48.2% to 58.9%) and OCT had lower sensitivity (75.4%, 95% CI 71.6% to 78.9%) but higher specificity (41.0%, 95% CI 35.8% to 46.3%) values than HRT-GPS and HRT-MRA]. Likelihood ratios (and 95% CI) showed evidence of all four triage tests being able to rule in and out the presence of abnormalities for all four triage tests (CIs did not contain 1.0). DORs ranged from 2.1 for GDx to 3.9 for HRT-GPS.

Participant preference for type of imaging test was collected for 890 participants (94%). Almost half of responders (48.2%) had no preference. Of those participants who expressed a preference, OCT was ranked as most preferred (27.6%), followed by GDx (11.9%) and HRT (5.1%). Average time taken to perform the test varied from 5.2 minutes (SD 3.0 minutes) for OCT to 7.6 minutes (SD 5.0 minutes) for HRT.

Economic analysis results

All triage strategies were more cost-effective than current practice but resulted in reduced health because of missing cases (i.e. fewer expected QALYs). The base-case results suggest that, of the triage pathways modelled, a triage including IOP, VA and HRT-MRA is the most cost-effective strategy. Triage including GDx was shown to be the least costly and least effective. Triage including OCT and HRT-GPS were not cost-effective. Compared with GDx, the cost per QALY gained for HRT-MRA was £22,904. The cost per QALY gained with current practice was £156,985 compared with HRT-MRA. Large savings could be made by implementing HRT-MRA but some benefit to patients would be forgone.

These results should be interpreted with some caution, particularly in terms of differences among triage strategies, since the diagnostic accuracy of all tests (except GDx) and their unit costs are very similar. The incremental cost-effectiveness of the triage strategies compared with current practice is very sensitive to the costs included in the model. Indeed, current practice becomes cost-effective when the total cost of a triage test increases to £30 and above. A key assumption used in the model was that clinicians are 100% accurate in their diagnostic ability. Relaxing this assumption increased further the ICER (favouring triage strategies).

Conclusions

Implications for health care

Imaging technologies can be effective to aid the diagnosis of glaucoma. An alternative pathway for patients referred from community to hospital eye services with possible glaucoma, using a triage test that includes imaging, IOP and VA, appears to be cost-effective compared with current practice. Our findings are based on a relatively inexpensive composite triage test (< £30). The most cost-effective strategy would include HRT-MRA imaging. However, triaging would be associated with a loss of health, and the acceptability of this option among users and clinicians has not been evaluated.

Recommendations for research

- Determine the acceptability to patients and health-care providers of implementing an efficient triage glaucoma diagnostic triage system but with reduced health.
- Obtain data on glaucoma disease progression, specifically including patients classified as having glaucoma suspects and ocular hypertension, associated utility, and cost of providing health care.
- Investigate varying the results of the imaging tests beyond the standard options, since the recommended classification may not be the one best suited to the population from which GATE recruited.
- Examine the effectiveness of implementation of a composite triage test.

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Chapter 1 Introduction

Glaucoma describes a group of eye diseases in which there is progressive damage of the optic nerve. It is characterised by a specific pattern of optic nerve head and visual field loss leading to impaired vision and sometimes blindness if inadequately treated. Primary glaucoma can be classified as open-angle glaucoma (OAG) or angle-closure glaucoma, the former being the more common.[1] Glaucoma is a significant public health problem, second only to macular degeneration as the most common cause of blindness in the UK,[2–4] and is the leading cause of irreversible blindness worldwide.[5] The impact on patients is considerable, with the risks of moderate visual field loss (which affects the ability to drive) and long-term blindness reported as the most important consequences.[6] Late detection is a major risk factor for glaucoma blindness.[7] However, if glaucoma is identified in the early stages, treatment is effective at reducing the progress of the disease.[8]

A a number of factors increase the risk of developing glaucoma, including elevated intraocular pressure (IOP), older age, ethnic background and family history of glaucoma. Of these, the level of IOP is the most important risk factor and is the only one which is treatable. Ocular hypertension (OHT), generally defined as an IOP of ≥ 21 mmHg [2 standard deviations (SDs) above the mean], used to be considered as a part of the definition of glaucoma, but population studies have consistently found that many people with glaucoma have an IOP below this level.[9–13] However, the risk of developing glaucoma, and of worsening of existing disease, increases with increasing IOP.[14–16] This is supported by the fact that those presenting with advanced glaucoma at diagnosis are more likely to have higher IOP.[12,17]

The estimated prevalence of glaucoma in the UK is over 1% of the population over 40 years of age.[18–21] Approximately 4000 new cases of severe sight impairment due to glaucoma are registered every year in the UK. Many more glaucoma patients have sight impairment not severe enough to be registered but with significant impact on their quality of life (e.g. loss of driving licence). In England and Wales, in 2007, there were over 5 million outpatient attendances at hospital eye services (around 10% of all annual outpatient attendances) in the NHS. Of these, approximately 1,400,000 were new patients (costing over £140M). As the population ages, these numbers are likely to increase.[22]

Estimates based on official population projections and epidemiological prevalence surveys have predicted that the number of glaucoma cases in England and Wales will increase by one-third by 2021 and continue to increase at a similar pace until 2031.[23]

Management of patients with glaucoma and those at risk of suffering from glaucoma constitutes a major part of the workload of any secondary care eye services. In two independent surveys, between 8%[24] and 13%[25] of all new referrals to secondary eye care were a result of glaucoma, and 25% of all follow-up attendances were glaucoma related. In England alone there are over 1 million glaucoma-related outpatient visits in the NHS hospital eye services annually (approximately 1% of all outpatient activity).[26] Currently, referrals for glaucoma suspect are usually initiated by a community optometrist and are assessed in hospital eye services by clinicians. However, the reported referral accuracy of glaucoma by optometrists is suboptimal. Fewer than one-quarter of people referred actually have glaucoma, and nearly half of referred individuals are discharged after the first visit.[27] Thus, many referrals are unnecessary and overburden the already busy hospital eye services. It also causes distress and worry to the patient that could be avoided. Interventions such as glaucoma training[28] or agreed guidelines[29] may not always have an effect in the rates of false-positive referrals by community optometrists.

Diagnosing glaucoma

Glaucoma is diagnosed primarily by detecting glaucomatous optic neuropathy (i.e. characteristic changes of the optic nerve head – the optic disc) and a compatible visual field defect. According to current National Institute for Health and Care Excellence (NICE) guidelines,[26] a definitive glaucoma diagnosis is based on the expertise of a clinician who subjectively interprets the appearance of the optic disc and the results of visual field testing. In addition to diagnosing glaucoma, the clinical examination will include a visual acuity (VA) test (to measure central vision), anterior chamber angle examination (to determine the mechanism of glaucoma, e.g. open-angle or angle-closure), and IOP measurement (which is a risk factor for glaucoma and also for disease progression).

Accurate clinical diagnosis of glaucoma is limited by subjectivity, reliance on the examiner's experience and a wide variation of optic disc structure in the population. Imaging techniques for assessment of the structural changes at the optic nerve head and retinal nerve fibre layer (RNFL) have emerged and are in routine use in the NHS: Heidelberg Retinal Tomography (HRT)-III, scanning laser polarimetry [glaucoma diagnostics (GDx; Carl Zeiss Meditec, Dublin CA, USA)] and spectral domain optical coherence tomography (SD-OCT; Heidelberg Engineering, Heidelberg, Germany). These techniques can be easily performed by trained technicians and provide an automatic glaucoma classification index. Some clinicians now routinely incorporate the information from such imaging technologies to help make a diagnosis of glaucoma, although there is no strong evidence of their effectiveness.

Using an automated imaging quantitative test for glaucoma diagnosis may have advantages over visual field testing in that the majority of people can be imaged.[18]

Comparison of glaucoma diagnostic technologies

In 1997, the Health Technology Assessment (HTA) programme funded a study entitled 'The effectiveness of the Heidelberg Retina Tomograph and laser diagnostic glaucoma scanning system (GDx) in detecting and monitoring glaucoma'.[30] At the time, this study was the largest and most rigorous head-to-head comparison of tests for diagnosing glaucoma. However, this study used the first prototypes of the HRT and GDx, now outdated. Another serious limitation was the small study sample (250 participants), in addition to a potentially biased selection of patients, as they were not consecutively selected.

A systematic review of the performance of technologies for detecting glaucoma as both screening and diagnostic tests for glaucoma identified that the evidence is of poor quality and that no one test was clearly superior.[18] In this systematic review it was also found that populations studied were varied and biased. Furthermore, only six studies performed a direct comparison of the available diagnostic instruments (and including, on average, fewer than 300 patients), the threshold for definitions of glaucoma cases was not consistent and there were no studies reporting on the performance of GDx and optical coherence tomography (OCT) that met the inclusion criteria for this systematic review. However, the review did suggest that some diagnostic technologies perform better than others (e.g. HRT performed relatively well), but the credible intervals around the estimates were wide, reflecting considerable uncertainty, and, therefore, it recommended that the available diagnostic tests be evaluated in an appropriately powered directly comparative study.

In the published NICE guideline,[26] the authors searched for evidence comparing the diagnostic performance of HRT, GDx and OCT with expert clinical examination. No studies met the inclusion criteria for the guideline review.

Triage tests in secondary care eye services

Considerable NHS resources are required to assess all patients referred to hospital eye services with glaucoma suspect. In June 2009, the chairman published on behalf of the Professional Standards Committee of the Royal College of Ophthalmology a statement that the interpretation of NICE glaucoma guidelines was putting considerable strain onto secondary care eye services through the increase in false-positive referrals from community optometrists. The statement proposed that eye departments should consider innovative and efficient clinics for the initial assessment of patients.[31]

If referrals could be triaged to identify suitable referrals and discharge unsuitable referrals in an effective and cost-effective manner, the resources could be better utilised for patient eye care services. Imaging technologies are being introduced into glaucoma services in both hospital and community settings, but their role in the diagnostic pathway as triage, replacement or add-on tests has not been evaluated. The tests to be evaluated in this study are the currently available imaging technologies with characteristics that suggest that they could be valuable triage tests and that are in current use in the NHS. They do not require patient input, are user-friendly,[32] provide automated quantitative classifications and potentially could reduce the need for an extensive examination by an expert glaucoma clinician. The diagnostic performance of these imaging technologies has not been evaluated in a triage setting and in a robust manner.

Aim and research objectives

Aim

To assess the relative performance and the cost-effectiveness of new diagnostic imaging technologies, as triage tests in secondary care, for identifying people with glaucoma.

Research objectives

Primary objective

To compare the performance of imaging technologies [HRT Moorfields regression analysis (HRT-MRA; Heidelberg Engineering, Heidelberg, Germany), HRT glaucoma probability score (HRT-GPS; Heidelberg Engineering, Heidelberg, Germany), GDx and OCT] as diagnostic and triage tests for patients referred to hospital eye services with possible glaucoma. Triage tests include an imaging technology, VA and IOP.

Secondary objectives

(a) To explore alternative thresholds for determining test positivity.
(b) To evaluate the diagnostic performance of combinations of the imaging tests.
(c) To evaluate the performance of the tests across the spectrum of glaucoma (mild, moderate and severe).
(d) To evaluate the cost-effectiveness of adopting individual tests or combination of tests as triage tests compared with the current practice of diagnostic examination by a clinician in a secondary care setting.
(e) To evaluate patient preferences of different imaging technologies.

Chapter 2 Methods

This chapter describes the Glaucoma Automated Tests Evaluation (GATE) study design and methods for the diagnostic performance evaluation, and follows the standards for the reporting of diagnostic accuracy studies (STARD).[33] The methods for the health-economic evaluation are described separately (see *Chapter 6*).

Overview of the study design

An overview of the GATE study design is shown in *Figure 1*. The GATE study is a pragmatic within-patient comparative diagnostic evaluation of four imaging techniques for glaucoma in patients referred to hospital eye services. Specifically, this study was designed to evaluate (1) diagnostic accuracy of imaging tests for detecting glaucoma in an eye and (2) diagnostic accuracy of triage tests that consisted of a combination of an imaging test, VA and IOP measurement, for identifying patients requiring referral to hospital eye services.

All patients recruited to the study received four different imaging tests (using three different devices), which were compared with a reference standard (i.e. a comprehensive clinical examination). The study was co-ordinated from a central study office in the Health Services Research Unit at the University of Aberdeen.

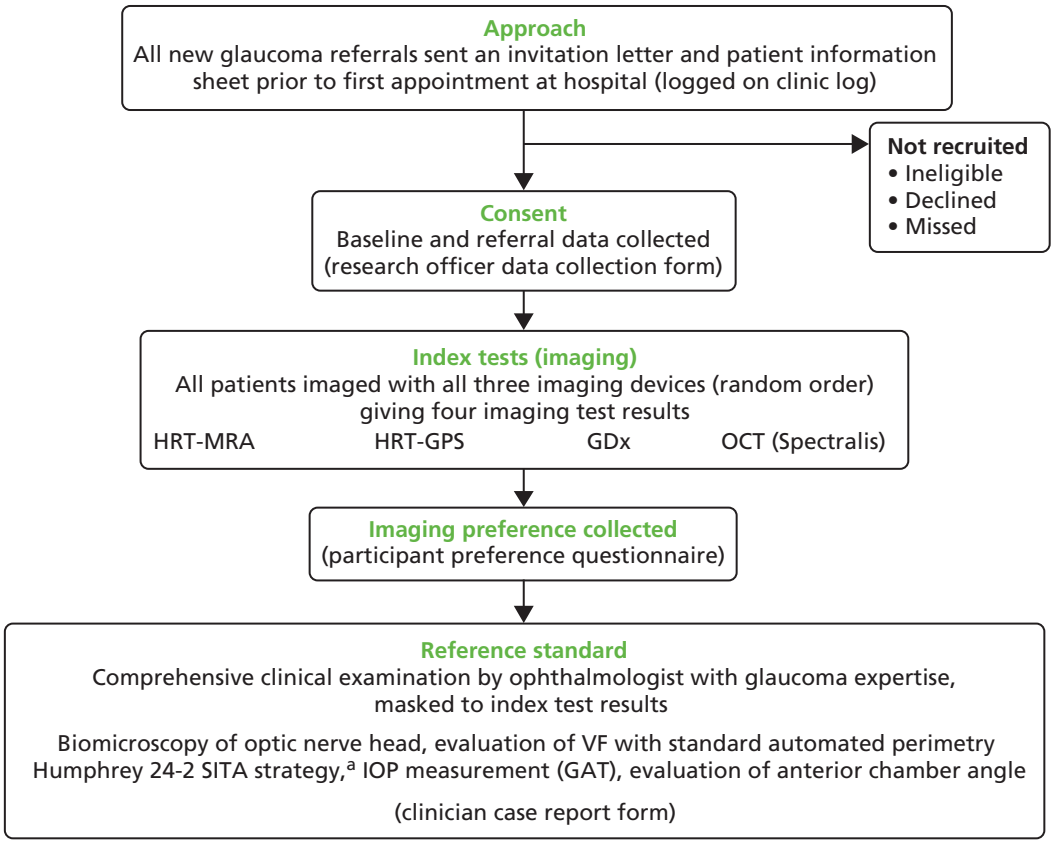

FIGURE 1 Overview of study design. GAT, Goldman applanation tonometry; VF, visual field. a, Carl Zeiss Meditec, Dublin, CA, USA.

Participants

Inclusion criteria

Adult patients referred from community optometrists or general practitioners to hospital eye services with any glaucoma-related findings, including those with OHT.

Exclusion criteria

Patients referred to hospital eye services because of other ocular disease; patients < 18 years old; patients who could not give informed consent; patients who had already been diagnosed with glaucoma; and patients referred from within secondary care.

Setting

Five NHS hospital eye services in the UK participated in this study: Aberdeen Royal Infirmary (Aberdeen), Bedford Hospital (Bedfordshire), Hinchingbrooke Hospital (Cambridgeshire), Moorfields Eye Hospital (London) and St Paul's Eye Unit (Liverpool). The participating units consisted of three academic units of different sizes and two district general hospitals (Hinchingbrooke and Bedford).

Identification of participants and recruitment process

Consecutive eligible patients referred from community optometrists to hospital eye services with a glaucoma-related finding were identified by the research officer in each centre at the time of referral. Patients were identified from their referral letter as being referred with a possible glaucoma diagnosis or glaucoma-related finding, including high IOP, possible abnormalities in the optic disc or visual field tests, and possible narrow anterior chamber angle. To ensure that a full cross-section of referrals were identified, existing referral refinement schemes in two of the participating centres were suspended for the duration of the study in order not to introduce selection bias. In the largest centre (Moorfields Eye Hospital) only those patients booked to see a clinician trained in the study protocol to provide the reference standard were identified as eligible. Information about this study was sent to potentially eligible patients together with the date of the appointment (see *Appendix 1*). Patients were approached by the local research officer on their first visit to hospital eye services to discuss the study and those patients who agreed to participate and signed the consent form (see *Appendix 1*) were enrolled (i.e. before their consultation with the ophthalmologist). Each research centre kept a clinic log of eligible patients invited (see *Appendix 2*), which included patient demographics (age and sex) and, for those who declined to take part or were found to be ineligible, reason for not taking part if given.

Diagnostic technologies being assessed (index tests)

Four diagnostic tests from three imaging devices were evaluated:

1. HRT-III, confocal laser scanning imaging technology, used by the Heidelberg Retinal Tomograph (Heidelberg Engineering, Heidelberg, Germany), exploits the principle of confocal laser scanning to allow quantitative structural information of the optic disc anatomy. The topographic image is derived from multiple optical sections at consecutive focal depth planes. Each image consists of numerous pixels, with each pixel corresponding to the retinal height at its location. Images are given a measure of quality: the mean topography SD which the manufacturer recommends should be ≤ 40 µm. There are two main classification tools to define normality/outside normal limits: (1) MRA,[34] which requires the

user to draw a contour line to define the optic disc boundary, and (2) glaucoma probability score (GPS),[35] which is fully automated and independent of operator input.

   i. The HRT-MRA produces an overall ('global') classification as well as by six segments ('temporal', 'temporal superior', 'temporal inferior', 'nasal', 'nasal superior' and 'nasal inferior') of the eye. Each a classification of 'within normal limits', 'borderline' and 'outside normal limits' is given based on whether or not the observed value is within the 95.0% prediction interval, between the 95.0% and the 99.9% prediction interval or below the 99.9% prediction interval of the preset data, respectively. The final classification is based on the most abnormal of any of the seven classifications. If any one of these is 'outside normal limits' then the overall classification is 'outside normal limit'. Where there is no 'outside normal limits' but at least one 'borderline' then the final classification is 'borderline'. Only where the global and all six segment probabilities are 'within normal limits' is the final classification 'within normal limits'.

2. HRT-GPS produces an overall probability of the presence of glaucoma ('global') and by segment ('temporal', 'temporal superior', 'temporal inferior', 'nasal', 'nasal superior' and 'nasal inferior') for each eye. The default 'final' classification is based on applying cut-off to the overall and six segment probabilities: < 0.28 is 'within normal limits', ≥ 0.28 and < 0.65 is 'borderline' and ≥ 0.65 is 'outside normal limits'.[35] If any one of these is 'outside normal limits' then overall classification is 'outside normal limit'. Where there is none 'outside normal limits' but at least one 'borderline' then the final classification is 'borderline'. Only where the global and all six segment probabilities are 'within normal limits' is the final classification 'within normal limits'.
3. GDx-Enhanced Corneal Compensation (ECC) (Carl Zeiss Meditec, Dublin, CA, USA) scanning laser polarimetry measures the RNFL thickness. Measurements are based on the birefringent properties of the RNFL, which has its neurotubules disposed in an organised, parallel fashion. The software provides a discriminating classifier of glaucoma/normality, the nerve fibre indicator (NFI) value, which is fully automated and is calculated for each eye. The manufacturers' reported cut-offs for the GDx-ECC NFI value are based on 95% and 99% coverage of the normative database population and are 1–35 ('normal'), 36–55 ('abnormal 95') and ≥ 56 ('abnormal 99').[36] The difference between 'abnormal 95' and 'abnormal 99' may be viewed in a similar manner to the 'borderline' category for HRT-GPS, HRT-MRA and OCT classifications. The temporal, superior, nasal, inferior, temporal (TSNIT) parameters used in the calculation of the NFI are also produced overall and by eye segment (superior and inferior) and an inter-eye symmetry is also produced. Images are given a quality figure, which the manufacturer recommends should be ≥ 7. In this study, GDx-ECC measurements were made using either the GDx-Pro (three centres) or the GDx-VCC with updated ECC module (two centres).
4. OCT: SD-OCT (Spectralis®, Heidelberg Engineering, Heidelberg, Germany) is an optical imaging technique capable of providing high-resolution, cross-sectional imaging of the human retina in a fashion analogous to B-scan ultrasonography but using light instead of sound. OCT uses the principles of low-coherence interferometry using light echoes from the scanned structure to determine the thickness of the tissue. The glaucoma detection software of the Spectralis® machine used in this study produces an average RNFL thickness value for the global and six segments of the eye and automatically compares sectors of RNFL thickness with a normative database. An overall assessment of 'within normal limits', 'borderline' or 'outside normal limits' is produced[34] based on the global classification and the six individual segments. Inter-eye symmetry is also produced for each segment. Images are given a quality figure, which the manufacturer recommends should be > 15.

Sample reports generated by each of the imaging tests are shown in *Appendix 3*.

Reference standards

Eye level (for the diagnostic performance analysis)

The glaucoma diagnosis reference standard chosen for this study represents current clinical practice in the UK, which consists of clinical examination (biomicroscopy) of the appearance of the optic nerve head and evaluation of the visual field with standard automated perimetry Humphrey 24–2 SITA (Carl Zeiss Meditec, Dublin, CA, USA) strategy by an ophthalmologist with glaucoma expertise. In addition, the clinician measured the IOP and examined the anterior chamber angle. The imaging tests were not available to the ophthalmologist when measuring the reference standard. The clinician recorded the status of each eye as described in *Table 1* (i.e. glaucoma, OHT, glaucoma suspect, other eye morbidities or normal). If a clinical diagnosis could not be established at the first visit (e.g. unreliable visual field measurement requiring repeated measurement at a further appointment), an inconclusive diagnosis was recorded. In order to ensure valid and consistent application of the agreed reference standard, a limited number of consultant ophthalmologists provided the reference standard (one or two clinicians in four centres, and five different clinicians at one centre). Principal investigators collaborating in each of the participating units gathered at the start of the project to review and agree on the reference standard (definitions of glaucoma, OHT, glaucoma suspect and

TABLE 1 Clinical diagnosis definitions

Diagnosis	Definition
Glaucoma	
Severe	Evidence of glaucomatous optic neuropathy[a] and a characteristic VF loss.[b] Severe: MD worse than or equal to –12.01 dB
Moderate	Evidence of glaucomatous optic neuropathy[a] and a characteristic VF loss.[b] Moderate: MD between –6.01 dB and –12 dB
Mild	Evidence of glaucomatous optic neuropathy[a] and a characteristic VF loss.[b] Mild: MD better than or equal to –6 dB
Glaucoma suspect	
Disc suspect	Appearance suggestive of glaucomatous optic neuropathy but may also represent a variation of normality, with normal VFs (with or without high IOP)
VF suspect	VF loss suggestive of glaucoma, but may also represent a variation of normality, with normal appearance of the optic disc (with or without high IOP)
VF and disc suspect	Both the optic disc and VF have some features that resemble glaucoma but may also represent a variation of normality (with or without high IOP)
OHT	When both the VF and optic nerve appear normal in the presence of elevated pressure > 21 mmHg
PAC	Closed anterior chamber angle (appositionally or synechial) in at least 270°, and at least one of the following: IOP > 21 mmHg and/or presence of peripheral anterior synechiae. Both VF and optic nerve appear normal
PAC suspect	Closed anterior chamber angle (appositionally without any synechiae) in at least 270°, with IOP ≤ 21 mmHg. Both VF and optic nerve appear normal

MD, mean deviation; PAC, primary angle closure; VF, visual field.

a Evidence of optic nerve damage from any of the following: optic disc or RNFL 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 localised abnormalities of the peripapillary RNFL, especially at the inferior or superior poles; disc rim or peripapillary RNFL haemorrhages; optic disc neural rim asymmetry of the two eyes consistent with loss of neural tissue.

b Reliable VF abnormality considered a valid representation of the subject's functional status. VF damage consistent with RNFL damage (e.g. nasal step, arcuate field defect or paracentral depression in clusters of test sites). VF loss in one hemifield that is different from the other hemifield, that is across the horizontal midline (in early/moderate cases). Absence of other known explanations.

Note

Reference standard: for the eye-level analysis, reference standard positive was classified as a diagnosis of glaucoma. Sensitivity analyses explored the diagnostic performance of the tests when also including glaucoma suspects in the definition of reference standard positive (see *Statistical analysis methods* for full details).

normal) and how to define the spectrum of the disease (mild, moderate and severe). For this purpose, training material was used including a series of cases with glaucoma-related findings and also with normal subjects. Clinicians who were incorporated into the study at a later date to recruit and provide the reference standard were trained individually by the chief investigator with the same material.

For the eye-level analysis, reference standard positive was classified as a diagnosis of glaucoma based on the 'worse' eye. Sensitivity analyses explored the diagnostic performance of the tests when also including glaucoma suspects in the definition of reference standard positive along with using the 'better' eye (see *Statistical analysis methods* for full details).

Patient level (for the triage performance analysis)

For each patient the clinical management decision made was recorded, that is 'discharge' or 'do not discharge'. Additionally, the reason for non-discharge [and which eye(s) it refers to] of 'treatment' or 'monitoring' was also collected. Clinicians were advised to follow NICE guidelines in deciding whether to discharge or not.[26]

Outcomes

For each of the four tests (HRT-MRA, HRT-GPS, GDx and OCT) the following outcomes were measured.

Diagnostic performance of imaging technologies

The primary diagnostic performance outcomes were sensitivity and specificity. Secondary diagnostic performance outcomes were likelihood ratio and diagnostic odds ratio (DOR). The overall diagnostic performance of combinations of these four tests was also evaluated (HRT-MRA with each of the other three tests) as well as their relative performance. The diagnostic performance of the tests (and corresponding combinations) was also assessed according to the spectrum of glaucoma (mild, moderate and severe), as defined by the glaucoma expert.

Other outcomes

The proportions of indeterminacy results, low-quality imaging according to the manufacturer's recommendation and the participant's preference regarding the four tests were recorded for each test. Additionally, the number of participants who required pupil dilatation to perform the imaging was also recorded. Dilatation was attributed to the first imaging technology. Where a high-quality test result was not available for a participant ('no result'), one of the following categorises applied:

(a) test performed and imaging report produced but quality is lower than manufacturer quality cut-off
(b) test performed and imaging report produced but no overall classification generated by machine
(c) test performed but there was a clear imaging artefact on the report
(d) test attempted but no imaging could be acquired from the patient's eyes – no report generated
(e) missing imaging output (owing to study-related or data-collection issues).

Indeterminacy of the result was calculated as categories (b) to (d), divided by the total number of non-missing cases. The proportion of low-quality imaging was (a) divided by the total number of non-missing cases minus categories (a) to (d).

Diagnostic performance of a triage test (imaging test, visual acuity and intraocular pressure measurement)

As for the diagnosis analyses, the primary diagnostic performance outcomes of the triage test were sensitivity and specificity in correctly identifying patients who would be discharged from secondary care. Clinicians were advised to follow NICE guidelines in deciding whether to discharge or not.[26] Secondary diagnostic performance outcomes included likelihood ratios and DOR.

Delivery of interventions and data collection

Enrolled participants attended a diagnostic station for imaging (index test) and visual field measurement immediately prior to their meeting with the ophthalmologist. In three centres (Hinchingbrooke, Bedford and Liverpool), the visual field and imaging measurements took place on a separate day prior to the ophthalmologist appointment (within 2 weeks). Pupils were not routinely dilated. However, in those patients in whom adequate quality imaging could not be obtained, pupil dilatation could be used to try to improve image quality. In exceptional circumstances, where dilatation was required in centres offering split visits, some or all of the imaging tests could be delayed until the clinic appointment but always ahead of the clinical reference standard. Imaging technicians and the patient were therefore masked to the patient's underlying condition at the time of testing. In the remaining two centres (Aberdeen and Moorfields) all measurements were undertaken on the same day. All participants in each of the centres underwent testing with the three imaging devices, in a random order (to avoid bias when collecting participant preference) in one sitting. The random test order was automatically generated for each patient from the study website.

Imaging technicians employed at each centre performed the imaging tests. One to three technicians were identified at each centre and trained in study procedures prior to recruitment (see *Appendix 4*). There was no restriction on the same technician performing all imaging tests on an individual. Across all centres, most technicians were experienced in performing the test prior to the study; if technicians were not already experienced, they received training from the manufacturer or local imaging lead prior to collecting study data.

With the exception of HRT-MRA, which required an experienced user to identify a contour line at the optic disc margin, all imaging tests generated the glaucoma classification automatically once an image had been acquired. The research officer kept printed copies of the images and uploaded the imaging results to the study website. Imaging reports were identified using a unique study number and date of birth.

The participant was asked to grade the tests in order of preference, or to record no preference, using a standard form (see *Appendix 2*). Visual field measurements were undertaken with standard perimetry Humphrey SITA 24-2 strategy for each participant after all imaging tests had been completed. In exceptional circumstances, visual field measurements were undertaken ahead of the imaging tests because of clinic demand for equipment. Participants were then examined by an experienced glaucoma clinician who performed a comprehensive ocular examination including IOP measurement with Goldmann applanation tonometry (GAT), gonioscopy and biomicroscopic examination of the optic disc (with pupil dilated in patients without narrow anterior chamber angle) and evaluated the visual field test results. The clinician provided the reference standard masked to the results of the imaging technologies and completed a clinical data collection form (see *Appendix 2*).

The research officer collated the results for each participant (see *Appendix 2*) including a copy of the visual field test, completed forms for each participant, uploaded the information onto the web page and posted original consent forms to the central office. Information uploaded onto the web page included demographics, referral IOP, refractive error, patient preference, need for pupil dilatation, and Humphrey visual field reliability and global indices mean deviation (MD), pattern standard deviation (PSD) and visual field index (VFI).

Data management

A web-based secure study database was developed for the GATE study which research staff could access remotely. Password-protected access was provided such that centres could view data only from their own centre. All data collected during the course of the research were kept strictly confidential and accessed only by members of the study team. Minimal patient details were recorded and were stored under the guidelines of the 1998 Data Protection Act.[37] Patients were allocated an individual study number and this number was used to identify study paperwork. Study data were entered and imaging reports uploaded onto the database by the research officer working in each centre. Whenever possible, drop-down boxes were employed to select appropriate responses and minimise typographical errors. Automated range checks and validation were built in to ensure that inappropriate values could not be recorded.

Staff in the study office monitored data centrally and worked closely with local research officers to ensure that the data were as complete and accurate as possible. Missing forms and primary outcome data were automatically identified on the study website and distributed to local research officers on a regular basis. Uploaded imaging reports for each participant were checked by the central office, following an agreed checklist, and errors flagged for correction to the appropriate research team on a regular basis. This resulted in a low percentage of missing primary outcome data (1% reference standard: 1–3% imaging data). The content of approximately 50 case report forms and imaging reports selected at random was checked against entered data to ensure data entry accuracy. If consistent errors or discrepancies were found, this triggered a further training session with the research officer to discuss and resolve data collection and entry issues.

The chief investigator checked a random sample of HRT-MRA imaging reports from each centre (five reports for each operator at each centre) for accurate location of the optic disc margin. A high error rate (more than two of five checked) at one centre triggered a complete check of the data at that centre: images with incorrectly placed contour lines were excluded from the default analysis and classified as artefact, as described in *Chapter 4*.

Statistical analyses

Sample size

The sample size calculation and analysis were based on standard diagnostic accuracy study methods.[38] The sensitivity and specificity of each of the automated imaging tests were compared. A 5% significance level based on a two-sided test was used in the sample size calculations. A study of 897 individuals would have 90% power to detect a difference in accuracy of 9% for the primary outcome of diagnosis of glaucoma. This is based on conservative assumptions of a probability of disagreement of 0.18 (maximum level possible), a glaucoma rate of 25% (as seen in similar populations) and a sensitivity of 86% (as found in a systematic review for HRT[18]). Given this sample size, there would also be 80% power to detect a 6% difference in accuracy should the sensitivity be 93% (the current best estimate from meta analyses of high-quality diagnostic studies). For specificity, we would have over 90% power to detect a 5% difference. Based on current available evidence, a rate of 6% indeterminacy of tests results was assumed, which increased the sample size to 954 in total. A sample of this size would be of sufficient size for other measures of diagnostic performance [e.g. the sensitivity and specificity of individual technologies would be estimated to 95% confidence intervals (CIs) of width 10% and 5%, respectively].

Overview of planned analyses

To address the primary objective, two sets of preplanned statistical analyses and sensitivity analyses of the diagnostic performance were carried out. They were:

1. 'glaucoma diagnosis' analyses focused on the clinical diagnosis of glaucoma (see *Chapter 4*)
2. 'triage' analyses focused on the clinical discharge decision (see *Chapter 5*).

Glaucoma diagnosis analyses of diagnostic performance

The diagnostic performance of the four imaging tests (HRT-GPS and HRT-MRA outputs, GDx-ECC and OCT) from three imaging devices for detecting glaucoma was calculated and compared. The 'worse' eye of each participant as defined by the clinical reference standard was used in these analyses, except for one sensitivity analysis, which used the 'better' eye of each participant. The reference standard was a clinical diagnosis of glaucoma (mild, moderate or severe) by an ophthalmologist (see *Reference standards*). Diagnosis was ranked in order of decreasing severity as severe glaucoma, moderate glaucoma, mild glaucoma, glaucoma suspect (of any kind), primary angle closure (PAC), OHT or normal (including all other diagnoses). The 'worse' eye, on the basis of comparing eyes using this ranking, was used. If the two eyes had a similar spectrum of disease then a random eye was chosen. The primary analysis definition did not include glaucoma suspects (whether disc- or visual field-based suspicion or both). The initial 'positive' test

definition under the imaging assessment was a test result of 'outside normal limits' for HRT-MRA, HRT-GPS, OCT and NFI ≥ 56 for GDx, with borderline cases classified as 'negative'.

Triage analyses of diagnostic performance

This set of analyses focused on the clinical decision for the management of a participant (discharged or not discharged). The reference standard for these analyses was a person-level clinical decision ('not discharged' or 'discharged'). 'Not discharged' was defined as a 'positive' test result for the reference standard. The decision to 'not discharge' a patient may have been a result of the diagnosis of an eye condition which needs treatment (glaucoma or otherwise) or the need for monitoring in one or both eyes. As VA and IOP influence the clinical decision to discharge or not discharge a patient for conditions other than glaucoma and are routinely collected, these data were incorporated and a composite triage test was defined. In these analyses, the discharge status of the patient was compared with a composite 'test' which is a combination of results from an imaging test, the measurement of IOP and VA.

Following the statistical analysis plan, the diagnosis results (according to diagnosis performance and proportion of indeterminate tests) were considered prior to conduct of the triage analysis. Corresponding triage analyses of all four imaging tests were then conducted according to the following definitions. An 'abnormal' result for the imaging component was defined as including borderline as 'abnormal'. An 'abnormal' result for the IOP measurement component was a pressure > 21 mmHg as measured by the ophthalmologist. Similarly, for VA, an 'abnormal' test result was defined as 6/12 or poorer as measured prior to referral by an optometrist. The VA cut-off point (6/12) was chosen because below this level patients would not be able to drive and would merit further investigation to justify the reduced vision. VA was assumed not to be abnormal if it was not mentioned in the referral letter. The composite test was classified as 'abnormal' if any of three components tests were judged to be abnormal for either eye.

Statistical analysis methods

Diagnostic performance analysis methods

Diagnostic measures (sensitivity, specificity, likelihood ratios and DORs) were calculated for each test with appropriate CI.[39,40] All analyses were conducted at a 5% (two-sided) significance level, with 95% CIs produced where appropriate. Under the diagnoses analyses, the diagnostic performance (sensitivity and specificity) of the alternative imaging tests was compared using McNemar's test (default analyses only).[38] Corresponding CIs for the paired difference were generated.[41] No missing imaging, IOP or reference standard data were imputed. VA was assumed not to meet the abnormal criteria if not reported.

Sensitivity analyses of diagnostic performance

A range of sensitivity analyses were conducted for the diagnosis and/or triage analyses. These were:

- Varying the imaging test cut-off to explore possible threshold effects. This was done by classifying borderline as diseased for the overall classification and also by using the parameters reported by each imaging test. A receiver operating characteristic (ROC) curve and the area under the curve (AUC) with the corresponding 95% CI was calculated for each parameter using a non-parametric approach (SAS, SAS Institute Inc., Cary, NC, USA; Logistic command). The results of the threshold assessment are given in *Appendix 5* (diagnosis analysis only).
- Varying the reference standard definition of abnormal (e.g. inclusion of glaucoma suspects for diagnosis analyses) (both diagnosis and triage analyses).
- Removing the imaging quality requirement and/or assuming indeterminate results were abnormal (both diagnosis and triage analyses).
- Using a combination of (two) tests for diagnostic performance. The choice of combinations was informed by the individual imaging test glaucoma diagnosis analyses (diagnosis analysis only).
- Assess the impact of using 'better' eye instead of the 'worse' eye for each participant as defined by the clinical reference standard (diagnosis analysis).

- Varying the IOP cut-off value for the pressure component of the test to be classified as 'abnormal'. A further analysis using a cut-off point of IOP > 25 mmHg was carried out (triage analysis only).
- Using the referral IOP measurement instead of the ophthalmologist's measurement to define the positive IOP component of the triage test. For this analysis IOP > 21 mmHg will be used as the cut-off point for OHT (triage analysis only).
- Varying the threshold for the VA component of the composite test to be classified as 'abnormal' (triage analyses only).
- Using a composite test without a VA component (i.e. only imaging and IOP components) (triage analyses only).

Diagnostic analyses to populate the health economic model

A third set of analyses were produced in order to provide the most appropriate diagnostic performance data to populate the economic model (see *Appendix 6* for the results). Under these analyses, the reference standard was detection of glaucoma and those 'at risk' of glaucoma (i.e. a patient who was a glaucoma suspect of any kind, PAC or OHT). This is because people with these potential diagnoses need to remain monitored in secondary care according to the NICE guidelines. Any modelled triage system would need to reflect standard practice.[26]

Other outcomes

Two other outcomes were used to evaluate each of the four tests: indeterminacy of tests and participant preferences. Indeterminacy of tests was quantified as the proportion of tests that are indeterminate for each of the four imaging tests. This outcome was calculated in two ways: those which meet the manufacturer's suggested quality requirements and those for which a test result was produced. Participants' preference ranking of the three imaging technologies was summarised.

Patient and public involvement

Representatives from a UK-based charity for glaucoma patients, the International Glaucoma Society, were involved in the study oversight throughout the project through the steering committee. This included review and development of the study protocol and patient paperwork; monitoring the study progress; review and discussion of the final results of the study, including the care pathways and sensitivity analyses for the economic analyses, with particular reference to the patient perspective; and proposing further research priorities, particularly the acceptability of this new model of care. Additionally, a patient with glaucoma reviewed and commented on the lay summary of the report.

Study oversight and management arrangements

The University of Aberdeen sponsored the study. An independent Trial Steering Committee (TSC) was established. The TSC comprised an independent chairperson (ophthalmologist and senior academic), three further independent members (two ophthalmologists and the chief executive of a UK-based charity for glaucoma patients, the International Glaucoma Association) and the study grant holders. The TSC met approximately annually over the course of the study. A patient (IR) agreed to provide advice on certain aspects of the study, but was not a member of the TSC. No data monitoring committee was used, as there were no safety concerns; the diagnostic technologies under evaluation were non-invasive, they were routinely performed in clinical settings and patient management did not change.

The day-to-day running of the study was the responsibility of the chief investigator (AAB) supported by the research manager, research fellow and data support staff. A project management group consisting of the coapplicants provided strategic, management and content expertise to the study.

Ethical arrangements and regulatory approvals

The study and subsequent amendments were reviewed and given a favourable opinion by the North of Scotland Research Ethics Committee (reference 10/S0801/58) and local research and development departments. The study was conducted according to the principles of good clinical practice.

Protocol amendments after study initiation

A number of minor protocol revisions were made after study initiation (*Box 1*).

BOX 1 Versions of the study protocol

- Version 1, 28 July 2010.
- Version 1.1, 31 January 2011 (minor typographical changes).
- Version 1.2, 17 April 2012 (extension of recruitment time scale).
- Version 1.3, 11 April 2013 (extension of recruitment time scale).
- Version 1.4, 4 July 2013 (updated list of grant holders and TSC members).

Chapter 3 Participant characteristics

This chapter provides an overview of the baseline characteristics of participants in the GATE study.

Recruitment of participants

Between April 2011 and July 2013, 2088 participants were identified as potentially eligible to take part in the study: 2013 were sent letters of invitation and patient information sheets. Of those invited, 966 (48%) agreed to take part, and 265 (13%) expressed a preference for not participating. Characteristics of non-participants are detailed in *Table 2*.

Following consent, 11 participants were subsequently excluded from the study: 10 were ineligible (four had pre-existing glaucoma, four were referred from secondary care and two were not referred for glaucoma) and one person withdrew from the study. Therefore, 955 participants were available for the index test comparison. Additionally, owing to administrative and research processes, imaging was not implemented for all imaging tests in 12 participants, and these participants were excluded from all analyses. The baseline measurements presented in this chapter relate to the remaining 943 participants.

Figure 2 shows a diagram of the enrollment following the STARD reporting guidelines. Full details of patient flow through the diagnostic performance analysis are described within the results (see *Chapters 4* and *5*).

Aberdeen and Hinchingbrooke were the highest-recruiting centres (*Table 3*). Over two-thirds of GATE participants were recruited from these two sites.

TABLE 2 Characteristics of non-participants

Characteristic	Value
N	1122
Age (years),[a] mean (SD)	61.7 (15.1)
Female, *n* (%)	592 (52.8)
Reasons for not taking part,* n *(%)	
Screened but not sent information sheet	75 (6.7)
Refusal	265 (23.6)
Equipment malfunction	33 (2.9)
Missed	93 (8.3)
Non-attendance	134 (11.9)
Other reason	247 (22.0)
Reason not given	275 (24.5)

a Age calculated as year of test – year of birth.

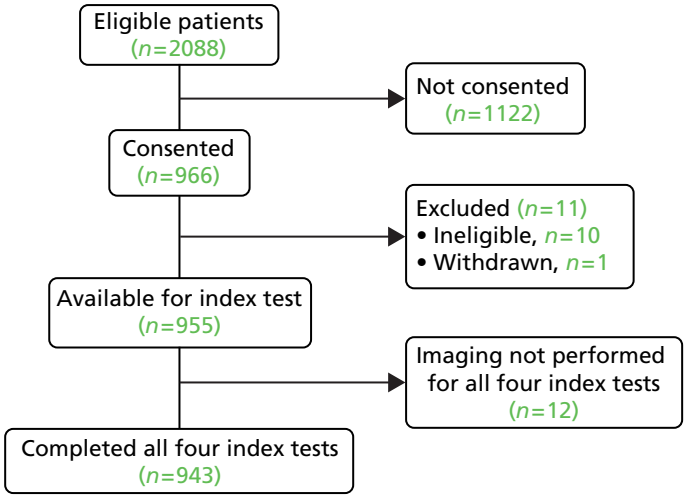

FIGURE 2 Diagram showing recruitment to the study.

TABLE 3 Centre recruitment

Centre	Participants recruited, *n* (%)
Aberdeen Royal Infirmary	353 (37.0)
Bedford Hospital	74 (7.7)
Hinchingbrooke Hospital NHS Trust	343 (35.9)
Moorfields Eye Hospital	157 (16.4)
Royal Liverpool Hospital	28 (2.9)
Total	955

Baseline characteristics of participants

Demographic characteristics of participants and non-participants were similar, with an average age slightly above 60 years (*Tables 2* and *4*) and similar gender distribution. Among participants, nearly 90% were of white British ethnicity (self-reported ethnicity; *Table 4*).

Ocular characteristics recorded in the referral letter from the optometrist are detailed in *Table 5*. In the majority of referrals (77%), the optometrist had highlighted abnormalities in both eyes (referral eye). The average IOP at referral was 20 mmHg. Where the method of IOP measurement was reported on the referral letter (52%), the most commonly reported method of measurement was non-contact tonometry.

Data on VA and refractive error at referral are summarised in *Table 5*.

TABLE 4 Baseline demographics of included participants

Characteristic	Value		
	All participants	Glaucoma	Non-glaucoma
N	943	158	770
Age (years), mean (SD)	60.5 (13.8)	67.4 (12.7)	59.2 (13.6)
Female, *n* (%)	482 (51.1)	74 (46.8)	401 (52.1)
Ethnicity,*[a] n *(%)			
Black or Black Caribbean	25 (2.7)	4 (2.5)	21 (2.7)
Black or Black British-African	20 (2.1)	6 (3.8)	14 (1.8)
Asian or Asian British-Indian	18 (1.9)	5 (3.2)	13 (1.7)
Asian or Asian British-Pakistani	4 (0.4)	0 (0)	4 (0.5)
Chinese	1 (0.1)	1 (0.6)	0 (0)
Other Asian background	4 (0.4)	1 (0.6)	3 (0.4)
Mixed White and Black African	1 (0.1)	1 (0.6)	0 (0)
White British	826 (89.2)	140 (88.6)	686 (89.1)
Other	29 (3.1)	0 (0)	29 (3.8)

a There was no ethnicity recorded in 15 participants.

TABLE 5 Ocular characteristics of participants at referral

Characteristic		
Referral eye,* n/N *(%)		
Right	97/939 (10.3)	
Left	116/939 (12.3)	
Both eyes	725/939 (76.9)	
Not answered	1/939 (0.1)	
Method of IOP assessment,* n/N *(%)		
Non-contact tonometry	260/943 (27.6)	
GAT	231/943 (24.5)	
Other[a]	452/943 (47.9)	
IOP on referral (mmHg)	***Right eye***	***Left eye***
IOP, mean (SD)	19.6 (5.7), 918	19.9 (5.6), 918
Refraction		
Mean sphere (dp), mean (SD), *n*	0.4 (3.3), 571	1.0 (3.6), 561
Myopia greater than –5 dp, *n/N* (%)	37/943 (3.9)	36/943 (3.8)
Hyperopia greater than +5 dp, *n/N* (%)	38/943 (4.0)	51/943 (5.4)
Astigmatism greater than 3 dp, *n/N* (%)	16/943 (1.7)	16/943 (1.7)
***VA, mean (SD),* n**		
BCVA, Snellen chart	1.0 (0.3), 925	1.0 (0.3), 926
LogMAR	0.0 (0.3), 925	0.0 (0.3), 926

BCVA, best corrected VA; logMAR, logarithm of the minimum angle of resolution.
a Includes those where the method of assessment was not recorded on referral.

Reference standard diagnosis characteristics

Tables 6–14 describe the tests used to determine the reference standard and the diagnoses in the GATE population. The average clinician IOP measured with GAT was similar to the referral IOP (see *Table 6*) and highest among patients with OHT and glaucoma (see *Table 7*). Visual field testing was outside the manufacturer-recommended reliability in one-quarter of participants. The average MD among those diagnosed with glaucoma and with reliable visual field tests was –6.0 dB (SD 6.4 dB) in the right eye and –7.5 dB (SD 6.8 dB) in the left eye (see *Table 7*).

Table 8 displays the diagnosis of the GATE population per eye according to the agreed reference standard (see *Chapter 2*). The most common diagnosis (at approximately 40%) was 'no glaucoma-related findings'. Glaucoma was diagnosed in about 11% of eyes. Comorbidities were uncommon, except for cataract, which was reported in approximately 8% of eyes (see *Table 9*).

Among those eyes with glaucoma, mild disease was most prevalent (above half), while severe glaucoma was diagnosed in a relatively small proportion of eyes with the disease (28 out of 219 eyes, 12.8%; see *Table 10*).

Over one-third of the GATE participants were discharged after the first visit (see *Table 11*). *Table 13* describes the diagnosis by worse eye (ranked in the order shown) and by better eye. Glaucoma was diagnosed in at least one eye in 16.8% of the GATE cohort and 6.5% had glaucoma in both eyes at referral (see *Table 12*).

TABLE 6 Data from HES examination: VF and IOP

Characteristic	Right eye	Left eye
***VF reliability,*[a] n/N (%)**		
Reliable	706/941 (75.0)	707/940 (75.2)
Unreliable	212/941 (22.5)	210/940 (22.3)
Not done	23/941 (2.4)	23/940 (2.4)
***Reliable VF measures, mean (SD),* n**		
MD (dB)	–1.9 (4.0), 703	–2.2 (4.1), 702
PSD (dB)	2.8 (2.6), 703	2.8 (2.6), 702
VFI (%)	95.0 (10.1), 688	94.9 (10.3), 682
***VF measures including unreliable, mean (SD),* n**		
MD (dB)	–1.8 (4.0), 893	–2.0 (4.1), 887
PSD (dB)	2.8 (2.5), 893	2.8 (2.5), 887
VFI (%)	95.0 (10.2), 866	95.0 (10.1), 859
***IOP: ophthalmologist GAT, mean (SD),* n**		
IOP (mmHg)	19.2 (5.1), 932	19.3 (5.1), 932

HES, hospital eye service; VF, visual field.
a VF reliability as defined by Humphrey VF output.

TABLE 7 Data from HES examination: IOP and MD by diagnosis

Diagnosis	Right eye, mean (SD), *n*	Left eye, mean (SD), *n*
IOP (mmHg) GAT		
Glaucoma	23.0 (6.4), 116	22.6 (6.9), 103
Glaucoma suspect	17.9 (4.4), 201	18.8 (5.2), 194
OHT	25.2 (3.5), 122	25.2 (3.1), 123
PAC/PAC suspect	17.8 (4.1), 120	17.8 (3.8), 126
Normal	17.1 (3.2), 367	17.2 (3.1), 379
Reliable VF MD (dB)		
Glaucoma	–6.0 (6.4), 85	–7.5 (6.8), 77
Glaucoma suspect	–2.2 (3.4), 150	–2.2 (3.4), 153
OHT	–0.6 (2.2), 85	–0.8 (2.0), 92
PAC/PAC suspect	–1.1 (3.0), 91	–1.4 (2.9), 89
Normal	–1.1 (3.0), 280	–1.3 (3.0), 279
All VF MD (dB) including unreliable		
Glaucoma	–5.6 (6.1), 103	–7.2 (6.6), 89
Glaucoma suspect	–2.2 (3.5), 195	–2.0 (3.3), 187
OHT	–0.3 (2.3), 113	–0.7 (2.1), 111
PAC/PAC suspect	–0.9 (2.9), 115	–1.3 (2.9), 121
Normal	–1.1 (3.4), 352	–1.4 (3.4), 364

HES, hospital eye service; VF, visual field.

TABLE 8 Data from HES examination: diagnosis

Diagnosis	Right eye, *n* (%)	Left eye, *n* (%)
N	932	931
Glaucoma	116 (12.4)	103 (11.1)
Disc suspect	146 (15.6)	126 (13.5)
VF suspect	29 (3.1)	35 (3.8)
VF + disc suspect	26 (2.8)	33 (3.5)
OHT	122 (13.0)	123 (13.2)
PAC	30 (3.2)	29 (3.1)
PAC suspect	90 (9.6)	97 (10.4)
No glaucoma-related findings	367 (39.2)	379 (40.7)
Undetermined	6 (0.6)	6 (0.6)

HES, hospital eye service; VF, visual field.

TABLE 9 Data from HES examination: comorbidity

Comorbidity	Right eye, *n* (%)	Left eye, *n* (%)
N	936	936
Age-related macular degeneration	7 (0.7)	11 (1.2)
Cataract	78 (8.3)	70 (7.4)
Neurological	6 (0.6)	8 (0.8)
Other	65 (6.9)	63 (6.7)

HES, hospital eye service.

TABLE 10 Data from HES examination: glaucoma severity

Glaucoma severity[a]	Right eye, *n* (%)	Left eye, *n* (%)
N	116	103
Mild	69 (59.5)	53 (51.5)
Moderate	31 (26.7)	29 (28.2)
Severe	11 (9.5)	17 (16.4)
Severity not recorded	5 (4.3)	4 (3.9)

HES, hospital eye service.
a See *Chapter 2* for severity definitions.

TABLE 11 Data from HES examination: action after first consultation

Action	*n* (%)	
N	933	
Discharged – person level	357 (38.3)	
For those not discharged	***Right eye***	***Left eye***
Treat	291 (31.2)	287 (30.8)
Monitor only	214 (22.9)	216 (23.2)
Repeat assessment required	33 (3.5)	39 (4.1)
Not recorded	37 (4.0)	33 (3.5)

HES, hospital eye service.

TABLE 12 Data from HES examination: diagnosis by worse eye and better eye

Diagnosis/comorbidity/action	Worse eye, *n* (%)	Better eye, *n* (%)
N	932	931
Diagnosis by clinician		
Glaucoma	158 (17.0)	61 (6.6)
Disc suspect	170 (18.2)	102 (11.0)
VF suspect	36 (3.9)	28 (3.0)
VF + disc suspect	36 (3.9)	23 (2.5)
OHT	115 (12.3)	130 (14.0)
PAC	31 (3.3)	28 (3.0)
PAC suspect	83 (8.9)	104 (11.2)
No glaucoma-related findings	299 (32.1)	447 (48.0)
Undetermined	4 (0.4)	8 (0.8)
Comorbidity		
Age-related macular degeneration	9 (1.0)	9 (1.0)
Cataract	75 (8.0)	73 (7.7)
Neurological	7 (0.7)	7 (0.7)
Other	68 (7.2)	60 (6.4)
Action		
Treat	320 (33.9)	258 (27.4)
Monitor only	210 (22.3)	220 (23.3)
Repeat assessment required	39 (4.1)	33 (3.5)

HES, hospital eye service; VF, visual field.

TABLE 13 Data from HES examination: severity of disease by worse and better eye for those diagnosed with glaucoma

Glaucoma severity	Worse eye, *n* (%)	Better eye, *n* (%)
N	158	61
Mild	78 (49.4)	19 (31.1)
Moderate	45 (28.5)	27 (44.3)
Severe	26 (16.5)	15 (24.6)
Severity not recorded	9 (5.7)	0 (0)

HES, hospital eye service.

TABLE 14 Data from HES examination: glaucoma mechanism for those diagnosed with glaucoma or glaucoma suspect, by worse and better eye

Clinical diagnosis	Worse eye	Better eye
Glaucoma, n/N (%)	***158/936 (16.8)***	***61/936 (6.5)***
Open angle, *n*	123	46
Angle closure, *n*	26	12
Other, *n*	1	0
Missing, *n*	8	3
Disc suspect, n/N (%)	***170/936 (18.0)***	***102/936 (10.8)***
Open angle, *n*	150	94
Angle closure, *n*	11	6
Other, *n*	2	0
Missing, *n*	7	2
VF suspect, n/N (%)	***36/936 (3.8)***	***28/936 (3.0)***
Open angle, *n*	27	21
Angle closure, *n*	6	5
Other, *n*	1	2
Missing, *n*	2	0
VF + disc suspect, n/N (%)	***36/936 (3.8)***	***23/936 (2.4)***
Open angle, *n*	33	21
Angle closure, *n*	3	2
Other, *n*	0	0
Missing, *n*	0	0

HES, hospital eye service; VF, visual field.

Chapter 4 Diagnostic analysis results

Overview

This chapter reports the results of the diagnosis analyses which aimed to assess the diagnostic performance of the four imaging tests (HRT-MRA, HRT-GPS, GDx and OCT) and the other outcomes associated with the imaging tests (indeterminacy and participant preference). The results of the triage analyses are provided in *Chapter 5*. The specific diagnostic performance analyses covered in this chapter are the default diagnosis analysis (*Table 15*, 'Default diagnostic analysis'), six sensitivity analyses (see *Table 15*, 'Diagnosis sensitivity analyses 1–6') and the use of a combination of the imaging tests (see *Table 15*, 'Combination of tests analysis') for a list with definitions. The default analysis was defined as one where the reference standard definition of disease was a clinical diagnosis of glaucoma only. The imaging test definition of an abnormal result was 'outside normal limits' for the overall classification of the imaging test (see *Chapter 2*).

TABLE 15 Diagnosis analyses

Analysis	Reference standard definition of disease	Abnormal test result	Handling of 'no result' categories	Figure number	Table number
Default diagnostic analysis	Glaucoma in the 'worse' eye	Outside normal limits	A–E excluded	*3*	*16*, *17*, *18*, *19*
Diagnosis sensitivity analysis 1	Glaucoma in the 'worse' eye	Outside normal limits or borderline	A–E excluded	*4*	*22*
Diagnosis sensitivity analysis 2	Glaucoma or glaucoma suspect in the 'worse' eye	Outside normal limits	A–E excluded	*5*	*23*
Diagnosis sensitivity analysis 3	Glaucoma or glaucoma suspect in the 'worse' eye	Outside normal limits or borderline	A–E excluded	*6*	*24*
Diagnosis sensitivity analysis 4	Glaucoma or glaucoma suspect in the 'worse' eye	Outside normal limits or borderline	A imaging classification B–D abnormal E excluded	*7*	*25*
Diagnosis sensitivity analysis 5	Glaucoma in the 'worse' eye	Outside normal limits	A imaging classification B–D abnormal E excluded	*8*	*26*
Diagnosis sensitivity analysis 6	Glaucoma in the 'better' eye	Outside normal limits	A–E excluded	*9*	*27*
Combinations of diagnosis imaging tests	Glaucoma in the 'worse' eye	Outside normal limits	A–E excluded	*10*	*28*

No result categories: A, test performed and imaging report produced but quality is lower than manufacturer quality cut-off point; B, test performed and imaging report produced but no overall classification generated by machine; C, test performed but there was a clear imaging artefact on the report; D, test attempted but no imaging could be acquired from the patient's eyes – no report generated; E, missing imaging output (because of study-related or data-collection issues).

Additionally, only cases where there was a good-quality image with an overall classification available were included (see *Chapter 2*). The six sensitivity analyses assessed the impact of varying assumptions made in the default analysis relating to the reference standard definition of disease (including all types of glaucoma suspects as diseased), the definition of an abnormal test result (including borderline results as abnormal), and how cases where the test did not produce an overall classification were handled in the analysis. In addition to missing data, there were four test-related reasons why an overall classification may not have been available (see *Table 15*, 'Handling of no results categories'). Sensitivity analyses also assessed the impact of removing the requirement of a 'good'-quality image and using the provided assessment, along with setting other cases which did not produce an overall classification result as abnormal.

The combination of test analyses investigated using pairs of imaging tests to produce a composite imaging test result, under the same assumptions as the default analysis. Given the findings of the default and sensitivity analyses, only three pairs of test combinations were evaluated: HRT-MRA with each of the other tests. For all analyses, a STARD flow diagram[33,38] was produced which shows the flow of participants. The subset of participants who received all four tests and were considered in the statistical analyses is separated out into three groups according to whether each imaging test result was 'abnormal', 'normal' or 'no result' (the imaging test result being not available because either the test was inconclusive or because the result was missing). For each of these three groups, the group status according to the reference standard ('glaucoma present' or 'glaucoma absent') for each participant is given or alternatively the reference standard was stated to be missing or inconclusive. The final categorisations of the imaging test result by reference standard status provides the four possible combinations (true and false positive, and false and true negative) from which the diagnostic performance can be assessed. Sensitivity, specificity, likelihood ratios and DOR are provided with associated 95% CIs summarised for each analysis.

Of the 966 (46%) who agreed to take part in GATE, 11 were excluded from the study: 10 were ineligible and one person withdrew prior to participating in the study.

Additionally, owing to administrative and research processing errors, imaging was not implemented for all four imaging tests in 12 participants and these participants were excluded from all analyses. The analyses in this chapter pertain to the remaining 943 participants. Of these, no reference standard finding was available for 11 participants, with an inconclusive finding in a further four cases.

Default diagnosis analysis

The results for the default diagnosis analysis are presented in three sections:

- diagnostic performance of the imaging tests
- paired comparisons of imaging tests
- diagnostic performance with restricted reference standard definition of disease.

Diagnostic performance of the imaging tests

For the default analysis, abnormal imaging test results were those classified as 'outside normal limits' and the corresponding reference standard definition of disease was a diagnosis of glaucoma in the 'worse' eye. Only participants with an imaging test output with an overall classification which met the manufacturer quality criteria were included in the analysis.

The flow of study participants according to the default diagnosis analysis is shown in *Figure 3*, with the corresponding number of abnormal, normal and no result cases by imaging test, and the corresponding reference standard finding shown. Of the 943 patients for whom all four tests were performed, 158 were classified as disease positive and 770 as disease negative. The reference standard was missing and inconclusive for 11 and four participants, respectively. The diagnostic performance for the four tests is

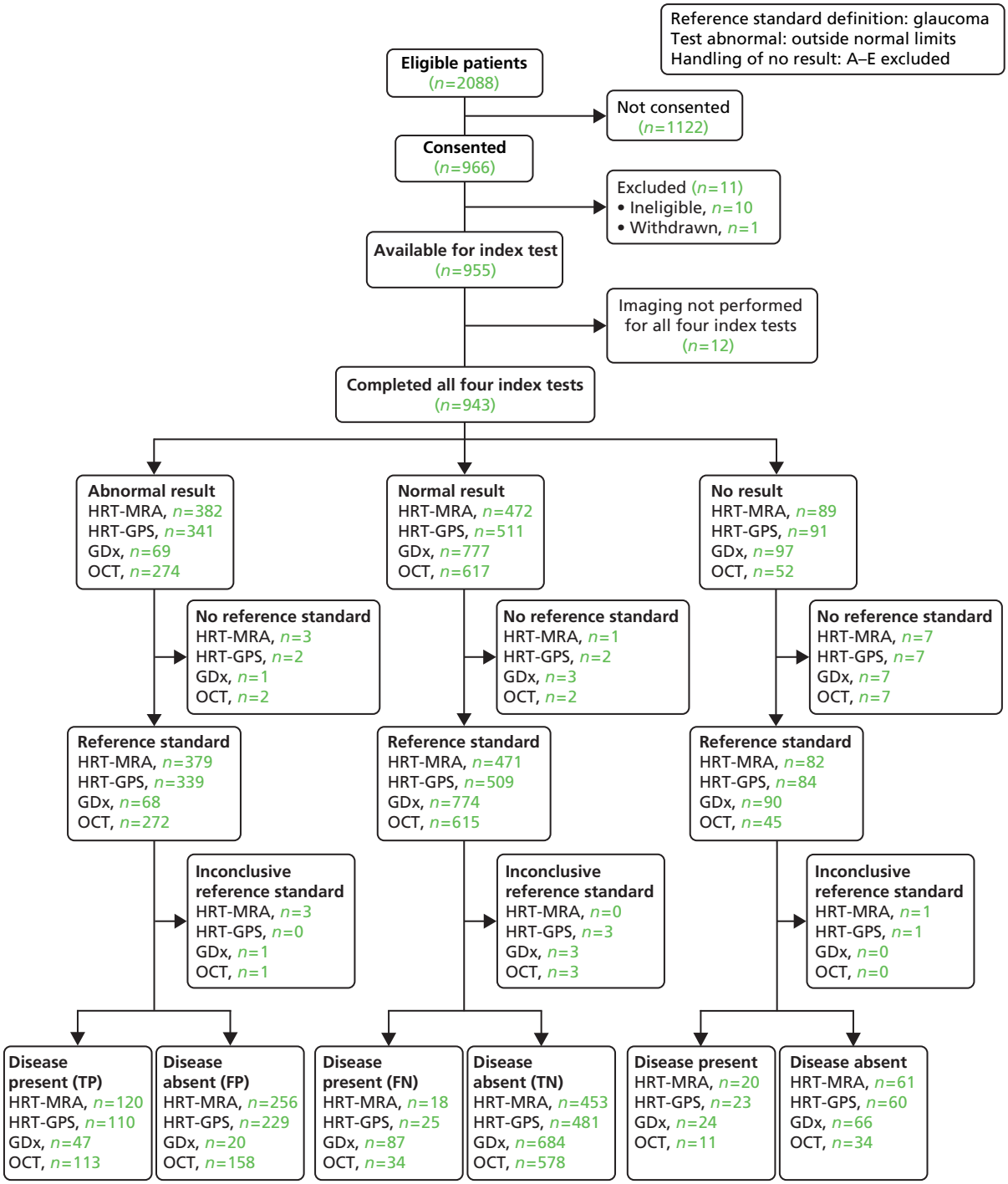

FIGURE 3 Flow diagram: default diagnostic analysis. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

given in *Table 16*. The results showed a trade-off between detection of glaucoma and correctly identifying non-glaucoma cases: HRT-MRA had the highest sensitivity (87.0%, 95% CI 80.2% to 92.1%) but the lowest specificity (63.9%, 95% CI 60.2% to 67.4%), GDx had the lowest sensitivity (35.1%, 95% CI 27.0% to 43.8%) but the highest specificity (97.2%, 95% CI 95.6% to 98.3%) and the other two tests provided intermediate results (HRT-GPS values were very similar to the HRT-MRA results and OCT had very similar sensitivity and specificity values). Likelihood ratios (and 95% CI) showed evidence of being able to both rule in and rule out the presence of glaucoma for all four imaging tests (CIs did not contain 1.0). DORs ranged from 9.24 for HRT-GPS to 18.48 for GDx.

Paired comparisons of imaging tests

Table 17 shows the paired difference (with 95% CI) and corresponding McNemar's test *p*-value for comparisons between pairs of tests. There was evidence that the sensitivity of all tests differed from each other except for HRT-GPS versus OCT.

The highest sensitivity was in HRT-MRA and the lowest sensitivity in GDx. Differences varied from –6.7% (HRT-GPS vs. HRT-MRA) to 55.6% (HRT-MRA vs. GDx). Similarly there was evidence that all specificities of all tests varied from each other (according to McNemar's test);[38] the 95% paired difference CI for HRT-GPS versus HRT-MRA just overlapped with zero.

TABLE 16 Diagnostic performance: default diagnosis analysis

Test	Diagnostic parameter	Point estimate	95% CI
HRT-MRA	Sensitivity (%)	87.0	80.2 to 92.1
	Specificity (%)	63.9	60.2 to 67.4
	Positive likelihood ratio	2.41	2.14 to 2.71
	Negative likelihood ratio	0.20	0.13 to 0.32
	DOR	11.80	7.02 to 19.81
HRT-GPS	Sensitivity (%)	81.5	73.9 to 87.6
	Specificity (%)	67.7	64.2 to 71.2
	Positive likelihood ratio	2.53	2.21 to 2.89
	Negative likelihood ratio	0.27	0.19 to 0.39
	DOR	9.24	5.82 to 14.67
GDx	Sensitivity (%)	35.1	27.0 to 43.8
	Specificity (%)	97.2	95.6 to 98.3
	Positive likelihood ratio	12.35	7.57 to 20.14
	Negative likelihood ratio	0.67	0.59 to 0.76
	DOR	18.48	10.46 to 32.63
OCT	Sensitivity (%)	76.9	69.2 to 83.4
	Specificity (%)	78.5	75.4 to 81.4
	Positive likelihood ratio	3.58	3.04 to 4.22
	Negative likelihood ratio	0.29	0.22 to 0.40
	DOR	12.16	7.97 to 18.54

TABLE 17 Paired comparisons of sensitivity and specificity between the imaging tests

Tests compared	Parameter	Test	Value (%) (95% CI)	*p*-value (McNemar's)
HRT-GPS vs. GDx	Sensitivity	HRT-GPS	81.1 (74.2 to 88.1)	–
		GDx	34.4 (26.0 to 42.9)	–
		Difference	46.7 (37.0 to 54.9)	< 0.001
	Specificity	HRT-GPS	67.5 (64.0 to 71.1)	–
		GDx	97.5 (96.3 to 98.7)	–
		Difference	–30.0 (–33.6 to –26.3)	< 0.001
GDx vs. OCT	Sensitivity	GDx	36.4 (28.1 to 44.7)	–
		OCT	77.5 (70.3 to 84.7)	–
		Difference	–41.1 (–49.2 to –31.6)	< 0.001
	Specificity	GDx	97.5 (96.3 to 98.7)	–
		OCT	79.8 (76.8 to 82.8)	–
		Difference	17.7 (14.9 to 20.8)	< 0.001
GDx vs. HRT-MRA	Sensitivity	GDx	33.1 (24.8 to 41.3)	–
		HRT-MRA	88.7 (83.1 to 94.3)	–
		Difference	–55.6 (–63.8 to –45.6)	< 0.001
	Specificity	GDx	97.3 (96.1 to 98.5)	–
		HRT-MRA	63.7 (60.1 to 67.4)	–
		Difference	33.6 (29.8 to 37.3)	< 0.001
HRT-GPS vs. HRT-MRA	Sensitivity	HRT-GPS	81.3 (74.7 to 87.9)	–
		HRT-MRA	88.1 (82.6 to 93.5)	–
		Difference	–6.7 (–13.2 to –0.6)	< 0.001
	Specificity	HRT-GPS	67.8 (64.3 to 71.3)	–
		HRT-MRA	64.1 (60.5 to 67.6)	–
		Difference	3.7 (–0.1 to 7.5)	< 0.001
HRT-MRA vs. OCT	Sensitivity	HRT-MRA	86.5 (80.7 to 92.3)	–
		OCT	75.2 (67.8 to 82.5)	–
		Difference	11.3 (3.4 to 19.2)	< 0.001
	Specificity	HRT-MRA	63.9 (60.3 to 67.5)	–
		OCT	79.4 (76.4 to 82.4)	–
		Difference	–15.5 (–19.8 to –11.2)	< 0.001
HRT-GPS vs. OCT	Sensitivity	HRT-GPS	82.3 (75.7 to 88.9)	–
		OCT	75.4 (68.0 to 82.8)	–
		Difference	6.9 (–1.6 to 15.4)	0.106
	Specificity	HRT-GPS	67.7 (64.2 to 71.2)	–
		OCT	79.7 (76.7 to 82.7)	–
		Difference	–12.0 (–16.3 to –7.6)	< 0.001

Impact of severity of disease

Two further analyses looked at the impact of changing the reference standard definition of disease to moderate and severe glaucoma and to severe glaucoma only (see *Chapter 2* for disease definitions). The only change from the default analysis was in terms of the reference standard. The diagnostic performance for the four imaging tests where the reference standard definition of disease was moderate and severe glaucoma only is given in *Table 18*.

The results showed a trade-off between detection of glaucoma and correctly identifying non-glaucoma cases: HRT-GPS had the highest sensitivity (92.7%, 95% CI 82.4% to 98.0%) but the second lowest specificity (63.5%, 95% CI 60.1% to 66.9%), GDx had the lowest sensitivity (60.0%, 95% CI 45.9% to 73.0%) but the highest specificity (95.7%, 95% CI 94.0% to 97.0%) and the other two tests provided intermediate results (HRT-MRA values were very similar to the HRT-GPS results and OCT had a similar sensitivity but higher specificity). Likelihood ratios (and 95% CIs) showed evidence of being able to both rule in and rule out the presence of glaucoma for all four imaging tests (CIs did not contain 1.0). DORs ranged from 12.44 for HRT-MRA to 33.04 for GDx. Compared with the default analysis, the diagnostic performances of GDx and OCT were both better and those of HRT-GPS and HRT-MRA poorer.

TABLE 18 Diagnostic performance: default diagnosis analysis (reference standard definition of disease of moderate and severe glaucoma)

Test	Diagnostic parameter	Point estimate	95% CI
HRT-MRA	Sensitivity (%)	89.7	78.8 to 96.1
	Specificity (%)	58.9	55.4 to 62.4
	Positive likelihood ratio	2.18	1.93 to 2.46
	Negative likelihood ratio	0.18	0.08 to 0.38
	DOR	12.44	5.28 to 29.30
HRT-GPS	Sensitivity (%)	92.7	82.4 to 98.0
	Specificity (%)	63.5	60.1 to 66.9
	Positive likelihood ratio	2.54	2.26 to 2.86
	Negative likelihood ratio	0.11	0.04 to 0.29
	DOR	22.22	7.95 to 62.12
GDx	Sensitivity (%)	60.0	45.9 to 73.0
	Specificity (%)	95.7	94.0 to 97.0
	Positive likelihood ratio	13.82	9.32 to 20.47
	Negative likelihood ratio	0.42	0.30 to 0.58
	DOR	33.04	17.43 to 62.65
OCT	Sensitivity (%)	89.1	78.8 to 95.5
	Specificity (%)	73.9	70.7 to 76.9
	Positive likelihood ratio	3.41	2.95 to 3.94
	Negative likelihood ratio	0.15	0.07 to 0.30
	DOR	23.02	10.34 to 51.25

The diagnostic performance of the four imaging tests in cases where the reference standard definition of disease was severe glaucoma only is given in *Table 19*. The results showed a trade-off between detection of glaucoma and correct identification of non-glaucoma cases: OCT had the highest sensitivity (95.2%, 95% CI 76.2% to 99.9%) and the second highest specificity (70.9%, 95% CI 67.7% to 73.9%), GDx had the lowest sensitivity (78.9%, 95% CI 54.4% to 93.9%) but the highest specificity (93.7%, 95% CI 91.8% to 95.2%) and the other two tests provided intermediate results (HRT-GPS and HRT-MRA results were very similar and had a similar sensitivity to OCT although a lower specificity). Likelihood ratios (and 95% CI) showed evidence of being able to rule in the presence of glaucoma for all four imaging tests (CIs did not contain 1.0) but could not always rule out the disease. DORs ranged from 23.63 for HRT-MRA to 48.69 for OCT. Compared with the default analysis, the sensitivity of the tests was better and the specificity poorer.

TABLE 19 Diagnostic performance: default diagnosis analysis (reference standard definition of disease of severe glaucoma)

Test	Diagnostic parameter	Point estimate	95% CI
HRT-MRA	Sensitivity (%)	94.7	74.0 to 99.9
	Specificity (%)	56.8	53.3 to 60.2
	Positive likelihood ratio	2.19	1.92 to 2.50
	Negative likelihood ratio	0.09	0.01 to 0.63
	DOR	23.63	3.14 to 177.85
HRT-GPS	Sensitivity (%)	94.7	74.0 to 99.9
	Specificity (%)	61.1	57.7 to 64.5
	Positive likelihood ratio	2.44	2.13 to 2.79
	Negative likelihood ratio	0.09	0.01 to 0.58
	DOR	28.32	3.76 to 213.16
GDx	Sensitivity (%)	78.9	54.4 to 93.9
	Specificity (%)	93.7	91.8 to 95.2
	Positive likelihood ratio	12.43	8.75 to 17.66
	Negative likelihood ratio	0.22	0.09 to 0.54
	DOR	55.31	3.76 to 172.63
OCT	Sensitivity (%)	95.2	76.2 to 99.9
	Specificity (%)	70.9	67.7 to 73.9
	Positive likelihood ratio	3.27	2.84 to 3.77
	Negative likelihood ratio	0.07	0.01 to 0.2
	DOR	48.69	6.50 to 364.73

Other outcomes

Indeterminacy results are shown in *Table 20*. GDx had the highest percentage of low-quality imaging results, followed by HRT-GPS and HRT-MRA, with OCT giving the lowest percentage of low-quality results.

Table 21 shows the participants' preference ranking of imaging tests (HRT-GPS and HRT-MRA have the same results), time taken to conduct the test and the proportion who received dilatation. Participant preference was collected for 890 participants (94%). Almost half of responders (48.2%) had no preference. Among those participants who gave a preference, OCT was ranked as most preferred (27.6%), followed by GDx (11.9%), and HRT-GPS/HRT-MRA had the lowest preference (5.1%). Average time taken to perform the test varied from 5.2 minutes (OCT) to 7.6 minutes (HRT-GPS/HRT-MRA). More participants received dilatation under HRT-GPS/HRT-MRA (2.2%) than the other two tests. No adverse events were reported during the study.

TABLE 20 Classification and quality of imaging results (default analysis)

Class	HRT-MRA, *n* (%) (*N* = 943)	HRT-GPS, *n* (%) (*N* = 943)	GDx, *n* (%) (*N* = 943)	OCT, *n* (%) (*N* = 943)
Normal	319 (33.8)	310 (32.9)	640 (67.9)	447 (47.4)
Borderline	153 (16.2)	201 (21.3)	137 (14.5)	170 (18.0)
Abnormal	382 (40.5)	341 (36.2)	69 (7.3)	274 (29.1)
Indeterminacy (no result categories A–D)	58 (6.3)	75 (8.0)	79 (8.4)	40 (4.2)
Missing data (no result category E)	31 (3.2)	16 (1.7)	18 (1.9)	12 (1.3)
Quality[a]	**N = *887***	**N = *887***	**N = *907***	**N = *906***
Good quality	854 (96.3)	852 (96.1)	846 (93.3)	891 (98.3)
Low quality	33 (3.7)	35 (3.9)	61 (6.7)	15 (1.7)

a Excluding no result categories B–E.

TABLE 21 Participant preference, test conduct time and dilatation results

Test	Order	Preference (*n* preferred) *n* (%) (*N* = 890)	Test conduct time (minutes), mean (SD)	Dilatation, *n* (%) (*N* = 918)
HRT (MRA/GPS)	1	49 (5.1)	*N* = 900	20 (2.2)
	2	150 (15.6)	7.6 (5.0)	–
	3	229 (23.9)	–	–
GDx	1	114 (11.9)	*N* = 886	16 (1.7)
	2	162 (16.9)	7.5 (5.1)	–
	3	152 (15.8)	–	–
OCT[a]	1	265 (27.6)	*N* = 904	6 (0.7)
	2	116 (12.1)	5.2 (3.0)	–
	3	44 (4.6)	–	–
All	Preference	462 (48.2)	–	–

a Three participants did not give a ranking for OCT.

Diagnosis sensitivity analysis 1

Diagnosis sensitivity analysis 1 differed from the default analysis in that a borderline finding on the imaging test was also classified as an abnormal result.

For diagnosis sensitivity analysis 1, abnormal imaging test results were those classified as 'outside normal limits' and 'borderline', and the corresponding reference standard definition of disease was a diagnosis of glaucoma in the 'worse' eye. Only participants with an imaging test output with an overall classification which met the manufacturer quality cut-off point were included in the analysis.

The flow of study participants according to sensitivity analysis 1 is shown in *Figure 4*, with the corresponding number of abnormal, normal and no result cases given by imaging test, and the corresponding reference standard finding shown. Of the 943 patients in whom all four tests were performed, 158 were classified as disease positive and 770 as disease negative. The reference standard was missing and inconclusive for 11 and four participants, respectively. The diagnostic performance for the four tests is given in *Table 22*. The results showed a trade-off between detection of glaucoma and correctly identifying non-glaucoma cases: HRT-MRA had the highest sensitivity (94.9%, 95% CI 89.8% to 97.9%) but the second lowest specificity (43.9%, 95% CI 40.2% to 47.6%), GDx had the lowest sensitivity (60.4%, 95% CI 51.6% to 68.8%) but the highest specificity (82.8%, 95% CI 79.8% to 85.5%), and the other two tests provided intermediate results (HRT-GPS values were very similar to the HRT-MRA results although marginally lower and OCT had a high sensitivity and moderate specificity in relation to the other tests). Sensitivity was higher for all tests than under the default analysis but with corresponding lower specificity. Likelihood ratios (and 95% CI) showed evidence of being able to both rule in and rule out the presence of glaucoma for all four imaging tests (CIs did not contain 1.0). DORs ranged from 7.36 for GDx to 14.62 for HRT-MRA.

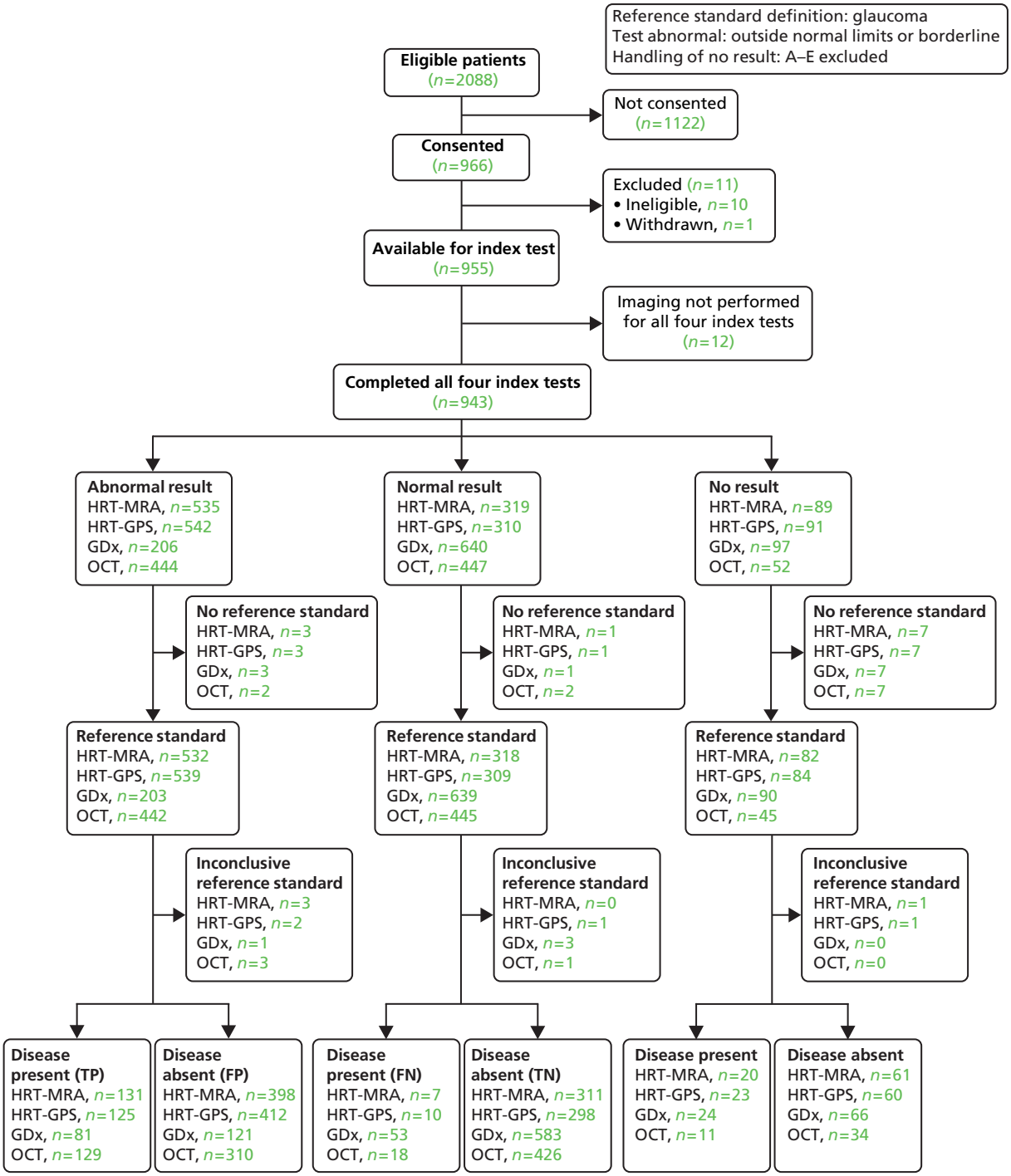

FIGURE 4 Flow diagram: diagnostic sensitivity analysis 1. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

TABLE 22 Diagnostic performance: diagnosis sensitivity analysis 1

Test	Diagnostic parameter	Point estimate	95% CI
HRT-MRA	Sensitivity (%)	94.9	89.8 to 97.9
	Specificity (%)	43.9	40.2 to 47.6
	Positive likelihood ratio	1.69	1.57 to 1.82
	Negative likelihood ratio	0.12	0.06 to 0.24
	DOR	14.62	6.74 to 31.73
HRT-GPS	Sensitivity (%)	92.6	86.8 to 96.4
	Specificity (%)	42.0	38.3 to 45.7
	Positive likelihood ratio	1.60	1.47 to 1.73
	Negative likelihood ratio	0.18	0.10 to 0.32
	DOR	9.04	4.67 to 17.51
GDx	Sensitivity (%)	60.4	51.6 to 68.8
	Specificity (%)	82.8	79.8 to 85.5
	Positive likelihood ratio	3.52	2.84 to 4.35
	Negative likelihood ratio	0.48	0.39 to 0.59
	DOR	7.36	4.95 to 10.96
OCT	Sensitivity (%)	87.8	81.3 to 92.6
	Specificity (%)	57.9	54.2 to 61.5
	Positive likelihood ratio	2.08	1.88 to 2.31
	Negative likelihood ratio	0.21	0.14 to 0.33
	DOR	9.85	5.89 to 16.49

Diagnosis sensitivity analysis 2

Diagnosis sensitivity analysis 2 differed from the default analysis in that the reference standard definition of disease incorporated all participants with glaucoma suspect (irrespective of type). For diagnosis sensitivity analysis 2, abnormal imaging test results were those classified as 'outside normal limits' and the corresponding reference standard definition of disease was a diagnosis of glaucoma in the 'worse' eye. Only participants with an imaging test output with an overall classification which met the manufacturer quality cut-off point were included in the analysis.

The flow of study participants according to sensitivity analysis 2 is shown in *Figure 5*, with the corresponding number of abnormal, normal and 'no result' cases by imaging test, and the corresponding reference standard finding shown. Of the 943 patients in whom all four tests were performed, 400 were classified as disease positive and 528 as disease negative. The reference standard was missing and inconclusive for 11 and four participants, respectively. The diagnostic performance of the four tests is given in *Table 23*. The results showed a trade-off between detection of glaucoma and correctly identifying non-glaucoma cases: HRT-MRA had the highest sensitivity (74.0%, 95% CI 69.1% to 78.5%) but lowest specificity (76.5%, 95% CI 72.5% to 80.1%), GDx had the lowest sensitivity (16.5%, 95% CI 12.8% to 20.8%) but the highest specificity (98.2%, 95% CI 96.5% to 99.2%) and the other two tests provided

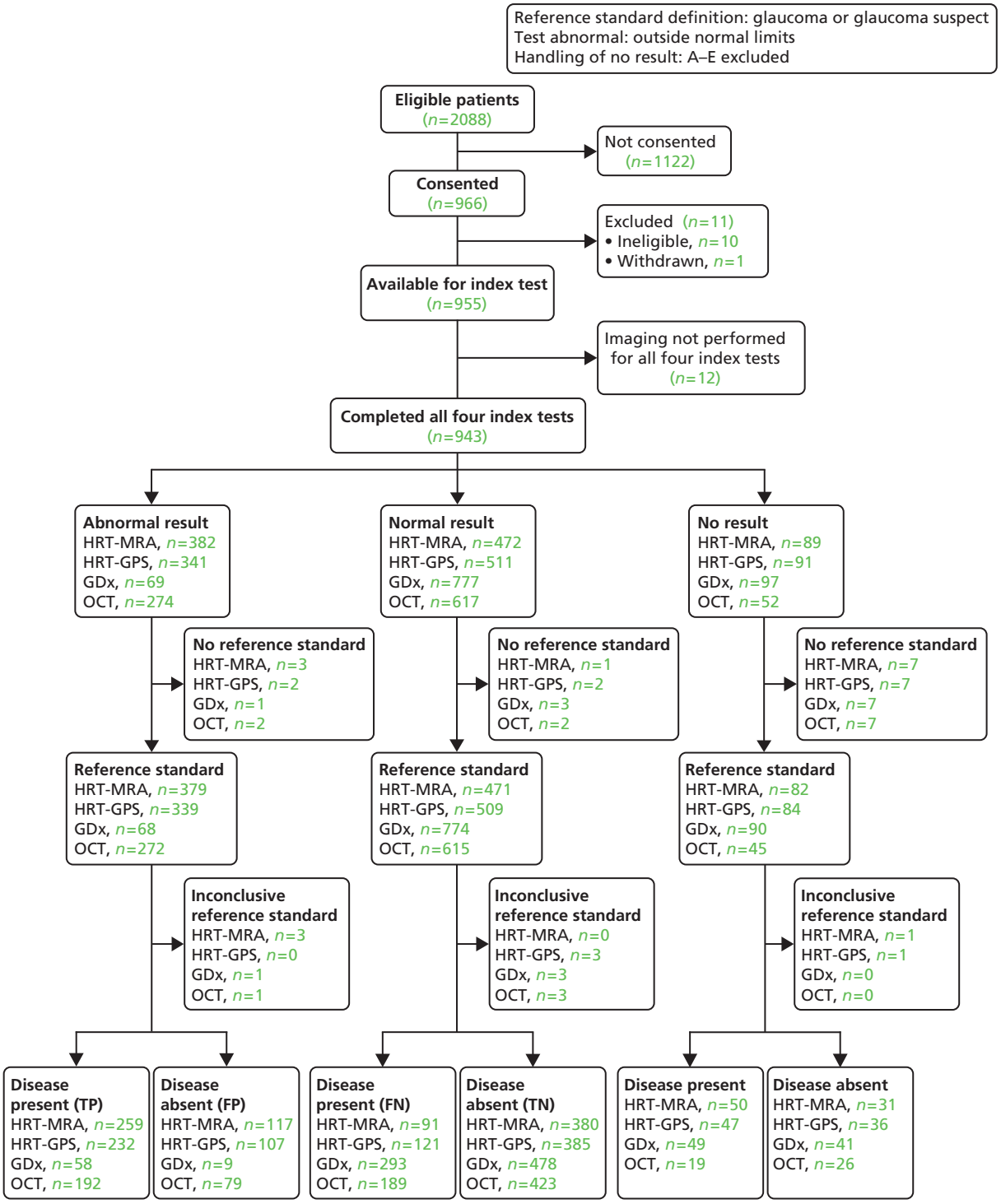

FIGURE 5 Flow diagram: diagnostic sensitivity analysis 2. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

TABLE 23 Diagnostic performance: diagnosis sensitivity analysis 2

Test	Diagnostic parameter	Point estimate	95% CI
HRT-MRA	Sensitivity (%)	74.0	69.1 to 78.5
	Specificity (%)	76.5	72.5 to 80.1
	Positive likelihood ratio	3.14	2.65 to 3.73
	Negative likelihood ratio	0.34	0.28 to 0.41
	DOR	9.24	6.74 to 12.68
HRT-GPS	Sensitivity (%)	65.7	60.5 to 70.7
	Specificity (%)	78.3	74.3 to 81.8
	Positive likelihood ratio	3.02	2.51 to 3.63
	Negative likelihood ratio	0.44	0.38 to 0.51
	DOR	6.90	5.08 to 9.38
GDx	Sensitivity (%)	16.5	12.8 to 20.8
	Specificity (%)	98.2	96.5 to 99.2
	Positive likelihood ratio	8.94	4.49 to 17.80
	Negative likelihood ratio	0.85	0.81 to 0.89
	DOR	10.51	5.13 to 21.54
OCT	Sensitivity (%)	50.4	45.3 to 55.5
	Specificity (%)	84.3	80.8 to 87.3
	Positive likelihood ratio	3.20	2.56 to 4.01
	Negative likelihood ratio	0.59	0.53 to 0.66
	DOR	5.44	3.98 to 7.44

intermediate results (HRT-GPS had lower sensitivity than HRT-MRA but a slightly higher specificity and OCT had the second lowest sensitivity but the second highest specificity values). Sensitivity was lower for all tests than under the default analysis but with correspondingly higher specificity. Likelihood ratios (and 95% CI) showed evidence of being able to both rule in and rule out the presence of glaucoma for all four imaging tests (CIs did not contain 1.0). DORs ranged from 5.44 for OCT to 10.51 for GDx.

Diagnosis sensitivity analysis 3

Diagnosis sensitivity analysis 3 differed from the default analysis in that a borderline finding on the imaging test was classified as an abnormal test result and the reference standard definition of disease incorporated all glaucoma suspects (irrespective of type).

For diagnosis sensitivity analysis 3, abnormal imaging test results were those classified as 'outside normal limits' or 'borderline' and the corresponding reference standard definition of disease was a diagnosis of glaucoma or glaucoma suspect in the 'worse' eye. Only participants with an imaging test output with an overall classification which met the manufacturer quality cut-off point were included in the analysis.

The flow of study participants according to sensitivity analysis 3 is shown in *Figure 6*, with the corresponding number of abnormal, normal and no result cases by imaging test, and the corresponding reference

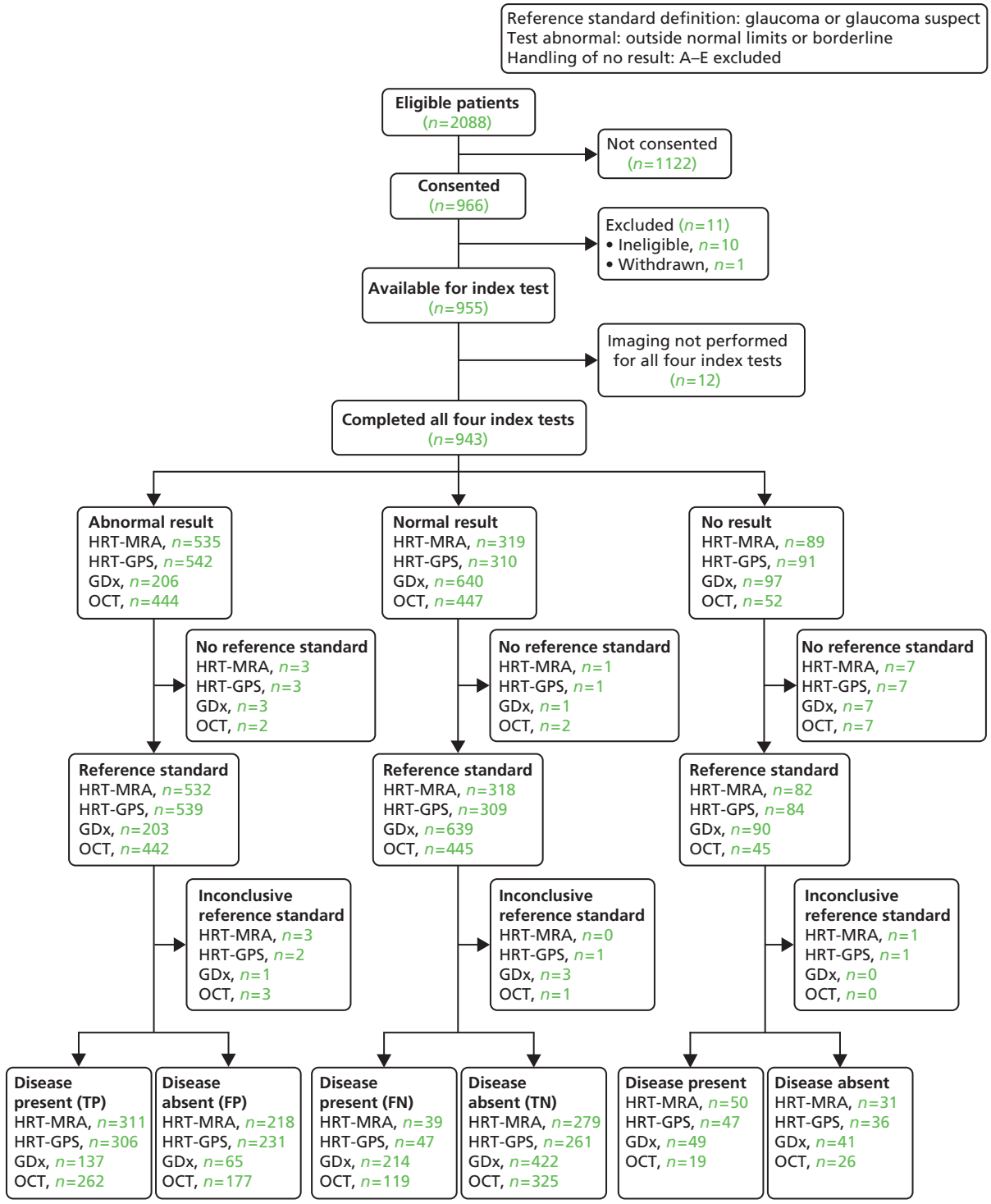

FIGURE 6 Flow diagram: diagnostic sensitivity analysis 3. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

standard finding shown. Of the 943 patients in whom all four tests were performed, 400 were classified as disease positive and 528 as disease negative. The reference standard was missing and inconclusive for 11 and four participants, respectively. The diagnostic performance of the four tests is given in *Table 24*. The results showed a trade-off between detection of glaucoma and correctly identifying non-glaucoma cases: HRT-MRA had the highest sensitivity (88.9%, 95% CI 85.1% to 92.0%) but the second lowest specificity (56.1%, 95% CI 51.6% to 60.6%), GDx had the lowest sensitivity (39.0%, 95% CI 33.9% to 44.4%) but the highest specificity (86.7%, 95% CI 83.3% to 89.5%) and the other two tests provided intermediate results (HRT-GPS values were very similar to the HRT-MRA results and OCT had very similar sensitivity and specificity values). Sensitivity was slightly higher for GDx, HRT-GPS and HRT-MRA than under the default analysis but with correspondingly lower specificity. OCT, however, had a slightly lower sensitivity and specificity than under the default analysis.

Likelihood ratios (and 95% CI) showed evidence of being able to both rule in and rule out the presence of glaucoma for all four imaging tests (CIs did not contain 1.0). DORs ranged from 4.04 for OCT to 10.21 for HRT-MRA.

TABLE 24 Diagnostic performance: diagnosis sensitivity analysis 3

Test	Diagnostic parameter	Point estimate	95% CI
HRT-MRA	Sensitivity (%)	88.9	85.1 to 92.0
	Specificity (%)	56.1	51.6 to 60.6
	Positive likelihood ratio	2.03	1.82 to 2.25
	Negative likelihood ratio	0.20	0.15 to 0.27
	DOR	10.21	7.00 to 14.88
HRT-GPS	Sensitivity (%)	86.7	82.7 to 90.1
	Specificity (%)	53.0	48.5 to 57.5
	Positive likelihood ratio	1.85	1.67 to 2.05
	Negative likelihood ratio	0.25	0.19 to 0.33
	DOR	7.36	5.16 to 10.49
GDx	Sensitivity (%)	39.0	33.9 to 44.4
	Specificity (%)	86.7	83.3 to 89.5
	Positive likelihood ratio	2.92	2.25 to 3.80
	Negative likelihood ratio	0.70	0.64 to 0.77
	DOR	4.16	2.96 to 5.83
OCT	Sensitivity (%)	68.8	63.8 to 73.4
	Specificity (%)	64.7	60.4 to 68.9
	Positive likelihood ratio	1.95	1.70 to 2.24
	Negative likelihood ratio	0.48	0.41 to 0.57
	DOR	4.04	3.04 to 5.37

Diagnosis sensitivity analysis 4

Diagnosis sensitivity analysis 4 has the same reference standard and definition of an abnormal imaging test as sensitivity analysis 3 differing by including the imaging test-related 'no result' cases (the overall classification was used irrespective of the quality indicator and the types were all classified as abnormal).

For diagnosis sensitivity analysis 4, abnormal imaging test results were those classified as 'outside normal limits' or 'borderline' and the corresponding reference standard definition of disease was a diagnosis of glaucoma or glaucoma suspect in the 'worse' eye. The analysis included participants with a low-quality imaging output if a classification was given; other imaging test results which did not provide an overall classification were included as abnormal.

The flow of study participants according to sensitivity analysis 4 is shown in *Figure 7*, with the corresponding number of abnormal, normal and no result cases and the corresponding reference standard finding shown. Of the 943 patients in whom all four tests were performed, 400 were classified as disease positive and 528 as disease negative. The reference standard was missing and inconclusive for 11 and four participants, respectively. The diagnostic performance for the four tests is given in *Table 25*.

The results showed a trade-off between detection of glaucoma and correctly identifying non-glaucoma cases: HRT-MRA had the highest sensitivity (89.2%, 95% CI 85.7% to 92.1%) but second lowest specificity (55.1%, 95% CI 50.7% to 59.5%), GDx had the lowest sensitivity (41.9%, 95% CI 37.0% to 47.0%) but the highest specificity (85.6%, 95% CI 82.3% to 88.5%) and the other two tests provided intermediate results (HRT-GPS values were similar to the HRT-MRA results and OCT had similar sensitivity and specificity values). Sensitivity was higher for all tests than under the default analysis but with correspondingly lower specificity. Likelihood ratios (and 95% CI) showed evidence of being able to both rule in and rule out the presence of glaucoma for all four imaging tests (CIs did not contain 1.0). DORs ranged from 3.89 for OCT to 10.19 for HRT-MRA.

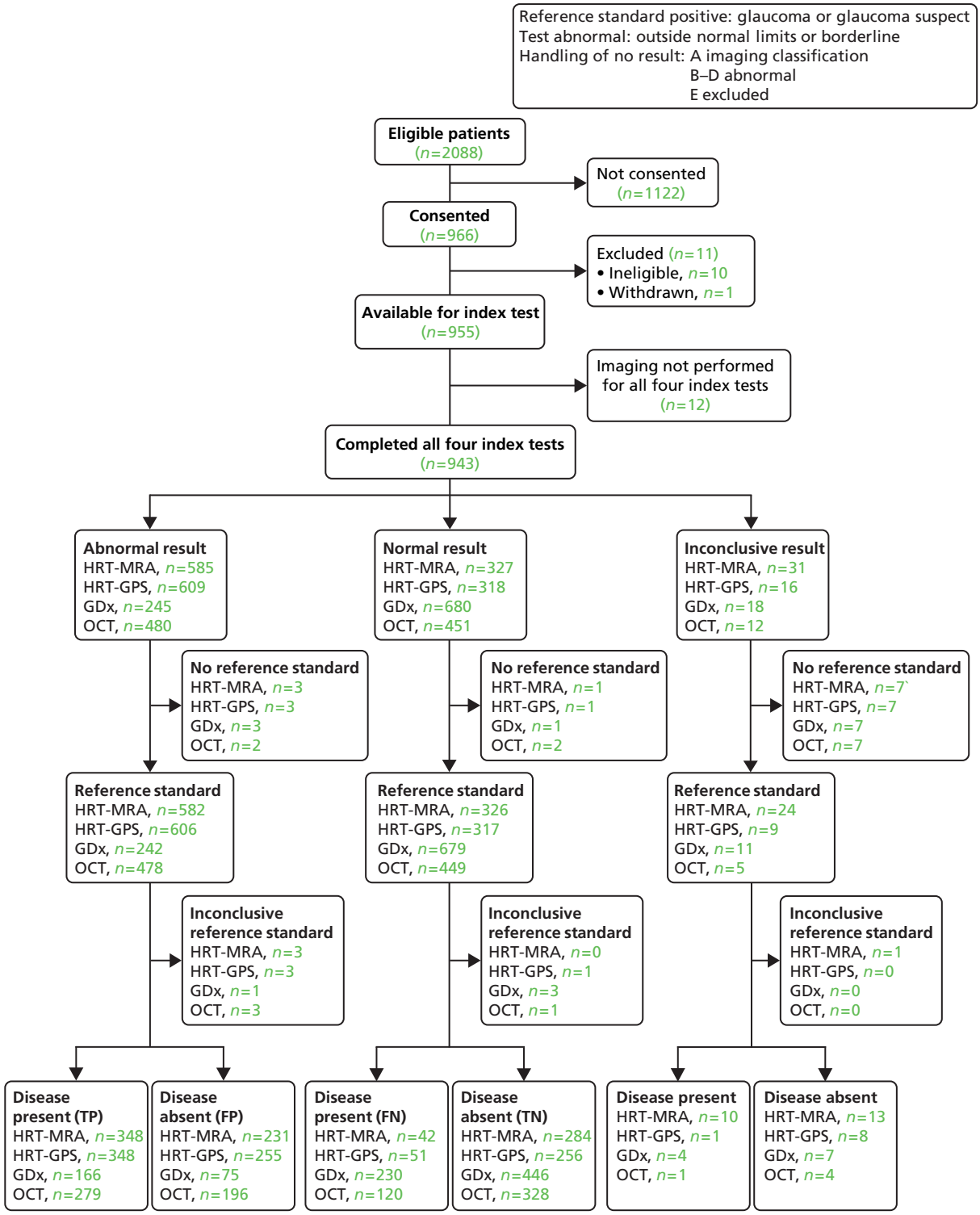

FIGURE 7 Flow diagram: diagnostic sensitivity analysis 4. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

TABLE 25 Diagnostic performance: diagnosis sensitivity analysis 4

Test	Diagnostic parameter	Point estimate	95% CI
HRT-MRA	Sensitivity (%)	89.2	85.7 to 92.1
	Specificity (%)	55.1	50.7 to 59.5
	Positive likelihood ratio	1.99	1.80 to 2.20
	Negative likelihood ratio	0.20	0.15 to 0.26
	DOR	10.19	7.08 to 14.66
HRT-GPS	Sensitivity (%)	87.2	83.5 to 90.3
	Specificity (%)	51.0	46.6 to 55.3
	Positive likelihood ratio	1.78	1.62 to 1.96
	Negative likelihood ratio	0.25	0.19 to 0.33
	DOR	7.09	5.04 to 9.97
GDx	Sensitivity (%)	41.9	37.0 to 47.0
	Specificity (%)	85.6	82.3 to 88.5
	Positive likelihood ratio	2.91	2.29 to 3.70
	Negative likelihood ratio	0.68	0.62 to 0.74
	DOR	4.29	3.13 to 5.89
OCT	Sensitivity (%)	69.9	65.2 to 74.4
	Specificity (%)	62.6	58.3 to 66.7
	Positive likelihood ratio	1.87	1.64 to 2.12
	Negative likelihood ratio	0.48	0.41 to 0.57
	DOR	3.89	2.95 to 5.14

Diagnosis sensitivity analysis 5

Diagnosis sensitivity analysis 5 differed from the default analysis in that the imaging test-related 'no result' cases were included as above for sensitivity analysis 4.

For sensitivity analysis 5, abnormal imaging test results were those classified as 'outside normal limits' and the corresponding reference standard definition of disease was a diagnosis of glaucoma in the 'worse' eye. The analysis included participants with a low-quality imaging output if a classification was given; other imaging test results which did not provide an overall classification were included as abnormal.

The flow of study participants according to sensitivity analysis 5 is shown in *Figure 8*, with the corresponding number of abnormal, normal and no result cases by imaging test, and the corresponding reference standard finding shown. Of the 943 patients in whom all four tests were performed, 158 were classified as disease positive and 770 as disease negative. The reference standard was missing and inconclusive for 11 and four participants, respectively. The diagnostic performance of the four tests is given in *Table 26*. The results showed a trade-off between detection of glaucoma and correctly identifying non-glaucoma cases: HRT-MRA had the highest sensitivity (87.3%, 95% CI 81.0% to 92.0%) but lowest specificity (61.8%, 95% CI 58.2% to 65.3%), GDx had the lowest sensitivity (37.6%, 95% CI 30.0% to 45.7%) but the highest specificity (95.4%, 95% CI 93.7% to 96.8%) and the other two tests provided intermediate results (HRT-GPS values were very similar to

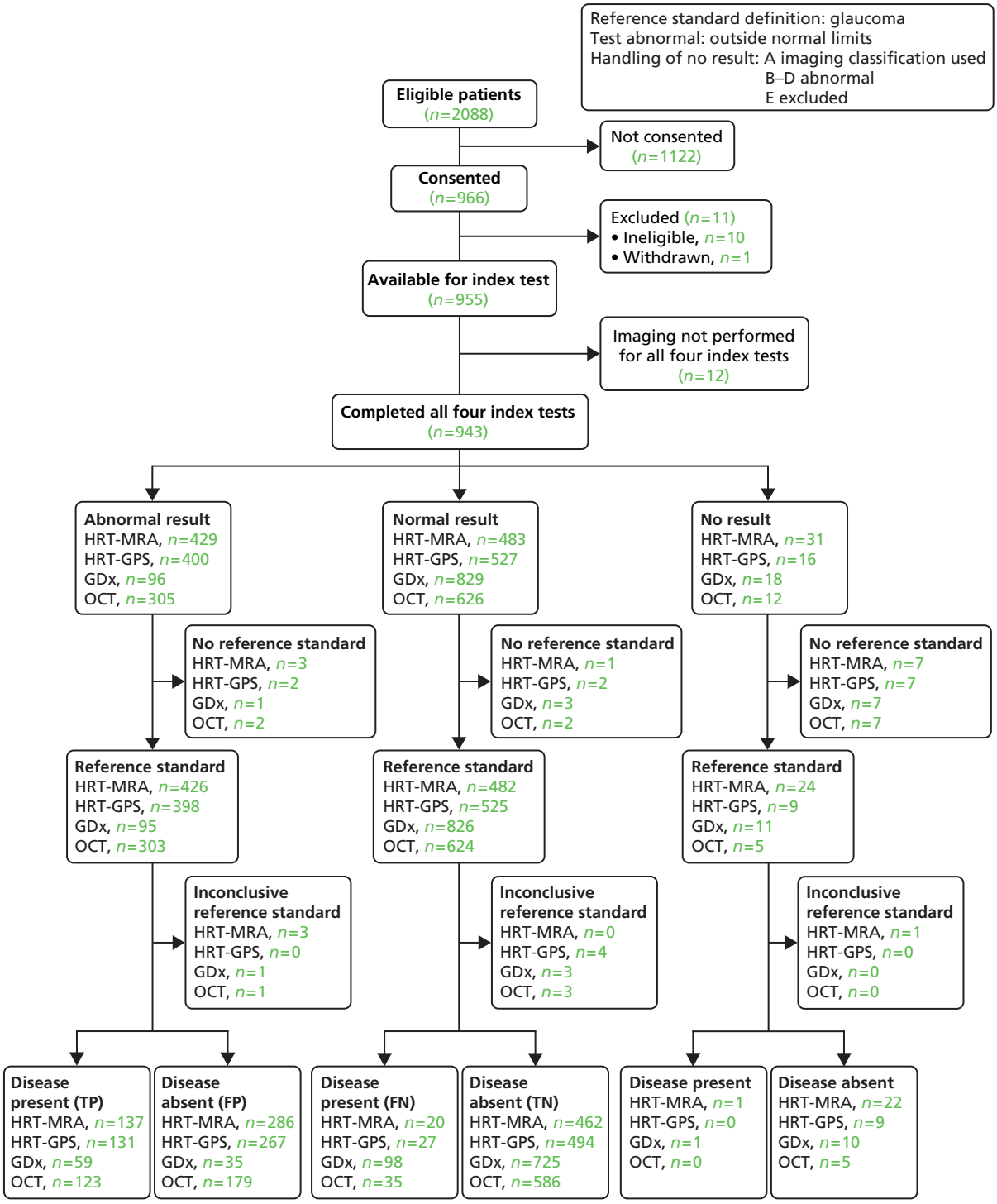

FIGURE 8 Flow diagram: diagnostic sensitivity analysis 5. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

TABLE 26 Diagnostic performance: diagnosis sensitivity analysis 5

Test	Diagnostic parameter	Point estimate	95% CI
HRT-MRA	Sensitivity (%)	87.3	81.0 to 92.0
	Specificity (%)	61.8	58.2 to 65.3
	Positive likelihood ratio	2.28	2.05 to 2.54
	Negative likelihood ratio	0.21	0.14 to 0.31
	DOR	11.07	6.77 to 18.09
HRT-GPS	Sensitivity (%)	82.9	76.1 to 88.4
	Specificity (%)	64.9	61.4 to 68.3
	Positive likelihood ratio	2.36	2.10 to 2.66
	Negative likelihood ratio	0.26	0.19 to 0.37
	DOR	8.96	5.78 to 13.94
GDx	Sensitivity (%)	37.6	30.0 to 45.7
	Specificity (%)	95.4	93.7 to 96.8
	Positive likelihood ratio	8.16	5.57 to 11.95
	Negative likelihood ratio	0.65	0.58 to 0.74
	DOR	12.47	7.81 to 19.2
OCT	Sensitivity (%)	77.8	70.6 to 84.1
	Specificity (%)	76.6	73.4 to 80.0
	Positive likelihood ratio	3.33	2.86 to 3.88
	Negative likelihood ratio	0.29	0.22 to 0.39
	DOR	11.50	7.63 to 17.35

the HRT-MRA results and OCT had very similar sensitivity and specificity values). Likelihood ratios (and 95% CI) showed evidence of being able to both rule in and rule out the presence of glaucoma for all four imaging tests (CIs did not contain 1.0). DORs ranged from 8.96 for HRT-GPS to 12.47 for GDx.

Diagnosis sensitivity analysis 6

Diagnosis sensitivity analysis 6 differed from the default analysis in that the diagnosis of the participants' 'better' eye according to the reference standard was used. Abnormal imaging test results were those classified as 'outside normal limits' and the corresponding reference standard definition of disease was a diagnosis of glaucoma. Only participants with an imaging test output with an overall classification which met the manufacturer quality cut-off point were included in the analysis.

The flow of study participants according to sensitivity analysis 6 is shown in *Figure 9*, with the corresponding number of abnormal, normal and 'no result' cases by imaging test, and the corresponding reference standard finding shown. Of the 943 patients in whom all four tests were performed, 61 were classified as disease positive and 862 as disease negative. The reference standard was missing and inconclusive for 12 and 8 participants, respectively. The diagnostic performance of the four tests is given in *Table 27*. The results showed a trade-off between detection of glaucoma and correctly identifying non-glaucoma cases: HRT-GPS had the highest sensitivity (82.4%, 95% CI 69.1% to 91.6%) but also the second lowest specificity

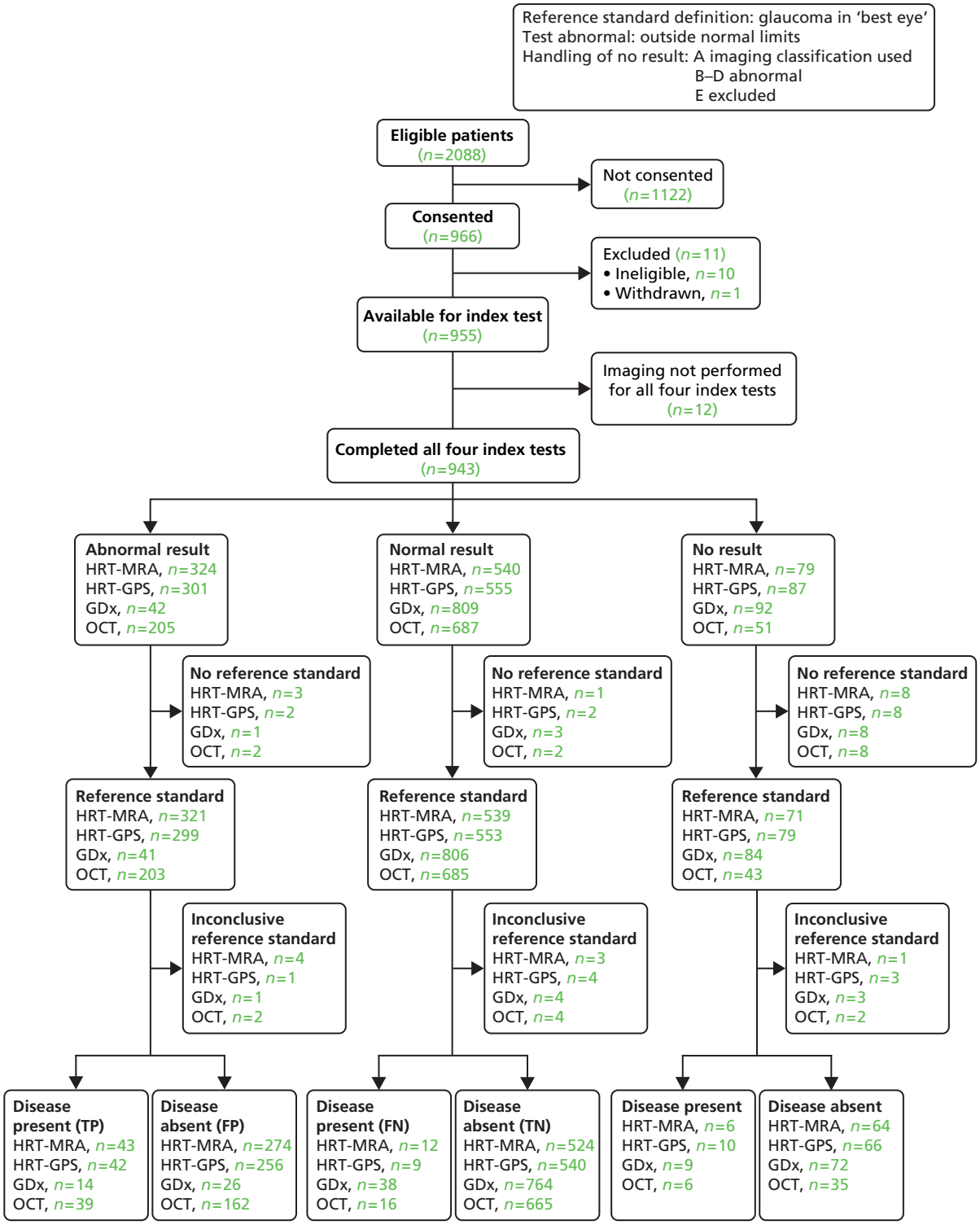

FIGURE 9 Flow diagram: diagnostic sensitivity analysis 6. FN, false negative; FP, false positive; TN, true negative, TP, true positive.

TABLE 27 Diagnostic performance: diagnosis sensitivity analysis 6

Test	Diagnostic parameter	Point estimate	95% CI
HRT-MRA	Sensitivity (%)	78.2	65.0 to 88.2
	Specificity (%)	65.7	62.3 to 69.0
	Positive likelihood ratio	2.28	1.92 to 2.70
	Negative likelihood ratio	0.33	0.20 to 0.55
	DOR	6.85	3.55 to 13.21
HRT-GPS	Sensitivity (%)	82.4	69.1 to 91.6
	Specificity (%)	67.8	64.5 to 71.1
	Positive likelihood ratio	2.56	2.18 to 3.01
	Negative likelihood ratio	0.26	0.14 to 0.47
	DOR	9.84	4.72 to 20.53
GDx	Sensitivity (%)	26.9	15.6 to 41.0
	Specificity (%)	96.7	95.2 to 97.8
	Positive likelihood ratio	8.18	4.55 to 14.70
	Negative likelihood ratio	0.76	0.64 to 0.89
	DOR	10.83	5.23 to 22.39
OCT	Sensitivity (%)	70.9	57.1 to 82.4
	Specificity (%)	80.4	77.5 to 83.1
	Positive likelihood ratio	3.62	2.91 to 4.50
	Negative likelihood ratio	0.36	0.24 to 0.55
	DOR	10.01	5.45 to 18.35

(67.8%, 95% CI 64.5% to 77.1%), GDx had the lowest sensitivity (26.9%, 95% CI 15.6% to 41.0%) but the highest specificity (96.7%, 95% CI 95.2% to 97.8%) and the other two tests provided intermediate results (HRT-MRA had a slightly lower sensitivity and specificity than HRT-GPS but a slightly higher specificity and OCT had the second lowest sensitivity but the second highest specificity values). Sensitivity was slightly lower for all HRT-MRA, GDx and OCT than under the default analysis but with a slightly higher specificity. HRT-GPS has very similar sensitivity analysis results to the default (primary) analysis. Likelihood ratios (and 95% CI) showed evidence of being able to both rule in and rule out the presence of glaucoma for all four imaging tests (CIs did not contain 1.0). DORs ranged from 6.85 for HRT-MRA to 10.83 for GDx.

Combinations of imaging tests

The HRT-MRA test was combined with the other imaging tests to form three combined tests and the diagnostic performance was assessed. The reference standard and the definition of an abnormal imaging test result was the same as for the default analysis (abnormal imaging test 'outside normal limits'; reference standard diagnosis of glaucoma in the 'worse' eye; and only participants with an imaging test output with an overall classification which met the manufacturer quality cut-off point were included in the analysis). The corresponding flow of study participants is shown in *Figure 10*, with the corresponding number of abnormal, normal and no results cases by combination imaging test and the corresponding reference standard finding shown. The diagnostic performance of the four tests is given in *Table 28*.

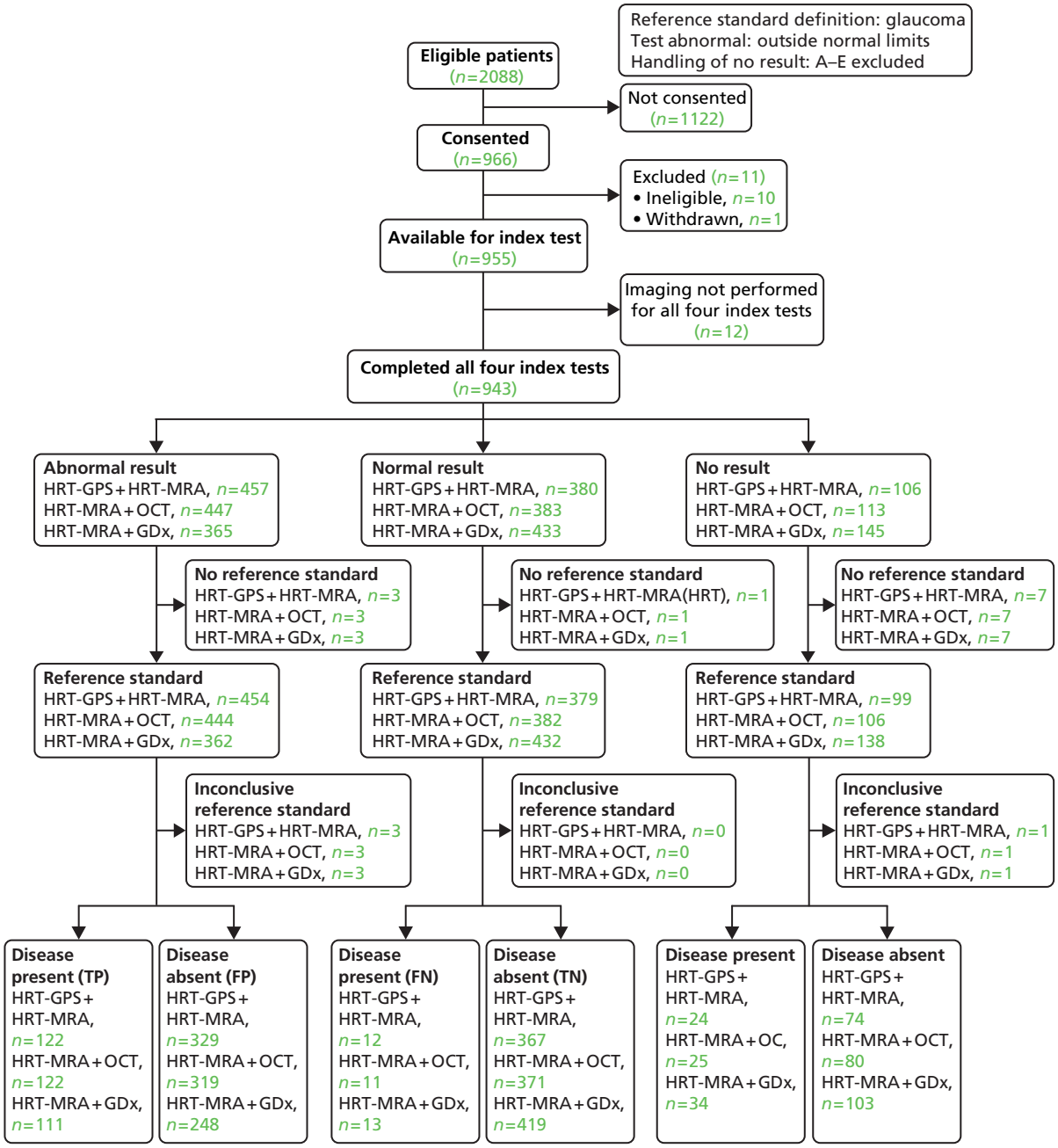

FIGURE 10 Flow diagram: combination of imaging tests. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

TABLE 28 Diagnostic performance: diagnostic performance of test combinations

Test	Diagnostic parameter	Point estimate	95% CI
HRT-MRA + HRT-GPS	Sensitivity (%)	91.0	84.9 to 95.3
	Specificity (%)	52.7	48.9 to 56.5
	Positive likelihood ratio	1.93	1.75 to 2.12
	Negative likelihood ratio	0.17	0.10 to 0.29
	DOR	11.34	6.15 to 20.90
HRT-MRA + GDx	Sensitivity (%)	89.5	82.7 to 94.3
	Specificity (%)	62.8	59.0 to 66.5
	Positive likelihood ratio	2.41	2.14 to 2.70
	Negative likelihood ratio	0.17	0.10 to 0.28
	DOR	14.43	7.95 to 26.17
HRT-MRA + OCT	Sensitivity (%)	91.7	85.7 to 95.8
	Specificity (%)	53.8	50.0 to 57.5
	Positive likelihood ratio	1.98	1.80 to 2.18
	Negative likelihood ratio	0.15	0.09 to 0.27
	DOR	12.90	6.84 to 24.34

The results showed a trade-off between detection of glaucoma and correctly identifying non-glaucoma cases: HRT-MRA combined with OCT had the highest sensitivity (91.7%, 95% CI 85.7% to 95.8%) but the second lowest specificity (53.8%, 95% CI 50.0% to 57.5%) and HRT-MRA combined with GDx had the lowest sensitivity (89.5%, 95% CI 82.7% to 94.3%) but the highest specificity (62.8%, 95% CI 59.0% to 66.5%). Likelihood ratios (and 95% CI) showed evidence of being able to both rule in and rule out the presence of glaucoma all three combination imaging tests (CIs did not contain 1.0). DORs ranged from 11.34 for HRT-MRA combined with HRT-GPS, to 14.43 for HRT-MRA combined with GDx.

Discussion

The diagnostic performance of four imaging tests (HRT-MRA, HRT-GPS, GDx and OCT) for the detection of glaucoma was compared for the GATE population of referrals to a glaucoma clinic in secondary care. The sensitivity and specificity of the four imaging tests for the default diagnosis analysis and sensitivity analyses (see *Table 15* for details) are summarised in *Figures 11* and *12*, respectively.

All four imaging tests had some value in terms of ruling in and ruling out the presence of glaucoma. However, the diagnostic performance of the imaging tests differed in the ability to correctly diagnose glaucoma (sensitivity) and non-glaucoma cases (specificity). HRT-MRA had the highest sensitivity across analyses, except when the reference standard diagnosis was moderate and severe glaucoma only, when HRT-GPS was higher, but at a cost of lower specificity compared with other tests. In contrast, GDx consistently had the best specificity but the lowest sensitivity. HRT-GPS results were typically similar to HRT-MRA as might be expected given that their analysis is based on the same imaging machine. The sensitivity of OCT was generally of a similar magnitude to its specificity. When the reference standard definition of disease excluded mild glaucoma, OCT displayed better diagnostic performance than HRT-GPS and HRT-MRA, with GDx providing the best specificity. The choice of which imaging test is to be preferred reflects the inherent trade-off regarding diagnostic testing, when the desire not to miss glaucoma when present must be balanced again the desire to correctly identify those who are without disease.

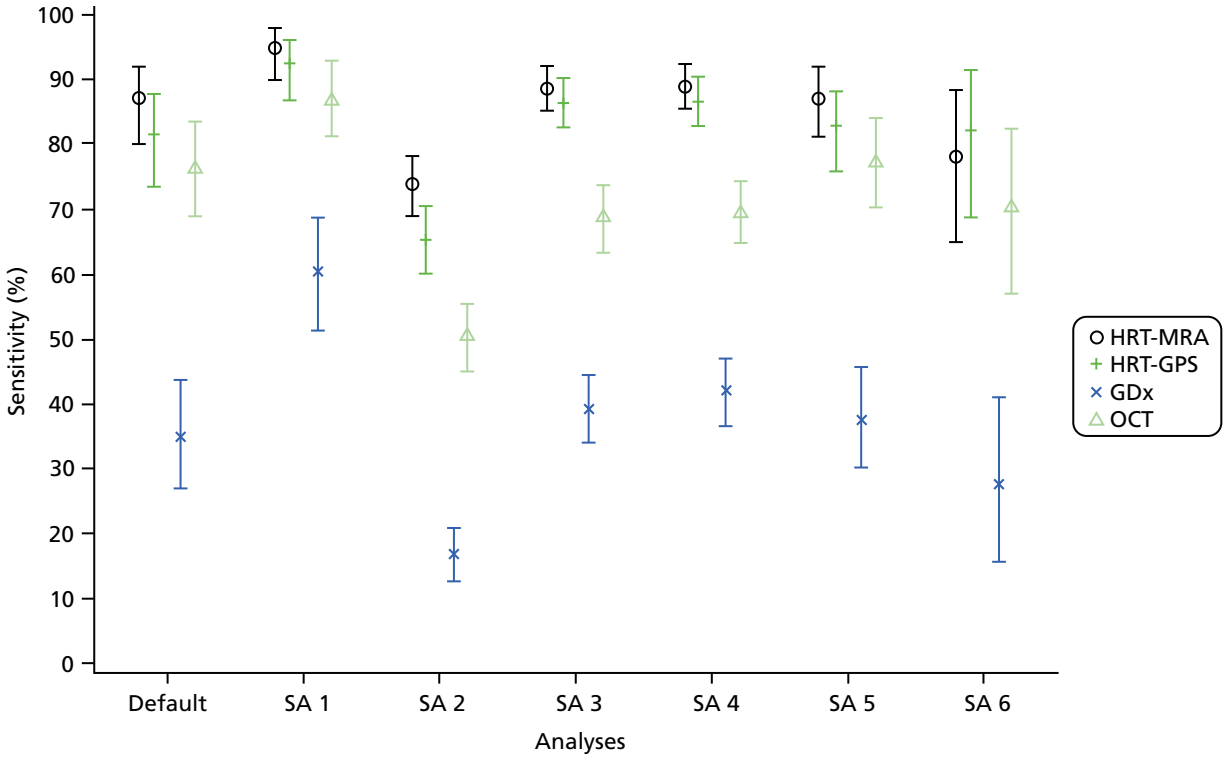

FIGURE 11 Summary of the sensitivity of imaging tests across all diagnosis analyses. SA, sensitivity analyses.

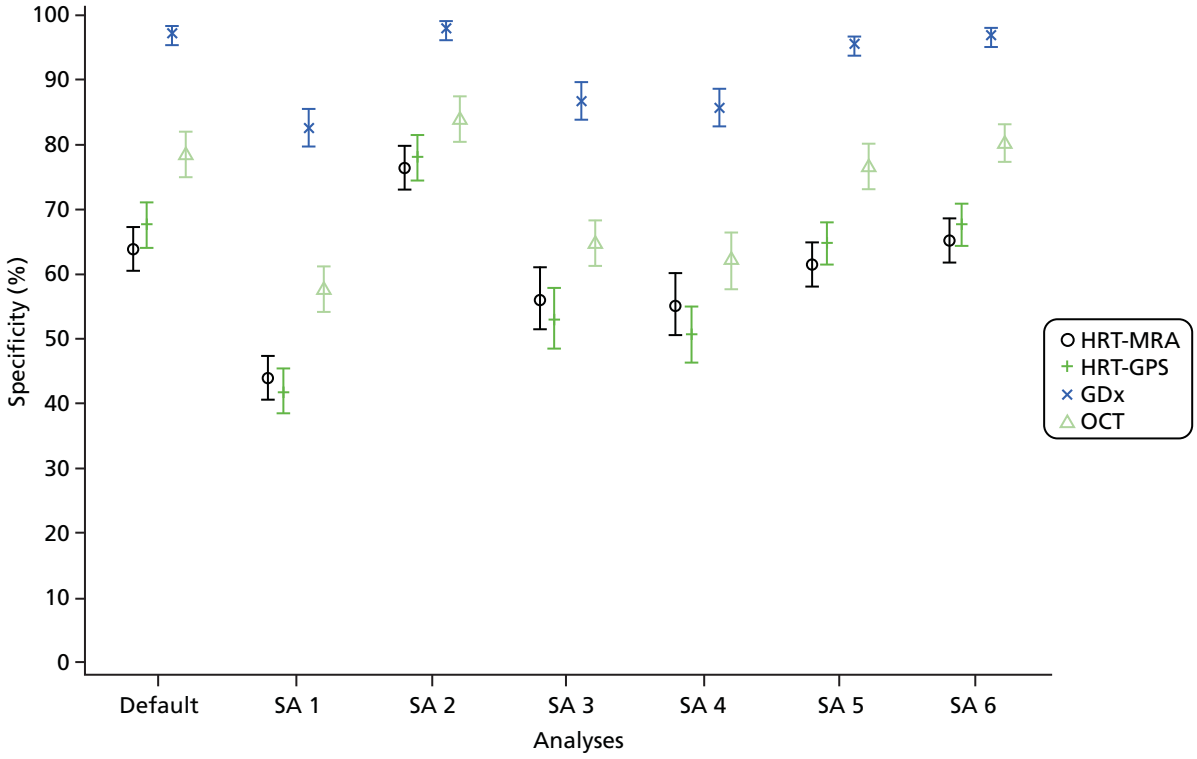

FIGURE 12 Summary of the specificity of imaging tests across all diagnosis analyses. SA, sensitivity analyses.

The non-diagnostic outcomes tended to favour OCT. OCT had the lowest number of low-quality imaging results, with GDx having the highest. Average time taken to conduct the tests was lowest for OCT with the other tests taking a similar length of time. Less dilatation was required for OCT, followed by GDx then the HRT tests. Considering the time taken and need for dilatation, patient preference tended to favour OCT followed by GDx, although almost one-half of participants did not have a preference.

Glaucome Automated Test Evaluation was a large prospective paired diagnostic study and provided diagnostic tests in this desired setting. This is reflected in the precision in which the sensitivity and specificity were calculated with differences between every pair of tests identified for one if not both sensitivity and specificity. McNemar's test[38] was used to compare the sensitivity and specificity of the tests. Following the rationale of others in effectiveness studies, the paired comparisons were not adjusted for multicomparisons. Even if such a correction were to have been applied such was the strength of evidence there would still be evidence of differences in the diagnostic performance of the different imaging tests.

A number of sensitivity analyses were carried out to assess the robustness of the findings of the default analysis. Varying the test definition of an abnormal imaging result by including the borderline category was carried out; this had the anticipated impact of improving the detection of glaucoma, although at the expense of more participants without glaucoma being falsely classified as having glaucoma. This resulted in very high detection of glaucoma for HRT-MRA, HRT-GPS and OCT but with low to moderate diagnosis of non-glaucoma cases. GDx provided moderate performance for both detecting glaucoma and correctly diagnosing non-glaucoma cases. Additionally, the impact of also seeking to diagnose glaucoma suspect (based on optic disc and/or visual field findings as described in *Chapter 2*) was assessed both with and without classifying borderline imaging findings as abnormal. When the test definition of abnormal incorporated the borderline category, the net impact was a slight increase in sensitivity for GDx, HRT-GPS and HRT-MRA, with the sensitivity of OCT slightly reduced compared with the default analysis, suggesting that the OCT test deals less well with glaucoma suspect cases. The diagnostic performance on the better eye gave similar results, although with generally a lower sensitivity and slightly higher specificity than for the worse eye. HRT-GPS diagnostic performance for these data was remarkably similar to when the worse eye was used.

Finally, the impact of using a combination of tests was assessed. Given the findings of the default diagnosis analysis and associated sensitivity analyses, this was restricted to an assessment of whether or not using another imaging test in addition to HRT-MRA appeared to be beneficial. Although the additional use of another test led to improved detection of glaucoma, the improvement was marginal and smaller than the loss in terms of the handling of non-diseased cases and although the use of two tests in combination did have some benefit in terms of reducing the number of no result cases, the change in diagnostic performance coupled with the additional practical and cost implications in terms of training and staff time, and an additional requirement of equipment (for two of the three combinations) suggests that the use of a single test is to be preferred.

A number of assumptions underpinned the analysis and interpretation of the results. Most importantly, the reference standard was assumed to be perfect although it is widely recognised that diagnosis of glaucoma is difficult and uncertainty exists even among specialists. While consensus was sought through structured training, some assessor differences may have remained between the sites. Additionally, the diagnosis and clinical management of patients with glaucoma suspect is uncertain; in particular, the risk of conversion of such individuals is not known. Nevertheless, the findings provide evidence reflective of current clinical practice in NHS glaucoma clinics.

A number of areas for further research are clear. Further investigation of varying the results of the imaging tests beyond the standard options could be undertaken, as the recommended classification may not be the one best suited to the population that GATE recruited from. The definition and clinical management of glaucoma suspects is also an area in which further research is needed, in particular quantifying the proportion that will convert or will be discharged from clinical care over subsequent years. Finally, the diagnosis value of using an imaging test explicitly in a triage scenario with the additional use of an IOP measurement and VA to form a composite triage test requires evaluation.

Chapter 5 Triage analysis results

Overview

This chapter reports the results of the triage analyses, which aimed to assess the diagnostic performance of the four imaging tests in a triage setting. The specific diagnostic performance analyses covered in this chapter are the default triage analysis (*Table 29*, *Default triage analysis*) along with eight sensitivity analyses (see *Table 29*, *Triage sensitivity analyses 1–8*) for a list with definitions. A further set of three analyses specifically to inform the economic model are described in *Appendix 6*. The default triage analysis was defined as one in which the reference standard was the person-level clinical decision ('not discharged' or 'discharged').

TABLE 29 Triage analyses

Analysis	Reference standard definition	Test abnormal	Handling of 'no result' categories	Figure number	Table number
Default triage analysis	Not discharged	Imaging (outside normal limits) or IOP > 21 mmHg or VA 6/12 or poorer	A–D for referral E excluded	*13*	*30*, *31*
Triage sensitivity analysis 1	Not discharged	Imaging (outside normal limits or borderline) or IOP > 21 mmHg or VA 6/12 or poorer	A–D for referral E excluded	*14*	*32*
Triage sensitivity analysis 2	Not discharged	Imaging (outside normal limits) or IOP > 21 mmHg or VA 6/12 or poorer	A use imaging classification B for referral C–E excluded	*15*	*33*
Triage sensitivity analysis 3	Not discharged	Imaging (outside normal limits or borderline) or IOP > 21 mmHg or VA 6/12 or poorer	A use imaging classification B for referral C–E excluded	*16*	*34*
Triage sensitivity analysis 4	Not discharged	Imaging (outside normal limits) or IOP > 21 mmHg (referred IOP) or VA 6/12 or poorer	A–D for referral E excluded	*17*	*35*
Triage sensitivity analysis 5	Not discharged	Imaging (outside normal limits) or VA 6/12 or poorer	A–D for referral E excluded	*18*	*36*
Triage sensitivity analysis 6	Not discharged	Imaging (outside normal limits) or IOP > 21mmHg	A–D for referral E excluded	*19*	*37*
Triage sensitivity analysis 7	Not discharged	Imaging (outside normal limits) or IOP > 26 mmHg or VA 6/12 or poorer	A–D for referral E excluded	*20*	*38*
Triage sensitivity analysis 8	Not discharged	Imaging (outside normal limits) or IOP > 21 mmHg or VA 6/18 or poorer	A–D for referral E excluded	*21*	*39*

No result categories: A, test performed and imaging report produced but quality is lower than manufacturer quality cut-off; B, test performed and imaging report produced but no overall classification generated by machine; C, test performed but there was a clear imaging artefact on the report; D, test attempted but no imaging could be acquired from the patient's eyes – no report generated; E, missing imaging (because of study-related or data-collection issues).

The test was defined as categorising a patient as requiring to be referred on ('for referral') if any of the elements of the composite triage test (imaging, IOP and/or VA) were themselves 'abnormal': imaging outside normal limits on the overall classification of the imaging test (see *Chapter 2*), IOP > 21 mmHg or VA of 6/12 or poorer under the default triage analysis.

If the imaging test did not produce an overall classification or its quality was poor, the imaging test result was again defined as abnormal and, therefore, the patient was classified as 'for referral'. The eight sensitivity analyses assessed the impact of varying assumptions made in the default triage analysis relating to the definition of a positive test result, modifying or removing the IOP and/or VA components of the triage test, and how cases where the test did not produce an overall classification were handled in the analysis.

The analyses in this chapter pertain to the 943 participants remaining in the study (see *Chapter 4*). The reference standard was available for 933 cases. For all analyses, a STARD diagram shows the flow of participants. The subset of participants who received all four tests and were considered in the statistical analyses are separated out into three groups according to whether each triage test result was 'abnormal', 'normal' or 'no result' (the triage test result was not available because either the test was inconclusive or the result was missing). For each of these three groups the group status according to the reference standard ('discharged' or 'not discharged') for each participant is given or alternatively the reference standard was stated to be missing or inconclusive. The final categorisations of the triage test result by reference standard status provides the four possible combinations (true and false positive, false and true negative) from which the diagnostic performance was assessed. Sensitivity, specificity, likelihood ratios and DOR are provided with associated 95% CIs for each analysis.

Default triage analysis

The results for the default triage analysis are presented in two sections:

- diagnostic performance of the triage tests, and
- paired comparisons of triage tests.

Diagnostic performance of the triage tests

For the default triage analysis, the triage test is classified as abnormal if (1) the imaging test result is classified as 'outside normal limits', (2) IOP is > 21 mmHg or (3) VA is 6/12 or poorer. Imaging test results that did not provide an overall classification were included as abnormal. The corresponding reference standard definition is a clinical decision not to discharge the patient.

The flow of study participants according to the default triage analysis is shown in *Figure 13*, with the corresponding numbers of referral, not for referral and no result cases by triage test and the corresponding reference standard finding shown. Of the 943 participants in whom all four tests were performed, 576 were not discharged and 357 were discharged and the discharge status was missing for 10 participants. The diagnostic performance of the four tests is given in *Table 30*. The results showed a trade-off between the detection of patients who need to be referred and the discharge of those who do not need to be referred: HRT-GPS had the highest sensitivity (86.0%, 95% CI 82.8% to 88.7%) but lowest specificity (39.1%, 95% CI 34.0% to 44.5%), GDx had the lowest sensitivity (64.7%, 95% CI 60.7% to 68.7%) but the highest specificity (53.6%, 95% CI 48.2% to 58.9%), and the other two tests provided intermediate results [HRT-MRA values were very similar to the HRT-GPS results, as might be expected given that they use the same machine, and OCT had lower sensitivity (75.4%, 95% CI 71.9 to 78.9) but higher specificity (41%, 95% CI 35.8 to 46.3) values than HRT-GPS and HRT-MRA]. Likelihood ratios (and 95% CI) showed evidence of being able to both rule in and rule out the presence of glaucoma for all four triage tests (CIs did not contain 1.0). DORs ranged from 2.12 for GDx and OCT to 3.94 for HRT-GPS.

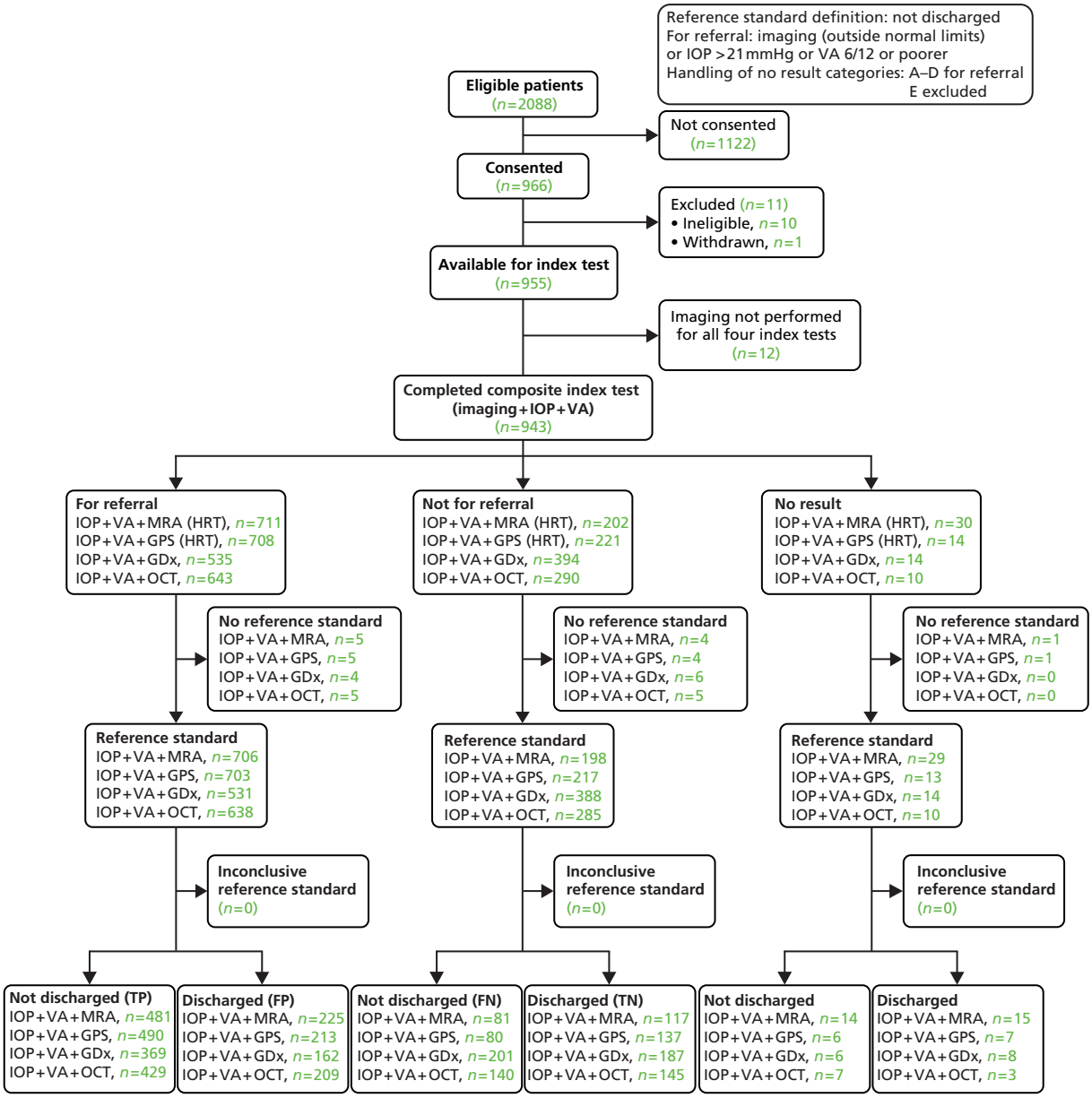

FIGURE 13 Flow diagram: default triage analysis. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

TABLE 30 Diagnostic performance: default triage analysis

Test	Diagnostic parameter	Value	95% CI
HRT-MRA	Sensitivity (%)	85.6	82.4 to 88.4
	Specificity (%)	34.2	29.20 to 39.5
	Positive likelihood ratio	1.3	1.20 to 1.41
	Negative likelihood ratio	0.4	0.33 to 0.54
	DOR	3.09	2.23 to 4.27
HRT-GPS	Sensitivity (%)	86.0	82.8 to 88.7
	Specificity (%)	39.1	34.0 to 44.5
	Positive likelihood ratio	1.41	1.29 to 1.55
	Negative likelihood ratio	0.36	0.28 to 0.46
	DOR	3.94	2.86 to 5.42
GDx	Sensitivity (%)	64.7	60.7 to 68.7
	Specificity (%)	53.6	48.2 to 58.9
	Positive likelihood ratio	1.39	1.23 to 1.59
	Negative likelihood ratio	0.66	0.57 to 0.76
	DOR	2.12	1.62 to 2.78
OCT	Sensitivity (%)	75.4	71.6 to 78.9
	Specificity (%)	41.0	35.8 to 46.3
	Positive likelihood ratio	1.28	1.16 to 1.41
	Negative likelihood ratio	0.60	0.50 to 0.73
	DOR	2.13	1.60 to 2.83

Paired comparisons of imaging tests

Table 31 shows the paired difference (with 95% CI) and corresponding McNemar's tests *p*-value for comparisons between pairs of tests. There was evidence that the sensitivity of all tests differed from each other, except for HRT-GPS versus HRT-MRA.

The highest sensitivity was found in HRT-GPS and HRT-MRA, and HRT-MRA and GDx had the lowest sensitivity. Differences varied from 0.2% (HRT-GPS vs. HRT-MRA) to 21.3%. (HRT-GPS vs. GDx). Similarly, there was evidence that specificities for all the tests varied from each other (according to McNemar's test), except for HRT-GPS versus OCT.

TABLE 31 Paired comparisons of sensitivity and specificity between the triage tests

Tests compared	Diagnostic parameter	Test	Value, % (95% CI)	*p*-value (McNemar's)
HRT-GPS vs. GDx	Sensitivity	HRT-GPS	85.8 (82.9 to 88.7)	–
		GDx	64.5 (60.6 to 68.5)	–
		Difference	21.3 (17.7 to 24.9)	< 0.0001
	Specificity	HRT-GPS	39.6 (34.4 to 44.7)	–
		GDx	53.8 (48.5 to 59.0)	–
		Difference	–14.2 (–19.0 to –9.2)	< 0.0001
GDx vs. OCT	Sensitivity	GDx	64.8 (60.9 to 68.8)	–
		OCT	75.1 (71.6 to 78.7)	–
		Difference	–10.3 (–13.5 to –7.0)	< 0.0001
	Specificity	GDx	53.4 (48.2 to 58.7)	–
		OCT	41.1 (35.9 to 46.3)	–
		Difference	12.4 (7.9 to 16.7)	< 0.0001
GDx vs. HRT-MRA	Sensitivity	GDx	64.9 (61.0 to 68.9)	–
		HRT-MRA	85.4 (82.5 to 88.4)	–
		Difference	–20.5 (–24.3 to –16.7)	< 0.0001
	Specificity	GDx	53.3 (47.9 to 58.6)	–
		HRT-MRA	34.3 (29.3 to 39.4)	–
		Difference	18.9 (13.8 to 23.9)	< 0.0001
HRT-GPS vs. HRT-MRA	Sensitivity	HRT-GPS	85.7 (82.8 to 88.6)	–
		HRT-MRA	85.5 (82.6 to 88.4)	–
		Difference	0.2 (–2.4 to 2.8)	0.8907
	Specificity	HRT-GPS	39.3 (34.1 to 44.5)	–
		HRT-MRA	34.3 (29.3 to 39.3)	–
		Difference	5.0 (0.3 to 9.6)	< 0.0001
HRT-MRA vs. OCT	Sensitivity	HRT-MRA	85.6 (82.7 to 88.5)	–
		OCT	75.2 (71.6 to 78.8)	–
		Difference	10.4 (7.1 to 13.8)	< 0.0001
	Specificity	HRT-MRA	34.2 (29.2 to 39.2)	–
		OCT	40.9 (35.7 to 46.1)	–
		Difference	–6.7 (–12.2 to –1.2)	0.0171
HRT-GPS vs. OCT	Sensitivity	HRT-GPS	86.1 (83.2 to 88.9)	–
		OCT	75.3 (71.8 to 78.9)	–
		Difference	10.8 (7.4 to 14.2)	< 0.0001
	Specificity	HRT-GPS	39.1 (34.0 to 44.3)	–
		OCT	41.1 (36.0 to 46.3)	–
		Difference	–2.0 (–7.4 to 3.5)	0.4726

Triage sensitivity analysis 1

Triage sensitivity analysis 1 differed from the default triage analysis in that a borderline finding on the imaging test was also classified as an abnormal result.

For triage sensitivity analysis 1, the triage test is classified as abnormal if (1) the imaging test result is classified as 'outside normal limits' or 'borderline', (2) IOP is > 21 mmHg or (3) VA is 6/12 or poorer. Imaging test results which did not provide an overall classification were included as abnormal. The corresponding reference standard definition is a clinical decision not to discharge the patient.

The flow of study participants according to triage sensitivity analysis 1 is shown in *Figure 14*, with the corresponding numbers of referral, not for referral and no result cases by triage test, and the corresponding reference standard finding shown. Of the 943 participants in whom all four tests were performed, 576 were not discharged and 357 were discharged and the discharge status was missing for 10 participants. The diagnostic performance for the four tests is given in *Table 32*. The results generally showed a trade-off between the detection of patients who need to be referred and the discharge of those who do not need to be referred: HRT-GPS had the highest sensitivity (94.0%, 95% CI 91.8% to 95.8%) but second lowest specificity (24.9%, 95% CI 20.4% to 29.7%), GDx had the lowest sensitivity (74.9%, 95% CI 71.1% to 78.4%) but the highest specificity (45%, 39.7% CI 39% to 50.4%), and the other two tests provided intermediate results (HRT-MRA values were very similar though marginally inferior to the HRT-GPS results, and OCT had lower sensitivity (84.2%, 95% CI 80.9 to 87.1) but slightly higher specificity than HRT-GPS and HRT-MRA). Likelihood ratios (and 95% CI) showed evidence of being able to both rule in and rule out the presence of glaucoma for all four triage tests (CIs did not contain 1.0). DORs ranged from 2.04 for OCT to 5.21 for HRT-GPS.

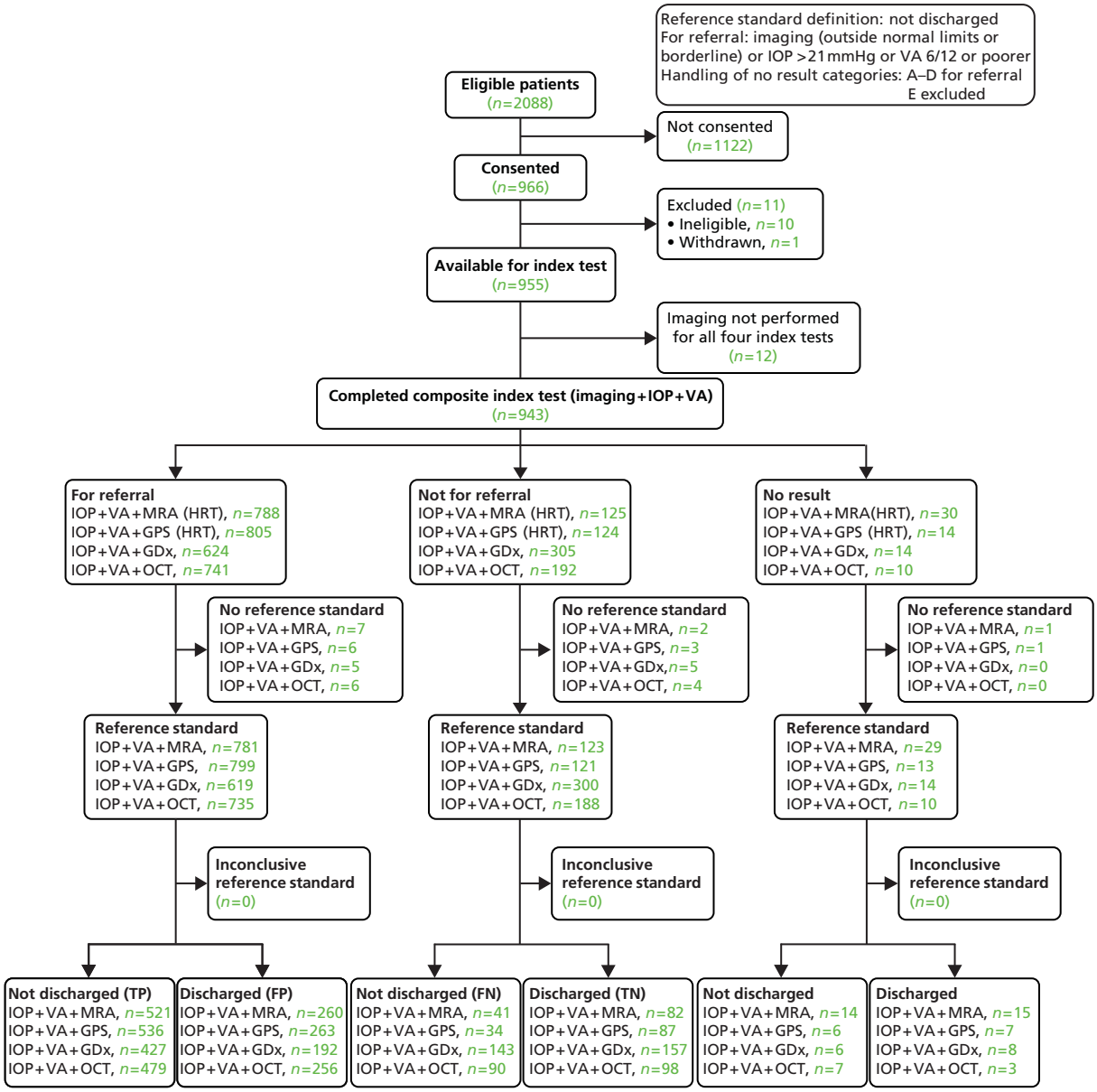

FIGURE 14 Flow diagram: triage sensitivity analysis 1. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

TABLE 32 Diagnostic performance: triage sensitivity analysis 1

Test	Diagnostic parameter	Value	95% CI
HRT-MRA	Sensitivity (%)	92.7	90.2 to 94.7
	Specificity (%)	24.0	19.5 to 28.9
	Positive likelihood ratio	1.2	1.14 to 1.30
	Negative likelihood ratio	0.30	0.21 to 0.43
	DOR	4.01	2.68 to 6.00
HRT-GPS	Sensitivity (%)	94.0	91.8 to 95.8
	Specificity (%)	24.9	20.4 to 29.7
	Positive likelihood ratio	1.25	1.17 to 1.33
	Negative likelihood ratio	0.24	0.17 to 0.35
	DOR	5.21	3.42 to 7.96
GDx	Sensitivity (%)	74.9	71.1 to 78.4
	Specificity (%)	45.0	39.7 to 50.4
	Positive likelihood ratio	1.36	1.22 to 1.51
	Negative likelihood ratio	0.56	0.46 to 0.67
	DOR	2.44	1.84 to 3.24
OCT	Sensitivity (%)	84.2	80.9 to 87.1
	Specificity (%)	27.7	23.1 to 32.7
	Positive likelihood ratio	1.16	1.08 to 1.51
	Negative likelihood ratio	0.57	0.44 to 0.74
	DOR	2.04	1.47 to 2.82

Triage sensitivity analysis 2

Triage sensitivity analysis 2 has the same reference standard and definition of abnormal test result as the default analysis but did not include all no result cases (see *Table 33*).

For triage sensitivity analysis 2, the triage test is classified as abnormal if (1) the imaging test result is classified as 'outside normal limits', (2) IOP is > 21 mmHg or (3) VA is 6/12 or poorer. Poor-quality imaging test results were included, and those where an image was acquired but no classification generated were included as abnormal. All other missing imaging results were excluded. The corresponding reference standard definition is a clinical decision not to discharge the patient.

The flow of study participants according to triage sensitivity analysis 2 is shown in *Figure 15*, with the corresponding numbers of referral, not for referral and no result cases by triage test and the corresponding reference standard finding shown. Of the 943 participants in whom all four tests were performed, 481 were not discharged and 562 were discharged and the discharge status was missing for 10 participants. The diagnostic performance for the four tests is given in *Table 33*. The results generally showed a trade-off between the detection of patients who need to be referred and the discharge of those who do not need to be referred: HRT-GPS had the highest sensitivity (84.6%, 95% CI 81.4% to 87.5%) but the second lowest specificity (39.7%, 95% CI 34.6% to 45.1%), GDx had the lowest sensitivity (61.1%, 95% CI 56.9% to 65.1%) but the highest specificity (59.0%, 95% CI 53.7% to 64.2%) and the other two tests provided intermediate results [HRT-MRA values were very similar, although slightly inferior to the HRT-GPS

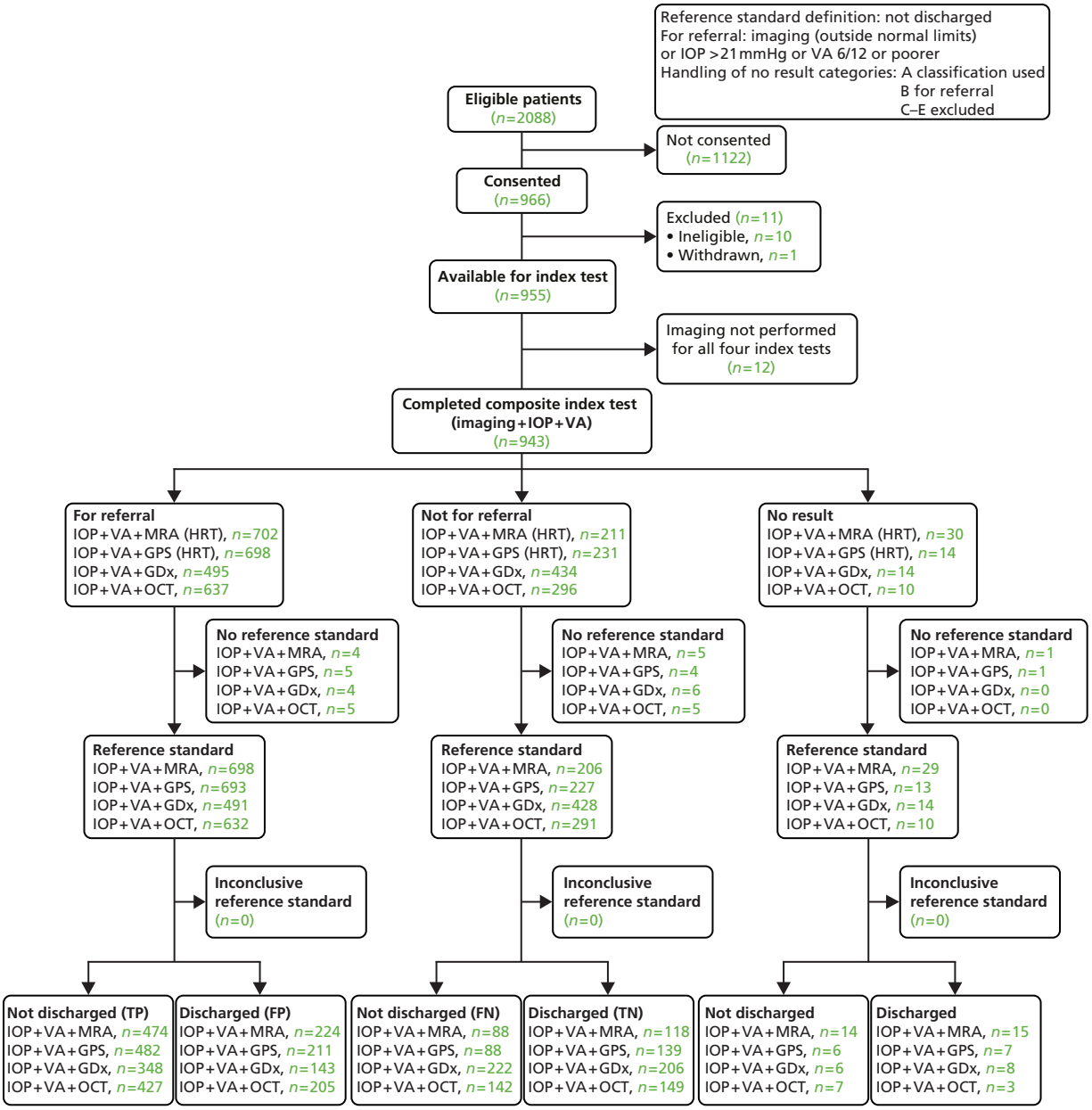

FIGURE 15 Flow diagram: triage sensitivity analysis 2. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

TABLE 33 Diagnostic performance: triage sensitivity analysis 2

Test	Diagnostic parameter	Value	95% CI
HRT-MRA	Sensitivity (%)	84.3	81.1 to 87.2
	Specificity (%)	34.5	29.5 to 39.8
	Positive likelihood ratio	1.29	1.18 to 1.40
	Negative likelihood ratio	0.45	0.36 to 0.58
	DOR	2.84	2.06 to 3.90
HRT-GPS	Sensitivity (%)	84.6	81.4 to 87.5
	Specificity (%)	39.7	34.6 to 45.1
	Positive likelihood ratio	1.40	1.28 to 1.54
	Negative likelihood ratio	0.39	0.31 to 0.49
	DOR	3.61	2.64 to 4.93
GDx	Sensitivity (%)	61.1	56.9 to 65.1
	Specificity (%)	59.0	53.7 to 64.2
	Positive likelihood ratio	1.49	1.29 to 1.72
	Negative likelihood ratio	0.66	0.58 to 0.76
	DOR	2.26	1.72 to 2.96
OCT	Sensitivity (%)	75.0	71.3 to 78.5
	Specificity (%)	42.1	36.9 to 47.4
	Positive likelihood ratio	1.30	1.17 to 1.43
	Negative likelihood ratio	0.59	0.49 to 0.72
	DOR	2.19	1.65 to 2.90

results, and OCT had the second lowest sensitivity (75.0%, 95% CI 71.3% to 78.5%) but the second highest specificity (42.1%, 95% CI 36.9% to 47.4%) values]. Likelihood ratios (and 95% CI) showed evidence of being able to both rule in and rule out the presence of glaucoma for all four triage tests (CIs did not contain 1.0). DORs ranged from 2.19 for GDx to 3.61 for OCT.

Triage sensitivity analysis 3

Triage sensitivity analysis 3 was the same as triage sensitivity analysis 2 except that 'borderline' test results were also classified as abnormal.

For triage sensitivity analysis 3, the triage test is classified as abnormal if (1) the imaging test result is classified as 'outside normal limits' or 'borderline', (2) IOP is > 21 mmHg or (3) VA is 6/12 or poorer. Poor-quality imaging test results were included, and those where an image was acquired but no classification generated were included as abnormal. All other missing imaging results were excluded. The corresponding reference standard definition is a clinical decision not to discharge the patient.

The flow of study participants according to triage sensitivity analysis 3 is shown in *Figure 16*, with corresponding numbers of referral, not for referral and no result cases by triage test and the corresponding reference standard finding shown. Of the 943 participants in whom all four tests were performed, 481 were not discharged and 562 were discharged and the discharge status was missing for 10 participants.

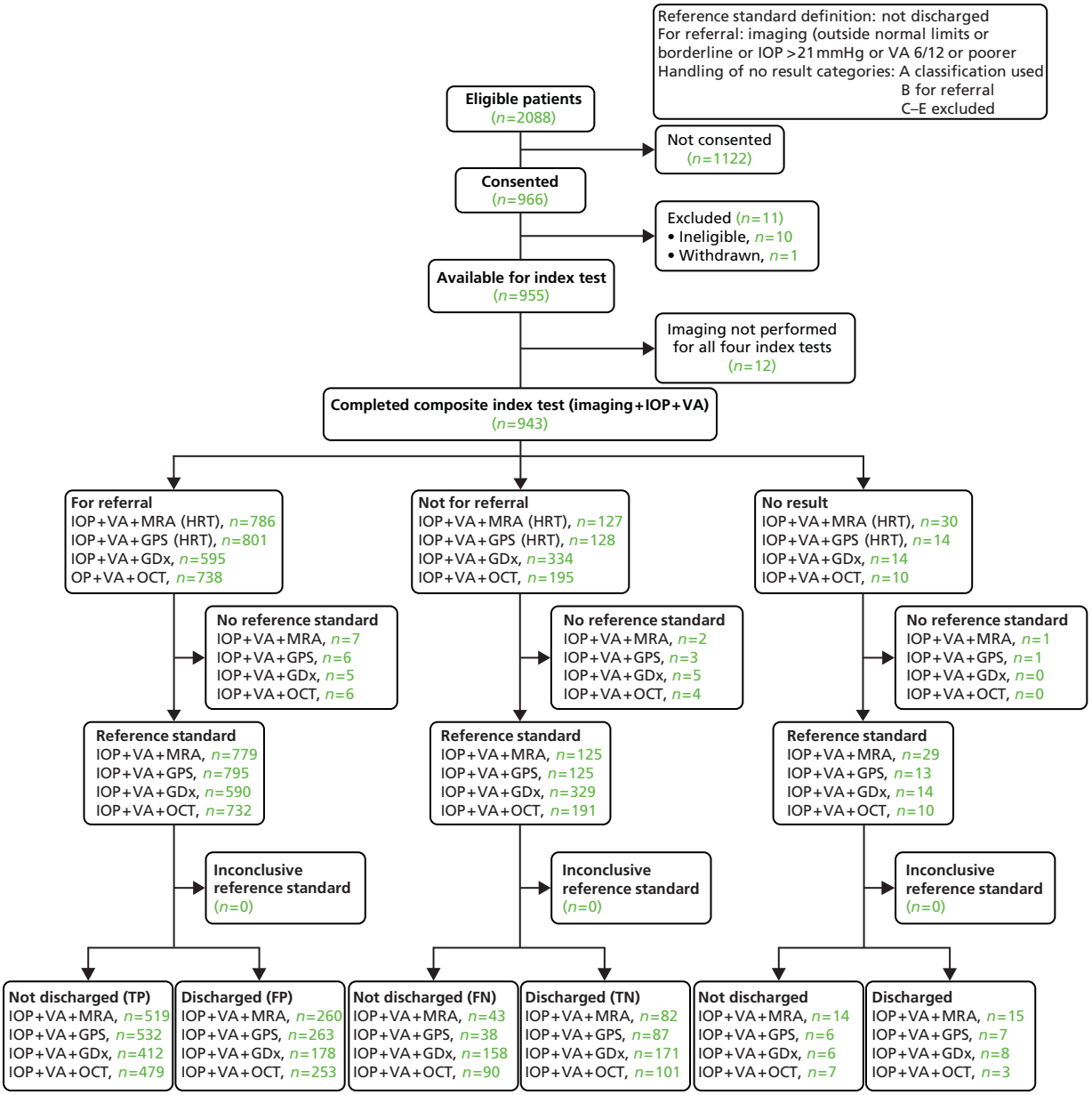

FIGURE 16 Flow diagram: triage sensitivity analysis 3. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

The diagnostic performance for the four tests is given in *Table 34*. The results generally showed a trade-off between the detection of patients who need to be referred and the discharge of those who do not need to be referred: HRT-GPS had the highest sensitivity (93.3%, 95% CI 91.0% to 95.2%) but second lowest specificity (24.9%, 95% CI 20.4% to 29.7%), GDx had the lowest sensitivity (72.3%, 95% CI 68.4% to 75.9%) but the highest specificity (49.0%, 95% CI 43.6% to 54.4%) and the other two tests provided intermediate results [HRT-MRA values were very similar to the HRT-GPS results, although slightly inferior, and OCT had the second lowest sensitivity (84.2%, 95% CI 80.9% to 87.1%) but the second highest specificity]. Likelihood ratios (and 95% CI) showed evidence of being able to both rule in and rule out the presence of glaucoma for all four triage tests (CIs did not contain 1.0). DORs ranged from 2.12 for OCT to 4.63 for HRT-GPS.

TABLE 34 Diagnostic performance: triage sensitivity analysis 3

Test	Diagnostic parameter	Value	95% CI
HRT-MRA	Sensitivity (%)	92.3	89.8 to 94.4
	Specificity (%)	24.0	19.5 to 28.9
	Positive likelihood ratio	1.21	1.14 to 1.03
	Negative likelihood ratio	0.32	0.23 to 0.45
	DOR	3.81	2.56 to 5.67
HRT-GPS	Sensitivity (%)	93.3	91.0 to 95.2
	Specificity (%)	24.9	20.4 to 29.7
	Positive likelihood ratio	1.24	1.16 to 1.32
	Negative likelihood ratio	0.27	0.19 to 0.38
	DOR	4.63	3.08 to 6.97
GDx	Sensitivity (%)	72.3	68.4 to 75.9
	Specificity (%)	49.0	43.6 to 54.4
	Positive likelihood ratio	1.42	1.26 to 1.59
	Negative likelihood ratio	0.57	0.48 to 0.67
	DOR	2.51	1.90 to 3.31
OCT	Sensitivity (%)	84.2	80.9 to 87.1
	Specificity (%)	28.5	23.9 to 33.5
	Positive likelihood ratio	1.18	1.09 to 1.27
	Negative likelihood ratio	0.55	0.43 to 0.71
	DOR	2.12	1.54 to 2.93

Triage sensitivity analysis 4

Triage sensitivity analysis 4 differed from the default triage analysis in that referral IOP > 21 mmHg rather than clinician IOP > 21 mmHg was used to identify abnormal tests. The triage test is classified as abnormal if (1) the imaging test result is classified as 'outside normal limits', (2) referral IOP is > 21 mmHg or (3) VA is 6/12 or poorer. Imaging test results which did not provide an overall classification were included as abnormal. The corresponding reference standard definition is a clinical decision not to discharge the patient.

The flow of study participants according to triage sensitivity analysis 4 is shown in *Figure 17*, with the corresponding numbers of referral, not for referral and no result cases by triage test and the corresponding reference standard finding shown. Of the 943 participants in whom all four tests were performed, 481 were not discharged and 562 were discharged and the discharge status was missing for 10 participants. The diagnostic performance for the four tests is given in *Table 35*. The results generally showed a trade-off between the detection of patients who need to be referred and the discharge of those who do not need to be referred: HRT-GPS had the highest sensitivity (86.5%, 95% CI 83.4% to 89.2%) but second lowest specificity (24.0%, 95% CI 19.6% to 28.8%), GDx had the lowest sensitivity (67.2%, 95% CI 63.2% to 71.0%) but the highest specificity (35.8%, 95% CI 30.8% to 41.1%) and the other two tests provided intermediate results (HRT-MRA values were very similar to the HRT-GPS results, although slightly inferior, and OCT had the second lowest sensitivity (76.8%, 95% CI 73.1% to 80.2%) but the second highest specificity (27.7%, 95% CI 23.1% to 32.7%). Likelihood ratios (and 95% CI) showed evidence of being able to both rule in and rule out the presence of glaucoma for all four triage tests (CIs did not contain 1.0). DORs ranged from 1.14 for GDx to 2.02 for HRT-GPS.

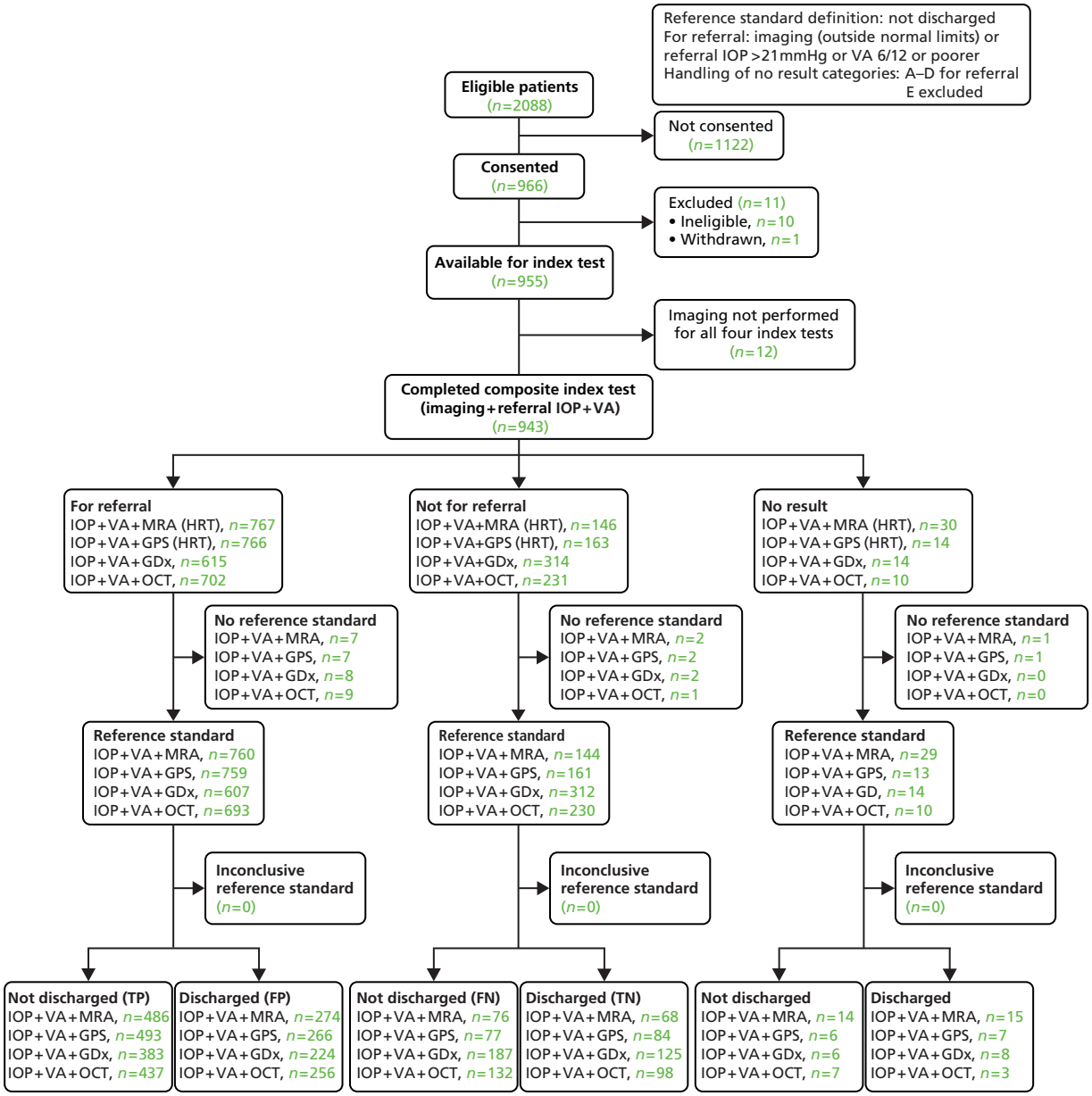

FIGURE 17 Flow diagram: triage sensitivity analysis 4. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

TABLE 35 Diagnostic performance: triage sensitivity analysis 4

Test	Diagnostic parameter	Value	95% CI
HRT-MRA	Sensitivity (%)	86.5	83.4 to 89.2
	Specificity (%)	19.9	15.8 to 24.5
	Positive likelihood ratio	1.08	1.01 to 1.15
	Negative likelihood ratio	0.68	0.50 to 0.92
	DOR	1.59	1.11 to 2.27
HRT-GPS	Sensitivity (%)	86.5	83.4 to 89.2
	Specificity (%)	24.0	19.6 to 28.8
	Positive likelihood ratio	1.14	1.06 to 1.22
	Negative likelihood ratio	0.56	0.43 to 0.74
	DOR	2.02	1.43 to 2.85
GDx	Sensitivity (%)	67.2	63.2 to 71.0
	Specificity (%)	35.8	30.8 to 41.1
	Positive likelihood ratio	1.05	0.95 to 1.15
	Negative likelihood ratio	0.92	0.76 to 1.10
	DOR	1.14	0.86 to 1.51
OCT	Sensitivity (%)	76.8	73.1 to 80.2
	Specificity (%)	27.7	23.1 to 32.7
	Positive likelihood ratio	1.06	0.98 to 1.15
	Negative likelihood ratio	0.84	0.67 to 1.05
	DOR	1.27	0.94 to 1.72

Triage sensitivity analysis 5

Triage sensitivity analysis 5 differed from the default triage analysis in that the IOP component was removed from the composite triage test. The triage test is classified as abnormal if the imaging test result is classified as (1) 'outside normal limits' or (2) VA is 6/12 or poorer. Imaging test results which did not provide an overall classification were included as abnormal. The corresponding reference standard definition is a clinical decision not to discharge the patient.

The flow of study participants according to triage sensitivity analysis 5 is shown in *Figure 18*, with the corresponding numbers of referral, not for referral and no result cases by triage test and the corresponding reference standard finding shown. Of the 933 participants in whom all four tests were performed, 481 were not discharged and 562 were discharged. The discharge status was missing for 10 participants. The diagnostic performance for the four tests is given in *Table 36*. The results generally showed a trade-off between the detection of patients who need to be referred and the discharge of those who do not need to be referred: HRT-MRA had the highest sensitivity (68.9%, 95% CI 64.9% to 72.7%) but the lowest specificity (52.3%, 95% CI 46.9% to 57.7%), GDx had the lowest sensitivity (32.8%, 95% CI 29.0% to 36.8%) but the highest specificity (81.1%, 95% CI 76.6% to 85.1%) and the other two tests provided intermediate results (HRT-GPS values were very similar to the HRT-MRA results and OCT had the second lowest sensitivity but the second highest specificity). Likelihood ratios (and 95% CI) showed evidence of being able to both rule in and rule out the presence of glaucoma for all four triage tests (CIs did not contain 1.0). DORs ranged from 1.80 for OCT to 2.91 for HRT-GPS.

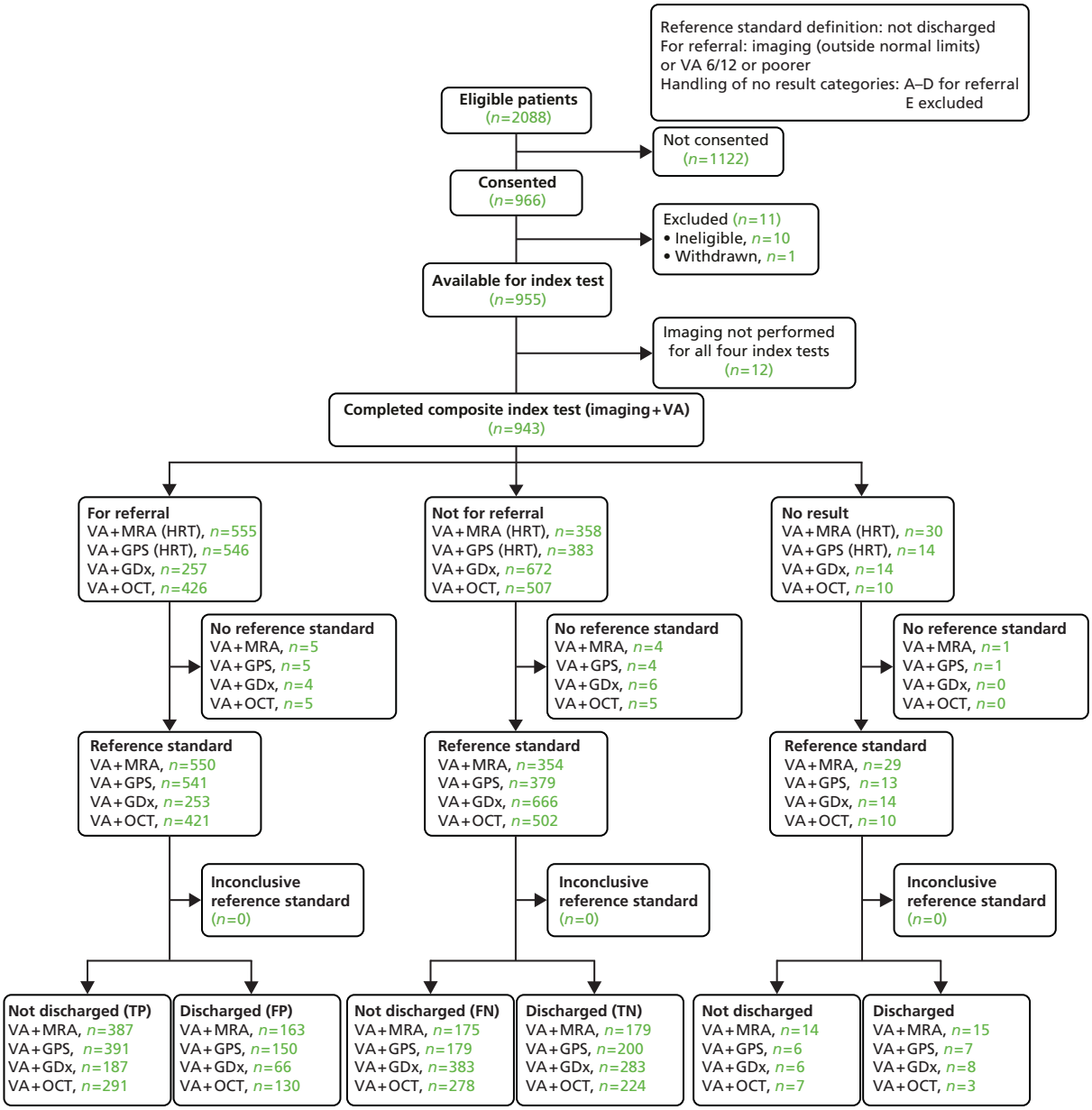

FIGURE 18 Flow diagram: triage sensitivity analysis 5. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

TABLE 36 Diagnostic performance: triage sensitivity analysis 5

Test	Diagnostic parameter	Value	95% CI
HRT-MRA	Sensitivity (%)	68.9	64.9 to 72.7
	Specificity (%)	52.3	46.9 to 57.7
	Positive likelihood ratio	1.44	1.28 to 1.64
	Negative likelihood ratio	0.59	0.51 to 0.70
	DOR	2.43	1.84 to 3.20
HRT-GPS	Sensitivity (%)	68.6	64.6 to 72.4
	Specificity (%)	57.1	51.8 to 62.4
	Positive likelihood ratio	1.60	1.40 to 1.83
	Negative likelihood ratio	0.55	0.47 to 0.64
	DOR	2.91	2.21 to 3.84
GDx	Sensitivity (%)	32.8	29.0 to 36.8
	Specificity (%)	81.1	76.6 to 85.1
	Positive likelihood ratio	1.73	1.36 to 2.22
	Negative likelihood ratio	0.83	0.77 to 0.89
	DOR	2.09	1.52 to 2.88
OCT	Sensitivity (%)	51.1	47.0 to 55.3
	Specificity (%)	63.3	58.0 to 68.3
	Positive likelihood ratio	1.39	1.19 to 1.63
	Negative likelihood ratio	0.77	0.69 to 0.87
	DOR	1.80	1.37 to 2.37

Triage sensitivity analysis 6

Triage sensitivity analysis 6 differed from the default triage analysis in that the VA component was removed from the composite triage test. The triage test is classified as abnormal if (1) the imaging test result is classified as 'outside normal limits' or (2) IOP is > 21 mmHg. Imaging test results which did not provide an overall classification were included as abnormal. The corresponding reference standard definition is a clinical decision not to discharge the patient.

The flow of study participants according to triage sensitivity analysis 6 is shown in *Figure 19*, with corresponding numbers of referral, not for referral and no result cases by triage test and the corresponding reference standard finding shown. Of the 943 participants in whom all four tests were performed, 481 were not discharged and 562 were discharged and the discharge status was missing for 10 participants. The diagnostic performance for the four tests is given in *Table 37*. The results generally showed a trade-off between the detection of patients who need to be referred and the discharge of those who do not need to be referred: HRT-MRA had the highest sensitivity (84.9%, 95% CI 81.9% to 87.7%) but second lowest specificity (37.4%, 95% CI 32.3% to 42.8%), GDx had the lowest sensitivity (60.5%, 95% CI 56.4% to 64.6%) but the highest specificity (57.6%, 95% CI 52.2% to 62.8%), and the other two tests provided intermediate results (HRT-GPS values were very similar to the HRT-MRA results and OCT had the second lowest sensitivity but the second highest specificity). Likelihood ratios (and 95% CI) showed evidence of being able to both rule in and rule out the presence of glaucoma for all four triage tests (CIs did not contain 1.0). DORs ranged from 2.03 for OCT to 3.97 for HRT-GPS.

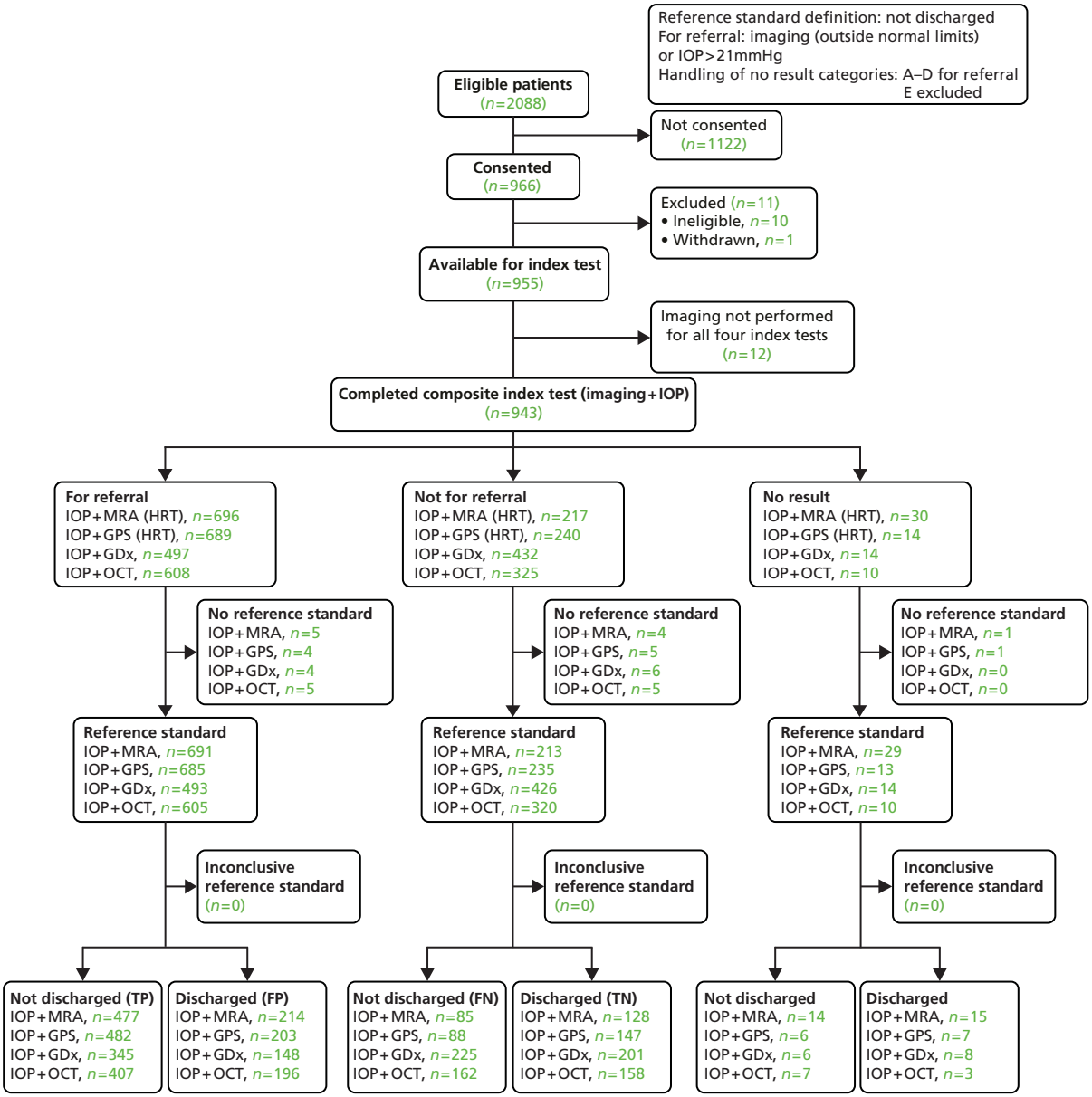

FIGURE 19 Flow diagram: triage sensitivity analysis 6. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

TABLE 37 Diagnostic performance: triage sensitivity analysis 6

Test	Diagnostic parameter	Value	95% CI
HRT-MRA	Sensitivity (%)	84.9	81.6 to 87.7
	Specificity (%)	37.4	32.3 to 42.8
	Positive likelihood ratio	1.36	1.24 to 1.48
	Negative likelihood ratio	0.40	0.32 to 0.48
	DOR	3.36	2.44 to 4.61
HRT-GPS	Sensitivity (%)	84.6	81.3 to 87.4
	Specificity (%)	42.0	36.8 to 47.4
	Positive likelihood ratio	1.46	1.32 to 1.60
	Negative likelihood ratio	0.37	0.29 to 0.46
	DOR	3.97	2.91 to 5.41
GDx	Sensitivity (%)	60.5	56.4 to 64.6
	Specificity (%)	57.6	52.2 to 62.8
	Positive likelihood ratio	1.43	1.24 to 1.64
	Negative likelihood ratio	0.69	0.60 to 0.79
	DOR	2.08	1.59 to 2.73
OCT	Sensitivity (%)	71.5	67.6 to 75.2
	Specificity (%)	44.6	39.4 to 50.0
	Positive likelihood ratio	1.29	1.16 to 1.44
	Negative likelihood ratio	0.64	0.54 to 0.76
	DOR	2.03	1.53 to 2.67

Triage sensitivity analysis 7

Triage sensitivity analysis 7 differed from the default triage analysis in that a higher IOP threshold of 26 mmHg rather than 21 mmHg was used to identify abnormal tests. The triage test is classified as abnormal if (1) the imaging test result is classified as 'outside normal limits', (2) IOP is > 26 mmHg or (3) VA is 6/12 or poorer. Imaging test results which did not provide an overall classification were included as abnormal. The corresponding reference standard definition is a clinical decision not to discharge the patient.

The flow of study participants according to triage sensitivity analysis 7 is shown in *Figure 20*, with the corresponding numbers of referral, not for referral and no result cases by triage test and the corresponding reference standard finding shown. Of the 943 participants in whom all four tests were performed, 481 were not discharged and 562 were discharged and the discharge status was missing for 10 participants. The diagnostic performance for the four tests is given in *Table 38*. The results generally showed a trade-off between the detection of patients who need to be referred and the discharge of those who do not need to be referred: HRT-MRA had the highest sensitivity (77.2%, 95% CI 73.5% to 80.6%) but second lowest specificity (51.8%, 95% CI 46.3% to 57.2%), GDx had the lowest sensitivity (47.9%, 95% CI 43.7% to 52.1%) but the highest specificity (79.1%, 95% CI 74.4% to 81.2%), and the other two tests provided intermediate results (HRT-GPS values were very similar to the HRT-MRA results and OCT had very similar sensitivity and specificity). Likelihood ratios (and 95% CI) showed evidence of being able to both rule in and rule out the presence of glaucoma for all four triage tests (CIs did not contain 1.0). DORs ranged from 2.61 for OCT to 4.03 for HRT-GPS.

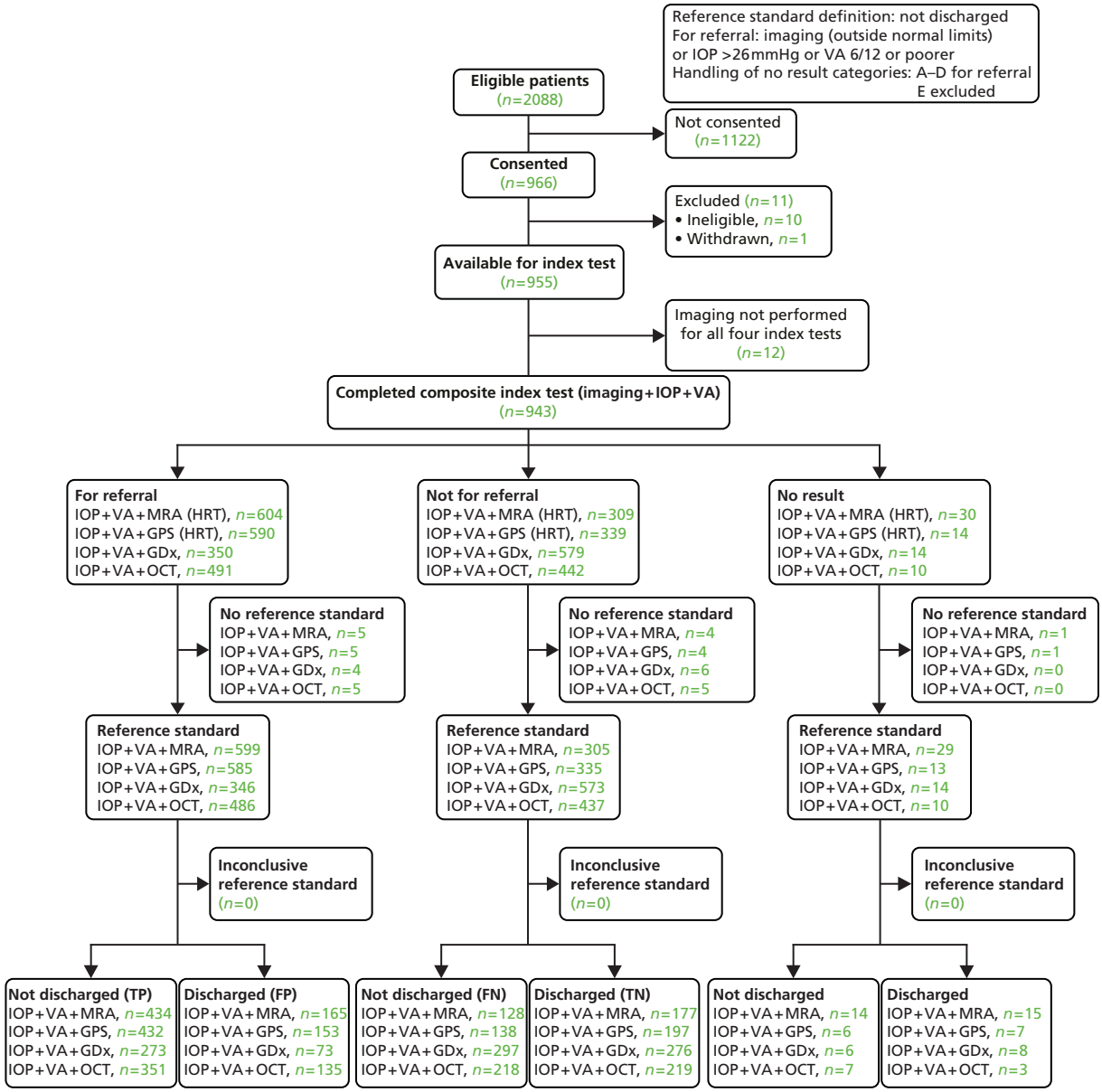

FIGURE 20 Flow diagram: triage sensitivity analysis 7. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

TABLE 38 Diagnostic performance: triage sensitivity analysis 7

Test	Diagnostic parameter	Value	95% CI
HRT-MRA	Sensitivity (%)	77.2	73.5 to 80.6
	Specificity (%)	51.8	46.3 to 57.2
	Positive likelihood ratio	1.60	1.42 to 1.80
	Negative likelihood ratio	0.44	0.37 to 0.53
	DOR	3.64	2.72 to 4.86
HRT-GPS	Sensitivity (%)	75.8	72.1 to 79.3
	Specificity (%)	56.3	50.9 to 61.6
	Positive likelihood ratio	1.73	1.53 to 1.97
	Negative likelihood ratio	0.43	0.36 to 0.51
	DOR	4.03	3.03 to 5.36
GDx	Sensitivity (%)	47.9	43.7 to 52.1
	Specificity (%)	79.1	74.4 to 81.2
	Positive likelihood ratio	2.29	1.84 to 2.86
	Negative likelihood ratio	0.66	0.60 to 0.72
	DOR	3.48	1.99 to 3.43
OCT	Sensitivity (%)	61.7	57.6 to 65.7
	Specificity (%)	61.9	56.6 to 66.9
	Positive likelihood ratio	1.62	1.40 to 1.87
	Negative likelihood ratio	0.62	0.54 to 0.71
	DOR	2.61	1.99 to 3.43

Triage sensitivity analysis 8

Triage sensitivity analysis 8 differed from the default triage analysis in that a higher VA threshold of VA 6/18 or poorer was used to identify abnormal tests. The triage test is classified as abnormal if (1) the imaging test result is classified as 'outside normal limits', (2) IOP is > 21 mmHg or (3) VA is 6/18 or poorer. Imaging test results which did not provide an overall classification were included as abnormal. The corresponding reference standard definition is a clinical decision not to discharge the patient.

The flow of study participants according to triage sensitivity analysis 8 is shown in *Figure 21*, with the corresponding numbers of referral, not for referral and no result cases by triage test and the corresponding reference standard finding shown. Of the 943 participants in whom all four tests were performed, 481 were not discharged and 562 were discharged and the discharge status was missing for 10 participants. The diagnostic performance for the four tests is given in *Table 39*. The results showed a trade-off between the detection of patients who need to be referred and the discharge of those who do not need to be referred: HRT-MRA had the highest sensitivity (85.1%, 95% CI 81.8% to 87.9%) but lowest specificity (35.1%, 95% CI 30.0% to 40.4%), GDx had the lowest sensitivity (61.9%, 95% CI 57.8% to 65.9%) but the highest specificity (55.6%, 95% CI 50.2% to 60.9%) and the other two tests provided intermediate results (HRT-GPS values were very similar to the HRT-MRA results, and OCT had the second lowest sensitivity (72.9%, 95% CI 69.1% to 76.5%) but the second highest specificity (42.9%, 95% CI 37.7% to 48.3%). Likelihood ratios (and 95% CI) showed evidence of being able to both rule in and rule out the presence of glaucoma for all four triage tests (CIs did not contain 1.0). DORs ranged from 2.03 for OCT to 3.80 for HRT-GPS.

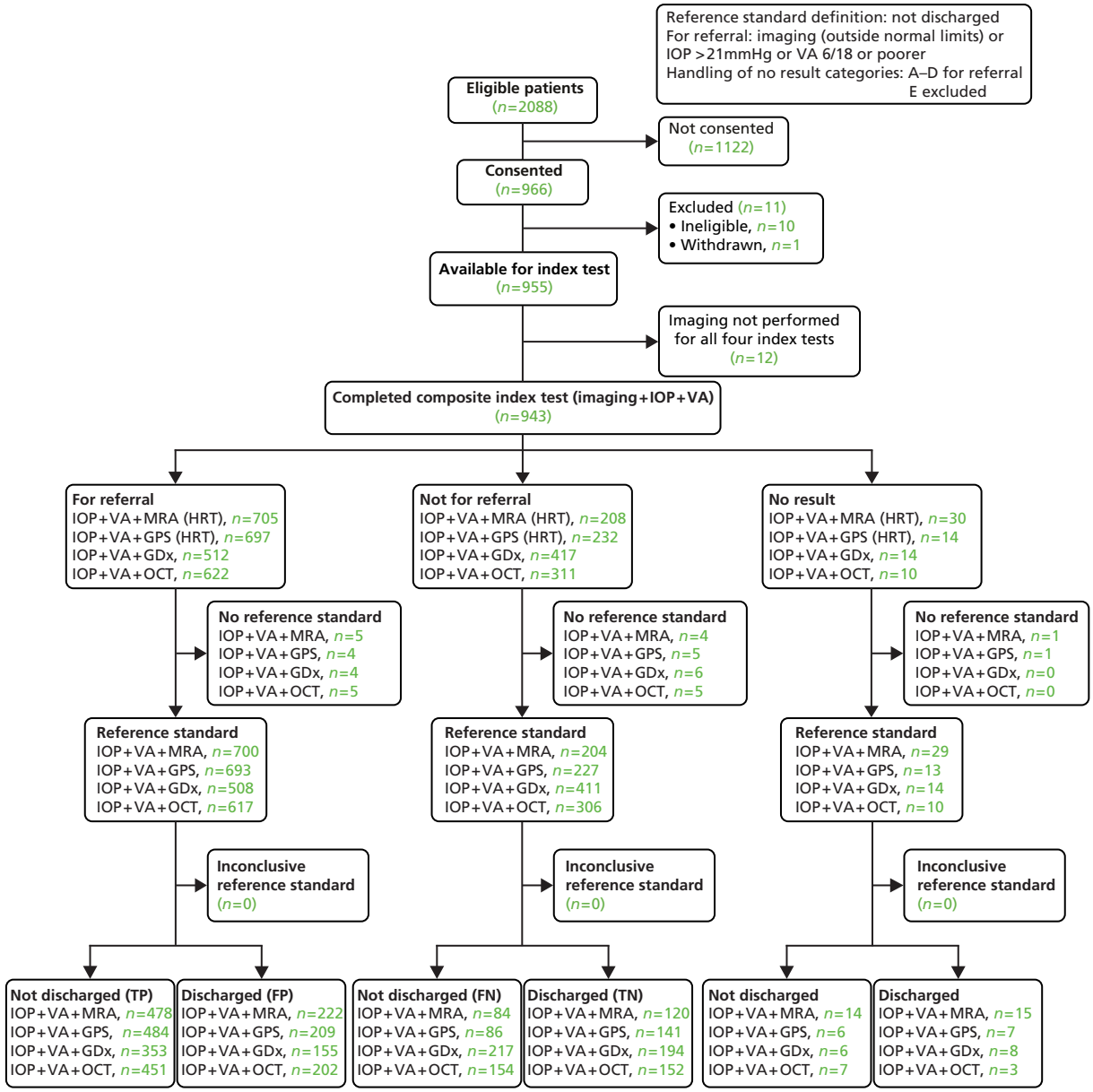

FIGURE 21 Flow diagram: triage sensitivity analysis 8. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

TABLE 39 Diagnostic performance: triage sensitivity analysis 8

Test	Diagnostic parameter	Value	95% CI
HRT-MRA	Sensitivity (%)	85.1	81.8 to 87.9
	Specificity (%)	35.1	30.0 to 40.4
	Positive likelihood ratio	1.31	1.20 to 1.43
	Negative likelihood ratio	0.43	0.33 to 0.54
	DOR	3.08	2.23 to 4.24
HRT-GPS	Sensitivity (%)	84.9	81.7 to 87.8
	Specificity (%)	40.3	35.1 to 45.6
	Positive likelihood ratio	1.42	1.30 to 1.56
	Negative likelihood ratio	0.37	0.30 to 0.47
	DOR	3.80	2.78 to 5.19
GDx	Sensitivity (%)	61.9	57.8 to 65.9
	Specificity (%)	55.6	50.2 to 60.9
	Positive likelihood ratio	1.39	1.22 to 1.59
	Negative likelihood ratio	0.68	0.60 to 0.79
	DOR	2.04	1.55 to 2.67
OCT	Sensitivity (%)	72.9	69.1 to 76.5
	Specificity (%)	42.9	37.7 to 48.3
	Positive likelihood ratio	1.28	1.15 to 1.42
	Negative likelihood ratio	0.63	0.53 to 0.76
	DOR	2.03	1.53 to 2.68

Discussion

Four composite triage (imaging, IOP measurement and VA assessment) tests were compared with regard to their diagnostic performance for determining who should be referred for further assessment or discharged using the GATE population of referrals to a glaucoma clinic in secondary care.

The sensitivity and specificity of the four triage tests incorporating each of the imaging technologies along with IOP and VA for the default triage analysis and sensitivity analyses (see *Table 29* for details) are summarised in *Figures 22* and *23*, respectively.

All four triage tests had value in terms of ruling in and ruling out the need for referral on to a consultant ophthalmologist. The diagnostic performance of the triage tests differed with substantial differences in the ability to correctly detect those who need to be referred and those who do not. HRT-GPS and HRT-MRA consistently had the highest sensitivities across analyses but at a cost of lower specificity than other tests. HRT-GPS had the slightly higher specificity. In contrast, GDx consistently had the best specificity, although the lowest sensitivity. HRT-GPS results were typically similar to HRT-MRA. OCT generally had similar levels of sensitivity and specificity. The choice of which triage test is to be preferred reflects the inherent trade-off regarding diagnostic testing, where the desire to refer onwards when referral is needed must be balanced again the desire to discharge those who do not need a further assessment. A formal assessment of this trade-off and the consequences in terms of health outcome and costs is covered in *Chapters 6* and *7*.

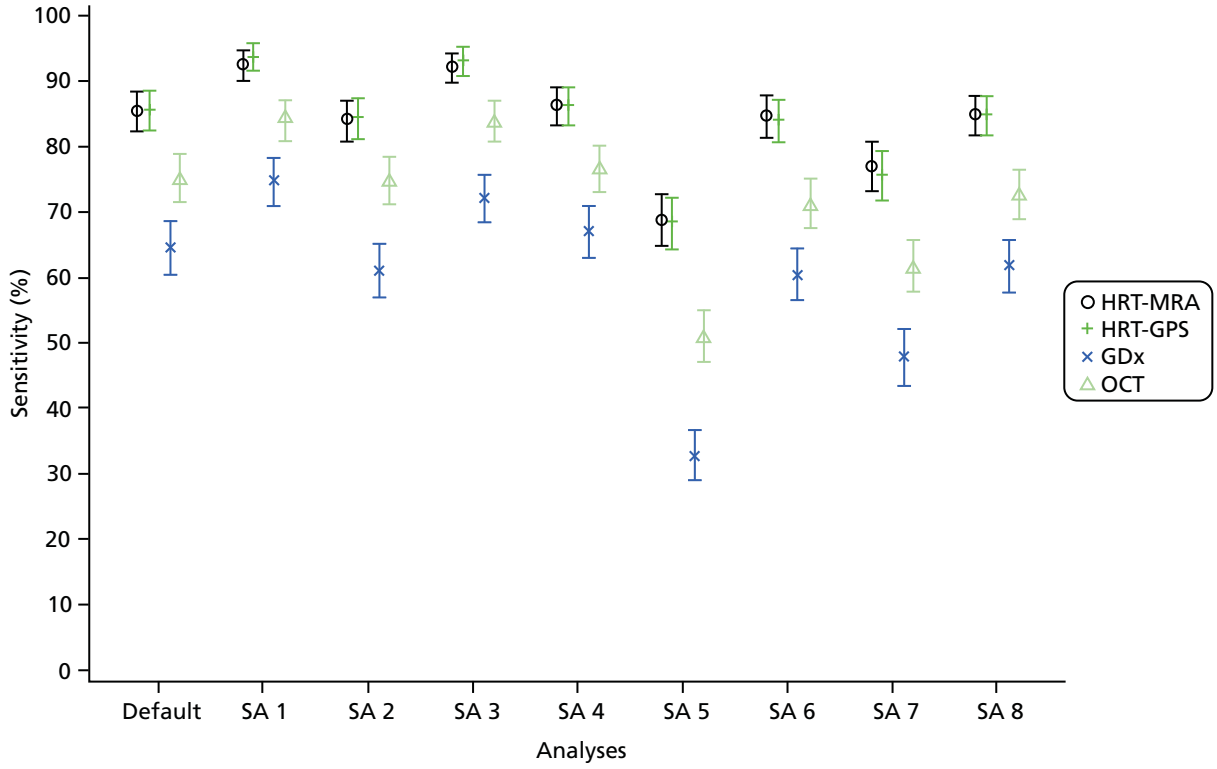

FIGURE 22 Summary of the sensitivity of the composite test across all triage analyses. SA, sensitivity analysis.

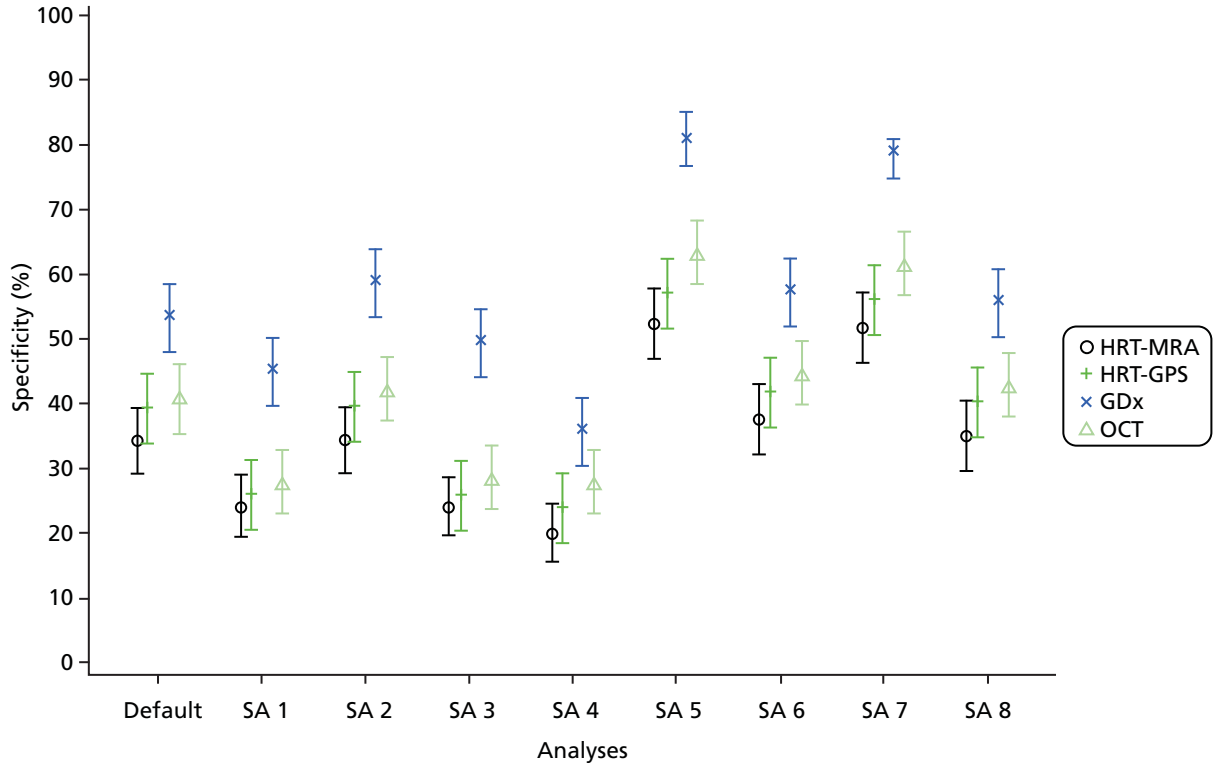

FIGURE 23 Summary of the specificity of the composite test across all triage analyses. SA, sensitivity analysis.

The triage was formed from three components, an imaging test as evaluated in *Chapter 4*, a measurement of IOP and VA measurement. The elements were combined in an additive manner where an individual was referred if any one of the three components met the relevant referral criteria. A number of sensitivity analyses were carried out to assess the robustness of the findings of this default triage analysis. Varying the imaging test definition of a positive result by including the borderline category of imaging test result was carried out; this had the expected impact of improving the detection of glaucoma, although at the cost of more non-glaucoma cases being falsely identified as having glaucoma. This resulted in very high detection of glaucoma for HRT-MRA, HRT-GPS and high sensitivities for GDx and OCT but the consequence of lower specificities (GDx had a higher specificity value than the other three triage tests). Additionally, the impact of using the classification from the imaging test when the quality criterion was not met was assessed. The impact was at most a small reduction in sensitivity with an increase in specificity (only GDx had more than a nominal change in values). The added value of the IOP and VA components was assessed by dropping one of the components, varying the cut-off point used to define abnormality, and, for the IOP component, using the referral IOP measurement in place of the ophthalmologist's. Removal of the IOP component had a noticeable impact on the diagnostic performance with exclusion leading to a reduction in sensitivity, although a gain in specificity. Modifying the IOP cut-off value changed the balance in terms of sensitivity and specificity as expected. When the referral IOP was used in place of the ophthalmologist's IOP the specificity was reduced. Such an impact is unsurprising given the known variability in IOP measurements[42] and the use of an absolute cut-off will lead to a regression to the mean effect when another measurement is taken (in this case by a different observer). Removing the VA component had very little impact on the diagnostic accuracy with a slight reduction in the sensitivity and corresponding increase in specificity. This impact may have been limited by the method of data collection (referral letter quotation) as opposed to complete data capture of a new VA measurement.

A number of assumptions underpinned the analyses and interpretation of these results in addition to those highlighted previously for diagnoses analyses. The reference standard here was the clinical decision to discharge or not, which will vary to some degree between individual clinicians and centres according to policies and practices (perhaps most noteworthy for individuals with glaucoma suspect). Components of the triage test were combined in an additive manner which reflects an implicit desire to favour sensitivity over specificity. No other options were assessed, although arguably this approach reflects clinical practice. The use of the ophthalmologist's measurement does not reflect the reality of how a triage system would be implemented where, if a measurement was taken in hospital eye services, it would be by another individual (e.g. a technician). Using the referral IOP did have a substantial impact, although most if not all of this impact might be attributed to the inevitable variability between measurements taken at different times by different observers and the impact of regression to the mean. The finding does suggest there is value in taking a measurement upon referral to hospital eye services.

Chapter 6 Economic evaluation methods

The objective of this chapter is to present the economic evaluation of four automated optic nerve and RNFL imaging tests (HRT-MRA, HRT-GPS, GDx and OCT), hereafter referred to as imaging technologies. These were evaluated in the GATE study as triage diagnostic stations in hospital eye services (secondary care), compared with current practice, for patients referred to hospital eye services for possible glaucoma. The triage diagnostic station included an imaging test, a VA test and an IOP measurement.

The model

The cost-effectiveness of the different imaging technologies and their subsequent care management pathways was assessed using a multistate Markov model. As glaucoma is a chronic condition, which progresses slowly over time, the model reflects the timing of both diagnostic testing and disease progression. This approach allowed modelling of the logical and temporal sequence of events (e.g. diagnosis or monitoring visits) following the initial diagnostic strategy.

Typically, Markov models have states (Markov states) in which individuals stay for a period of time called a 'cycle'. The cycle must be a period relevant to the condition considered (e.g. 6 months, 1 year). At the end of each cycle, individuals can remain in the state in which they started the cycle or move to a different state. The probabilities of moving from one state to another are called transition probabilities. In each state, the model will assign costs and benefits for each individual according to different interventions and/or time spent in the state. In these models, there must be at least one absorbing state, typically death, from which the individual will not be able to leave. The sum of the cost in each year and the product of the utilities in each year were summed over 50 years of the simulated patient cohort to compute total cost and quality-adjusted life-year (QALY) for that cohort.

The purpose of this model was to compare and contrast different imaging technologies (used as part of a wider triage station) for the identification of patients who should be referred for a clinician-led diagnostic examination. We can thus compare and contrast these with standard care where all patients receive a clinician-led diagnosis based on clinical examination and visual field assessment (automated perimetry). The model was constructed such that different sensitivities and specificities of each diagnostic strategy would determine if glaucoma was correctly identified or not, the health state patients would move to and the associated progression of any underlying glaucoma. The consequences could then be considered in terms of the monetary costs (of testing and subsequent management of the patient's condition) to the NHS and in terms of the effects on quality of life (by assigning utility weights). Combining these data with information of the probabilities of events occurring over time-enabled cost, patient outcomes and QALYs to be estimated for a hypothetical cohort of patients undergoing each triage strategy.

The results of the model are presented in *Chapter 7* and are presented as incremental cost per QALYs and incorporate (1) costs (of testing) and diagnostic outcomes, (2) costs (of testing and subsequent management) and (3) QALYs.

Figure 24 shows the possible health states in ovals, while the arrows show the possible directions in which individuals can move at the end of each cycle, depending on the transition probabilities. The states considered in the model were those thought to reflect possible paths for individuals classified as normal, at risk of glaucoma or suffering from glaucoma at different stages (see *Figure 24*). Each state, other than normal and death, is divided into two categories. The treated states on the right-hand side of *Figure 24* represent those individuals whose condition has been identified and is being treated, and the untreated states on the left-hand side represent those individuals whose condition has not yet been identified and thus who are not receiving treatment. The treatment health states refer to treated disease at each stage of glaucoma. The modality of treatment, IOP-lowering eye drops, laser or surgery or any combination thereof, is not specified for a glaucoma-related treatment state. A treatment state refers to any modality or combination treatment for each stage of glaucoma severity. There are three treatment states for the three stages of manifest glaucoma and a treatment state for sight impairment. The 'at risk of glaucoma' treatment state includes those individuals who are suspected of having glaucoma and those who have OHT and PAC. Among the 'at risk of glaucoma' group, we have assumed that all patients with OHT will be treated in the same way and that treatment incorporates annual outpatient appointments for observation, with all OHT individuals receiving continuous latanoprost (eye drops, once a day).

Depending on their underlying condition, individuals will start in the model in a normal state, an untreated 'at risk of glaucoma' state or an untreated glaucoma disease state (mild, moderate, severe or sight impaired). Each individual will then enter a diagnosis process that will differ according to the compared strategies used to diagnose their condition (i.e. for current practice in the form of consultant-led diagnosis and care or a triage station including one of the imaging technologies under consideration; see *Figure 24*). The sensitivity and specificity of each diagnostic strategy determine the Markov state an individual will move to. In particular, it will determine if an individual enters a treated or untreated disease state and the possible transitions associated with these. In general, as time passes, the normal or 'at risk of glaucoma' individuals could develop glaucoma, while those with glaucoma could progress to a more severe disease state until they eventually become visually impaired.

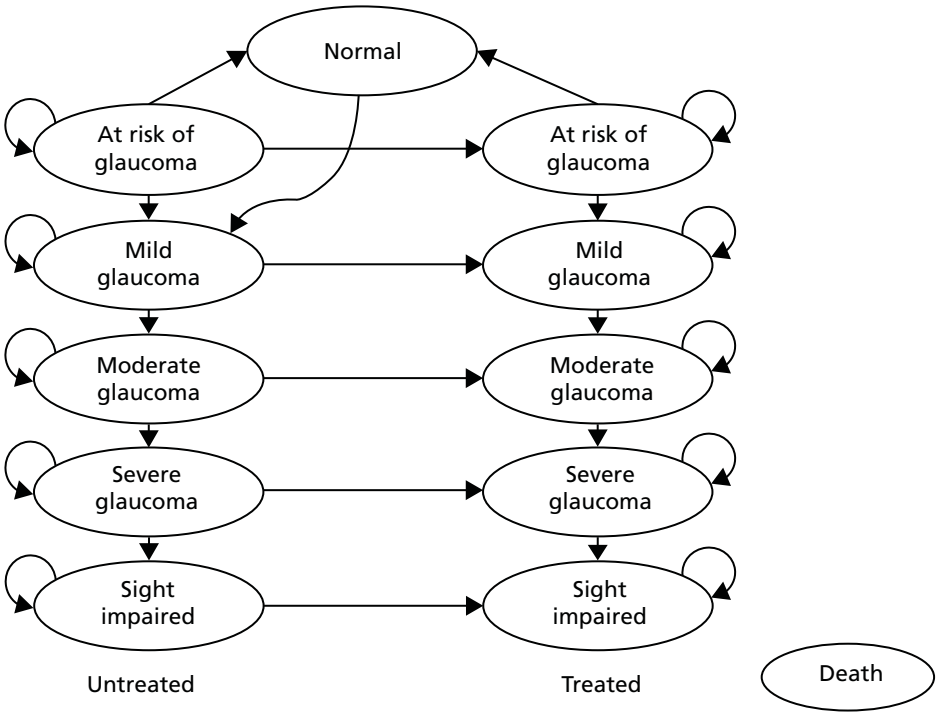

FIGURE 24 Schematic diagram of model states and possible transitions.

Glaucoma is not reversible and this is reflected in the model (see *Figure 24*). However, individuals can return to a normal state after a number of model cycles within the 'at risk of glaucoma' Markov state. The absorbing state in the model is death. Any individual can move into this state from any other state in the model.

The model allows for a cohort of the population, some with glaucoma, to pass through different diagnostic strategies. The intuitive idea behind the model is to identify the strategy that leads to the largest proportion of individuals with glaucoma being correctly diagnosed and being in treatment to reduce disease progression and visual loss.

Definition of health states used in the model

Glaucoma states were defined in terms of severity of disease, namely mild, moderate and severe glaucoma, and sight impaired. The agreed glaucoma severity definitions used for the GATE study data collection were used for the economic model (*Table 40*). Furthermore, an additional disease state defined as 'at risk of glaucoma' was included in the model to represent those individuals who do not have manifest glaucoma but have a higher risk of developing glaucoma (glaucoma suspects, those with OHT and those with PAC).

TABLE 40 Definition of health states for the economic evaluation

Health state	Definition
'At risk of glaucoma' health state: glaucoma suspect, OHT or PAC	
Glaucoma suspect	Either the optic disc or VF, or both, have some features that are suggestive of glaucoma but may also represent a variation of normality (with or without high IOP)
OHT	Both the VF and optic nerve appear normal in the presence of elevated pressure > 21 mmHg
PAC	Closed anterior chamber angle (appositionally or synechial) in at least 270°, and at least one of the following: IOP > 21 mmHg and/or presence of peripheral anterior synechiae. Both VF and optic nerve appear normal
'Glaucoma': different health states according to MD index of the VF test	
'Mild glaucoma'	Evidence of glaucomatous optic neuropathy and a characteristic VF loss. MD better than or equal to –6 dB
'Moderate glaucoma'	Evidence of glaucomatous optic neuropathy and a characteristic VF loss. MD between –6.01 dB and –12 dB
'Severe glaucoma'	Evidence of glaucomatous optic neuropathy and a characteristic VF loss. MD worse than or equal to –12.01 dB
'Sight impaired' health state: sight impaired and severely sight impaired	
Sight impaired	Poor VA (3/60 to 6/60) with full field of vision; or slightly reduced VA (up to 6/24) and reduced field of vision or blurriness/cloudiness in central vision; or relatively good VA (up to 6/18) but significantly reduced field of vision
Severely sight impaired	Very poor VA (less than 3/60) with full field of vision; or poor VA (between 3/60 and 6/60) and severely reduced field of vision; or slightly reduced VA (6/60 or better) and significantly reduced field of vision

VF, visual field.

Description of the health-care diagnostic strategies and management pathways considered within the model

The care pathways modelled within the Markov model following diagnosis were developed in consultation with the study team and the independent steering committee members. The main study team for this element of the work comprised two ophthalmologists (AA-B, JB), and three health economists (RH, PM, JG), and a health services researcher (KB). Over a number of meetings, the group mapped out the sequence of events for patients potentially eligible for treatment or monitoring following the diagnostic strategies under consideration. Additional information came from our previous models in this area, notably our model comparing alternative screening strategies for OAG[18] reviewed guidelines and expert opinion. These care pathways were then presented to the steering committee and revised to reflect the comments received.

Current practice care pathway

Patients enter the model as a cohort who have been identified with signs of, for example possible glaucoma or OHT by a community optometrist or GP and who have been referred to secondary care. Within hospital eye services, all individuals will see a nurse, who will perform a VA examination, and a technician, who will perform a visual field test. All individuals will then see a clinician (typically an ophthalmologist), who will measure IOP (using GAT), look at the visual field results and perform a fundus examination to examine the optic disc and the posterior retina. *Figure 25* shows the care pathway.

Considering all the clinical information, the clinician will decide on a diagnosis as described in *Chapter 2*. For the purpose of the model, these diagnoses have been grouped into five health states (described further in *Table 40*): mild glaucoma, moderate glaucoma, severe glaucoma, at risk of glaucoma and normal. Furthermore, the 'at risk of glaucoma' health state includes those with a diagnosis of OHT or glaucoma suspect or PAC.

Individuals who are diagnosed by the clinician to be in the normal health state are discharged from secondary care. Individuals diagnosed with glaucoma remain in secondary care under treatment and enter the relevant glaucoma-treated health state. Individuals diagnosed as 'at risk of glaucoma' also remain in secondary care and enter into the 'at risk of glaucoma' treatment state. The subset of 'at risk of glaucoma' patients with OHT are all assumed to be undergoing treatment.

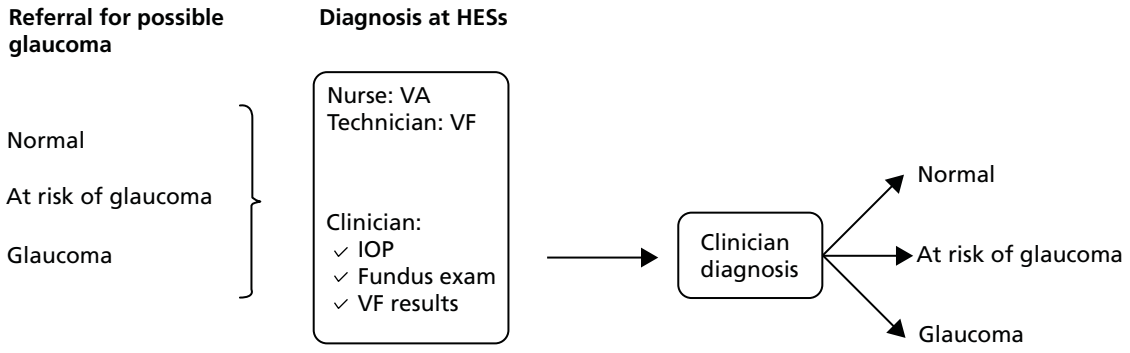

FIGURE 25 Care pathway: current practice. HES, hospital eye service; VF, visual field.

Triage care pathway

As described in *Chapter 2*, the triage pathway used IOP, imaging and VA to identify patients who could be discharged from secondary care if all tests were normal. IOP and VA are routinely collected in primary and/or secondary care and used to inform the clinical decision-making process as to whether to discharge a patient or not. At hospital eye services the individuals will be seen by a nurse that will perform VA examination and IOP measurement. They will also be seen by a technician who will perform the index (imaging) test (HRT-MRA, HRT-GPS, GDx or OCT depending on triage strategy). *Figure 26* shows the care pathway for the triage strategies.

The results of these three examinations are combined into a composite triage test result as follows. If any of the VA or IOP or imaging test results is abnormal, then the composite test is assumed to be positive or abnormal. Only if all three tests (VA, IOP and imaging test) are normal is the composite test result negative or normal. Individuals with normal (negative) composite triage test results are discharged from secondary care. Individuals with abnormal (positive) test results are referred to the clinician to make a diagnosis. Definitions of abnormal (positive) test results for the elements of the composite test are as follows: IOP > 21 mmHg, VA 6/12 or worse, imaging technology classification abnormal or borderline.

Individuals who have been discharged with normal (negative) composite triage test results can be either truly normal (true negative) or have been incorrectly diagnosed as normal when they do in fact have disease (false negative). Individuals with an abnormal (positive) composite triage test result are then referred to the clinician, who will make a definitive diagnosis. Perfect information by the clinician is assumed in the model; therefore, individuals will be correctly identified as having glaucoma (e.g. mild, moderate, severe or visually impaired), as being at risk of glaucoma or without any of these conditions (e.g. normal). Normal individuals are discharged while all others are kept under monitoring or observation. The perfect information assumption is explored in sensitivity analysis with the possibility of misdiagnoses by the clinician (e.g. false-positive and false-negative results).

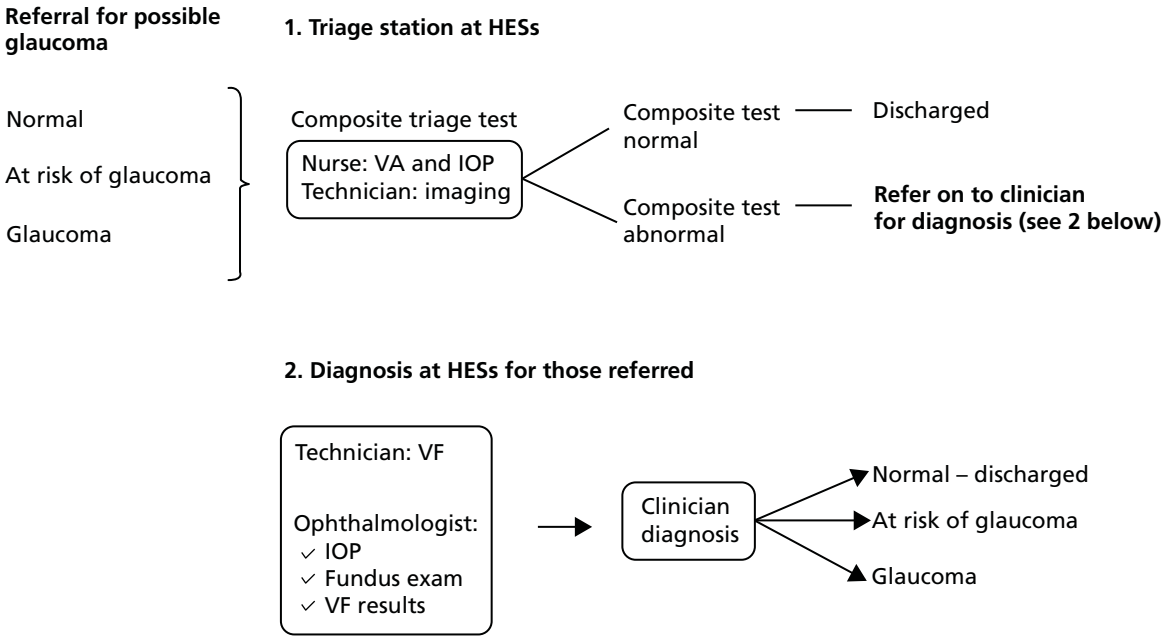

FIGURE 26 Care pathway: triage strategies. HES, hospital eye service; VF, visual field.

Model strategies

Five diagnostic strategies are explicitly considered in the model (see *Table 41*). The comparator in the model reflects the current practice. In this strategy, all patients referred to secondary care for possible glaucoma see a clinician for diagnosis of their condition.

Four diagnostic imaging technologies (HRT-MRA, HRT-GPS, GDx, OCT) used as part of a composite triage test which includes an assessment of IOP and VA are evaluated within the model. The diagnostic strategies and associated care pathways used in the economic model are summarised in *Table 41*.

Estimation of parameters used within the model

This section summarises the parameter values used in the economic evaluation model.

Data regarding the cohort in terms of prevalence, incidence and progression are reported first, followed by diagnostic triage test performance data, with subsequent sections regarding data on cost and utilities also reported.

Cohort data: prevalence, incidence and progression data

Table 42 shows data on prevalence, incidence and progression of glaucoma used in the model.

Prevalence data and proportion of glaucoma subjects by severity of disease were based on the GATE study population (see *Chapter 3*). Incidence data and progression data as well as relative rate of progression between treated and untreated individuals were obtained from previous models of glaucoma management and surveillance.[18,42,43] The annual probability of having an eye test was informed by Burr *et al.*,[18] who used data on eye test, sex and age from the British Household Panel Survey[45] to estimate the annual probabilities in different age groups of having an eye test by a community optometrist. We used the average of two probabilities estimated in the report, 0.248 per year for those in the 40–59 years range and 0.3769 per year for those in the 60–75 years age range, to give 0.312 visits per year.

TABLE 41 Diagnostic strategies and associated care pathways

Strategy	Triage stage (composite test)	Diagnosis stage (clinician)	Treatment	Note
Current practice/ standard care	N/A	VA by nurse and VF by technician. Then IOP measured (GAT) and fundus examination conducted by a clinician who will make diagnosis decision (together with VF and VA information)	• Treatment/monitoring according to NICE guidelines[26] • All glaucoma patients treated according to severity • Assume all OHT treated with latanoprost (xalatan®, Pfizer) • Glaucoma suspects monitored only	–
Triage 1: HRT-MRA	HRT-MRA test by technician; IOP and VA by nurse. If all three tests negative, discharge. If any of HRT-MRA or IOP or VA test positive, refer on to diagnosis stage (clinician examination)	VF test by technician, IOP measured (GAT) and fundus examination conducted by a clinician who will make diagnosis decision (together with VF and VA information)	• Treatment/monitoring according to NICE guidelines[26] • All glaucoma patients treated according to severity • Assume all OHT treated with latanoprost • Glaucoma suspects monitored only	• MRA positive: 'outside normal limits' or 'borderline' classification • IOP positive: > 21 mmHg • VA positive: 6/12 or poorer
Triage 2: HRT-GPS	HRT-GPS test by technician; IOP and VA by nurse. If all three tests negative, discharge. If any of HRT-GPS or IOP or VA test positive, refer on to diagnosis stage (clinician examination)	VF test by technician; IOP measured (GAT) and fundus examination conducted by a clinician who will make diagnosis decision (together with VF and VA information)	• Treatment/monitoring according to NICE guidelines[26] • All glaucoma patients treated according to severity • Assume all OHT treated with latanoprost • Glaucoma suspects monitored only	• GPS positive: 'outside normal limits' or 'borderline' classification • IOP positive: > 21 mmHg • VA positive: 6/12 or poorer
Triage 3: GDx	GDx test by technician; IOP and VA by nurse. If all three tests negative, discharge. If any of GDx or IOP or VA test positive, refer on to diagnosis stage (clinician examination)	VF test by technician; IOP measured (GAT) and fundus examination conducted by a clinician who will make diagnosis decision (together with VF and VA information)	• Treatment/monitoring in accordance with NICE guidelines[26] • All glaucoma patients treated according to severity • Assume all OHT treated with latanoprost • Glaucoma suspects monitored only	• GDx positive: NFI > 35 • IOP positive: > 21 mmHg • VA positive: 6/12 or poorer
Triage 4: OCT	OCT test by technician; IOP and VA by nurse. If all three tests negative, discharge. If any of OCT or IOP or VA test positive, refer on to diagnosis stage (clinician examination)	VF test by technician; IOP measured (GAT) and fundus examination conducted by a clinician, who will make diagnosis decision (together with VF and VA information)	• Treatment/monitoring according to NICE guidelines[26] • All glaucoma patients treated according to severity • Assume all OHT treated with latanoprost • Patients with glaucoma suspect monitored only	• OCT positive: 'outside normal limits' or 'borderline' classification • IOP positive: > 21 mmHg • VA positive: 6/12 or poorer

N/A, not applicable; VF, visual field.

TABLE 42 Cohort data: prevalence, incidence and progression

Probability	Value	Source
Cohort start age (years)	40	Base-case assumption
Prevalence of glaucoma	0.17	GATE study
Proportion of normal	0.412	GATE study
Prevalence of 'at risk of glaucoma'	0.418	GATE study
Proportion of mild glaucoma	0.523	GATE study
Proportion of moderate glaucoma	0.302	GATE study
Proportion of severe glaucoma	0.174	GATE study
Progression to mild glaucoma from 'at risk of glaucoma'	0.002	Expert opinion from clinical experts in the research team (AA-B and JB)
Progression to moderate glaucoma	0.129	Burr *et al.* 2014[43]
Progression to severe glaucoma	0.048	Burr *et al.* 2014[43]
Progression to sight impaired	0.042	Burr *et al.* 2014[43]
Reduction in risk of progression from any medical treatment for glaucoma	0.65	Burr *et al.* 2014[43]
Mortality	Various	Interim life tables[44]
Incidence of glaucoma		
50 years old	0.0003	Burr *et al.* 2007[18]
60 years old	0.0008	Burr *et al.* 2007[18]
70 years old	0.00181	Burr *et al.* 2007[18]
80 years old	0.00414	Burr *et al.* 2007[18]

Test performance data

Table 43 shows data on the test performances of each of the triage strategies that incorporated the different diagnostic technologies plus IOP and VA measurement and the current strategy in the form of clinician diagnosis. Although the imaging technology is used to define the strategy, all performance measures are calculated based on a composite test result which combines imaging, IOP and VA test results (see *Appendix 6*).

For current clinical practice, diagnosis by a clinician was assumed to be 100% sensitive and specific. The remaining composite test performances for detecting glaucoma, 'at risk of glaucoma' and normal individuals were informed by statistical analysis of the GATE study specifically carried out to inform the economic model. Triage accuracy data for the four triage strategies (e.g. sensitivity and specificity) were calculated for glaucoma, 'at risk of glaucoma' and normal groups (see *Appendix 6*).

Estimation of costs used within the model

All costs were estimated based on resource-use inputs and unit costs for the 2012–13 financial year and are reported in UK pounds sterling. With the exception of treatment costs, which were taken from the literature, costs included in the model were estimated using a micro-costing exercise or using NHS Reference Costs.[22] The data used in this exercise were then subsequently checked by the steering committee members. Specific costs to the NHS relevant to the diagnostic strategies, subsequent treatment pathways and events included diagnostic imaging, staff time, treatment, equipment and capital costs. With the exception of capital costs, which were sourced from specific commercial providers, most unit costs were sourced from NHS Reference Costs,[22] Unit Costs of Health and Social Care[46] and Agenda for Change.[47] Where costs were not reported in 2012–13 values, they were inflated by the Hospital and Community Health Sector inflation index.[46]

TABLE 43 Accuracy parameters of the triage test used in the model

Probability	Value	Source
Sensitivity for all glaucoma individuals		
HRT-MRA	0.99	GATE study
HRT-GPS	0.99	GATE study
GDx	0.88	GATE study
OCT	0.97	GATE study
Sensitivity for all 'at risk of glaucoma' individuals		
HRT-MRA	0.97	GATE study
HRT-GPS	0.97	GATE study
GDx	0.77	GATE study
OCT	0.87	GATE study
Specificity for all normal individuals		
HRT-MRA	0.30	GATE study
HRT-GPS	0.28	GATE study
GDx	0.51	GATE study
OCT	0.35	GATE study
Sensitivity and specificity of current practice (diagnosis by an ophthalmologist) for all individuals (glaucoma, 'at risk of glaucoma' and normal)		
Sensitivity	1	Assumption
Specificity	1	Assumption

All capital costs for each of the diagnostic imaging technologies were costed using current market prices obtained from various commercial providers to the NHS (see explanations below in the *Costs of diagnosis pathway: triage strategies* section). These initial outlay costs were annuitised over the useful working lifespan of the piece of equipment (assumed to be 10 years for all equipment) applying an annual discount factor of 3.5%[47] to account for the opportunity cost of the investment over time.

The equivalent annual cost of each piece of equipment was divided by its estimated maximum number of uses per annum (from NHS providing units and expert opinion) to give cost per use estimates.

Tables 44–46 show the cost estimates used in the model for diagnosis by current practice, diagnosis by the triage strategies and treatment costs.

TABLE 44 Costs of current practice diagnosis used in the model

Costs	Value (£)	Source
Nurse-led VA test	2.45	Agenda for Change[47]
Technician VF test	2.72	Agenda for Change[47]
Ophthalmology first outpatient appointment	106	NHS Reference Costs[22]

VF, visual field.

TABLE 45 Costs of triage strategies used in the model

Costs	Value (£)	Source
Triage appointment costs		
Nurse-led VA and IOP test	2.45	Agenda for Change[47]
Technician-led index test (e.g. OCT, GDx or HRT)	2.72	Agenda for Change[47]
Capital cost OCT diagnostic technology	1.32	Micro-costed
Capital cost of HRT-III (GPS and MRA) and GDx diagnostic technologies	0.79	Micro-costed
Appointment costs for those triaged and referred to the clinician		
Technician VF test	2.72	Agenda for Change[47]
Ophthalmology first outpatient appointment	106	NHS Reference Costs[22]

VF, visual field.

TABLE 46 Annual cost of treatment

Costs	Value (£)	Source
Glaucoma-related treatment costs		
Glaucoma mild treatment	499.80	Burr *et al.* 2007[18]
Glaucoma moderate treatment	562.87	Burr *et al.* 2007[18]
Glaucoma severe treatment	447.44	Burr *et al.* 2007[18]
Sight impaired annual cost	796.11	Burr *et al.* 2007[18]
'At risk of glaucoma' state treatment costs		
Multiprofessional follow-up ophthalmology outpatient appointment	87.00	NHS Reference Costs[22]
Latanoprost	23.64	*British National Formulary*[49]

Costs of diagnosis pathway: current practice

The costs of the current practice diagnostic pathway are presented in *Table 44*. At hospital eye services, all individuals see a nurse, who will perform a VA examination, and a technician, who will perform a visual field test. It was assumed that the VA test would take 10 minutes of a band 5 (mid-point scale) nurse's time and the visual field test would take 15 minutes of a band 3 (mid-point scale) technician's time. The unit costs for these were taken from Agenda for Change[47] and inflated to 2012–13 prices. All individuals will then see a clinician, and the cost of this was based on the NHS Reference Cost (HRG WF01B) of a first consultant-led ophthalmology outpatient appointment.

Costs of diagnosis pathway: triage strategies

The costs of the GATE triage diagnostic strategies are specified in *Table 45*. All individuals will see a nurse, who will perform a VA and an IOP test. It was assumed that this would take 10 minutes of a band 5 (mid-point scale) nurse's time. All patients would then go on to have one of the four index tests (diagnostic technologies). We assumed that these imaging tests would be performed by a band 3 technician (mid-point scale) and would take 15 minutes of staff time. As stated previously, the unit costs of staff time were calculated from Agenda for Change[46] and inflated to 2012–13 values.

The capital costs for the UK for the OCT Spectralis® (Heidelberg Engineering, Heidelberg, Germany) and HRT-III diagnostic imaging technologies and associated installation and maintenance costs were obtained from Heidelberg Engineering Ltd (www.HeidelbergEngineering.co.uk) (Tosh Vadhia, Regional Business Manager – South, 2013, personal communication). These initial outlay costs were annuitised over the useful working lifespan of the piece of equipment (assumed to be 10 years for all equipment) applying an annual discount factor of 3.5%[47] to account for the opportunity cost of the investment over time. The equivalent annual cost of each piece of equipment was divided by its estimated maximum number of uses per annum (from NHS providing units and expert opinion) to give cost per use estimates. The expected number of uses per annum was based on 253 working days per year, with each use taking a 15-minute slot over a 7.5 hour working day. This assumption was based on information provided by Moorfields Eye Hospital NHS Foundation Trust (Edward White, Chief Ophthalmology Technician, 2013, personal communication). During the course of the study, we were unable to obtain data on capital cost of the GDx diagnostic technology. As such, we assumed that, because of the competitive nature of the pricing from suppliers to the NHS, this technology had the same capital, installation and associated maintenance contract costs as the HRT-III machine.

In each triage diagnostic strategy, patients who were diagnosed with a positive composite test result were referred for a first consultant-led ophthalmology outpatient appointment, the cost of which was based on NHS Reference Costs (HRG WF01B).[22] This outpatient visit would also involve visual field testing by a technician (costs as for the standard care strategy detailed above). Thereafter, those who were identified by the ophthalmologist as being normal were then assumed to be discharged from secondary care.

Costs of treatment

Table 46 shows costs of treatment, which are separated into two distinct categories: those related to glaucoma-related states (mild, moderate, severe and sight impaired) and those for the 'at risk of glaucoma' state.

The costs of treating the glaucoma-related states (mild, moderate, severe, sight impaired) were taken from a related study[18] and inflated to 2013–14 prices. The authors used costs estimates based on the study of Traverso *et al.*,[50] which was a Europe-based study and includes data for the UK by severity of glaucoma. Treatment costs related to the 'at risk of glaucoma' state (i.e. individuals who are glaucoma suspects or

diagnosed with OHT) were based on a number of assumptions and expert opinion and were micro-costed to get an average annual cost per patient. It was assumed that all individuals in the 'at risk of glaucoma' state would be given an annual multiprofessional follow-up ophthalmology outpatient appointment, the cost of which was taken from NHS Reference Costs (WF02 A).[22] Furthermore, it was assumed that all individuals with OHT would be treated (based on advice from our expert advisory group) with latanoprost for the rest of their lives or until their condition progressed, with annual costs of £23.64.[49]

Estimation of utilities used within the model

Quality-adjusted life-years are calculated by weighting life-years with utility values, to reflect individuals' preferences for the health-related quality of life that they experience. There are various methods and tools that can be used to elicit utility values. NICE recommends, in its methods guide,[48] the use of the European Quality of Life-5 Dimensions (EQ-5D).

Previous research by members of the study team used the EQ-5D to value quality-of-life states for those with mild, moderate or severe glaucoma and sight impaired and these data were used in the model to value time in these health states. The EQ-5D 3 Level data were obtained from responses from 640 participants with OHT and glaucoma sampled from a secondary glaucoma service.[42] Similar to the study by Burr *et al.*,[42] who suggested that the degree of visual impairment for mild glaucoma is minimal, it was assumed that the score for those individuals in the 'at risk of glaucoma' state would be the same as the score for those with mild glaucoma. *Table 47* shows the utility weights used in the model.

Validation of the model

Our model was developed from that successfully used by Burr *et al.*[18] Developing the model from a pre-existing model meant that much of the structure had been previously validated. However, this approach also meant that there was no scope to make methodological changes to the way the previous model was implemented. Therefore, the Markov model was developed in TreeAge (TreeAge Software, Inc., Williamstown, MA, USA) 2013 using the same core structures and transition probabilities as Burr *et al.*[18] TreeAge is a frequently used tool for the type of model used in the economic evaluation and allows the documentation of our model and simplifies its use by other researchers.

To validate the model structure where changes were made to that of Burr *et al.*,[18] a simple Markov model was developed in R (The R Foundation for Statistical Computing, Vienna, Austria) in order to make comparisons with the model developed in TreeAge.

TABLE 47 Utility weights used in the model

Health state	Utility weight	Source/note
Normal	1	Assumption
Mild glaucoma	0.8371	Burr *et al.* 2012[42]
Moderate glaucoma	0.7919	Burr *et al.* 2012[42]
Severe glaucoma	0.7156	Burr *et al.* 2012[42]
Sight impaired	0.5367	Burr *et al.* 2012[42]
At risk of glaucoma	0.8371	Assumed equal to glaucoma mild individuals

Base-case analysis

The base-case analysis was run for a cohort of 40-year-old males. Although the choice of this start age was arbitrary, it was felt that it covered the range over which diagnostic strategies for glaucoma might be considered, and would cover most of prevalent cases of glaucoma, which is an age-related disease. Sex-specific variables were not available for any of the model parameters except for mortality, and a decision was made to use male mortality rates in the base-case analysis, consistent with good modelling practice, as they are a conservative assumption for this enhanced case detection study. The model was run for a range of possible prevalence values and for a 50-year time horizon. Cycle length was set at 1 year. Costs are presented in 2012–13 UK pounds sterling and effectiveness in QALYs. A discount rate of 3.5% for costs and benefits was used following guidelines for technology assessment by NICE.[48] The results are presented in incremental cost-effectiveness ratios (ICERs). This measure is a ratio of the difference in costs divided by the difference in the effectiveness between two alternative strategies. These data can be interpreted as how much society would have to pay for an extra unit of effectiveness. Central to the assessment of cost-effectiveness is the value that society would put on gaining an additional QALY. NICE states that 'Below a most plausible ICER of £20,000 per QALY, judgements about the acceptability of a technology as an effective use of NHS resources are based primarily on the cost-effectiveness estimate.'[48] Between £20,000 per QALY and £30,000 per QALY, judgements about the acceptability of the technology should take into account factors such as

- the degree of uncertainty surrounding the calculation of ICERs
- the innovative nature of the technology
- the particular features of the condition and population receiving the technology
- where appropriate, the wider societal costs and benefits.

Above an ICER of £30,000 per QALY, the case for supporting the technology on these factors has to be increasingly strong.[47] In the absence of a more definitive statement this report focuses on a willingness-to-pay threshold of £30,000 for a QALY.

Sensitivity analysis

We addressed uncertainty by conducting deterministic (e.g. one-way) sensitivity analyses. In consultation with the independent advisory group, the following deterministic sensitivity analyses were considered:

1. The base-case analysis assumed that the annual probability of having an eye test is 31.2%. All patients who are discharged by the diagnosing clinician or discharged by the triage station for the triage strategies would therefore be expected to be picked up in the community and would return to the secondary care triage station approximately every 3 years. In this analysis, based on clinical opinion, the impact of changing this probability and thus the diagnostic screening interval within a range of 1–10 years inclusive was explored.
2. In the base case, the diagnostic triage strategies were micro-costed and included staff time and capital costs of the diagnostic technologies. However, owing to the relatively large cost differential of these triage strategies compared with current practice, it was deemed appropriate to explore the effects on cost-effectiveness of introducing an NHS Reference Cost for a non-consultant-led first outpatient appointment (£85) to the costs of the triage strategies. This was further varied from £10 to £85 in £5 intervals to explore if this changed either the diagnostic strategies that were deemed cost-effective or the magnitude of effect.
3. The base-case analysis included a cohort of men with an age of 40 years to be modelled for 50 years. The impact of modelling older cohorts of men was explored by varying the start age from 45 to 70 years in 10-year intervals.

4. The base-case analysis was conducted on the basis that all glaucoma patients and those at risk of glaucoma (including glaucoma suspects, OHT and PAC) would be monitored and treated depending on their definitive diagnosis. It was discussed and agreed in a meeting between the study team and the independent steering committee that there was a need to explore the effects of a hypothetical secondary care service where those patients diagnosed as 'at risk' would be discharged from the service, thus potentially reducing the diagnostic, monitoring and/or treatment costs.
5. The base-case analysis assumed that clinicians were 100% sensitive and specific in their diagnosis of patients. The sensitivity and specificity was varied between 0.85 and 1 to explore the impact for patients who would not always being seen in secondary care by an ophthalmologist with glaucoma expertise and thus having 100% diagnostic accuracy.
6. A threshold analysis was conducted in order to explore the impact of increasing the costs of the triage strategies and discharging those patients that are given a diagnosis of 'at risk of glaucoma'.
7. The base-case analysis incorporated point estimates for the sensitivities and specificities of each of the imaging technologies that were estimated from the GATE study. We varied sensitivity and specificity of each triage strategy to create a best-case diagnostic scenario (+ 10% sensitivity and + 5% specificity) and a worse-case diagnostic scenario (–10% sensitivity and –5% specificity) for each of the imaging technologies as shown in *Table 48* to explore the impact on the ICERs. These values were decided on by the research study team on the basis of variations in the CIs in the base-case analysis.
8. The base-case analysis assumed the prevalence of glaucoma in the referred population, which was estimated from the GATE study. However, no referral refinement schemes were in place during the GATE study. Other measures to improve the accuracy of glaucoma referrals are constantly being explored, with a reduction in false-positive rates. The impact of adding an imaging-based composite triage system to a referred population with lower false-positives rates was explored by decreasing the proportion of normal diagnoses in the cohort from 0.412 to 0.212 and increasing the glaucoma prevalence from 0.17 to 0.27 and the 'at-risk' group from 0.418 to 0.518.
9. The base-case analysis assumed that the utility weights for the 'at-risk' health state were the same as mild glaucoma in the absence of literature addressing this issue. We explored the impact of a utility weight for the 'at-risk' health state being the same as normal health state.

TABLE 48 Alternative best case and worse case sensitivity and specificity values used to explore uncertainties in point estimates

Technology	'Glaucoma' sensitivity	'At-risk' sensitivity	'Normal' specificity
HRT-MRA			
Base case	0.99	0.97	0.3
Best case	1	1	0.35
Worst case	0.89	0.87	0.25
HRT-GPS			
Base case	0.99	0.97	0.28
Best case	1	1	0.33
Worst case	0.89	0.87	0.23
GDx			
Base case	0.88	0.77	0.51
Best case	0.98	0.87	0.56
Worst case	0.78	0.67	0.46
OCT			
Base case	0.97	0.87	0.35
Best case	1	0.97	0.4
Worst case	0.87	0.77	0.3

Chapter 7 Economic evaluation results

This chapter reports the results of the cost–utility analysis for four alternative triage strategies that incorporate each of the imaging tests evaluated in the GATE study (combined with IOP and VA data) to identify appropriate referrals to hospital eye services, compared with current practice, which is that all referred patients undergo assessment and diagnosis by a clinician in hospital eye services. Expected cost and expected QALYs, as well as ICERs, are presented for the base-case analysis and for sensitivity analyses conducted to explore uncertainties. Unless stated, ICERs are reported against the next least costly non-dominated strategy.

Base-case analysis

The base-case analysis was conducted for a cohort of male patients with a starting age of 40 years, who were assumed to have an eye test approximately once every 3 years, and clinicians in hospital eye services were assumed to have perfect diagnostic ability. *Table 49* shows the cost-effectiveness results for the base-case analysis. All triage strategies were less costly than the current strategy, but the triage strategies resulted in fewer expected QALYs than the current strategy when a perfect diagnosis by the clinician was assumed. Triage with GDx was the strategy with lowest expected cost, followed, in order, by triage with OCT, HRT-MRA and HRT-GPS. Triage with OCT was extendedly dominated (i.e. a combination of triage with GDx or HRT-MRA could, in theory, produce more QALYs at lower expected costs than triage only with OCT alone). Triage with HRT-GPS strategy was dominated by HRT-MRA (i.e. HRT-GPS was more costly but did not produce more QALYs than HRT-MRA). This is further illustrated in *Figure 27*.

Incremental cost-effectiveness ratios were calculated for all non-dominated strategies. The ICER reported for current practice (£156,985) represents the comparison between HRT-MRA and current practice. It should be noted that the interpretation of this ICER is slightly different from the usual case. In moving from current practice to HRT-MRA, savings would be expected, but at the expense of lost QALYs.

The usual willingness-to-pay threshold value for an additional QALY has been stated to be around £30,000 for the UK.[47] However, it is not clear what decision rule should be applied when resources are saved in exchange for fewer QALYs. One possible interpretation is that of a similar threshold (e.g. £30,000 saved at the expense of a QALY), and this has been adopted in this chapter. Therefore, with this interpretation, adopting a triage with HRT-MRA strategy would be worthwhile (e.g. resources would be freed and could be used elsewhere in the health-care system to obtain QALYs at the threshold value of £30,000 per QALY).

TABLE 49 Incremental cost-effectiveness ratios: base case

Intervention	Cost (£)	QALYs	ICER
GDx	2791	19.7701	–
OCT	2917	19.7746	Extendedly dominated[a]
HRT-MRA	2952	19.7771	22,904
HRT-GPS	2961	19.7771	Dominated[b]
Current practice	3084	19.778	156,985

a Extendedly dominated: a combination of a less costly and less effective intervention and a more costly and more effective intervention would be more efficient.
b Dominated: an intervention is more costly but is less effective or as effective as an intervention that is less costly.

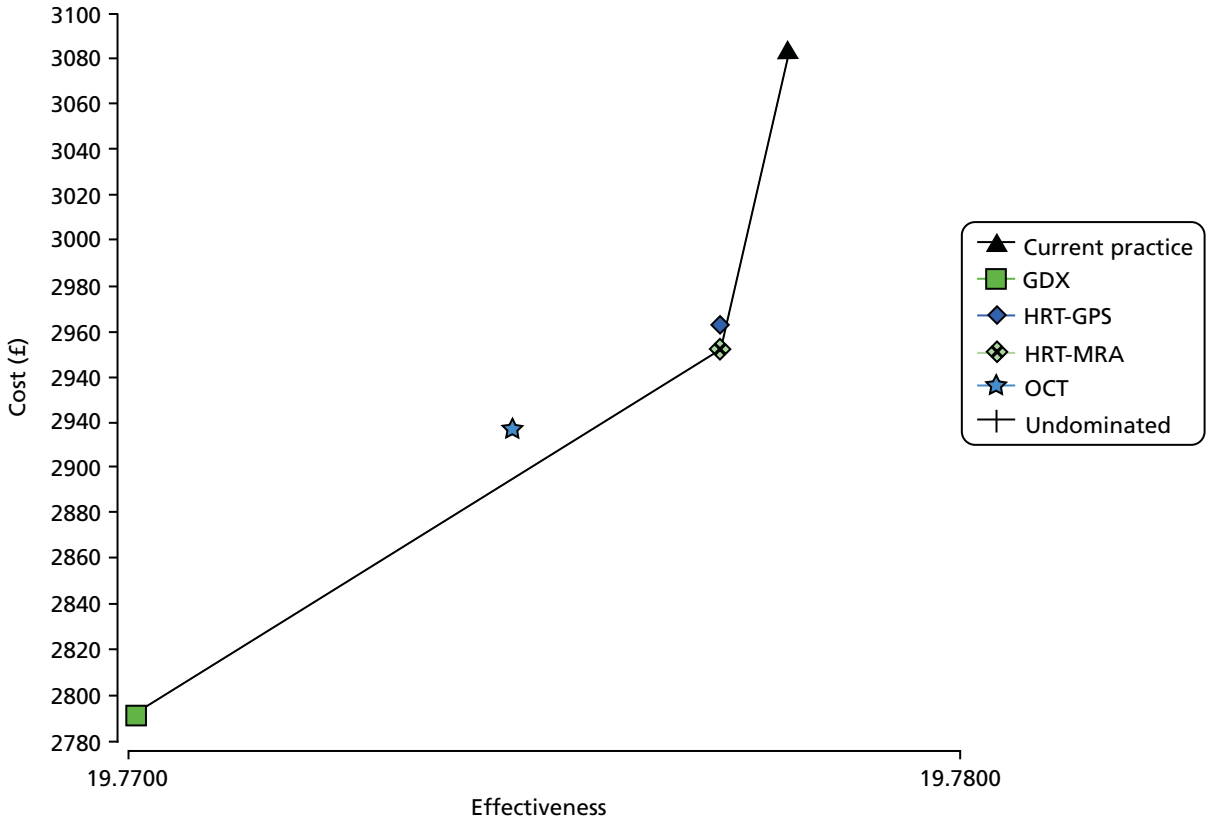

FIGURE 27 Base-case cost-effectiveness analysis results.

As shown in *Figure 27*, the results show that GDx is the least costly, least effective strategy and that OCT is extendedly dominated by GDx and HRT-MRA. This means that if it was possible to provide a mix of GDx and HRT-MRA, then a combination of provision of these two strategies would be dominant. Therefore, in economic evaluation we can disregard OCT from further consideration. In considering if it is worthwhile providing HRT-MRA in preference to GDx, we refer to the ICER. Relative to GDx, the ICER of HRT-MRA is £22,904 and is below the typical £30,000 value considered to be cost-effective in the UK.[48] In other words, moving from a triage strategy with HRT-MRA to GDx would save only £22,904 but at the expense of a QALY. Given the £30,000 threshold, any saved resources would not be sufficient to allow the QALY lost to be regained elsewhere.

Sensitivity analyses

A number of sensitivity analyses were performed as described in the methods (see *Chapter 6*).

Changes to the annual probability of having an eye test

The base-case analysis assumed that the annual probability of having an eye test by a community optometrist is 31.2%. All patients who are discharged by the diagnosing clinician, or by the triage station for the triage strategies (false negatives), would therefore be expected to be picked up in the community and subsequently referred back to the triage station at hospital eye services approximately every 3 years. We assumed that the community optometrist would identify a potential abnormality and subsequently refer the patient back to hospital eye services. In this sensitivity analysis, the impact of changing the annual probability of attending a community optometrist was explored. The annual probability was varied from 10% to 100% inclusive, corresponding to a return period decreasing from 10 years to 1 year. Note that, as the annual probability increases, the time to return to community optometrist decreases. As shown in *Table 50*, as the annual probability increases, both costs and QALYs increase but the savings realised (at the expense of a QALY) decrease. For instance, for HRT-MRA changing from a 20% probability (once every

TABLE 50 Incremental cost-effectiveness ratios for the cohort of 40-year-old males by varying annual probabilities of having a community optometrist eye test

Probability (%)	Strategy	Cost (£)	QALYs	ICER
10	GDx	1853	19.7253	–
	OCT	1960	19.7295	25,407
	HRT-MRA	1989	19.7313	15,503
	HRT-GPS	1992	19.7313	Dominated[a]
	Current practice	2038	19.7320	71,187
20	GDx	2451	19.7527	–
	OCT	2564	19.7165	Dominated[a]
	HRT-MRA	2596	19.7596	20,876
	HRT-GPS	2602	19.7596	Dominated[a]
	Current practice	2684	19.7604	106,392
30	GDx	2763	19.7686	–
	OCT	2886	19.7731	27,427
	HRT-MRA	2921	19.7756	13,738
	HRT-GPS	2930	19.7756	Dominated[a]
	Current practice	3048	19.7765	150,869
40	GDx	2972	19.7794	–
	OCT	3111	19.7837	32,321
	HRT-MRA	3149	19.7862	15,635
	HRT-GPS	3162	19.7862	Dominated[a]
	Current practice	3317	19.7870	208,159
50	GDx	3134	19.7873	–
	OCT	3292	19.7913	39,267
	HRT-MRA	3335	19.7936	18,788
	HRT-GPS	3350	19.7936	Dominated[a]
	Current practice	3543	19.7943	282,447
60	GDx	3271	19.7932	–
	OCT	3449	19.7969	48,375
	HRT-MRA	3497	19.7990	23,231
	HRT-GPS	3516	19.7990	Dominated[a]
	Current practice	3746	19.7996	377,466
70	GDx	3393	19.7978	–
	OCT	3593	19.8012	59,823
	HRT-MRA	3647	19.8030	29,027
	HRT-GPS	3668	19.8030	Dominated[a]
	Current practice	3937	19.8036	495,605
80	GDx	3505	19.8015	–
	OCT	3728	19.8045	73,741
	HRT-MRA	3788	19.8061	36,177
	HRT-GPS	3813	19.8061	Dominated[a]
	Current practice	4119	19.8067	637,178

continued

TABLE 50 Incremental cost-effectiveness ratios for the cohort of 40-year-old males by varying annual probabilities of having a community optometrist eye test (*continued*)

Probability (%)	Strategy	Cost (£)	QALYs	ICER
90	GDx	3611	19.8044	–
	OCT	3858	19.8071	90,141
	HRT-MRA	3924	19.8086	44,594
	HRT-GPS	3952	19.8086	Dominated[a]
	Current practice	4297	19.8091	800,615
100	GDx	3713	19.8067	–
	OCT	3983	19.8092	108,907
	HRT-MRA	4057	19.8106	54,140
	HRT-GPS	4088	19.8106	Dominated[a]
	Current practice	4471	19.8110	983,958

a Dominated: an intervention is more costly but is less effective or as effective as an intervention that is less costly.

5 years) to 10% (once every 10 years), savings (at the expense of a QALY) decreased from £106,392 to £71,187. This is driven by a reduction in costs of the current practice and, since glaucoma progresses relatively slowly, there is only a small reduction in QALY for missed cases. Therefore, any reduction in total QALYs is more than offset by a reduction in costs.

Regardless of the annual probability of having an eye test, HRT-GPS is always dominated as this strategy is always more expensive and less effective than HRT-MRA. Moreover, when a higher proportion of the cohort comes back every year, it is less clear which triage strategy should be adopted. The extreme case is for the cohort to come back every year (100% annual probability), in which case adopting a triage strategy with HRT-MRA would represent savings of £983,958, but moving from HRT-MRA to OCT and from OCT to GDx would account for savings of £54,140 and £108,907, respectively, but at the expense of a QALY. Therefore, at a willingness-to-pay threshold value of £30,000 per QALY, GDx-based triage should be adopted. It should be noted that this is an extreme example.

Changes in the costs of the triage strategies

The costs of the triage strategies included in the base-case analysis were estimated on the basis of a bottom-up approach to costing and were therefore micro-costed. Owing to the relatively large cost differential between the triage strategies and current practice and that NHS secondary care providers charge for a non-consultant-led outpatient appointment, the effects of introducing an NHS Reference Cost for a non-consultant-led first outpatient appointment (£85) was explored.[22] The results are presented in *Table 51*.

These data suggest that increasing the cost of the triage strategies by including a NHS Reference Cost renders all strategies dominated by current practice. On the basis of this result, a threshold analysis was performed to explore the maximum NHS Reference Cost which could be applied to the triage strategies for them to become undominated compared with current practice. The additional cost was varied from £10 to £85 in £3 intervals. The results are presented in *Appendix 7* and suggest that, as the cost of the triage strategies increases, the incremental cost per QALY of current practice decreases. Once the reference cost of the triage strategies reaches £61, all triage strategies are dominated by current practice. The ICERs of current practice relative to GDx or OCT are below the value typically considered to be cost-effective in the UK[48] and HRT-GPS is always dominated. Triage (with HRT-MRA) is cost-effective if the NHS Reference Cost tariff lies below £22, given a willingness-to-pay threshold of £30,000 per QALY.

TABLE 51 Incremental cost-effectiveness ratios for an increase to the unit costs of the triage strategies

Intervention	Cost (£)	QALYs	ICER
Current practice	3084	19.778	–
GDx	3217	19.7701	Dominated[a]
OCT	3339	19.7746	Dominated[a]
HRT-MRA	3372	19.7771	Dominated[a]
HRT-GPS	3381	19.7771	Dominated[a]

a Dominated: an intervention is more costly but is less effective or as effective as an intervention that is less costly.

Changes to the start age of the cohort

The base-case analysis included a cohort of men with an age of 40 years to be modelled for 50 years. The impact of modelling older cohorts of men was explored by varying the start age from 40 to 70 years in 10-year intervals for the same 50-years time horizon. The results are shown in *Table 52*.

As the starting age of the cohort increases, the incremental cost per QALYs of all interventions increases. Incrementally, as the cohort ages, both costs and QALYs decrease, but decreases in costs are outweighed by decreases in QALYs. This can be explained by the fact that treating younger populations yields larger health gains.

TABLE 52 Incremental cost-effectiveness ratios for changes in the age of the cohort at referral

Start age (years)	Intervention	Cost (£)	QALYs	ICER
40	GDx	2791	19.7701	0
	OCT	2917	19.7746	27,904
	HRT-MRA	2952	19.7771	13,896
	HRT-GPS	2961	19.7771	Dominated[a]
	Current practice	3084	19.7780	156,985
50	GDx	2390	17.2356	0
	OCT	2503	17.2392	30,995
	HRT-MRA	2535	17.2412	16,016
	HRT-GPS	2544	17.2412	Dominated[a]
	Current practice	2647	17.2419	165,616
60	GDx	1886	13.9949	0
	OCT	1983	13.9975	36,940
	HRT-MRA	2011	13.9989	20,152
	HRT-GPS	2018	13.9989	Dominated[a]
	Current practice	2098	13.9994	180,864
70	GDx	1318	10.3259	0
	OCT	1395	10.3274	49,717
	HRT-MRA	1419	10.3283	29,376
	HRT-GPS	1423	10.3283	Dominated[a]
	Current practice	1478	10.3285	211,668

a Dominated: an intervention is more costly but is less effective or as effective as an intervention that is less costly.

Changes to the patients treated: not treating patients 'at risk'

The base-case analysis was conducted on the basis that all glaucoma patients and those 'at risk of glaucoma' (including those with glaucoma suspect, OHT and PAC) would be monitored and treated depending on their definitive diagnosis. Owing to the potential overload of hospital eye services, it was agreed there was a need to explore the effects of a hypothetical hospital eye service where those patients diagnosed as 'at risk of glaucoma' would be discharged from the service, thus potentially reducing the diagnostic, monitoring and/or treatment costs. This analysis was conducted for all diagnostic strategies. The results are presented in *Table 53*.

Compared with base case, all strategies have lower expected costs and lower expected QALYs. This is explained by the lower proportion of individuals that are under treatment. In addition, the ICERs for all interventions have increased; in moving from current practice to HRT-MRA, HRT-MRA to OCT and OCT to GDx, savings are £752,248, £83,590 and £68,362, respectively, but at the expense of a QALY.

The higher ICERs are a result of fewer people 'at risk of glaucoma' being referred to hospital eye services for rediagnosis and further savings from the triage strategies are expected compared with base-case analysis. In other words, there is not much benefit from referral to the clinician for the 'at risk of glaucoma' group, as the decision would always be to discharge these patients and wait until conversion to glaucoma in order to start treatment. Given the value of all ICERs, all the triage strategies except the dominated HRT-GPS can be considered cost-effective given the typical thresholds used for decision-making in the UK.[48]

Changes to the sensitivity and specificity of the clinician

The base-case analysis assumed that clinicians were 100% sensitive and specific in their diagnosis of patients. In this sensitivity analysis, the sensitivity and specificity of clinicians was varied between 0.85 and 1 incrementally for all cohorts to explore the impact for patients of not always being seen in hospital eye services by a consultant ophthalmologist with glaucoma expertise, and thus having the possibility of reduced diagnostic accuracy. In the triage strategies, the diagnostic performance of the diagnosing clinician was not altered: for those referred (i.e. with a positive result of the triage testing) the clinician diagnosis was assumed to be perfect. The results are presented in *Tables 54* and *55*.

As the sensitivity of the clinician decreases from 1 to 0.95, the incremental cost per QALY of moving from HRT-MRA to current practice increases from £156,985 to £2,068,661. The incremental effect in terms of QALYs lost decreases as fewer patients are being correctly diagnosed. Similarly, incremental costs decrease; this is because fewer patients are seen by a clinician, which is only partially offset by cost increases as a result of more people being referred back for diagnostic testing with more expensive treatments. The incremental cost-effective ratio decreases and is very sensitive to the performance of the clinician as the QALYs lost outweigh the cost gains. Once the sensitivity drops below 0.95, current practice along with HRT-GPS becomes dominated by HRT-MRA, which is cheaper and either more or equally effective. This is because the cost savings realised by not being seen by a clinician are outweighed by the higher sensitivity of the alternative triage strategy (HRT-MRA). The ICERs of moving to any of the other triage strategies are below the values that are deemed acceptable in the UK to be cost-effective (£30,000).[48]

TABLE 53 Incremental cost-effectiveness for treating glaucoma patients only and discharging those 'at risk'

Intervention	Cost (£)	QALYs	ICER
GDx	2673	19.7392	–
OCT	2794	19.741	68,362
HRT-MRA	2824	19.7414	83,590
HRT-GPS	2833	19.7414	Dominated[a]
Current practice	2954	19.7415	752,248

a Dominated: an intervention is more costly but is less effective or as effective as an intervention that is less costly.

TABLE 54 Incremental cost-effectiveness ratios for changes in sensitivity of clinicians

Sensitivity	Intervention	Cost (£)	QALYs	ICER
0.85	GDx	2791	19.7701	–
	OCT	2917	19.7746	27,904
	HRT-MRA	2952	19.7771	13,896
	HRT-GPS	2961	19.7771	Dominated[a]
	Current practice	3025	19.7754	Dominated[a]
0.90	GDx	2791	19.7701	–
	OCT	2917	19.7746	27,904
	HRT-MRA	2952	19.7771	13,896
	HRT-GPS	2961	19.7771	Dominated[a]
	Current practice	3046	19.7763	Dominated[a]
0.95	GDx	2791	19.7701	–
	OCT	2917	19.7746	27,904
	HRT-MRA	2952	19.7771	13,896
	HRT-GPS	2961	19.7771	Dominated[a]
	Current practice	3066	19.7772	2,068,661

a Dominated: an intervention is more costly but is less effective or as effective as an intervention that is less costly.

TABLE 55 Incremental cost-effectiveness ratios for changes in specificity of clinicians

Specificity	Intervention	Cost (£)	QALYs	ICER
0.85	GDx	3029	19.7706	–
	OCT	3227	19.7752	42,496
	HRT-MRA	3283	19.7778	22,333
	HRT-GPS	3302	19.7778	1,028,309
	Current practice	3542	19.7789	221,312
0.90	GDx	2952	19.7704	–
	OCT	3126	19.7750	37,961
	HRT-MRA	3176	19.7776	19,709
	HRT-GPS	3191	19.7776	1,278,469
	Current practice	3395	19.7786	201,885
0.95	GDx	2872	19.7703	–
	OCT	3023	19.7748	33,106
	HRT-MRA	3065	19.7773	16,902
	HRT-GPS	3078	19.7774	2,027,006
	Current practice	3243	19.7783	177,341

As the specificity of the clinician decreases from 1 to 0.85, the incremental cost per QALY of moving from current practice to another triage strategy increases from £156,985 to £221,312. The incremental effect in terms of QALYs lost increases as more patients, although being incorrectly diagnosed, who would go on eventually to develop glaucoma or be 'at risk' are already being monitored/treated. Incrementally, costs are also increasing because more patients are being seen by a clinician and are subsequently monitored/treated. The costs are sensitive to clinicians' specificity, as the cost increases are outweighed by the QALY gains. The values of ICERs for current practice and HRT-GPS are above the acceptable threshold in the UK. That is, the savings, but with the loss of a QALY, of moving from current practice to HRT-GPS and from this strategy to HRT-MRA exceed the willingness to pay for a QALY and, therefore, a movement to HRT-MRA would be worthwhile.

Changes in the costs of the triage strategies and not treating patients 'at risk'

A threshold analysis was conducted in order to explore the impact of increasing the costs of the triage strategies and discharging those patients who are given a diagnosis of 'at risk of glaucoma.' Full results are presented in *Appendix 7*.

Adding an NHS Reference Cost of £85 to the cost of the triage station has the impact of current practice dominating all strategies. This prevails until the unit cost of triage station falls below £64, when both current practice and GDx become undominated. Reducing the reference cost to around £46, GDx becomes cost-effective compared with current practice. OCT also becomes undominated when the unit cost of the triage strategy falls to £34. Adding a lower reference cost to the triage station makes the triage strategies with lower expected cost worthwhile. This is reflected in the values of the ICERs that, compared with the usual threshold value for cost-effectiveness in the UK,[48] would render higher expected cost strategies to be not cost-effective and, therefore, would make a triage with GDx worthwhile.

Changes to the diagnostic performance of the imaging technologies

The base-case analysis incorporated point estimates for the sensitivities and specificities of each of the imaging technologies that were estimated from the GATE study. We explored the impact of changing these to a best-case diagnostic scenario and a worst-case diagnostic scenario for each of the imaging technologies (see *Chapter 6*) on the ICERs. These figures were based on the CIs of diagnostic performance measures used in the base-case analysis and the results are presented in *Table 56*.

The results show that in all scenarios, current practice always has the highest undominated ICER, as it is always more costly and less cost-effective than any of the triage strategies. Furthermore, the order of the strategies, according to ascending cost, does not change, with GDx, even under a best-case scenario, always having the lowest expected cost and the fewest expected QALYs.

When considering the performance of OCT in a best-case scenario, it does not form part of the efficiency frontier and would never be considered as a triage strategy, as it is always dominated by other strategies. The worst-case scenario for OCT does not affect the ICER, as OCT was not on the base-case efficiency frontier.

Compared with base-case analysis, when the best-case diagnostic scenarios are applied to HRT-MRA and HRT-GPS technologies in turn, the particular triage technology either replaces the other as the dominant option or reinforces its position as the dominant technology. The results of the sensitivity analysis investigating the best-case scenarios show that the choice of strategies, in order of willingness to pay, is sensitive to the relative performance of HRT-MRA and HRT-GPS. Given the assumptions in the model about consultant performance, no strategy displaces it as the most effective treatment.

TABLE 56 Incremental cost-effectiveness ratios for exploring triage performance best- and worst-case scenarios

Strategy	Cost (£)	QALYs	ICER	Strategy	Cost (£)	QALYs	ICER
GDx best case				***GDx worst case***			
GDx	2778	19.7717	–	GDx	2696	19.7683	–
OCT	2917	19.7746	Extendedly dominated[a]	OCT	2917	19.7746	Extendedly dominated[a]
HRT-MRA	2952	19.7771	31,863	HRT-MRA	2952	19.7771	28,988
HRT-GPS	2961	19.7771	Extendedly dominated[a]	HRT-GPS	2961	19.7771	Extendedly dominated[a]
Current practice	3084	19.778	156,985	Current practice	3084	19.778	156,985
OCT best case				***OCT worst case***			
GDx	2791	19.7701	–	GDx	2791	19.7701	–
OCT	2928	19.7751	Extendedly dominated[a]	OCT	2925	19.7746	Extendedly dominated[a]
HRT-MRA	2952	19.7771	26,326	HRT-MRA	2952	19.7771	26,326
HRT-GPS	2961	19.7771	Extendedly dominated[a]	HRT-GPS	2961	19.7771	Extendedly dominated[a]
Current practice	3084	19.778	156,985	Current practice	3084	19.778	156,985
HRT-GPS best case				***HRT-GPS worst case***			
GDx	2791	19.7701	–	GDx	2791	19.7701	–
OCT	2917	19.7746	Extendedly dominated[a]	OCT	2917	19.7746	Extendedly dominated[a]
HRT-MRA	2952	19.7771	26,326	HRT-GPS	2921	19.7755	Extendedly dominated[a]
HRT-GPS	2965	19.7773	89,632	HRT-MRA	2952	19.7771	26,326
Current practice	3084	19.778	172,479	Current practice	3084	19.778	156,985
HRT-MRA best case				***HRT-MRA worst case***			
GDx	2791	19.7701	–	GDx	2791	19.7701	–
OCT	2917	19.7746	Extendedly dominated[a]	HRT-MRA	2905	19.7755	25,658
HRT-MRA	2955	19.7773	26,275	OCT	2917	19.7746	Dominated[b]
HRT-GPS	2961	19.7771	Dominated[b]	HRT-GPS	2961	19.7771	34,269
Current practice	3084	19.778	186,408	Current practice	3084	19.778	145,579

a Extendedly dominated: a combination of a less costly and less effective intervention and a more costly and more effective intervention would be more efficient.
b Dominated: an intervention is more costly but is less effective or as effective as an intervention that is less costly.

When the worst-case diagnostic scenarios are applied to all the imaging technologies in turn, with the exception of GDx and of OCT, which were dominated already, they all become dominated and are not cost-effective. This can be explained by the lower cost of the GDx imaging technology. However, HRT-MRA was always undominated, except in the worst-case diagnostic scenario, when it was replaced by HRT-GPS. This can be explained by the similarities in the diagnostic performance and CIs of these two imaging technologies. Identical to the base-case results, with the exception of reducing the diagnostic ability of HRT-MRA (see *Table 56*), GDx, HRT-MRA and current practice are all dominant strategies and have increasing ICERs relative to each other.

In summary, in terms of GDx and current practice having the lowest and highest ICERs, respectively, the base-case results are not sensitive to changes in the diagnostic accuracy of the imaging technologies. Similar to the base-case analysis, current practice is not deemed cost-effective in any scenario.[48] However, the results are sensitive to improvements in the diagnostic accuracy in all the imaging technologies. The corresponding ICERs rise and the best-case triage strategy becomes cost-effective. When the diagnostic accuracy of the imaging technologies is reduced, HRT-MRA remains the winning strategy. The exception to this is the worst-case scenario for HRT-MRA where HRT-GPS becomes cost-effective. This can be explained by the similarities in the diagnostic accuracy of these two technologies.

Changes to the prevalence of glaucoma and 'at-risk' groups in the referred population

The base-case analysis assumed that the prevalence of disease in the referred population was as found for the GATE study. We explored the impact of a more enriched referred population (with higher proportion of glaucoma and 'at-risk' patients and a lower proportion of normal patients) if the existing triage system was used alongside a referral refinement scheme to filter out normal cases before referral to secondary care. The results are reported in *Table 57* and show higher expected costs and lower expected QALYs for all strategies than the base-case analysis. This was expected as the proportions of glaucoma and 'at risk of glaucoma' individuals entering the model are higher than in the base-case analysis. In addition, and also compared with base-case analysis, triage strategies are less appealing (e.g. ICER for current practice compared with HRT-MRA of £156,985 for base case and £99,227 in *Table 57*); however, the ICER of £99,227 is still above the usual cost-effectiveness threshold.

Changes to the quality of life for the 'at-risk' health state

The base-case analysis assumed a quality of life for the 'at-risk' health state equal to the mild glaucoma health state (quality of life = 0.8371). We explored the impact of assuming that the 'at-risk' health state would have a quality of life equal to the normal health state (quality of life = 1). As expected, *Table 58* shows no changes in expected costs as well as higher values for expected QALYs for all strategies in the model. Moreover, there is no major impact on cost-effectiveness results, with ICERs being lower but close to the values observed for the base-case analysis. Hence, base-case results are robust to this sensitivity analysis.

TABLE 57 Incremental cost-effectiveness ratios of increasing the prevalence of glaucoma and 'at-risk' groups in the referred population

Intervention	Cost (£)	QALYs	ICER
GDx	3991	19.1070	–
OCT	4123	19.1131	Extendedly dominated[a]
HRT-MRA	4158	19.1163	18,152
HRT-GPS	4166	19.1163	Extendedly dominated[a]
Current practice	4266	19.1174	99,227

a Extendedly dominated: a combination of a less costly and less effective intervention and a more costly and more effective intervention would be more efficient.

TABLE 58 Incremental cost-effectiveness ratios of changing the quality of life for the 'at-risk' health state

Intervention	Cost (£)	QALYs	ICER
GDx	2791	20.1788	–
OCT	2917	20.1836	Extendedly dominated[a]
HRT-MRA	2952	20.1864	21,107
HRT-GPS	2961	20.1864	Dominated[b]
Current practice	3084	20.1873	142,873

a Extendedly dominated: a combination of a less costly and less effective intervention and a more costly and more effective intervention would be more efficient.
b Dominated: an intervention is more costly but is less effective or as effective as an intervention that is less costly.

Summary and discussion

This chapter reported the results of a cost–utility analysis of alternative composite triage strategies using alternative diagnostic imaging technologies compared with current practice for patients referred to hospital eye services for possible glaucoma.

The base-case results suggest that HRT-MRA is the most cost-effective strategy. Given that current practice represents standard care in the UK, large savings in costs (£156,985) could be made, but at the expense of a QALY. Furthermore, the ICER for current practice relative to HRT-MRA would exceed the value that is deemed to be cost-effective in the UK.

Another potential benefit is the release of clinicians' time, which could be used to deliver other interventions.

Moreover, the sensitivity analysis results show triage strategies to be a potential cost-effective use of resources if the triage station cost does not reach £30 per triage visit. However, sensitivity analysis results were inconclusive in signalling a unique cost-effective triage strategy. HRT-GPS was often dominated by HRT-MRA, but the expected QALYs that these two strategies produce were almost identical, with the difference in total expected costs at around £10, which is not surprising since the results were obtained from the same imaging machine.

Furthermore, on a cost-effectiveness basis, GDx (or even OCT on a few occasions) could not be completely ruled out. GDx is highly specific and in a resource-constrained health economy it could be an efficient use of resources. It should be noted, however, that clinically, this strategy may not be acceptable to clinicians and/or patients because of its poor diagnostic performance (with low sensitivity). Determining a minimum level of diagnostic accuracy that is acceptable for clinical staff and patient was beyond the aims of this study and could be the subject of further research.

The QALY outcomes of all strategies depend only on the sensitivities of the tests to identify glaucoma and those at risk of glaucoma. The sensitivities of the different triage strategies for glaucoma are very close to each other, with the exception of GDx, but there is a greater difference between the strategies in their ability to identify people at risk of glaucoma. The consequences, in QALY terms, of missing a diagnosis of glaucoma are greater than those that result from missing a diagnosis of being 'at risk of glaucoma'. For these reasons, the quality-of-life differences between triage strategies are small. The sensitivity of the triage strategies also means that the QALY differences between them and the base-case scenario are small. This was to a certain extent expected for a study in which triage strategies have similar diagnostic accuracies and a slow progression of disease. For example, this difference in the base-case analysis between current practice and HRT-MRA triage strategy was 0.0008 QALYs, representing less than 8 hours in full health. This small difference might make easier to accept a triage strategy that would result in loss of QALYs in exchange for potential savings.

Furthermore, the incremental cost-effectiveness of the triage strategies compared with current practice was very sensitive to costs included in the model. Unnecessary outpatient visits and associated treatment costs within current practice and, in particular, the costs of the actual triage strategies are model result drivers for the expected costs as well as the resulting ICERs. The cost-effectiveness of any triage strategy is heavily dependent on the unit cost of the triage station. As such, all these strategies were dominated by the current practice under the plausible assumption that an NHS provider of care would charge, for the triage station, an NHS Reference Cost tariff corresponding to an outpatient appointment. Indeed, current practice becomes dominant when the cost of an outpatient appointment increases to £61 and above.

A key assumption used in the model was that clinicians are 100% accurate in their diagnostic ability. Relaxing this assumption further increased the ICERs of current practice relative to other triage strategies above a level that would be deemed to be cost-effective in the UK.[48] Even under extreme scenarios, in which the diagnostic accuracy of the triage strategies was reduced, current practice could not be deemed the most cost-effective. Hence, in terms of diagnostic accuracy, no plausible scenarios rendered current practice the most cost-effective. A probabilistic sensitivity analysis was therefore not warranted. Only when the costs of the triage strategies increased with an NHS Reference Cost did current practice become cost-effective.

The strengths of this research are that an economic model has been developed and analysed using good modelling research practice.[51,52] The cost-effectiveness of the different imaging technologies and their subsequent care management pathways was assessed using a multistate Markov model. This modelling approach is highly relevant, as glaucoma is a chronic condition, which progresses slowly over time, allowing the model to reflect the timing of both diagnostic testing and disease progression following the initial diagnostic strategy. Furthermore, we believe that this is the first economic evaluation of these interventions to be conducted in this context.

There are limitations to this research. A key issue for the study is paucity of data regarding parameter inputs used in the model. As stated in the introduction (see *Chapter 1*), there is a lack of evidence regarding the diagnostic accuracy of imaging techniques in a triage setting and thus the parameter estimates regarding this have been based on the GATE study alone and not from multiple studies. Furthermore, the diagnostic accuracy of clinicians has been assumed to be perfect but explored in sensitivity analysis.

Only very limited data on the costs of diagnosis and treatment were available and, although efforts were made to identify the best data applicable to the UK, these were sparse. The model estimates would be more robust if further data were to become available and as previously stated by Burr *et al.*,[18] consideration should be given whether or not further primary research is needed. The model was very sensitive to the costs of the triage strategies and as stated above, adding additional costs to their unit costs renders triage not cost-effective compared with current practice.

The quality and usefulness of the economic model is dependent not only on the quality of the data, but also on the way in which the data are used. The data requirements and the use of the data were determined by the structure adopted for the model. The development of the economic model was, as described in *Chapter 6*, based on discussions with a number of key stakeholders. It then underwent a prolonged period of refinement during which the care pathways were critically examined and refined. The model structure applies to a UK context and may not be relevant to other country settings, although other strategies could be developed and readily added to the model.

As described in *Chapter 6*, the model structure was developed so that the assumptions made in the base-case analysis could be explored in future work. For example, in the base-case analysis it was assumed that the clinician would make a perfect diagnosis. The model structure has allowed for the possibility that this will not be the case and that the clinician might possibly initiate treatment when it is not required (a false positive) and fail to diagnose some cases of glaucoma (a false negative).

The model is a simplification of the care pathways that may follow. For example, the model structure does not include all possible health states that may be relevant in context, such as misdiagnosis of those at risk of glaucoma as true positives. A second simplification made in the model was the relatively small number of stages used to reflect the progression of this chronic condition. While this assumption may fail to represent the subtleties of disease progression, it was believed the health states were sufficient in number to reflect the relevant issues needed for this economic evaluation.

Estimates of the risk of progression between health states are based on data from one eye and do not necessarily represent the definition of the health states in the model, which is based on binocular visual field loss. The fellow eye may not have such advanced disease as the study eye and, therefore, the quality-of-life loss might be overestimated. While this is a limitation of the study, the alternative of using the better eye for the analysis would result in an underestimation of the risk of progressive binocular visual field loss. Furthermore, there were insufficient data to determine whether or not some of the parameter values varied between the stages of disease, for example the diagnostic performance of the diagnostic strategies. The model was, however, structured in such a way that, should such data become available in the future, the model could be readily adapted and the data incorporated.

A further simplification in the model structure was that, rather than modelling the full variety of treatments available for glaucoma, it has been assumed that the effect of treatment can be represented by a single relative effect size for treatment compared with no treatment. In addition, when interpreting the results of the economic evaluation it should be borne in mind that the estimates of cost-effectiveness relate to a male cohort. Sex-specific data were not available for any of the parameter estimates except for annual all-cause mortality.

Finally, there is no clear decision rule or willingness-to-accept threshold value to interpret cost–utility analysis results where savings are obtained at expense of QALY being lost. In this study, a similar threshold value to the one often used as willingness-to-pay for a QALY gained was assumed (i.e. £30,000). Although this is one value from many possible, in the great majority of the analyses the savings per QALY lost (ICERs) were well above this threshold. In other words, the adopted interpretation would be consistent with higher willingness-to-accept value should this become common practice.

Chapter 8 Discussion

The GATE study was a large multicentre study designed to evaluate the performance of a triage test for patients referred to hospital eye services with possible glaucoma. The triage test would include VA and IOP measurements, and one of four imaging tests from three different instruments [the HRT-III confocal scanning laser ophthalmoscope (HRT-GPS and HRT-MRA), GDx scanning laser polarimeter and a SD-OCT (Spectralis®)]. There were two diagnostic evaluations: (1) an estimation of the ability of imaging technologies to diagnose glaucoma at an eye level and (2) an assessment of the performance of a triage test. All instruments are currently available in the NHS.

Regarding the diagnostic ability to detect and rule out glaucoma, all four imaging tests had some value; HRT-MRA had the highest sensitivity but lower specificity than other tests. In contrast, GDx had the best specificity but the lowest sensitivity. HRT-GPS results were similar to HRT-MRA results, as might be expected given that their analysis is based on imaging the same structure (i.e. the optic disc). The sensitivity of OCT was very similar in magnitude to its specificity. OCT gave the lowest percentage of low-quality imaging results, and GDx the highest, according to the image quality classification provided in the device software. Average time taken to conduct the tests was lowest for OCT. Patient preference tended to favour OCT followed by GDx, although almost half of participants did not have a preference.

A number of sensitivity analyses were carried out to assess the robustness of the findings of the default analysis. Varying the test definition of an abnormal imaging result by including the borderline category had the expected impact of improving the detection of glaucoma, although at the expense of more non-glaucoma cases being falsely classified as glaucoma. The impact of combining two imaging tests improved detection of glaucoma, but the improvement was marginal and smaller than the loss of specificity.

Regarding the triage analysis, four composite triage tests – which each consisted of an imaging test, IOP measurement and VA assessment – were compared with regard to their performance for determining who should be referred to a clinician for further assessment or discharged. All four triage tests had value in terms of ruling in and ruling out the need for referral to a clinician. The diagnostic performance of the triage tests differed substantially. HRT-GPS with HRT-MRA consistently having the highest sensitivity across analyses but at the cost of lower specificity than other tests. In contrast, GDx consistently had the best specificity though the lowest sensitivity. OCT generally had similar levels of sensitivity and specificity. A number of sensitivity analyses were carried out that confirmed the robustness of the findings of this default triage analysis.

The economic analysis suggested that a composite triage test, introduced into the care pathway for patients referred from community with possible glaucoma, appears to be cost-effective compared with current practice, in which all referred patients are seen by a clinician. Our findings are based on a relatively inexpensive composite triage test (< £30) including an imaging technology, IOP and VA testing.

Triage using HRT-MRA was the most cost-effective strategy. Given that current practice in the model represented standard care in the UK, large savings in costs (£156,985) could be made for each QALY forgone. For the ICER, current practice, compared with HRT-MRA, would largely exceed the value that is deemed to be cost-effective in the UK. With the exception of GDx, the diagnostic accuracy of all the triage strategies and their unit costs are very similar. Using GDx in a triage test is the least costly and least effective diagnostic strategy but it was still cost-effective compared with current practice for a number of analyses.

A variety of sensitivity analyses were conducted. The ICER of the triage strategies compared with current practice was very sensitive to costs included in the model. With the exception of increasing, the costs of the triage stations to NHS commissioners, within the uncertainty analysis, triage was always more cost-effective than current practice. Furthermore, the present analysis is inconclusive on the decision about a particular imaging test to be included in a triage station. Further research on acceptability of the alternative imaging tests is warranted.

There are emerging models of eye care in the community that try to reduce the number of false-positive referrals to hospital eye services.[53–55] Their effectiveness, efficiency and acceptability need to be evaluated in primary research before implementing change. The GATE study provides robust data on how such services might be reconfigured.

Strengths and limitations

A number of strengths can be highlighted. GATE was a large prospective paired diagnostic study and it evaluated diagnostic tests in the desired setting. The benefit of the large sample size is reflected in the precision with which the sensitivity and specificity were calculated, with differences between every pair of tests identified for one if not both of sensitivity and specificity. McNemar's test was used to compare the sensitivity and specificity of the tests. Following the rationale of others in effectiveness studies, the paired comparisons were not adjusted for multicomparisons. Even if such a correction had been applied, such was the strength of evidence that there would still be evidence of differences in the diagnostic performance of the different imaging tests.

The population enrolled in GATE consisted of subjects without a known history of disease, which would reflect the potential clinical application of the triage test. Other reported studies evaluating the performance of diagnostic technologies have used a population of patients already diagnosed with glaucoma, which has a risk of selection bias. This study recruited patients before diagnosis, and the population tested had a broad spectrum of disease at presentation, from early through to severe glaucoma, and included a large percentage of healthy individuals. The healthy individuals in whom the test 'specificity' was determined were subjects referred from primary care with a possible glaucoma-related finding (either risk factor or suspected sign). Thus, the diagnostic performance reported here refers to a secondary care setting and may be different in an unselected population.

An intentional aspect of the study's design is the focus on both the diagnostic performance of imaging tests for the identification of individuals with glaucoma and the performance as a triage test where imaging tests would be used in conjunction with other routine measurements (IOP and VA). Both aspects are important for understanding the potential value of the imaging tests. We have also evaluated other important considerations for diagnostic technologies, such as interpretability, patient preference and time taken to perform the test.

The reference standard was provided by different ophthalmologists with glaucoma expertise. The ophthalmologists had been trained in the study protocols and agreed to a common set of criteria to define glaucoma and normality. By using different ophthalmologists working at different units, the results of the study are more likely to be generalisable than results from studies performed in a single unit. The participating units are likely to be representative of the NHS practice, including two district general hospitals and three academic units of different size: relatively small (Aberdeen), medium (Liverpool) and large (Moorfields).

The economic model was developed and analysed using good modelling research practice.[51,52] The cost-effectiveness of the different imaging technologies and their subsequent care management pathways were assessed using a multistate Markov model. This modelling approach is highly relevant as glaucoma is a chronic condition, which progresses slowly over time, allowing the model to reflect both the timing of diagnostic testing and the disease progression following the initial diagnostic strategy.

Among the limitations, we recognise that diagnosing glaucoma during the very early stage of disease is challenging, and ideally a longitudinal follow-up would provide the best possible reference standard. This was proposed by Medeiros *et al.*[34] who used optic nerve head progression on stereophotographic examination as the criterion for glaucoma diagnosis, but we could not contemplate this possibility in GATE, as years of follow-up would have been required. The reference standard was assumed to be perfect, although it is

widely recognised that diagnosis of glaucoma is difficult in early disease, and uncertainty exists even among specialists. While consensus was sought through structured training, some assessor differences may have remained between the sites. Adding central corneal thickness information for patients referred for high IOP could potentially add valuable information and help further refine the referral pathway of such patients.

There was lack of evidence base regarding some parameter inputs used in the economic model. Only very limited data on the costs of diagnosis and treatment were available and, although efforts were made to identify the best data applicable to the UK, these were sparse. Data with respect to health utilities were available, but it is unclear whether or not the EQ-5D is sensitive enough to detect clinically significant changes in glaucoma. The model is a simplification of the care pathways that may follow, with a relatively small number of stages used to reflect the progression of this chronic condition. Estimates of the risk of progression between health states were based on data from one eye and do not necessarily represent the definition of the heath states in the model, which is based on binocular visual field loss. A further simplification in the model structure is that, rather than modelling the full variety of treatments available for OAG, it has been assumed that the effect of treatment can be represented by a single relative effect size for treatment compared with no treatment.

Uncertainties

- The diagnosis, natural history and risk of conversion to glaucoma of untreated or treated patients classified as glaucoma suspects is unknown. It is likely this is a very heterogeneous group, as reflected in the categories of glaucoma suspect defined in GATE.
- The natural history and risk of conversion to glaucoma of untreated or treated patients with OHT undergoing standard care is unclear. Although there is evidence on the efficacy of treatment of OHT from large randomised controlled trials, the generalisability of their findings to routine clinical care in the NHS is ill defined.
- It is unclear how often people attend community optometrists for regular eye examinations. If they have glaucoma that is missed by the triage, it is unknown how quickly it would be detected by the optometrist and at what severity of disease. In our model we hypothesised that all those with a false-negative diagnosis at the triage stage would return to hospital eye services within 3 years.
- The triage analysis used the IOP information provided by a consultant ophthalmologist. A triage system would rely on IOP measurements taken by a technician or a nurse, and it is uncertain whether or not such IOP measurements, possibly obtained with different tonometers, will be significantly different and what impact this would have in the performance of the triage test. The diagnostic accuracy of clinicians is uncertain. Glaucoma is diagnosed clinically, relying on the experience of the examiner, and it is likely that the relative performance of the imaging technologies may be underestimated if the reference standard comparator consists of experienced glaucoma experts, as were used in GATE. Glaucoma in the NHS is diagnosed by a variety of health-care professionals, including optometrists, specialist nurses, senior ophthalmologists with variable glaucoma expertise and trainees.
- There are other OCT instruments in the market with glaucoma diagnostic capabilities and the results of this study using the Spectralis® device may not be fully applicable to other OCT technologies.

Chapter 9 Conclusions

Implications for health care

Automated imaging technologies can be effective tests to aid in the diagnosis of glaucoma among individuals referred from the community to hospital eye services with possible glaucoma. A model of care incorporating a triage composite test for diagnosing patients referred from the community appears to be cost-effective compared with current practice. Our findings are based on a relatively non-expensive composite triage test (< £30) including an imaging technology, IOP and VA testing. The most efficient strategy would include HRT-MRA imaging. However, a triage test would be associated with reduced health, and the acceptability of this option among users and clinicians has not been evaluated.

Recommendations for research

- Acceptability to patients and health-care providers of implementing an efficient triage glaucoma diagnostic system but with reduced health should be explored. A qualitative or mixed-methods study, for example including a discrete choice experiment and also incorporating public perspectives, would be suitable.
- Further data on the glaucoma disease progression under routine care, and specifically including patients classified as having glaucoma suspect or OHT, on associated utility, on the cost of providing health-care services and on sight loss are needed. A long-term longitudinal cohort study would be ideal to address these issues.
- Further investigation of varying the thresholds for classification of the imaging tests beyond the standard options presented in the software could be undertaken, as the standard classification may not be the one best suited to the population referred from the community to hospital eye services. Further analysis of GATE data or review of data from other relevant diagnostic studies would be able to answer this question.
- The effectiveness of implementing a triage test incorporating imaging, an IOP measurement and VA requires evaluation. A longitudinal diagnostic impact study is needed.

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Contributions of authors

Augusto Azuara-Blanco was the chief investigator of the study, had complete involvement and oversight of the study design, execution and data collection and provided clinical expertise, led the writing of all chapters with the exception of *Chapters 4–7* and was responsible for the final report.

Katie Banister was responsible for the day-to-day management of the study, contributed to the writing of *Chapter 2*, commented on all chapters and was responsible for the production of the final report.

Charles Boachie conducted the statistical analysis and contributed to the writing of *Chapters 4* and *5*.

Peter McMeekin developed the structure of the Markov model, conducted the economic analyses and contributed to the writing of *Chapters 6* and *7*.

Joanne Gray led the economic analysis and led the writing of *Chapters 6* and *7*.

Jennifer Burr provided clinical advice and methodological support through all stages of the project and commented on the final report.

Rupert Bourne, **David Garway-Heath** and **Mark Batterbury** were clinical leads, provided expert advice on clinical aspects of the study and commented on the final report.

Rodolfo Hernández had oversight of the health economic analysis, contributed to the writing of *Chapters 6* and *7* and commented on the report.

Gladys McPherson provided technical data collection expertise throughout the study and reviewed the final report.

Craig Ramsay provided methodological oversight through all stages of the project and commented on the final report.

Jonathan Cook provided methodological oversight for the whole project, led the writing of *Chapters 4* and *5*, contributed to *Chapter 2* and commented on the final report.

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Data sharing statement

All available data can be obtained from the corresponding author.

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Appendix 1 Information for patients

NHS Grampian

Evaluation of novel imaging techniques for the detection of Glaucoma.

Dear

Invitation to take part in a research study

I am currently undertaking a national study to evaluate the performance of three new automated eye tests for the diagnosis of glaucoma in conjunction with The Health Services Research Unit, University of Aberdeen. As you are coming to the eye out patients department for an appointment I would like to invite you to take part.

I have enclosed an information sheet about the study which will help you decide whether or not you would like to participate and would be most grateful if you could take a few minutes to read through the information.

If you agree to take part then you will be given three automated eye tests during your appointment which should take no longer than one hour to complete before being seen by the ophthalmologist as per a normal clinic appointment.

Although your involvement is very important to us we would like to stress that you are under no obligation to participate. We will be happy to discuss any aspect of the study with you at the clinic when we see you and if you have any questions about the study we will be pleased to answer them then.

Yours sincerely,

Augusto Azuara-Blanco
Consultant Ophthalmologist.

GATE study patient information leaflet

Evaluation of novel imaging techniques for the detection of Glaucoma (GATE study).

Information leaflet.

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish. Ask us anything that is not clear or if you would like more information. Take time to decide whether you wish to take part. Thank you for reading this.

What is the purpose of the Study?

Glaucoma can reduce vision and quality of life but if diagnosed early it can be treated and reduction of vision prevented. The main risk factor for a reduction in vision due to glaucoma is being diagnosed late and damage to the eyesight has already begun. New promising diagnostic imaging tests are available and are easy to perform. They use a laser to explore and analyse the structure of the optic nerve head and surrounding tissues in the back of the eye. However, which test is the best to use is uncertain at present and this project will evaluate the performance of three new imaging tests. If one of the tests proves to be accurate and easy to perform, it could be implemented in the community to reduce the risk of reduced vision from glaucoma.

Why have I been chosen?

As you are attending the eye out-patient clinic for an eye examination from an ophthalmologist we would like to invite you to take part.

Do I have to take part?

No. It is up to you to decide whether you take part. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part, you are still free to withdraw at any time and without giving a reason.

What will happen if I take part?

The study is carried out alongside your appointment in the local Eye Out-Patient Clinic. Depending on routine practice at your local clinic this may be one or two appointments. You will be given a visual fields test along with three imaging tests and finally a basic eye examination by an Ophthalmologist. The addition of the imaging tests may extend your appointment time by approximately one hour.

What do the imaging tests involve?

There will be three imaging tests carried out by a research technician. The imaging tests are non-invasive and do not usually require eye drops. During the test you will have to look at a fixation light for a short period whilst a series of images of the optic nerve head at the back of the eye are acquired. The imaging tests are rapid and take approximately 10 minutes to complete. In a small number of cases we may have to place some eye drops in your eyes to dilate your pupils. This can make it easier to take the image.

What are the possible disadvantages and risks of taking part in this study?

Most people will not need their pupils dilated. If we need to dilate your pupils it can sometimes cause some temporary blurring of vision and sensitivity to light. This is, however, a routine procedure which would normally be performed as part of your eye examination

Are there any benefits to taking part in the study?

There will be no direct benefit to yourself in taking part in the study, however if any of the tests prove to be accurate and easy to perform, they could be implemented in the community.

Will my taking part in this study be confidential?

All information which is collected about you for the study will be kept strictly confidential. Information for all participants in the study will be kept for a minimum of ten years in line with current research governance arrangements and then destroyed. Only researchers involved with the study will have access to your information

What happens to the results of the study?

The results of the research will be published in relevant scientific journals and a report will be sent to the funder of the research, the NHS Health Technology Assessment programme. We would also be happy to send you a short report when the study when the research is complete. You will not be identifiable in any publications from this research.

How do I Complain?

If you wish to complain or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal NHS complaints mechanisms are available to you.

Who has reviewed the study?

This study has been reviewed and approved by the North of Scotland Research Ethics Committee.

Thank you very much for considering taking part in this research.

Contact details for further information

Central office:

GATE Study Office
Health Services Research Unit
University of Aberdeen
Health Sciences Building
Foresterhill
Aberdeen AB25 2ZD
Tel: 01224 438196
Fax: 01224 438165
Email:gate@abdn.ac.uk

Local contact details:

[Contact details]
[for local researchers]
[Affix sticker here]

GATE study consent form

(Form to be on headed paper)

Participant Study Number: ☐☐☐☐☐

CONSENT FORM

Comparative study of new imaging technologies for the diagnosis of glaucoma: the GATE study

		Please initial box
1	I confirm that I have read and understand the information sheet dated ..... (version .....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
3	I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the University of Aberdeen, from regulatory authorities or from the NHS Trust/Health Board, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐
4	I understand that my personal details collected during the study will be held in a secure central database, and may be subject to audit and monitoring by University of Aberdeen or NHS Trust/Health Board staff, without breaching data confidentiality	☐
5	I agree to take part in the above study.	☐

Name of Patient		Date Signature

I confirm that I have explained to the person named above the nature and purpose of the GATE study and the procedures involved

Name of Person taking consent	Date	Signature

GATE study office, Health Services Research Unit, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD.
Tel: 01224 438196, Fax 01224 438165, Email: gate@abdn.ac.uk

Copies: Original to be returned to study office: 1 copy for patient; 1 copy to be filed with hospital notes

Appendix 2 GATE study case report forms

Glaucoma Automated Tests Evaluation

Inclusion criteria

- Adult patients (aged over 18 years old)
- New referral from primary care to glaucoma clinic

Clinic date

.....

Study Number	Patient Name	Year of birth	Gender M/F	Info. sheet sent	Date info. sent	Consented	*If not consented, state reason (A, B, C or D)*	*Assigned Test Order*		
								HRT	GDX	OCT
				Y N		Y N				
				Y N		Y N				
				Y N		Y N				
				Y N		Y N				
				Y N		Y N				
				Y N		Y N				
				Y N		Y N				
				Y N		Y N				
				Y N		Y N				
				Y N		Y N				

Reasons for not including

A: Non attendance (DNA/CNA)
B: Refusal – record reason if possible
C: Missed
D: Equipment not working (please record which machine is not working)

Research Officer Data Collection Form

Participant Study No

Research Officer Data Collection Form

CONFIDENTIAL

This study is funded by the NHS National Institute for Health Research Health Technology Assessment Programme

Research Officer Data Collection Form

Participant Study number | | | | | |

Date of Assessment D D / M M / Y Y Y Y

SECTION A - PATIENT DETAILS

CHI number (Scotland only) or NHS number | | | | | | | | | | |

Date of Birth D D / M M / Y Y Y Y

Gender ☐ Male ☐ Female

ETHNIC ORIGIN

Please note the following are the main classification categories used by the Census 2001. Please ask the patient how they would describe themselves.

Black or Black British-Caribbean	☐	
Black or Black British-African	☐	
Other Black Background	☐	Please specify _____
Asian or Asian British-Indian	☐	
Asian or Asian British-Pakistani	☐	
Asian or Asian British-Bangladeshi	☐	
Chinese	☐	
Other Asian Background	☐	Please specify _____
Mixed – White and Black Caribbean	☐	
Mixed – White and Black African	☐	
Mixed – White and Asian	☐	
White - British	☐	
Other	☐	Please specify _____

Has patient been fully consented? Yes ☐

Version 1 2 - 2 - 20-07-11

SECTION B – CLINICAL DATA

Referral Eye (please tick only one) Right ☐ Left ☐ Both ☐

IOP on referral (mmHg)

Right ☐ Left ☐

Method of assessment (please tick only one)

NCT ☐
GAT ☐
Other ☐ Please specify _____

Refraction

	+/-	Sphere		+/-	Cyl		Axis
Right eye	☐	☐☐ . ☐☐	/	☐	☐☐ . ☐☐	x	☐
Left eye	☐	☐☐ . ☐☐	/	☐	☐☐ . ☐☐	x	☐

Best corrected visual acuity (Snellen)

Right eye	Left eye
☐	☐

Visual fields *(Humphrey 24.2)*

SITA standard or SITA fast. Record reliability information defined by the Humphrey

Right Eye: Reliable ☐ Unreliable ☐ Not done ☐

Fixation losses	False pos errors (%)	False neg errors (%)	+/-	MD (dB)	PSD (dB)	VFI (%)
☐ / ☐	☐	☐	☐	☐	☐	☐

Left Eye: Reliable ☐ Unreliable ☐ Not done ☐

Fixation losses	False pos errors (%)	False neg errors (%)	+/-	MD (dB)	PSD (dB)	VFI (%)
☐ / ☐	☐	☐	☐	☐	☐	☐

Printout of Visual Fields for research site file attached to CRF. Yes ☐

SECTION C – IMAGING DATA

Test order

The order that tests should be performed is found on the study website clinic log for this study number. Please record the order in which the tests were performed (1=1st,2=2nd,3=3rd)

HRT ☐ **GDX** ☐ **OCT** ☐

HRT

Start time (24hr clock) H H : M M **End time** (24hr clock) H H : M M

Were pupils dilated? Yes ☐ No ☐

Right Eye: Completed ☐ Not performed ☐ Reason _____

Left Eye: Completed ☐ Not performed ☐ Reason _____

Raw data filename _____ Raw data saved to disk ☐ Hard copy report printed MRA right eye ☐ MRA left eye ☐ GPS ☐

GDX

Start time (24hr clock) H H : M M **End time** (24hr clock) H H : M M

Were pupils dilated? Yes ☐ No ☐

Right Eye: Completed ☐ Not performed ☐ Reason _____

Left Eye: Completed ☐ Not performed ☐ Reason _____

Raw data filename _____ Raw data saved to disk ☐ Hard copy report printed ☐

OCT

Start time (24hr clock) H H : M M **End time** (24hr clock) H H : M M

Were pupils dilated? Yes ☐ No ☐

Right Eye: Completed ☐ Not performed ☐ Reason _____

Left Eye: Completed ☐ Not performed ☐ Reason _____

Raw data filename _____ Raw data saved to disk ☐ Hard copy report printed (RNFL basic report OU) ☐

Has participant completed the GATE Participant Preference questionnaire? Yes ☐ No ☐

If No, why? _____

Participant Study No

Glaucoma Automated Tests Evaluation

Participant Preference Questionnaire

CONFIDENTIAL

This study is funded by the NHS National Institute for Health Research Health Technology Assessment Programme

Participant Study No

Participant Preference Questionnaire

Date of examination ☐☐ / ☐☐ / ☐☐☐☐

Now that you have had all three tests can you please give an order of preference from 1 for the most preferred test, to 3 for the least.

If you have no preference please tick the last box.

Optical Coherence Tomography

☐

Scanning laser polarimetry – GDx-VCC

☐

Heidelberg Retinal Tomography

☐

I have no preference ☐

Please note you may not have had your tests in the order above and may not remember which test is which. If you are unsure then ask the research nurse for help.

CLINICIAN CRF

CONFIDENTIAL

DO NOT LOOK AT IMAGING RESULTS BEFORE COMPLETING THIS FORM

Participant Study number | | | | | |

Date of Assessment D D / M M / Y Y Y Y

Glaucoma Automated Tests Evaluation

Clinician Name (Capitals) _____

IOP (mmHg)

Today	Right		Left	

DIAGNOSIS (tick only one category in each column)	**Right**	**Left**
Glaucoma		
Disc suspect		
VF suspect		
VF+disc suspect		
OHT (normal disc and field)		
PAC (normal disc and field)		
PAC suspect (normal disc and field)		
No glaucoma-related findings		
Undetermined (could not complete assessment)		

→ Severity of glaucoma

	R	**L**
Mild		
Moderate		
Severe		

Please specify reason

For glaucoma and suspects:		**R**	**L**
Please tick mechanism	Open angle		
	Angle closure		
	Other		

Co-morbidity – tick all that apply	**Right**	**Left**
AMD		
Cataract		
Neurological		
Other		

Please specify

ACTION (please tick)

Discharge? Yes ☐ No ☐

If NO please complete – tick only one box in each column

	Right	Left
Treat		
Monitor only		
Repeat assessment required		

Comments

Clinical diagnosis definitions

Glaucoma:
Evidence of glaucomatous optic neuropathy* and a characteristic visual field loss**

Glaucoma severity: according to Humphrey SITA standard perimetry of a reliable VF ***:

Mild: MD better than or equal to -6 dB;

Moderate: MD between -6.01dB and -12 dB

Severe: MD worse than or equal to -12.01 dB

Mechanism:

Open angle: includes POAG, NTG,

Angle closure: includes evidence of glaucomatous optic neuropathy combined with a characteristic visual field loss, and a closed anterior chamber angle (appositionally or synechial) in at least 270°

Other: pigmentary glaucoma, pseudoexfoliation glaucoma or any other type of glaucoma

Disc suspect: appearance suggestive of glaucomatous optic neuropathy but may also represent a variation of normality, with normal visual fields (with or without high IOP).

VF suspect: visual field loss suggestive of glaucoma, but may also represent a variation of normality, with normal appearance of the optic disc (with or without high IOP)

VF+disc suspect: both the optic disc and visual field have some features that resemble glaucoma but may also represent a variation of normality (with or without high IOP)

OHT: when both the visual field and optic nerve appear normal in the presence of elevated pressure, > 21 mmHg

PAC: Closed anterior chamber angle (appositionally or synechial) in at least 270°, and at least one of the following two: IOP > 21 mmHg and/or presence of peripheral anterior synechiae. Both visual field and optic nerve appear normal

PAC suspect: Closed anterior chamber angle (appositionally without any synechiae) in at least 270°, with IOP $\leq$ 21 mmHg. Both visual field and optic nerve appear normal

The decision to monitor/treat will be defined in accordance with the NICE guidelines

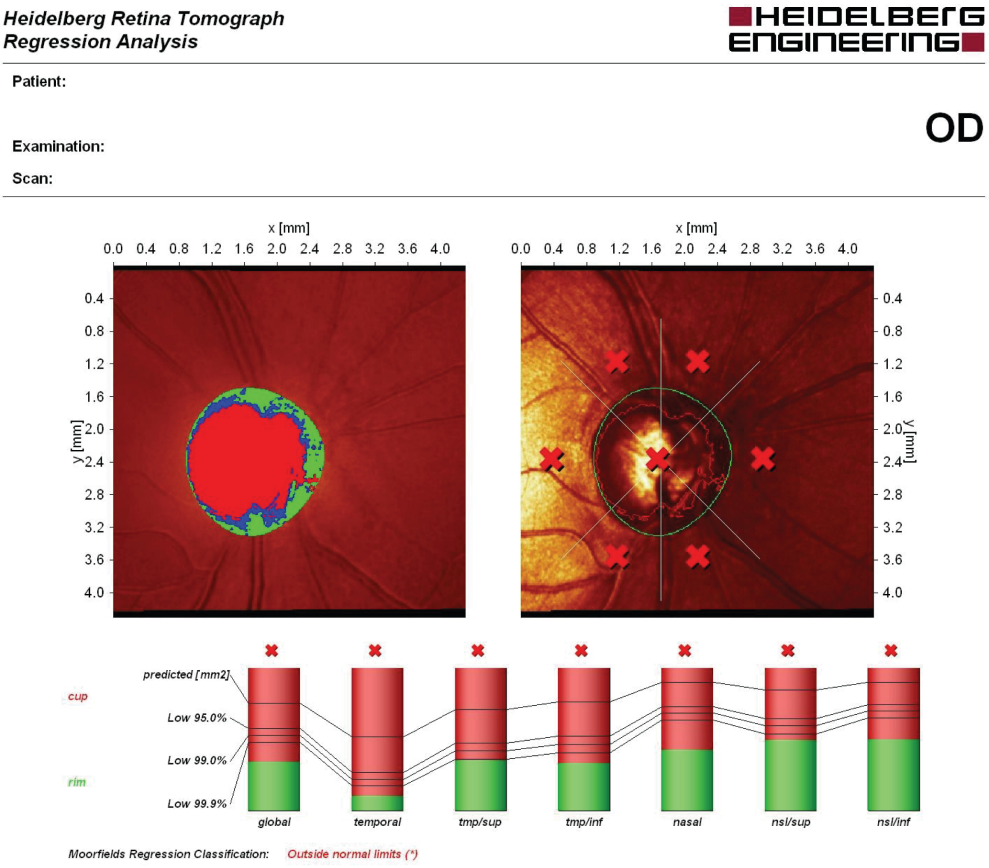
* Evidence of optic nerve damage from any of the following: Optic disc or retinal nerve fibre layer structural abnormalities. Diffuse thinning, focal narrowing, or notching of the optic disc rim, especially at the inferior or superior poles. Documented, progressive thinning of the neuroretinal rim with an associated increase in cupping of the optic disc. Diffuse or localized abnormalities of the peripapillary retinal nerve fibre layer, especially at the inferior or superior poles. Disc rim or peripapillary retinal nerve fibre layer haemorrhages. Optic disc neural rim asymmetry of the two 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 fibre layer damage (e.g., nasal step, arcuate field defect, or paracentral depression in clusters of test sites). Visual field loss in one hemifield that is different from the other hemifield, i.e., across the horizontal midline (in early/moderate cases). Absence of other known explanations.

***A reliable visual fields is classified as: False positive error <15% and no evidence for learning effect or poor performance which could impact on MD value (clinical judgement). In patients with unreliable visual field, the severity of glaucoma will be based upon clinical judgement.

Appendix 3 Example imaging report outputs from the four imaging tests

Heidelburgh Retinal Tomography glaucoma probability score (HRT-GPS)



Rim Area	global	temporal	tmp/sup	tmp/inf	nasal	nsl/sup	nsl/inf
actual [mm2]	0.81	0.06	0.11	0.11	0.25	0.14	0.15
predicted [mm2]	1.77	0.29	0.22	0.24	0.52	0.24	0.26
low 95.0% CI lim. [mm2]	1.35	0.15	0.15	0.17	0.42	0.18	0.22
low 99.0% CI lim. [mm2]	1.24	0.12	0.13	0.15	0.40	0.17	0.20
low 99.9% CI lim. [mm2]	1.12	0.10	0.11	0.13	0.37	0.15	0.19
actual/disc area [%]	34.6	10.7	35.2	33.2	42.7	49.6	50.0
predicted [%]	75.6	51.9	71.0	76.1	89.9	84.9	89.8
low 95.0% CI lim. [%]	57.8	27.2	47.6	52.5	73.2	64.8	74.3
low 99.0% CI lim. [%]	53.1	22.1	42.0	46.7	68.6	59.6	70.0
low 99.9% CI lim. [%]	48.1	17.4	36.3	40.7	63.6	54.0	65.3

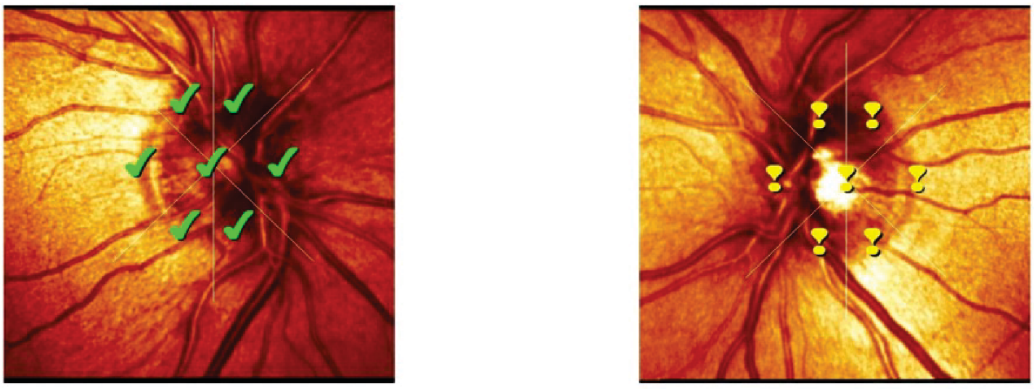
Heidelbergh Retinal Tomography Moorfields regression analysis (HRP-MRA)

Heidelberg Retina Tomograph
GPS Report

HEIDELBERG ENGINEERING

Quality: Very good (SD 13 µm)	Initial Report	**Quality:** Very good (SD 14 µm)
Focus: 4.00 dpt		**Focus:** 2.00 dpt
Operator: SN	**OD** **OS**	**Operator:** SN

Glaucoma Probability Score (GPS)



global	temporal	tmp/sup	tmp/inf	nasal	nsl/sup	nsl/inf	Parameter	global	temporal	tmp/sup	tmp/inf	nasal	nsl/sup	nsl/inf
0.11	0.10	0.10	0.09	0.11	0.11	0.11	Glaucoma prob.	0.52	0.52	0.51	0.52	0.50	0.55	0.51
0.00	-0.21	-0.12	0.05	-0.14	0.14	0.03	Rim steepness	-0.44	-0.21	-0.31	-0.06	-0.74	-0.68	-0.52
0.36	0.17	0.04	0.06	0.07	0.04	0.04	Cup size [mm²]	0.52	0.14	0.08	0.09	0.11	0.10	0.07
0.50	---	---	---	---	---	---	Cup depth [mm]	0.60	---	---	---	---	---	---
-0.01	---	---	---	---	---	---	H. RNFL curv.	-0.02	---	---	---	---	---	---
-0.09	---	---	---	---	---	---	V. RNFL curv.	-0.07	---	---	---	---	---	---
✓	✓	✓	✓	✓	✓	✓		?	?	?	?	?	?	?

Glaucoma Probability Score Classification:
Within normal limits

Glaucoma Probability Score Classification:
Borderline

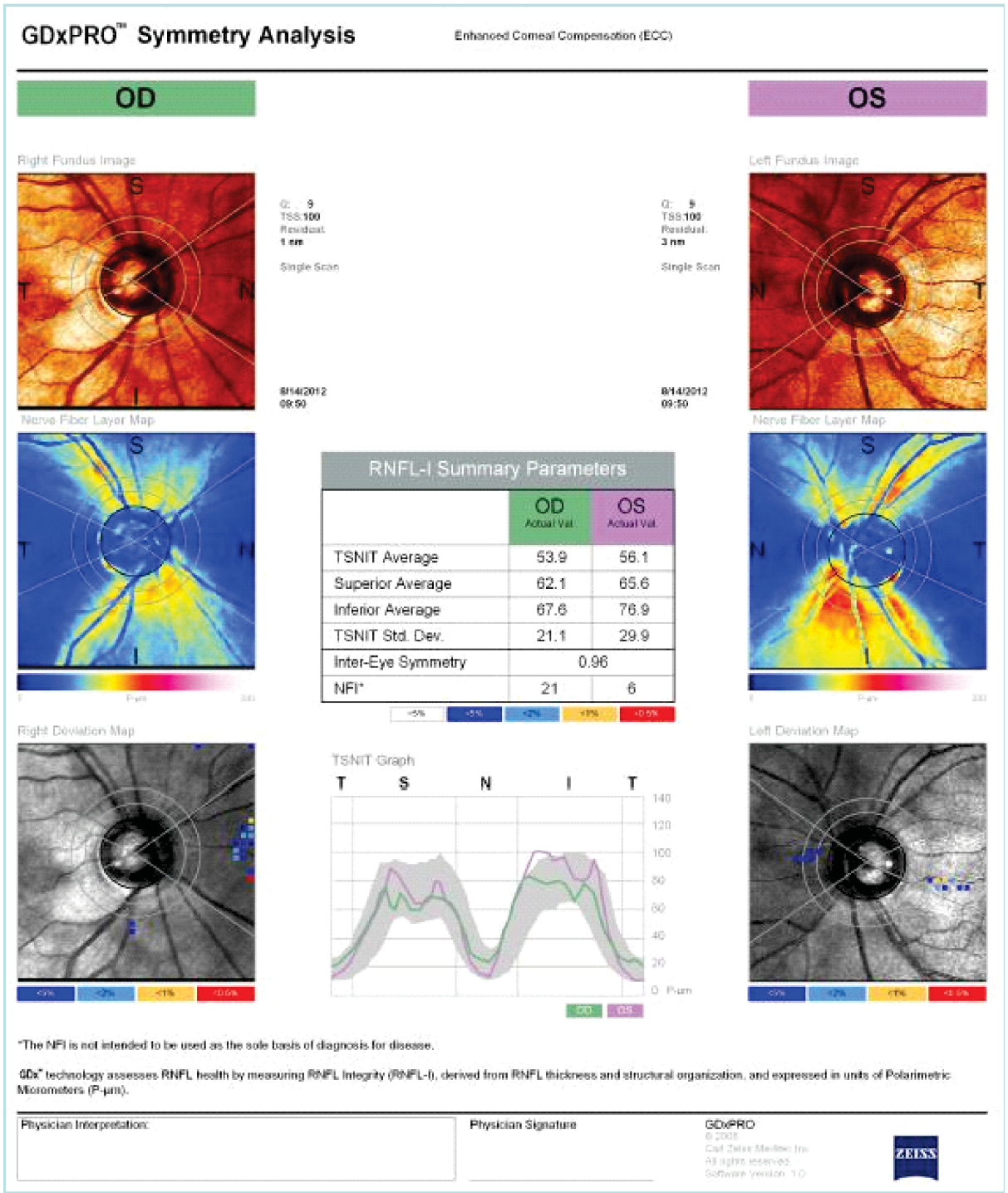
✓ Within normal limits
? Borderline
✖ Outside normal limits

Software Version: 3.1.2/5473
www.HeidelbergEngineering.com

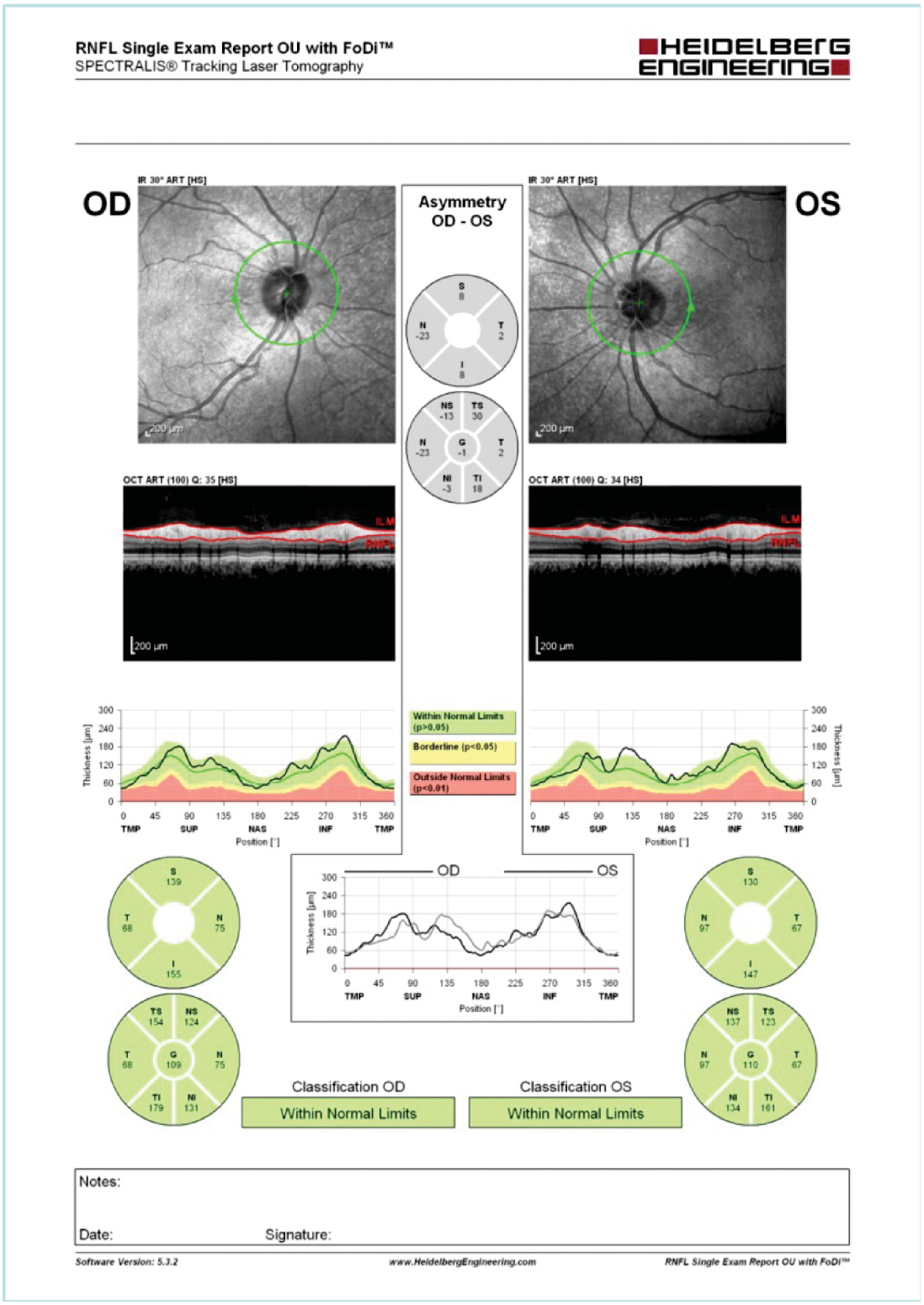
Comments:

Signature:
Date: 14/07/2011

Glaucoma diagnostics (GDx)



Spectralis optical coherence topography (OCT)



Appendix 4 Imaging standard operating procedures for the GATE study

STANDARD OPERATING PROCEDURES (SOP)

Image acquisition and storage

GATE: Glaucoma Automated Test Evaluation

Comparative study of new imaging technologies

for the diagnosis of glaucoma (HTA Reference Number: 09/22/111)

Sites:

1. Aberdeen Royal Infirmary
2. Hinchingbrooke Hospital
3. Moorfields Eye Hospital
4. St. Paul's Eye Unit, Liverpool
5. Bedford Hospital Trust

Instruments: HRT-III, GDx-PRO, Spectralis-OCT

Contact lens wear

There is currently no consensus as to whether a patient should be imaged with or without contact lenses. If a patient presents wearing contact lenses please follow local best practice.

Imaging Test order

Imaging should be performed in the random order allocated for each participant in the study. This can be found on the clinic log entry for that patient study ID on the GATE website.

Pupil dilation for imaging

Images should routinely be performed **without dilation** prior to clinician assessment and prior to visual field measurements. If pupil dilation is required to obtain an adequate quality HRT or OCT image then the GDx scan should be attempted prior to dilation (if not already performed). If an adequate quality GDx image is still not obtained prior to dilation the GDx scan should be repeated after pupil dilation. Whenever possible the random allocated test order should be used.

General indications for pupil dilation are media opacities and/or small pupils. However, the scan should always be attempted first to determine whether images are acceptable or if dilation is necessary.

Criteria for dilating the pupil are as follows:

- Unable to 'lock-on' to the pupil and save a scan
- Acceptability of best saved image is below requirements stated in SOP for that imaging technique

Acceptability criteria for each imaging technique are clearly detailed in the text for each technique below. Once an acceptable image has been obtained no further images should be acquired.

Acceptable quality criteria for imaging (summary)

HRT	Mean standard deviation ≤30, Image quality score: Good, Very Good, or Excellent
GDx	Q≥8
OCT	Q>15

Heidelberg Retina Tomograph (HRT-III)

Acquiring the image

Before imaging a subject on the HRT you should record their refraction (focimetry or auto-refraction. The focimetry/autorefraction is useful to guide the setting of the scan focus before image acquisition, but is not required to be input in the software.

Patients should not be imaged with their contact lenses in.

1. Ensure that IOP measurements (and other contact exams like gonioscopy) are done ***after*** HRT imaging.
2. Explain examination (method, time and requirements) to the patient.
3. Disinfect chin- and forehead supporting-stand.
4. Check optics for dirt or smudges, clean if required, with lint/oil-free lens paper moistened with a drop or two of photography quality lens cleaner.
5. Enter new patient details:

   a) Click on the new patient icon on the HEYEX tool bar to enter the subject's details and the operator initials. Enter the corneal curvature as an average of the two axes (i.e. 7.6 x 7.8 = 7.7) and enter the refractive error.

   The patient details need to be recorded as follows:
   - **Last Name:** 'GATE'
   - **First Name:** <site> e.g. 'Aberdeen'
   - **Title:** leave blank
   - **Date of birth:** enter patient date of birth
   - **Sex:** enter patient gender
   - **Patient ID:** enter < Participant study number>
   - **Ancestry:** enter the patient's ethnicity
6. Ensure that the table and the headrest are at the correct height for the subject. Adjust the chinrest height so that the patient's eyes are at the same level as the red canthus marks on the headrest posts. When the subject's details are entered the laser will activate and image acquisition can begin. As a starting point the focussing dial at the front of the HRT should be set to the subject's refraction.

7. Check that the subject is comfortable, and the scanning head is correctly aligned using the black adjustment handles on the HRT. The imaging distance between the HRT objective lens and the cornea is 1.5 cm; this can be judged by focussing the scanning beam on the iris (moving the scanning head towards or away from the eye). When the laser beam is focussed (sharp outline) on the iris, move the scanner sideways so the beam enters the pupil. All of the red light emitted from the HRT should be going straight into the pupil with little or none visible on the iris.

8. If cylinder correction exceeds ±0.75 diopter, place supplemental cylinder lens in front of the objective (image acquisition) lens. Note that the HRT will display a flashing alert on the refractive error correction dialog box if cylinder correction is recommended:

    a. click on the check box to display the recommended cylinder lens strength to be used. The lens should be oriented according to the axis provided by the autorefractometer.

    b. orientation of the cylinder may be adjusted manually during imaging in order to achieve the highest image quality on the screen (see point 9)

9. The HRT has an internal fixation point, a yellowy/green light which, when fixated by subject, should bring the optic disk into view on the screen. Once the scan is activated, the fixation point will appear on the subject's left for the right eye and on their right for the left eye (i.e. always towards the nose). Explain the fixation target (green light outside the red "carpet"). Once the subject is fixating, check the alignment of the laser in the pupil and make small adjustments to the focusing to optimise the image quality. The operator may also manually adjust the cylinder lens axis, if present, to achieve the best image quality.

    a. Images that are dark, have vignetting of the image corners or are grainy can be improved by dilation. If a good quality image cannot be obtained and dilation is required, delay the image acquisition until after clinical assessment as described in the flow chart in the GATE study procedures manual.

    b. In some cases where the internal fixation light cannot be seen by the patient, the external fixation device must be used. To use this, the opposite eye fixates on the green light which is manually positioned by the operator to display the optic nerve head in the centre of the screen.

10. Instruct the subject to blink as much as possible before you attempt to acquire a scan to avoid imaging a "dry eye" (drying of the corneal surface). The scan

duration is approx 6-8 seconds, during which time the subject should not blink and must maintain fixation. When ready, an image is acquired by pressing either the foot pedal or the grey button on the rear of the scan head.

11. Optimise image quality if necessary (artificial tears, elevate upper eyelids, re-adjust camera).

    a. Detector sensitivity should be as low as possible (<80)

    b. The image quality bar should be green for a good quality image and above 70%

12. The screen will display the progress of the scan; the HRT will take at least three scans of the optic nerve in one session.

    a. Monitor the progress of the scan to ensure that the subject's position and fixation is constant.

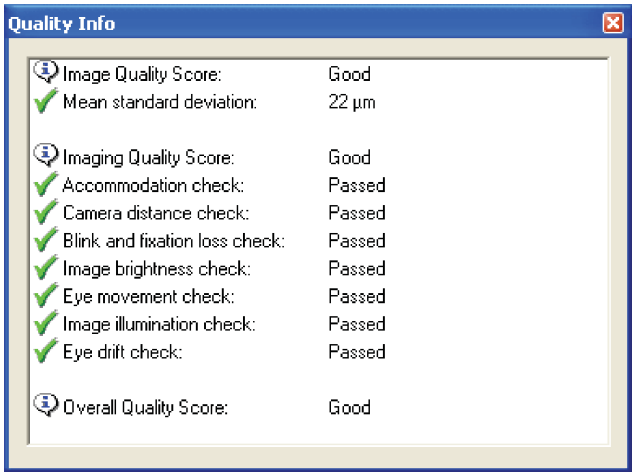
    b. The image series may be reviewed as a movie immediately after acquisition. HRT software can compensate for some movement but any scans containing large eye movements or blinks will have to be discarded and repeated.

    c. If you are satisfied with the scan select "save". Repeat to acquire another scan if image quality is not adequate.

    d. Move the machine over to image the fellow eye, the HRT software will recognise which eye you are scanning.

Checking image quality

Images acquired using the HRT III software allow the user to check the quality of the image by clicking on the **QC** icon in the right hand corner of the image:



a. Ensure that all elements are ticked. The overall quality score is given as one of Very Poor, Poor, Acceptable**, Good, Very Good, Excellent.** Ensure the overall quality score is Good or higher.

b. Check the **standard deviation** value displayed at the top of the topography. A value of **30 or below** is considered good image quality.

c. Repeat the image acquisition if required to obtain a good image quality.

d. If an acceptable image cannot be obtained after repeated attempts then the image acquisition should be attempted again after pupil dilation (please refer to study procedures document flow chart to ensure the order of clinical/imaging tests and visual field testing is correct)

Computing the topography

1. Once both eyes have been imaged, the topographies need to be computed.
   a. Exit from of the acquisition mode by clicking the "X" in the right hand corner of the acquisition window and you will be prompted to process the scans that have just been taken. When the scans are processed double click on the image to bring up the resulting topographical data in the examination results window

Drawing a contour line

1. Using the left mouse button select at least 3 points on the optic nerve rim to create a contour line and reposition to ensure the optic nerve rim is accurately located. Use the 3D viewer button to review your selection if required.
2. When you have located the optic nerve rim select 'Contour' then 'Accept Contour'
3. The contour and segment lines will appear.

HRT Report Printout:

Three printouts are required for the HRT scan,

1. Moorfields Regression Analysis (MRA) of right eye,
2. MRA of left eye and
3. GPS report

A hardcopy of each report should be filed in the study file for each participant.

An electronic copy of each report in **JPEG** format should also be saved to a memory stick and uploaded to the GATE study website.

The naming convention for filenames of any saved reports should be followed:

- MRA Right eye report: 'GATE<studyID>MRAright.jpg'
- MRA Left eye report: 'GATE<studyID>MRAleft.jpg'
- GPS report: 'GATE<studyID>GPS.jpg'

Printing a Moorfields Regression Analysis(MRA) Report

- Click the Moorfields classification tab
- Select 'Print'
- Select 'Examination report'
- Ensure the 'Moorfields report' is selected in the reports window
- Select 'preview'
- The Moorfields report for that eye will appear
- Select 'Save as'
- Enter the filename as 'GATE<studyID>MRAright.jpg' for right eye (or GATE<studyID>MRAleft.jpg for left eye)
- Select 'Save' to save the jpeg of the report
- Select 'print' to print a hardcopy report for the file
- Select other eye from Heidelberg Eye explorer window
- Repeat from start to print/save report from the other eye.

Printing a GPS report

- To print report select 'GPS classification' tab
- Select 'Print'
- Select 'Examination report'

To save as a jpeg file to upload to the GATE website

- Ensure GPS report is highlighted in the report window
- If more than one image is stored for the other eye, select the corresponding eye image for the GPS report
- Select Preview
- The GPS report will appear on the print preview screen
- Select 'Save as'
- Enter the filename as 'GATE<studyID>GPS.jpg'
- Select save to save the jpeg of the report

To print a hardcopy report

- Select 'Print'

HRT Data Export:

HRT imaging data should be exported on the same day every week. Export all the images since the last export.

1) From the main database screen select the patient you wish to export.
2) When the patient details appear on the right hand side of the screen double click the patient name.
3) Right click on the exam you wish to export and select the export option.
4) Select yes to export the 3D image series. Selecting this option could result in a prompt to retrieve the raw image data for that exam.
5) Select a folder to export using the browse option.
6) The file will export and appear as an *.E2E file in the selected export folder.
7) Save with filename 'GATE<studyID>rawHRTOS.e2e' for left eye, and 'GATE<studyID>rawHRTOD.e2e for right eye

GDx ECC/GDx Pro

Acquiring the image

1. Patients should not be imaged wearing their contact lenses. Ensure that IOP measurements and other contact exams like gonioscopy are performed after GDx imaging

2. With the GDx VCC and peripherals properly connected, the Access card inserted and the optics unlocked turn the machine on using the power switch on the side.

3. Disinfect face rest.

4. When the warm-up test is complete, the logo screen will be displayed. Select “new patient”.

5. The patient details need to be recorded as follows:
   - **Patient ID** - Use <GATE Participant study number>
   - **Last name –** ‘GATE’
   - **First name** – <site>e.g. Aberdeen
   - **Middle name** – leave blank
   - **DOB** – enter patient date of birth
   - **Doctor** –use any identifier usually used or leave blank

Press √ button to continue.

6. Input ancestry and gender information as prompted. Press √ button to continue.

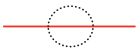
7. Check patient information for accuracy. If changes are needed press edit.

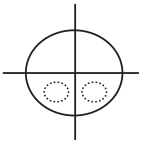
8. Select “full exam”.

9. Refraction input is needed for focusing purposes. Select Refraction. Press the **auto-refraction** button.

10. Position the subject in front of the GDx with the face placed comfortably against the face rest. For optimal positioning, ask the patient to place their brow bones on top of the upper rest “like wearing a mask”. Ask the subject to gaze at the blinking fixation target in the red field– located to the left hand side for the right eye and vice versa. The exam begins with the right eye as the default position.

11.

- Move the joystick , by pulling forwards and backwards, to vertically align the white focus dot on the horizontal red line 

- Centre the pupil in the target by moving the joystick up/down/ left/right and ensure that the 2 white dots are located in the bottom 2 quadrants of the target 

- Once aligned, ask the patient not to blink and press the **image acquisition button** on top of the joystick to scan the eye
- Once the refraction data is displayed on the top lhs select **image acquisition button** again to acquire refraction data from the other eye
- Click **image acquisition button** a 3rd time to display the ‘modify ellipse – measuring cornea’ screen

12. Following a cornea measurement, the “Modify Ellipse – Measuring Cornea” screen appears. The macular ellipse should be centred directly over the macula “bowtie”-pattern.

13. To change the macular ellipse position, use the arrow buttons. Do not change the size of the macular ellipse.

14. If the macula “bowtie” is not well defined, press the “Irregular Pattern” button to use an alternative cornea calculation based on the macula area within the dotted square which does not require macular ellipse placement (press the “Macular Ellipse” button to re-enable the macular ellipse placement options).

15. Press √ button to go to the “Modify Ellipse – Measuring Cornea” screen for the next eye. Optimise the placement of the cornea measurement ellipse in the same manner as for the first eye. Press √ button again when complete.

16. When ellipse modification is completed, the system displays the “Image Check-Measuring cornea” screen. The scan **quality score should be 8 and above**. If the scan quality is less than 8 then retake the image for that eye.

17. If image quality is acceptable then select “Accept”. The acquisition screen will now appear. If after repeating the GDx scan the image quality is still not acceptable then the image acquisition should be attempted again after pupil dilation (please refer to GATE study procedures flow chart to ensure the order of clinical/imaging tests is correct)

18. Move the joystick to vertically align the white focus dot on the horizontal red line and centre the pupil in the reticule. Once aligned, press the image acquisition button on top of the joystick to scan the eye. After the first image is captured the system will automatically move to the other eye.

19. Repeat step 18 for the left eye.

20. At the “Image Check” screen verify that the ellipses for both eyes are the correct size, shape and centred on the Optic Nerve Head (ONH). You can both change the ellipse diameter and shape using the arrow keys. (Note: While it is helpful to align the ellipse with the ONH margin, accurate centration is more important than perfect ellipse size).

21. When ellipse modification is completed, verify that the scans quality scores are 8 or above. If quality is less than 8, re-scan the patient. Proper ONH placement can influence image quality scores. Verify that placement is correct before deciding to retake an image.

22. If image quality is acceptable then select “Accept”.
    If not acceptable then the image acquisition should be attempted again after the clinician has dilated pupils for their routine clinical assessment (please refer to GATE study procedures flow chart to ensure the order of clinical/imaging tests is correct)

23. Press “print” or “save only” button.

GDx Printout

A printout of the GDx ECC report is required for the study file. Ensure that ECC is reported in the middle text box (white).

A hardcopy of each report should be filed in the study file for each participant.

A scanned electronic copy of each report in **JPEG** format should be uploaded to the GATE study website.
The naming convention for filenames of any saved reports should be followed:

- GDx ECC report: 'GATE<studyID>GDX.jpg'

After printing out the report you should select 'Save' to save the file for this patient

GDx Data Export

Data export is done on a floppy disk.

1. Select "existing patient".
2. Enter the patient ID number in the "Patient ID".
3. Press the "review" button
4. Use "Previous" and "Next" buttons to move through the list
5. Then using the "Select/Deselect" button highlight the chosen exam
6. Repeat 2 and 3 to select more then one exam
7. Press "review" button and then "export" button
8. Choose 'Export raw data'
9. You will be presented with a folder: My Computer. Press the tab key to get into the folder.
10. Using the arrow keys highlight the Floppy A Folder. Then press enter.
11. Name the folder (although the software will automatically save the data with Patient name and ID).
12. Press "√" button or the "enter" key.
13. You will be presented with the message: "Exporting Data" and when finished with the message "Export complete".

Optical Coherence Tomography Using: Heidelberg Spectralis OCT

Patients should not wear contact lenses

Acquiring the image

1. Explain examination (method and requirements) to the patient
2. Ensure that IOP measurements (and other contact exams like gonioscopy) are done **after** OCT imaging
3. Disinfect chin-and forehead-supporting stand
4. Check optics for dirt or smudges, clean if required/with lint/oil free lens paper moistened with a drop or two of photography quality lens cleaner
5. Ensure that the table and headrest are the correct height for the subject. Adjust the chinrest height so that the patient's eyes are at the same level as the red canthus marks on the headrest posts.

5. Create a new patient record by clicking on the ***New Patient*** button.

In the ***Patient File*** window you should enter the following patient details

- **Patient ID** - Use < Participant study number>
- **Patient Name** (Surname= 'GATE', Forename=<site> e.g. 'Aberdeen')
- **DOB** – enter patient date of birth
- Enter **Gender** and **Ethnicity** information

Examination Data Window

The ***Examination Data*** dialog opens before each exam, but can also be opened at any later stage using the ***Examination*** button in the patient file.
The respective ***Device Type*** for the examination must be selected from the dropdown menu; all other data is optional.

1. Select Spectralis OCT
2. Enter operator initials
3. Enter Study name as GATE

Eye Data Window

This window enables the entry of the eye parameters for both eyes. **Please Note**: Do NOT enter any data into this window.

1. Wait for the Laser On/Off button on the Control Panel to turn from Red to Yellow.
2. Press the Yellow On/Off button on the Control Panel to activate the Laser/OCT. Make sure that the OCT button is selected. (Note - On the Control Panel, Inactive/unselected buttons are Red; Active/Selected buttons are Blue).
3. Select the IR + OCT button.
4. Make sure that the Volume button is selected.
6. Field button should be at 30 degrees.
7. IR Intensity button will default to 100% but should be adjusted for patient media, typically 50% - 75%.
8. Always activate the ART Mean function when performing an OCT-Scan
9. Select **RNFL** preset on the monitor screen
10. Ensure HR for high resolution imaging is selected (not HS – high speed)
11. The OCT has a blue internal fixation point which when fixated by the subject should bring the optic disc into view on the screen
    a) slowly bring the camera towards the patient's eye,
    b) encourage the patient to blink just before a scan, since maintaining a good tear film is important for OCT image quality. In cases where the patient suffers from dry eye, or when the cornea cannot be kept moist enough by blinking alone, artificial tears may be used.
    c) Using the joystick (up, down, right or left) move the camera to the center of the pupil and adjust the distance between the objective and the examined eye to approx. 14 mm between the front edge of the objective and the cornea.
    d) Use the OCT Acquisition Window on the monitor to align the camera with the Optic disc Image on the left side of the window.
    e) Fine tune brightness and sharpness of the image using the focus knob. The optimum camera position is reached when no dark corners and overexposed areas are visible.

11. The bar above the OCT image will appear red if the OCT image touches the upper border. Move the camera further away from the patient if the OCT image is shown inverted. If the OCT image is tilted in a horizontal direction, move the camera slightly left/right (if capturing a horizontal scan) or up/down (if capturing a vertical scan). (Note in patients with moderate myopia, the scan can be tilted).

12 . The blue ***Quality bar*** in the lower part of the image indicates the signal strength. The quality score range is **0 (no image) to 40 (excellent quality)**. **Acceptable quality is**

>15. If the score is 15 or less, the quality bar turns red. If an acceptable quality image cannot be obtained, imaging should be repeated after pupil dilation (see flowchart in study procedures manual to determine test order)

13. To achieve optimum image quality, position the OCT image in the upper half of the ***Acquisition*** window. Using the joystick, move the camera slightly up/down and sideways until the optic disc and OCT image appear brightest and most evenly illuminated.

14. To acquire images, press the foot switch, the ***Acquire*** button on the control panel or the central button on the joystick. After acquiring images, save them using the ***Save images*** option in the top left corner of the ***Acquisition*** window. To end the acquisition session, exit the ***Acquisition*** window. The camera will automatically turn off.

OCT RNFL Basic Report OU Printout

- A hardcopy RNFL Basic Report OU should be filed in the study file for each participant.
- Add an image from each eye to the lightbox
- Select both images in the lightbox then select Print from the context menu
- The 'print spectralis report' window will appear
- Select the RNFL Basic Report option
- Select Preview
- Select Save to save a JPEG format then select Print to printout a hardcopy
- An electronic copy of each report in **JPEG** format should also be saved to a memory stick and uploaded to the GATE study website. The naming convention for filenames of any saved reports should be followed: OCT report: 'GATE<studyID>OCT.jpg'

OCT Data Export

OCT imagining data should be exported on the same day every week. Export all the images since the last export.

1) From the main database screen select the patient you wish to export
2) To export images and other data in an examination as an E2E file, select the desired thumbnail image(s) from the ***Patient File*** window, and select the item ***Export ► asE2E*** from the ***Context Menu*** in the ***Patient File***.

3) Save with filename ‘GATE<studyID>rawHRTOS.e2e’ for left eye, and ‘GATE<studyID>rawHRTOD.e2e for right eye
4) The *Batch* ► *Export E2E* feature in the *Database* window enables export of multiple patient records at once.

Appendix 5 Further assessment of threshold effects under diagnosis analysis using individual parameters from the imaging tests

As for default analysis, abnormal imaging test results were those classified as 'outside normal limits' and the corresponding reference standard definition of disease was a diagnosis of glaucoma of the worse eye. Only participants with an imaging test output with an overall classification which met the manufacturer quality cut-off point were included in the analysis.

The HRT-MRA parameters for which a ROC curve was produced and the AUC calculated were the global, temporal, temporal superior, temporal inferior, nasal, nasal superior and nasal inferior areas. For HRT-GPS and OCT, the probabilities and the RNFL thickness values were used for the same segments of the eye. For GDx, the TSNIT parameters (NFI, TSNIT average, superior average, inferior average, TSNIT SD were used).

The corresponding ROC curves are shown in *Figures 28–31* with the corresponding AUC with 95% CIs in *Table 59*. From visually assessment it can be seen that the OCT and GDx curves differed the most between parameters with the HRT tests, MRA and particularly GPS showing less variation in the curve shape between parameter. The point estimates for the AUC differed by only 0.02 for GPS, compared with GDx for 0.1 and 0.13 for OCT.

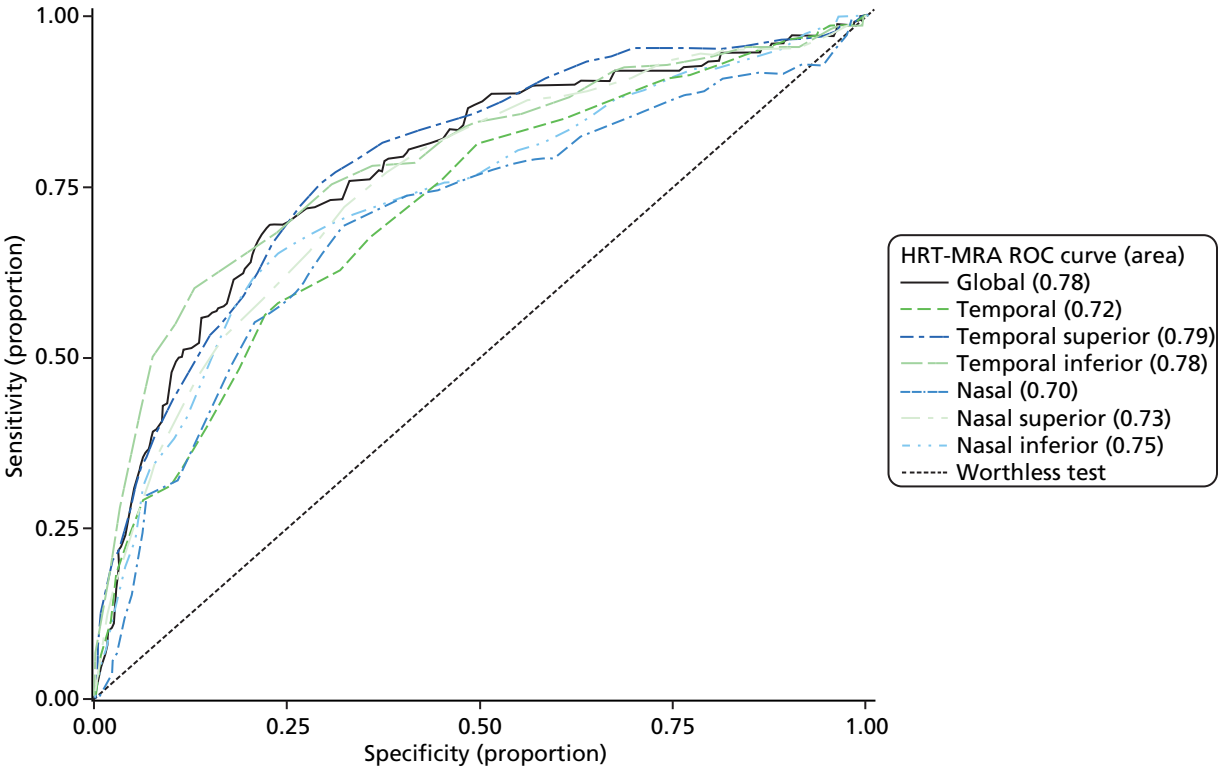


FIGURE 28 Receiver operating characteristic curve for HRT-MRA parameters.

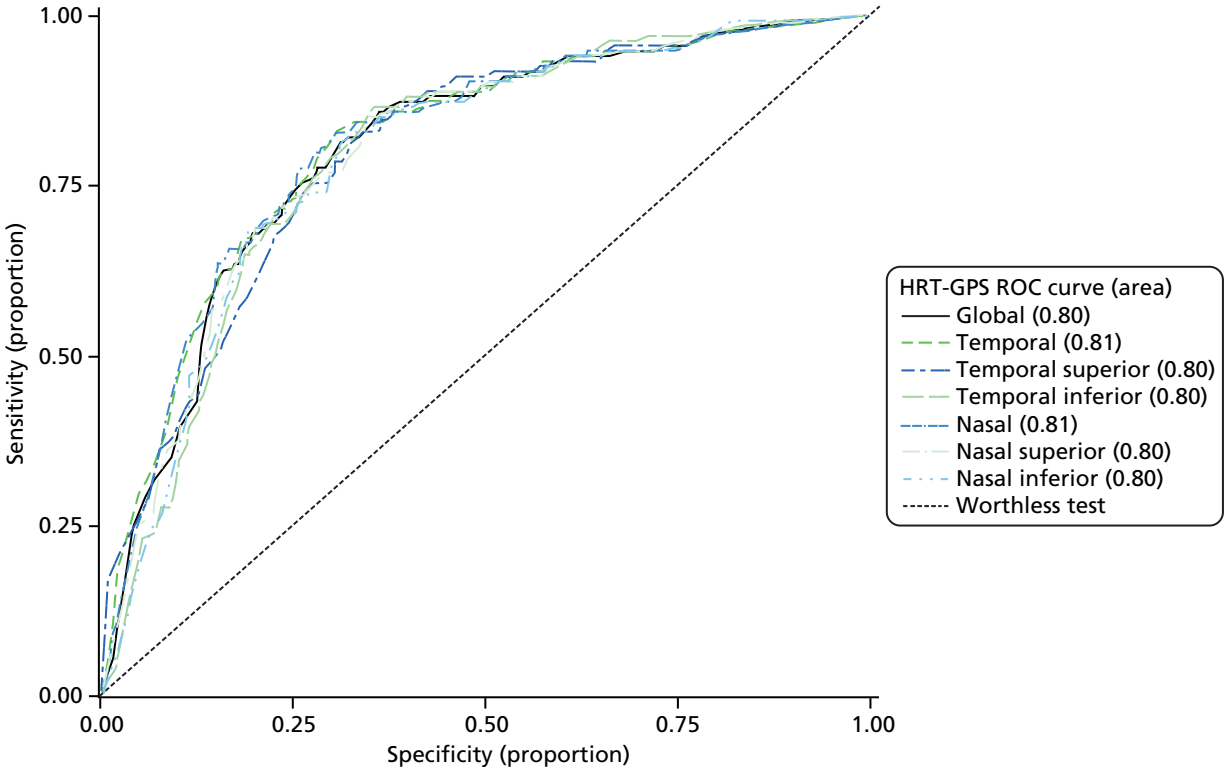


FIGURE 29 Receiver operating characteristic curve for HRT-GPS parameters.

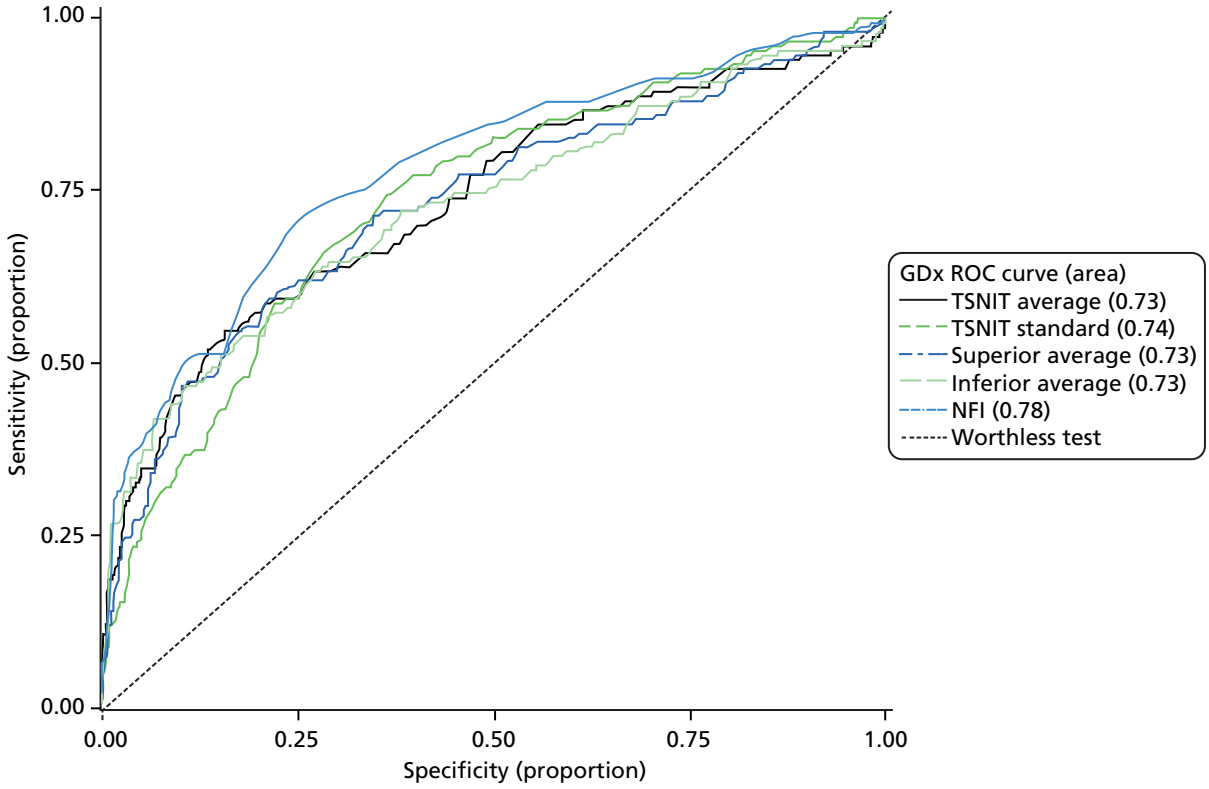


FIGURE 30 Receiver operating characteristic curve for GDx parameters.

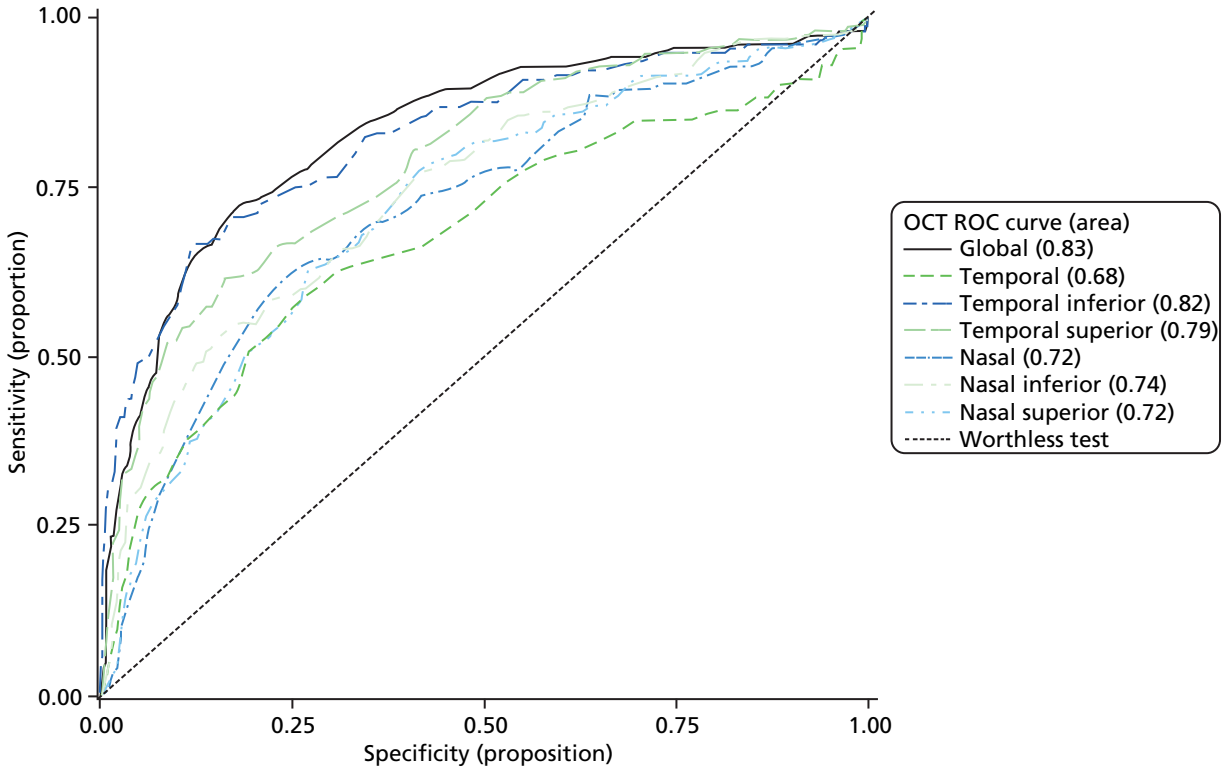


FIGURE 31 Receiver operating characteristic curve for OCT parameters.

TABLE 59 Area under the ROC curve using imaging test parameters for a diagnosis of glaucoma in the worse eye

Test	Parameter	Value	95% CI
HRT-MRA	Global area	0.78	0.73 to 0.82
	Temporal area	0.72	0.67 to 0.76
	Temporal superior area	0.78	0.74 to 0.83
	Temporal inferior area	0.79	0.74 to 0.83
	Nasal	0.70	0.65 to 0.75
	Nasal superior area	0.75	0.71 to 0.80
	Nasal inferior area	0.73	0.69 to 0.78
HRT-GPS	Global probability	0.80	0.77 to 0.84
	Temporal probability	0.81	0.77 to 0.85
	Temporal superior probability	0.80	0.76 to 0.84
	Temporal inferior probability	0.80	0.76 to 0.83
	Nasal probability	0.81	0.77 to 0.85
	Nasal superior probability	0.80	0.76 to 0.84
	Nasal inferior probability	0.79	0.76 to 0.83
GDx	NFI	0.78	0.74 to 0.83
	TSNIT average	0.73	0.69 to 0.78
	TSNIT SD	0.74	0.69 to 0.78
	Superior average	0.73	0.68 to 0.78
	Inferior average	0.73	0.68 to 0.78
OCT	Global thickness	0.83	0.79 to 0.87
	Temporal thickness	0.68	0.63 to 0.73
	Temporal superior thickness	0.79	0.75 to 0.83
	Temporal inferior thickness	0.82	0.78 to 0.86
	Nasal thickness	0.72	0.68 to 0.77
	Nasal superior thickness	0.72	0.68 to 0.77
	Nasal inferior thickness	0.74	0.70 to 0.79

Appendix 6 Additional triage analysis to inform the health economic model

Overview

An additional set of two statistical analyses (see *Triage sensitivity analyses 9 and 10*) were carried out to specifically inform the economic modelling for GATE. These were set up to mirror the model structure in terms of population (i.e. with the simplification of ignoring the presence of non-glaucoma-related comorbidities). The first additional analysis used a reference standard definition of disease of glaucoma, glaucoma suspect, OHT and PAC; the second analysis used diagnosis of glaucoma alone as the reference standard (*Table 60*). The test was a composite, as previously described in *Chapters 2* and *5*, of the imaging test result, IOP and VA measurements (referred to throughout this appendix by the name of imaging test used within the composite test, e.g. HRT-MRA, HRT-GPS, GDx or OCT). Where a classification was not provided by the imaging test, the patient was defined as a 'for referral'. For the first analysis, borderline imaging results were also classified as 'for referral', whereas for the second analysis they were classified 'not for referral'. Triage sensitivity analyses 9 and 10 represent the analyses used to populate the diagnostic accuracy results of the base case and the sensitivity analysis scenarios, respectively (see *Chapter 6* for further details). Subgroup sensitivity and specificity values were calculated for each diagnosis separately (e.g. glaucoma, 'at risk of glaucoma' and neither groups) breaking down the performances of the triage test to provide estimates for the economic model. 'At risk of glaucoma' was defined as being suspected of any type of glaucoma, or having OHT or PAC.

TABLE 60 Additional analyses carried out to inform the health economic model

Analysis	Reference standard definition of disease	Test 'for referral' definition	Handling of 'no result' categories	Figure number	Table number
Triage sensitivity analysis 9	Glaucoma, OHT, PAC and glaucoma suspect	Imaging (outside normal limits or borderline) or IOP > 21 mmHg or VA 6/12 or poorer	A–D for referral E excluded	*32*	*61*
Triage sensitivity analysis 10	Glaucoma	Imaging (outside normal limits)	A–D for referral E excluded	*33*	*62*

No result categories: A, test performed and imaging report produced but quality is lower than manufacturer quality cut-off point; B, test performed and imaging report produced but no overall classification generated by machine; C, test performed but there was a clear imaging artefact on the report; D, test attempted but no imaging could be acquired from the patient's eyes – no report generated; E, missing imaging output (because of study-related or data-collection issues).

Diagnostic performance of the triage tests

The diagnostic accuracy results of the two analyses are given in the following two sections.

Triage sensitivity analysis 9

The flow of study participants according to triage sensitivity analysis 9 is shown in *Figure 32* with corresponding numbers of referral, not for referral and no results cases by triage test. The diagnostic performance for the four tests is given in *Table 61*. The results showed a trade-off between the detection

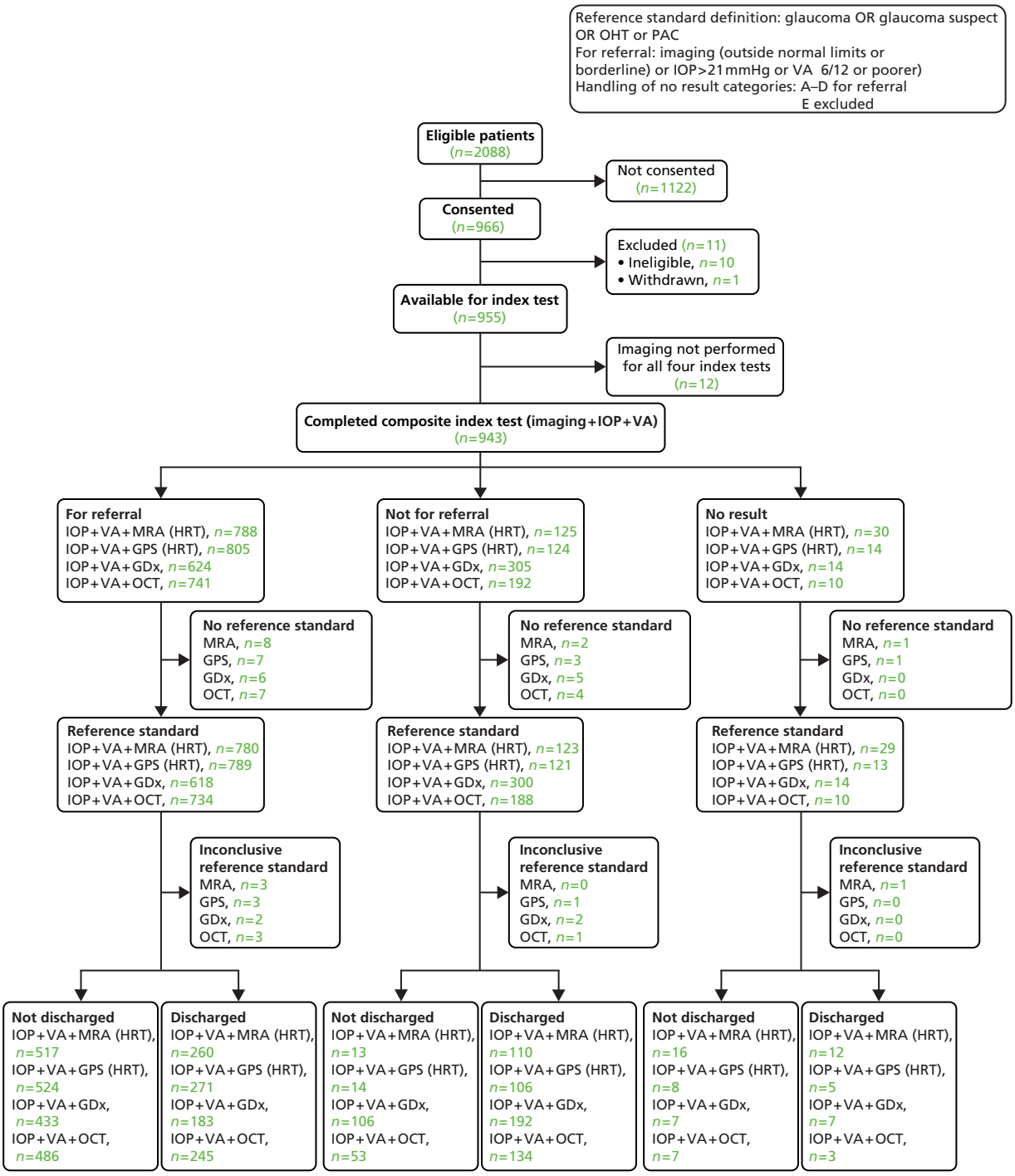


FIGURE 32 Flow diagram: triage sensitivity analysis 9.

TABLE 61 Triage sensitivity analysis 9

Test	Diagnostic parameter	Value	95% CI
HRT-MRA	Sensitivity (%)	97.5	95.8 to 98.7
	Specificity (%)	29.7	25.1 to 34.7
	Positive likelihood ratio	1.39	1.30 to 1.49
	Negative likelihood ratio	0.08	0.05 to 0.14
	DOR	16.83	9.29 to 30.47
HRT-GPS	Sensitivity (%)	97.4	95.7 to 98.6
	Specificity (%)	28.1	23.6 to 32.9
	Positive likelihood ratio	1.35	1.27 to 1.45
	Negative likelihood ratio	0.09	0.05 to 0.16
	DOR	14.64	8.23 to 26.05
GDx	Sensitivity (%)	80.3	76.7 to 83.6
	Specificity (%)	51.2	46.0 to 56.4
	Positive likelihood ratio	1.65	1.47 to 1.84
	Negative likelihood ratio	0.38	0.32 to 0.47
	DOR	4.29	3.2 to 5.75
OCT	Sensitivity (%)	90.2	87.3 to 92.5
	Specificity (%)	35.4	30.5 to 40.4
	Positive likelihood ratio	1.39	1.29 to 1.51
	Negative likelihood ratio	0.38	0.21 to 0.37
	DOR	5.02	3.52 to 7.14

of patients who need to be referred and the discharge of those who do not need to be referred: HRT-MRA had the highest sensitivity (HRT-GPS was only very slightly lower) but also the second lowest specificity (HRT-GPS had the lowest), GDx had the lowest sensitivity but the highest specificity and OCT provided intermediate results. Likelihood ratios (and 95% CI) showed evidence of being able to both rule in and rule out the presence of glaucoma for all four triage tests (CIs did not contain 1.0). DORs ranged from 4.29 for GDx to 16.83 for HRT-MRA.

From this analysis, the sensitivity for participants with glaucoma was calculated as 99%, 99%, 88% and 97% for HRT-MRA, HRT-GPS, GDx and OCT, respectively; similarly the sensitivity for participants 'at risk of glaucoma' was calculated as 97%, 97%, 77% and 87%, respectively, and the specificity for participants classified as normal (not glaucoma or 'at risk of glaucoma') was 30%, 28%, 51% and 35% for HRT-MRA, HRT-GPS, GDx and OCT, respectively.

Triage sensitivity analysis 10

The flow of study participants according to triage sensitivity analysis 10 is shown in *Figure 33*, with corresponding numbers of referral, not for referral and no results cases by triage test. The diagnostic performance for the four tests is given in *Table 62*. The results generally showed a trade-off between the detection of patients who need to be referred and the discharge of those who do not need to be referred: HRT-MRA had the highest sensitivity (HRT-GPS was only very slightly lower) but also the second lowest specificity (HRT-GPS had the lowest), GDx had the lowest sensitivity but the highest specificity and OCT provided intermediate results. Likelihood ratios (and 95% CI) showed evidence of being able to both rule in and rule out the presence of glaucoma for all four triage tests (CIs did not contain 1.0). DORs ranged from 5.11 for GDx to 12.83 for HRT-MRA.

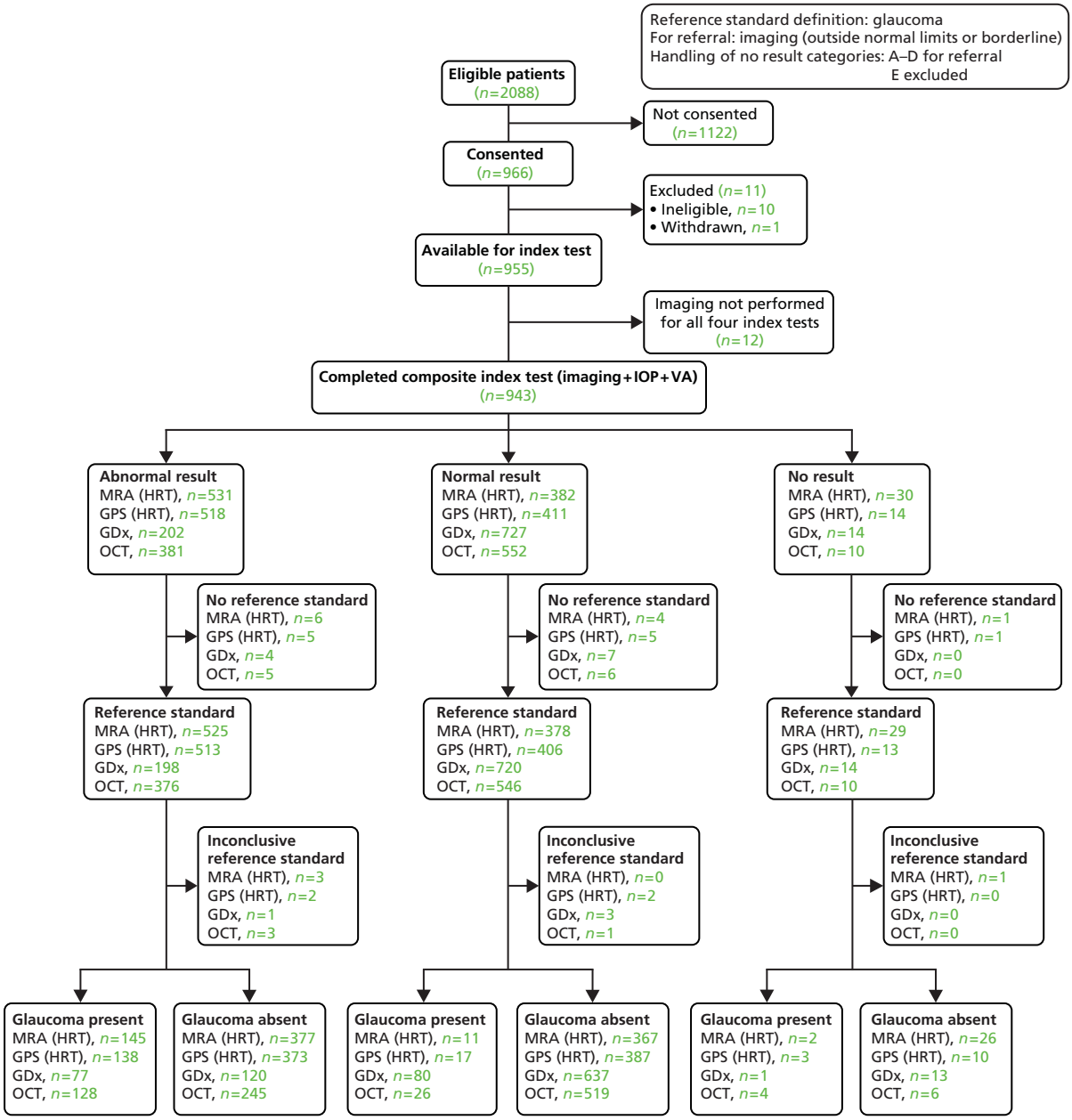


FIGURE 33 Flow diagram: triage analysis sensitivity 10.

TABLE 62 Triage sensitivity analysis 10

Test	Diagnostic parameter	Value	95% CI
HRT-MRA	Sensitivity (%)	92.9	87.7 to 96.4
	Specificity (%)	49.3	45.7 to 53.0
	Positive likelihood ratio	1.83	1.69 to 21.99
	Negative likelihood ratio	0.14	0.08 to 0.25
	DOR	12.83	6.84 to 24.08
HRT-GPS	Sensitivity (%)	89.0	83.0 to 93.5
	Specificity (%)	50.9	47.3 to 54.5
	Positive likelihood ratio	1.81	1.66 to 1.99
	Negative likelihood ratio	0.22	0.14 to 0.30
	DOR	8.42	4.99 to 14.88
GDx	Sensitivity (%)	49.0	41.0 to 57.1
	Specificity (%)	84.1	81.3 to 86.7
	Positive likelihood ratio	3.09	2.46 to 3.89
	Negative likelihood ratio	0.61	0.52 to 0.71
	DOR	5.11	3.53 to 7.39
OCT	Sensitivity (%)	83.1	76.2 to 88.7
	Specificity (%)	67.9	64.5 to 71.2
	Positive likelihood ratio	2.59	2.29 to 2.94
	Negative likelihood ratio	0.25	0.17 to 0.35
	DOR	10.43	6.66 to 16.33

From this analysis, the sensitivity for participants with glaucoma was 93%, 89%, 49% and 83% for HRT-MRA, HRT-GPS, GDx and OCT, respectively; the sensitivity for participants 'at risk of glaucoma' was calculated as 61%, 59%, 17% and 36%, respectively; and the specificity for participants in the normal health state (without glaucoma or 'at risk of glaucoma') was calculated as 60%, 61%, 85% and 72%, respectively.

Appendix 7 Cost-effectiveness supplementary tables

TABLE 63 Incremental cost-effectiveness for the base case with different NHS Reference Costs applied to the triage strategies

NHS Reference Cost (£)	Intervention	Cost (£)	QALYs	ICER
10	GDx	2841	19.7701	–
	OCT	2967	19.7746	27,812
	HRT-MRA	3001	19.7771	13,807
	HRT-GPS	3011	19.7771	Dominated[a]
	Current practice	3084	19.7780	98,231
13	GDx	2856	19.7701	–
	OCT	2982	19.7746	27,784
	HRT-MRA	3016	19.7771	13,780
	HRT-GPS	3026	19.7771	Dominated[a]
	Current practice	3084	19.7780	80,605
16	GDx	2872	19.7701	–
	OCT	2996	19.7746	27,757
	HRT-MRA	3031	19.7771	13,754
	HRT-GPS	3040	19.7771	Dominated[a]
	Current practice	3084	19.7780	62,979
19	GDx	2887	19.7701	–
	OCT	3011	19.7746	27,729
	HRT-MRA	3046	19.7771	13,727
	HRT-GPS	3055	19.7771	Dominated[a]
	Current practice	3084	19.7780	45,353
22	GDx	2902	19.7701	–
	OCT	3026	19.7746	27,701
	HRT-MRA	3060	19.7771	13,700
	HRT-GPS	3070	19.7771	Dominated[a]
	Current practice	3084	19.7780	27,727
25	GDx	2917	19.7701	–
	OCT	3041	19.7746	27,673
	HRT-MRA	3075	19.7771	13,673
	Current practice	3084	19.7780	10,101
	HRT-GPS	3085	19.7771	Dominated[a]

continued

TABLE 63 Incremental cost-effectiveness for the base case with different NHS Reference Costs applied to the triage strategies (*continued*)

NHS Reference Cost (£)	Intervention	Cost (£)	QALYs	ICER
28	GDx	2932	19.7701	–
	OCT	3056	19.7746	27,646
	Current practice	3084	19.7780	8313
	HRT-MRA	3090	19.7771	Dominated[a]
	HRT-GPS	3100	19.7771	Dominated[a]
31	GDx	2947	19.7701	–
	OCT	3071	19.7746	27,618
	Current practice	3084	19.7780	3853
	HRT-MRA	3105	19.7771	Dominated[a]
	HRT-GPS	3115	19.7771	Dominated[a]
34	GDx	2962	19.7701	–
	Current practice	3084	19.7780	15,579
	OCT	3086	19.7746	Dominated[a]
	HRT-MRA	3120	19.7771	Dominated[a]
	HRT-GPS	3129	19.7771	Dominated[a]
37	GDx	2977	19.7701	–
	Current practice	3084	19.7780	13,663
	OCT	3101	19.7746	Dominated[a]
	HRT-MRA	3135	19.7771	Dominated[a]
	HRT-GPS	3144	19.7771	Dominated[a]
40	GDx	2992	19.7701	–
	Current practice	3084	19.7780	11,747
	OCT	3116	19.7746	Dominated[a]
	HRT-MRA	3149	19.7771	Dominated[a]
	HRT-GPS	3159	19.7771	Dominated[a]
43	GDx	3007	19.7701	–
	Current practice	3084	19.7780	9831
	OCT	3130	19.7746	Dominated[a]
	HRT-MRA	3164	19.7771	Dominated[a]
	HRT-GPS	3174	19.7771	Dominated[a]
46	GDx	3022	19.7701	–
	Current practice	3084	19.7780	7315
	OCT	3145	19.7746	Dominated[a]
	HRT-MRA	3179	19.7771	Dominated[a]
	HRT-GPS	3189	19.7771	Dominated[a]

TABLE 63 Incremental cost-effectiveness for the base case with different NHS Reference Costs applied to the triage strategies (*continued*)

NHS Reference Cost (£)	Intervention	Cost (£)	QALYs	ICER
49	GDx	3037	19.7701	–
	Current practice	3084	19.7780	5999
	OCT	3160	19.7746	Dominated[a]
	HRT-MRA	3194	19.7771	Dominated[a]
	HRT-GPS	3204	19.7771	Dominated[a]
52	GDx	3052	19.7701	–
	Current practice	3084	19.7780	4083
	OCT	3175	19.7746	Dominated[a]
	HRT-MRA	3209	19.7771	Dominated[a]
	HRT-GPS	3218	19.7771	Dominated[a]
55	GDx	3067	19.7701	–
	Current practice	3084	19.7780	2168
	OCT	3190	19.7746	Dominated[a]
	HRT-MRA	3224	19.7771	Dominated[a]
	HRT-GPS	3233	19.7771	Dominated[a]
58	GDx	3082	19.7701	–
	Current practice	3084	19.7780	252
	OCT	3205	19.7746	Dominated[a]
	HRT-MRA	3238	19.7771	Dominated[a]
	HRT-GPS	3248	19.7771	Dominated[a]
61	Current practice	3084	19.7780	–
	GDx	3097	19.7701	Dominated[a]
	OCT	3220	19.7746	Dominated[a]
	HRT-MRA	3253	19.7771	Dominated[a]
	HRT-GPS	3263	19.7771	Dominated[a]
64	Current practice	3084	19.7780	–
	GDx	3112	19.7701	Dominated[a]
	OCT	3235	19.7746	Dominated[a]
	HRT-MRA	3268	19.7771	Dominated[a]
	HRT-GPS	3278	19.7771	Dominated[a]
67	Current practice	3084	19.7780	–
	GDx	3127	19.7701	Dominated[a]
	OCT	3250	19.7746	Dominated[a]
	HRT-MRA	3283	19.7771	Dominated[a]
	HRT-GPS	3292	19.7771	Dominated[a]

continued

TABLE 63 Incremental cost-effectiveness for the base case with different NHS Reference Costs applied to the triage strategies (*continued*)

NHS Reference Cost (£)	Intervention	Cost (£)	QALYs	ICER
70	Current practice	3084	19.7780	–
	GDx	3142	19.7701	Dominated[a]
	OCT	3265	19.7746	Dominated[a]
	HRT-MRA	3298	19.7771	Dominated[a]
	HRT-GPS	3307	19.7771	Dominated[a]
73	Current practice	3084	19.7780	–
	GDx	3157	19.7701	Dominated[a]
	OCT	3279	19.7746	Dominated[a]
	HRT-MRA	3313	19.7771	Dominated[a]
	HRT-GPS	3322	19.7771	Dominated[a]
76	Current practice	3084	19.7780	–
	GDx	3172	19.7701	Dominated[a]
	OCT	3294	19.7746	Dominated[a]
	HRT-MRA	3327	19.7771	Dominated[a]
	HRT-GPS	3337	19.7771	Dominated[a]
79	Current practice	3084	19.7780	–
	GDx	3187	19.7701	Dominated[a]
	OCT	3309	19.7746	Dominated[a]
	HRT-MRA	3342	19.7771	Dominated[a]
	HRT-GPS	3352	19.7771	Dominated[a]
82	Current practice	3084	19.7780	–
	GDx	3202	19.7701	Dominated[a]
	OCT	3324	19.7746	Dominated[a]
	HRT-MRA	3357	19.7771	Dominated[a]
	HRT-GPS	3367	19.7771	Dominated[a]
85	Current practice	3084	19.7780	–
	GDx	3217	19.7701	Dominated[a]
	OCT	3339	19.7746	Dominated[a]
	HRT-MRA	3372	19.7771	Dominated[a]
	HRT-GPS	3381	19.7771	Dominated[a]

a Dominated: an intervention is more costly but is less effective or as effective as an intervention that is less costly.

TABLE 64 Incremental cost-effectiveness ratios of increasing costs of triage strategies and not treating patients diagnosed as 'at risk'

Increasing cost of triage strategy (£)	Intervention	Cost (£)	QALYs	ICER
+10	GDx	2719	19.7393	–
	OCT	2840	19.7410	68,260
	HRT-MRA	2869	19.7414	83,488
	HRT-GPS	2879	19.7414	Dominated[a]
	Current practice	2954	19.7415	488,759
+13	GDx	2733	19.7393	–
	OCT	2853	19.7410	68,229
	HRT-MRA	2883	19.7414	83,457
	HRT-GPS	2893	19.7414	Dominated[a]
	Current practice	2954	19.7415	409,713
+16	GDx	2747	19.7393	–
	OCT	2867	19.7410	68,198
	HRT-MRA	2897	19.7414	83,426
	HRT-GPS	2906	19.7414	Dominated[a]
	Current practice	2954	19.7415	330,667
+19	GDx	2761	19.7393	–
	OCT	2881	19.7410	68,167
	HRT-MRA	2910	19.7414	83,396
	HRT-GPS	2920	19.7414	Dominated[a]
	Current practice	2954	19.7415	251,620
+22	GDx	2775	19.7393	–
	OCT	2895	19.7410	68,137
	HRT-MRA	2924	19.7414	83,365
	HRT-GPS	2934	19.7414	Dominated[a]
	Current practice	2954	19.7415	172,574
+25	GDx	2788	19.7393	–
	OCT	2908	19.7410	68,106
	HRT-MRA	2938	19.7414	83,335
	HRT-GPS	2947	19.7414	Dominated[a]
	Current practice	2954	19.7415	93,527
+28	GDx	2802	19.7393	–
	OCT	2922	19.7410	68,075
	HRT-MRA	2952	19.7414	83,304
	Current practice	2954	19.7415	14,481
	HRT-GPS	2961	19.7414	Dominated[a]

continued

TABLE 64 Incremental cost-effectiveness ratios of increasing costs of triage strategies and not treating patients diagnosed as 'at risk' (*continued*)

Increasing cost of triage strategy (£)	Intervention	Cost (£)	QALYs	ICER
+31	GDx	2816	19.7393	–
	OCT	2936	19.7410	68,044
	Current practice	2954	19.7415	34,813
	HRT-MRA	2965	19.7414	Dominated[a]
	HRT-GPS	2975	19.7414	Dominated[a]
+34	GDx	2830	19.7393	–
	OCT	2949	19.7410	68,014
	Current practice	2954	19.7415	8882
	HRT-MRA	2979	19.7414	Dominated[a]
	HRT-GPS	2989	19.7414	Dominated[a]
+37	GDx	2843	19.7393	–
	Current practice	2954	19.7415	48,341
	OCT	2963	19.7410	Dominated[a]
	HRT-MRA	2993	19.7414	Dominated[a]
	HRT-GPS	3002	19.7414	Dominated[a]
+40	GDx	2857	19.7393	0
	Current practice	2954	19.7415	42,328
	OCT	2977	19.7410	Dominated[a]
	HRT-MRA	3006	19.7414	Dominated[a]
	HRT-GPS	3016	19.7414	Dominated[a]
+43	GDx	2871	19.7393	–
	Current practice	2954	19.7415	36,314
	OCT	2991	19.7410	Dominated[a]
	HRT-MRA	3020	19.7414	Dominated[a]
	HRT-GPS	3030	19.7414	Dominated[a]
+46	GDx	2885	19.7393	–
	Current practice	2954	19.7415	30,300
	OCT	3004	19.7410	Dominated[a]
	HRT-MRA	3034	19.7414	Dominated[a]
	HRT-GPS	3043	19.7414	Dominated[a]
+49	GDx	2898	19.7393	–
	Current practice	2954	19.7415	24,287
	OCT	3018	19.7410	Dominated[a]
	HRT-MRA	3048	19.7414	Dominated[a]
	HRT-GPS	3057	19.7414	Dominated[a]

TABLE 64 Incremental cost-effectiveness ratios of increasing costs of triage strategies and not treating patients diagnosed as 'at risk' (*continued*)

Increasing cost of triage strategy (£)	Intervention	Cost (£)	QALYs	ICER
+52	GDx	2912	19.7393	–
	Current practice	2954	19.7415	18,273
	OCT	3032	19.7410	Dominated[a]
	HRT-MRA	3061	19.7414	Dominated[a]
	HRT-GPS	3071	19.7414	Dominated[a]
+55	GDx	2926	19.7393	–
	Current practice	2954	19.7415	12,260
	OCT	3045	19.7410	Dominated[a]
	HRT-MRA	3075	19.7414	Dominated[a]
	HRT-GPS	3084	19.7414	Dominated[a]
+58	GDx	2940	19.7393	–
	Current practice	2954	19.7415	6246
	OCT	3059	19.7410	Dominated[a]
	HRT-MRA	3089	19.7414	Dominated[a]
	HRT-GPS	3098	19.7414	Dominated[a]
+61	GDx	2954	19.7393	–
	Current practice	2954	19.7415	233
	OCT	3073	19.7410	Dominated[a]
	HRT-MRA	3102	19.7414	Dominated[a]
	HRT-GPS	3112	19.7414	Dominated[a]
+64	Current practice	2954	19.7415	–
	GDx	2967	19.7393	Dominated[a]
	OCT	3087	19.7410	Dominated[a]
	HRT-MRA	3116	19.7414	Dominated[a]
	HRT-GPS	3126	19.7414	Dominated[a]
+67	Current practice	2954	19.7415	–
	GDx	2981	19.7393	Dominated[a]
	OCT	3100	19.7410	Dominated[a]
	HRT-MRA	3130	19.7414	Dominated[a]
	HRT-GPS	3139	19.7414	Dominated[a]

a Dominated: an intervention is more costly but is less effective or as effective as an intervention that is less costly.

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