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Synopsis

Validating and updating the OHTS-EGPS model predicting 5-year glaucoma risk among patients with ocular hypertension using electronic medical records: a cohort study

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Abstract

Background: Ocular hypertension, that is intraocular pressure > 21 mmHg, is a risk factor for glaucoma. A glaucoma risk predictor, the Ocular Hypertension Study–European Glaucoma Prevention Study model, is available.

Objectives: (1) To validate and update the Ocular Hypertension Study–European Glaucoma Prevention Study risk prediction model in a United Kingdom population; (2) to assess the relative efficiency of alternative monitoring pathways according to glaucoma risk; (3) to determine the clinical and cost-effectiveness of treating people with ocular hypertension with intraocular pressure of 22 or 23 mmHg and (4) to elicit patient preferences for monitoring.

Design: (1) Retrospective data analysis of electronic medical records of ocular hypertension patients attending hospital eye services. The influence of the Ocular Hypertension Study–European Glaucoma Prevention Study predictors and additional ocular and systematic factors was explored. Validation: the Ocular Hypertension Study–European Glaucoma Prevention Study prediction model was applied. Update: the model was refitted by re-estimating baseline hazard and regression coefficients. (2, 3) Predictor versus standard care, with deterministic and probabilistic sensitivity analyses. Subgroup analysis for people with 22–23 mmHg intraocular pressure. (4) Discrete choice experiment.

Setting and participants: People with intraocular pressure 22–32 mmHg in either eye, at least four visual field tests, 5 years of follow-up, no significant ocular comorbidities. Data sourced from secondary clinical settings.

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Main outcome measures: Discriminative ability (c-index) and calibration (calibration slope) to predict conversion to glaucoma in 5 years. Quality-adjusted life-years, incremental cost-effectiveness ratio, preferences.
Data sources: Electronic medical records of 10 hospitals in England.
Results: (1) Of 9030 patients with ocular hypertension who fitted the inclusion criteria 1530 (16.9%) converted to glaucoma. The Ocular Hypertension Study–European Glaucoma Prevention Study model provided a pooled c-index of 0.61 (95% confidence interval: 0.60 to 0.63). The updated model had a pooled c-index of 0.67 (0.51 to 0.84). (2) In the economic model almost all (99%) patients were treated in the risk predictor strategy, and less than half (47%) in the standard care strategy. The risk predictor strategy produced higher costs, but also higher quality-adjusted life-years and is likely to be cost-effective compared with standard care. (3) Patients with ocular hypertension and intraocular pressure 22–23 mmHg had similar risk of conversion to the rest of the cohort. A treat-all strategy may not be cost-effective. (4) Three hundred and sixty patients were recruited from four NHS hospitals. Almost all respondents (92%) had experienced face-to-face monitoring at a hospital; fewer respondents had experienced virtual clinics (47%) or community optometrist monitoring (43%). Most patients preferred hospital-based monitoring services by health professionals rather than community-based by optometrists but patients with prior experience of community optometrist monitoring preferred it. Patients preferred options associated with lower risk of conversion and lower costs.
Limitations: Insufficient data to evaluate influence of ethnicity or ocular factors such as optic disc and retinal anatomy.
Conclusions: We validated the Ocular Hypertension Study–European Glaucoma Prevention Study predictor model in a large population with ocular hypertension achieving modest improvements. The use of a risk prediction tool is likely to be cost-effective. Reducing the risk of conversion was the most important preference for patients with ocular hypertension.
Future work: Future work should address the influence of genetic or other ocular factors in disease progression, evaluation of effectiveness and cost-effectiveness of different models of eye care, and on how to avoid late glaucoma presentation.
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Introduction

This report details the work undertaken to: (1) validate and update the the Ocular Hypertension Study (OHTS)–the European Glaucoma Prevention Study (EGPS) risk prediction model in a UK population with ocular hypertension (OHT); (2) assess the relative efficiency and patient preferences of alternative monitoring pathways for people with OHT; (3) determine the clinical and cost-effectiveness (CE) of treating people with OHT with intraocular pressure (IOP) of 22 or 23 mmHg; (4) evaluate patients preferences for monitoring services.

Rationale for research and background

Glaucoma is a chronic progressive optic neuropathy and a leading cause of irreversible blindness.[4] OHT is a risk factor for glaucoma and defined as an IOP of > 21 mmHg with normal optic disc and visual field (VF), with an open anterior chamber angle. According to the National Institute for Health and Care Excellence (NICE) 2017 updated glaucoma guideline around 1.3 million people aged over 40 in the UK have OHT. According to 'The Way Forward Project', commissioned by the Royal College of Ophthalmologists, from 2015 to 2035, the number of people in the UK with glaucoma will rise by 44% and with OHT by 16%, caused by a 'perfect storm of increased demand caused by more eye disease in an ageing population'.[5] Current standard practice is to monitor OHT in hospital eye service (HES), although there is potential for community optometrists to manage this condition, which could reduce pressures on HES, and waiting times for patients. NICE guidelines recommend treating patients with IOP of 24 mmHg and at risk of visual loss, but at present there is variability in the management of OHT in the UK. Robust data on the risk of developing glaucoma will be useful to develop monitoring strategies, for example from no or minimal follow-up to treatment and frequent follow-up.

A glaucoma risk prediction model based on the results of the OHTS[6] and the EGPS,[7] is available online: https://ohts.wustl.edu/risk/. This OHTS-EGPS risk calculator included age, IOP, central corneal thickness (CCT), a measure of the VF test [pattern standard deviation (PSD)] and the optic

nerve [(the vertical cup to disc ratio (VCDR)]. However, the 2017 NICE guidelines did not recommend the use of the OHTS-EGPS risk calculator because of its high risk of bias and uncertain generalisability to UK patients. Our study was designed to answer two research priorities by NICE: *'Validation of a risk prediction model for Ocular Hypertension'*, and *'What is the clinical and cost effectiveness of treating an IOP of 22 or 23 mmHg in people with normal optic discs and visual fields?'*. Validated risk prediction tools are used in other conditions to guide treatment decisions such as the need for lipid- lowering therapy to prevent cardiovascular disease.[8] The performance of a risk predictor can be measured using the c-index.[9] A c-index value generally considered useful in clinical practice is above 0.7; this indicates a model with good discriminatory ability. A risk prediction tool for OHT with high discriminatory ability will help inform decisions on optimal management. Finally, the use of a risk prediction tool will trigger service redesign and the alternative service delivery should be informed by patients' preferences.

Aims

The overall aim of this study was to validate and update a model to optimise the management of people in the UK with OHT using data on the risk of conversion to glaucoma and to compare the clinical and CE of different monitoring schemes proportionate to 5-year glaucoma risk.

Objectives

1. To validate and update the OHTS-EGPS risk prediction model in a large population of UK adults with OHT.
2. To assess the relative efficiency of alternative monitoring pathways for people with OHT (IOP of 24 mmHg or higher) according to glaucoma risk compared with standard practice.
3. To determine the clinical and CE of treating people with OHT who have IOP of 22 or 23 mmHg.
4. To elicit the preferences of patients with OHT for eye monitoring services in the UK.

Methods for data collection and analysis

Methods objective 1: to validate and update the OHTS-EGPS risk prediction model in a large population of UK adults with OHT

Population

We included adults with newly diagnosed OHT in one or both eyes, as recorded in the electronic medical records (EMRs). OHT was defined as an IOP ≥ 22 mmHg and ≤ 32 mmHg measured using Goldmann applanation tonometry (GAT), no clinical signs of primary open-angle glaucoma (OAG) (i.e. normal optic nerve examination and normal VF test), and no associated abnormalities on clinical exam (e.g. pigment dispersion or pseudoexfoliation). 'Normal' VF was defined as a reliable Standard Automated perimetry with Humphrey VFs (HVF) with a Glaucoma Hemifield Test (GHT) 'within normal limits'.

We excluded eyes with angle closure (including primary and secondary angle closure glaucoma) and those with clinically significant ocular comorbidity, such as maculopathies and patients with glaucoma (any type) in one eye at baseline. To match the original OHTS study,[6] those with IOP > 32 mmHg in either eye at baseline were excluded as 'glaucoma suspects'. We excluded those who did not have any VF testing and those without reliable VF testing. An unreliable VF was defined as a high frequency of false positives, more than 15%.[10] The unit of analysis was the person. Some patients contributed only one eye to the analysis.

Data extraction

Data were extracted from the EMRs for 10 hospital glaucoma services in England that used the Medisoft platform (Medisoft, Leeds, UK). Ethical approval for use of these data for this study was obtained (REC reference 21/EE/0109) and permissions received from each of the centres. Prior to extraction, all personal identifiers were removed and visit dates and dates of birth were perturbed (± 180 days) to preserve patient confidentiality. The records for each patient were perturbed by the same amount to preserve the temporal spacing of events.

Data were extracted for patients (n = 138,461) that attended any of the 10 hospital glaucoma services for the period November 1995–January 2022. Using the above inclusion and exclusion criteria (*Figure 1*), the analysis data set comprised 9030 patients (13,891 eyes). The cohort design excluded those that had received IOP-lowering medication prior to the start of OHT (the date of first IOP measurement > 21 mmHg). However, for some patients there was a delay before the start of VF follow-up (i.e. the date of first recorded normal VF). A total of 2722 (30%) of patients received medication from the date of OHT start to the date of VF start, inclusive, and were considered treated at the VF baseline.

Statistical analysis

The primary outcome was conversion to glaucoma within 5 years. We used VF tests to detect conversion to glaucoma, defined as two consecutive reliable abnormal VF examination results, that is GHT outside normal limits.[10–12] The date of conversion was the date of the first abnormal test result. Additionally, if an eye underwent surgery for glaucoma, even in the absence of VF conversion according to our definition, conversion to glaucoma was deemed to

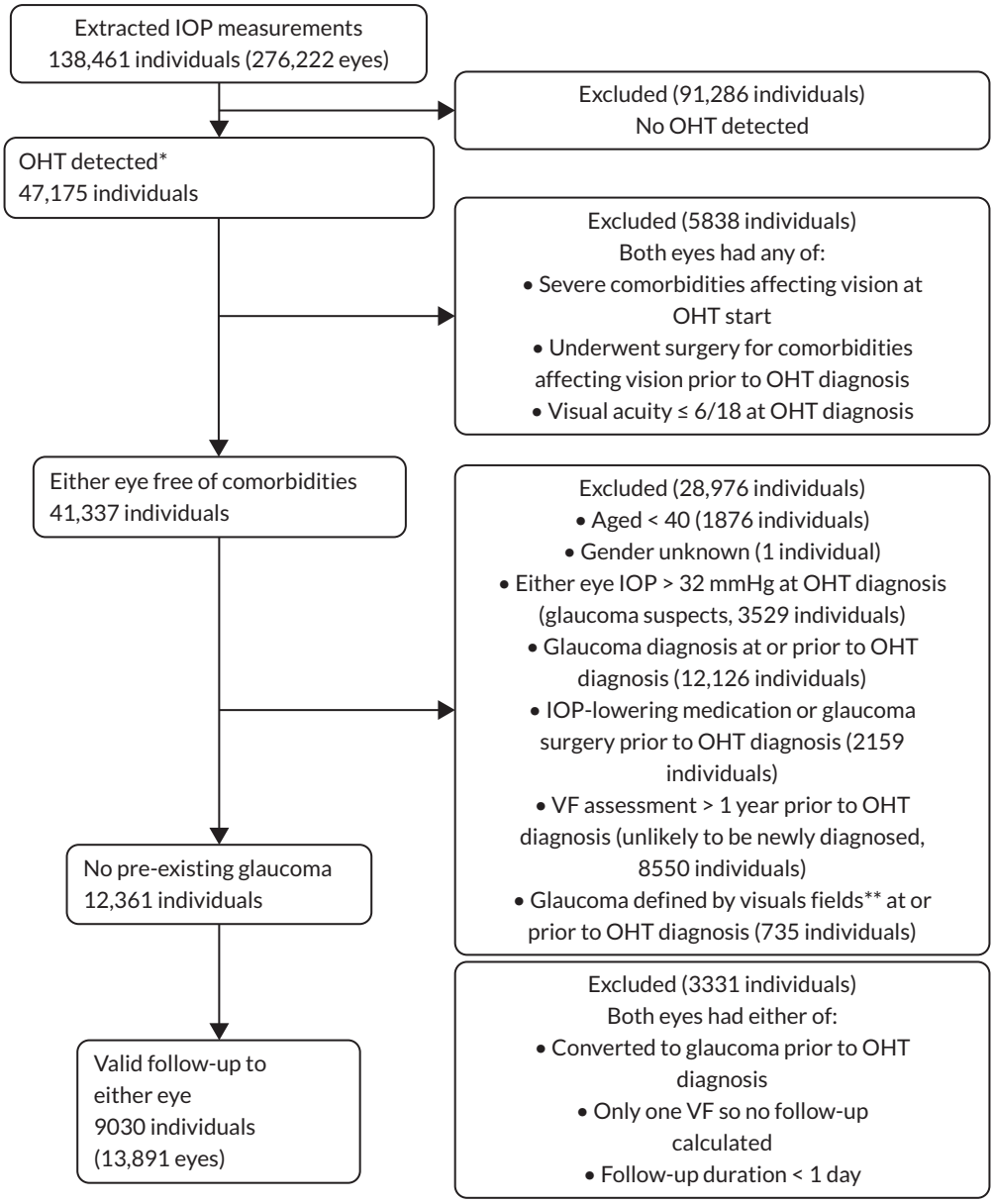


FIGURE 1 Flow chart describing construction of analysis cohort. Reproduced with permission from Wright *et al.*[1] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure above includes minor additions and formatting changes to the original text.* IOP measurement >21 mmHg followed by a reliable, normal visual field (glaucoma hemifield test - GHT within normal limits, false positive and negative rates <15%).
** Two consecutive reliable visual fields with GHT outside normal limits.

have occurred (at the earlier date). Patients were followed from date of the first normal VF test (after OHT diagnosis) until the date of glaucoma onset or censored at 5 years after first normal VF test, visual acuity dropping below 6/18 or diagnosis of an ocular copathology affecting VF (whichever was earliest).

Predictors

Data extracted included age, gender, ethnicity, history of glaucoma, diabetes, systemic hypertension, measurements of IOP, VFs and CCT. The predictors used in the OHTS-EGPS risk prediction model were available: (a) age (in years); (b) IOP (in mmHg, values outside 20–32 mmHg ignored); (c) CCT (in µm, values outside 475 to 658 µm ignored); (d) VF PSD (in dB, values 0.5–3 dB ignored); (e) VCDR in decimals, values outside 0.01–0.8 ignored). The average of both eyes was used for IOP, CCT, PSD and VCDR where available and appropriate. Also, additional potential predictors were available, including: (f) sex (male or female); (g) self-identified ethnicity (White, non-White or unknown); (h) family history (FH) of glaucoma (yes or no); (i) diabetes mellitus (self-reported, yes or no); (j) systemic hypertension (self-reported, yes or no); (k) treatment (received IOP-lowering medical treatment, yes or no).

Validation of the OHTS-EGPS model

First, the original OHTS-EGPS risk prediction model was applied to all 10 hospital glaucoma service data sets to calculate the predicted risk of developing glaucoma in 5 years for each participant as previously described:

$$\text{OHTS-EGPS predicted risk} = 1 - 0.92^{\exp(PI)}$$

$$PI = 0.23 \times (\text{agedecade} - 5.64) + 0.09 \times (IOP - 24.13) + 0.71 \times (T\_CCT + 14.33) + 0.12 \times (T\_PSD - 9.76) + 0.18 \times (T\_VCDR - 3.60),$$

$$PI = 4.91 + 0.23 \times (\text{agedecade}) + 0.09 \times (IOP) + 0.71 \times (T\_CCT) + 0.12 \times (T\_PSD) + 0.18 \times (T\_VCDR)$$

where agedecade is age in decades; IOP is in mmHg; CCT in µm is transformed using the equation T_CCT = −CCT/40; PSD is transformed using the equation T_PSD = PSD/0.2; and VCDR is transformed T_VCDR = VCDR/0.1.

Model performance was assessed by calculating measures of discriminative ability (Harrell's c-index) and calibration (using the calibration slope). The measures were calculated for each hospital and pooled across hospitals using random-effects meta-analysis. The calibration slopes were pooled on the original scale and the c-index was transformed to the logit scale before meta-analysis. Calibration plots of average observed risk against predicted 5-year risk were used to assess calibration at each hospital. Participants were divided by quintiles of predicted risk, and the average predicted risk for each quintile was compared with the corresponding Kaplan–Meier estimate of the observed risk within each hospital. To minimise the risk of bias due to missing data, missing CCT, VCDR and PSD values were imputed using multiple imputation by chained equations. Multiple imputation generates different imputed data sets to account for the uncertainty associated with the missing values. Ten imputations were applied. The imputation model was stratified by hospital and included all OHTS-EGPS predictors and the event indicator and cumulative hazard. Estimates were pooled across imputations using Rubin's rules. The analysis was repeated using complete cases as a sensitivity analysis.

Updating the OHTS-EGPS model

A new model was fitted using the five predictors in the OHTS-EGPS but re-estimating the baseline hazard and the regression coefficients in an attempt to improve both calibration and discrimination. Originally, the model was fitted in all 10 NHS hospitals and then validated separately in each hospital and the c-indices and calibration slopes pooled separately using meta-analysis. Internal–external cross-validation was used to validate this model. In this validation, the model was developed using a data set based on nine hospitals and validated in the hospital left out of the model development. This was repeated 10 times and meta-analysis models were then used to pool the c-index and calibration slope.

Further models were explored to attempt to improve prediction: including all additional predictors mentioned above, including all additional predictors except ethnicity (due to missing data), a model based on backward selection and a model excluding VCDR (because of concerns about reverse causation). A separate model was investigated including IOP of the worst eye (i.e. eye with highest IOP at baseline) to investigate the impact of average IOP across eyes in the main model. Another model was fitted including only patients with IOP ≤ 23. A separate model was fitted restricted to patients who had not received IOP treatments at baseline. Another model was restricted to those that never received IOP treatments.

Setting the risk prediction model in context. Influence of baseline variables on treatment

Treatment with IOP-lowering medication may influence the probability of conversion from OHT to glaucoma and hence performance of risk prediction models. The decision to start treatment with IOP-lowering medication for those with OHT is largely dependent on a small number of clinical characteristics: age, FH of glaucoma, CCT and IOP. To set the risk prediction models in context we modelled the associations between these variables and probability of having received IOP-lowering medication at baseline using logistic regression.

The following 10 NHS Trusts provided data for the study: Moorfields Eye Hospital NHS Foundation Trust, Nottingham University Hospitals NHS Trust, University Hospitals Bristol and Weston NHS Foundation Trust, Mid Yorkshire Hospitals NHS Trust, University Hospitals Plymouth NHS Trust, Gloucestershire Hospitals NHS Foundation Trust, Imperial College Healthcare NHS Trust, Wirral University Teaching Hospital NHS Foundation Trust, Bedford Hospital NHS Trust, Calderdale and Huddersfield NHS Foundation Trust.

Methods objective 2: to assess the relative efficiency of alternative monitoring pathways for people with ocular hypertension according to glaucoma risk compared with standard practice

We conducted a model-based economic evaluation to assess the CE of a monitoring pathway informed by the risk of conversion to glaucoma compared with standard care in the UK. We conducted a cost–utility analysis, and

our primary outcome was the incremental cost per quality-adjusted life-year gained.

Model structure

A discrete event simulation (DES) model was developed to model OHT and glaucoma monitoring and treatment. DES models offer flexibility and ability to explicitly evaluate monitoring frequency.[13–15] Diagnosed OHT (IOP ≥ 24 mmHg) patients entered the model with a set of predefined patient characteristics that depict their risk of conversion to glaucoma (*Figure 2*). A 'whether-to-treat' decision was assumed to be made by a hospital ophthalmologist/optometrist. Untreated patients had annual check-ups in the community and can be referred to the HES again when certain criteria are met (IOP out of control, or conversion to glaucoma). Treated but stable (IOP deemed on target after one checkup) OHT patients were referred from HES to community settings. 'Off-target' patients received treatment following a prespecified treatment sequence. Throughout the model, patients repeatedly faced three competing 'time-to-events': check-ups (eye tests), conversion to glaucoma (or progression to more advanced glaucoma for the OAG patients) or death, whichever the shortest would occur. These time-to-event values were recalculated each time an event occurred. For treated or untreated OHT patients monitored in community optometry, an unfavourable check-up would lead to a referral to the HES. Upon conversion to glaucoma, patients were followed up in HES. A schematic of the DES simulation is shown in *Figure 2*.

Care pathways

The clinical pathways for OHT monitoring were developed based on the 2022 NICE guidelines[16] and by members of the project management group: four ophthalmologists, two health economists and two statisticians. The two pathways considered are:

- standard care (SC)
- monitoring based on a risk prediction tool used by hospital ophthalmologists or optometrists in HES (RP).

All pathways comprise of both primary care (community optometry) and secondary care (HES) monitoring and treatment but differ in the criteria for accepting patients for treatment. For the SC pathway, the criteria for referring patients to HES were discussed in several meetings with the clinicians in the project management group, and a decision table was agreed based on the level of IOP, age, the cup-to-disk ratio and CCT. Those patients who met the initial treatment rule at the HES were treated with prostaglandin analogues (PGAs) (80% of them) or selective laser trabeculoplasty (SLT) (20% of them). Those who did not meet the referral criteria continued to be monitored in community optometry care without treatment.

Regarding monitoring, stable OHT patients (defined as 'on target' IOP, i.e. IOP reduced by 20% or more compared with the baseline IOP after treatment) were discharged from HES to community optometry after one clinical visit, while treatment was escalated for 'off-target' patients following a treatment sequence. For treated or untreated patients previously maintained at the community optometry settings, an observed conversion to glaucoma would trigger a referral to the HES, and an immediate eye assessment was assumed to be conducted by the hospital ophthalmologists to confirm the evidence of glaucoma. Patients with negative assessment results are referred back to the community optometry care and those with positive assessment results remain in HES. In addition, treated OHT patients maintained at community optometry with IOP measure deemed 'off target' would be referred to HES.

For the RP pathway, it was assumed that the risk prediction tool, developed and validated for Objective 1, was used by the hospital ophthalmologists or optometrists to make clinical decisions regarding the setting for eye care and whether to offer treatment to patients. The risk prediction tool was developed and validated using a large UK-based data set retrieved from the EMRs, which contains over 9000 OHT patients from 10 HES in the UK with at least 5 years of follow-up. The RP tool provides risk estimates of the 5-year risk of conversion to glaucoma used to inform monitoring and treatment decisions. Following Burr *et al.* risk classification,[17] patients were split into three groups based on the risk estimates: low risk (< 6%), intermediate risk (6–13%) and high risk (> 13%). Based on expert views, the high- and intermediate-risk groups were monitored and, if appropriate, treated in HES, and the low-risk groups were monitored in community optometry for regular eye check-ups without treatment. However, low-risk patients can be referred to the HES when their risk of conversion exceeds the threshold.

Baseline characteristics of the simulated cohort

A population of newly diagnosed OHT patients (defined as IOP ≥ 24 mmHg without sign of visual defect) were simulated according to a set of predefined patient characteristics depicting their risk of conversion to glaucoma (i.e. age, IOP, CCT, VCDR, PSD), which are key predictors of conversion.[18] Sampling was based on individual patient data extracted from the EMRs data set based on the UK OHT patients. Additional risk factors (i.e. whether a patient has hypertension, FH of glaucoma, diabetes, and biological gender) from the same data set were included.

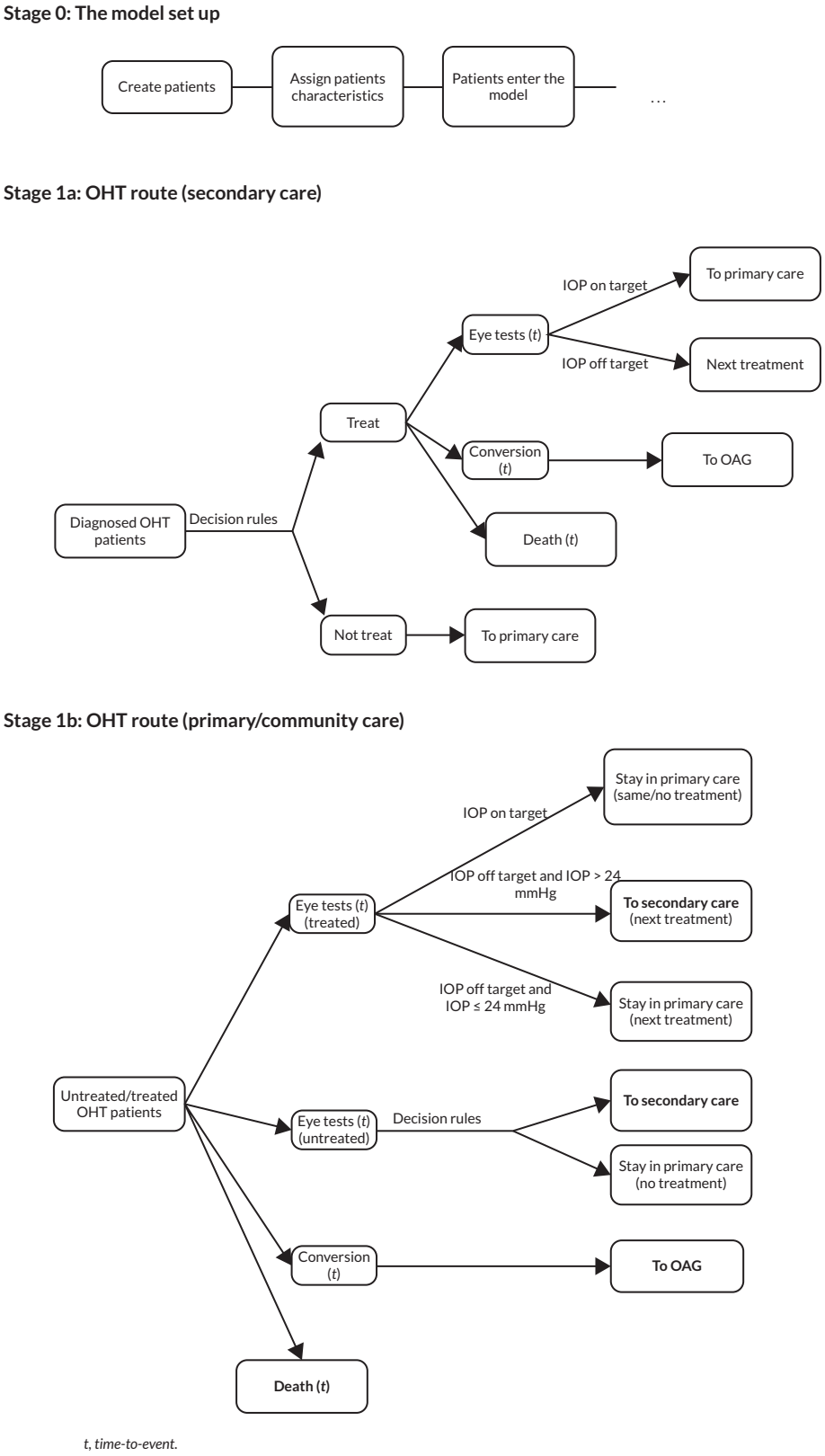
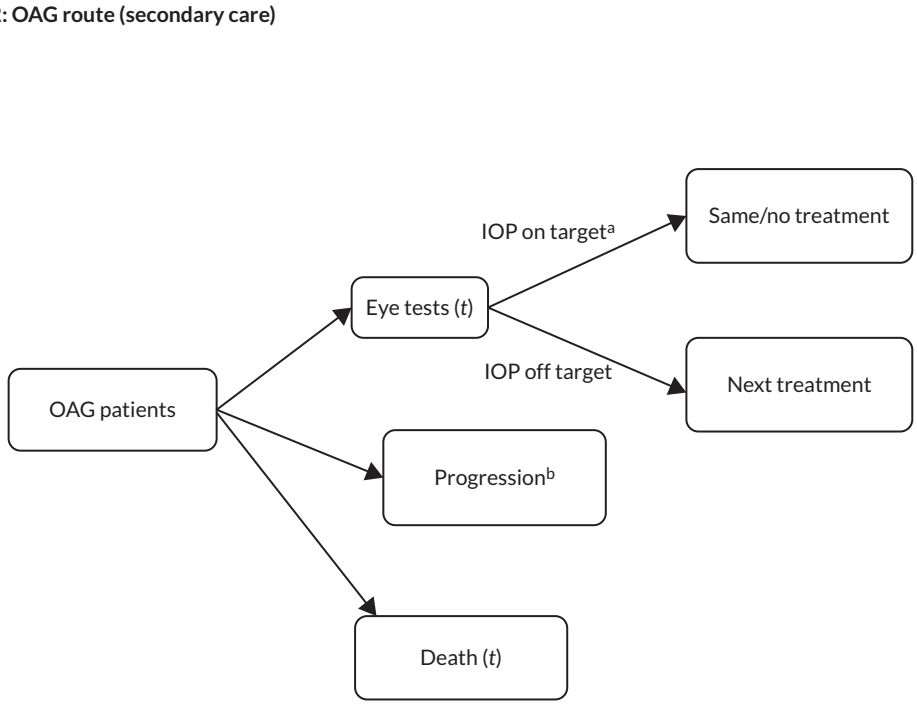


FIGURE 2 A schematic of the model structure. Reproduced with permission from Wu *et al.*[3] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure above includes minor additions and formatting changes to the original text.



t, time-to-event.

[a] *'On target' IOP means IOP reduced by 20% or more compared with the baseline IOP after treatment*

[b] *Progression to the next level of glaucomatous stage, which can be moderate, severe or visual impairment. Patients cannot progress further when reaching visual impairment.*

FIGURE 2 Continued

Mean deviation (MD) at conversion were drawn from a gamma distribution in which the mean and standard deviation (SD) are extracted from the data set (individual patient sampling was not used due to missing data). Life expectancy for each patient was drawn from the UK life table for the years of 2018–20,[19] which was then used to calculate time-to-death. *Table 1* shows the detailed statistics of the patient characteristics.

Modelling time-to-conversion and time-to-progression

Time-to-conversion to glaucoma and time-to-progression for OHT patients were estimated following the van Gestel *et al.* approach.[20] Time-to-conversion was calculated based on patients' risk profiles, current IOP and current age. The distribution of the time-to-conversion values were estimated based on a survival function adjusted at each time point of the time-to-conversion event. A key VF outcome, MDs, was used to model time-to-progression, which was linked to patients' IOP level. The higher a patient's IOP, the faster the patient would progress. Further details are reported in Wu *et al.*,[3] online supplemental material.

A widely used glaucomatous staging system was used to classify the VF outcome following Mills *et al.*,[21] which includes mild (MD between −0.01 and −6.00 dB), moderate (MD between −6.01 and −12.00 dB), severe glaucoma (MD between −12.01 and −20.00 dB) and visual impairment (MD smaller than −20.01 dB), each implying a different level of visual function corresponding to the patient's quality of life.

Treatment sequence and effectiveness

National Institute for Health and Care Excellence guidelines describe the treatment options for OHT and OAG patients;[16] however, clinical practice varies across the UK depending on patient-specific characteristics and disease progression. Therefore, a common sequence of treatment was developed based on the NICE guidelines and expert views (*Figure 3*). Initial medical treatment for OHT patients in the model was PGAs, followed by a combination of PGAs and beta-blocker (BB), and then followed by SLT. Treatment escalation was triggered if a patient's IOP was 'off target' (defined as a baseline IOP reduction of < 20%) or conversion to OAG was observed. A similar

TABLE 1 Baseline characteristics of the extracted individual patients

Baseline variables	Mean	SD	Data source
Age (years)	62.01	10.56	GRIP data set
CCT (μm)	558.66	35.83	
IOP (mmHg)	26.51	2.13	
PSD (dB)	1.63	0.34	
VCDR	0.46	0.17	
Hypertension (Y/N)	0.12	0.33	
FH of glaucoma (Y/N)	0.26	0.44	
Diabetes (Y/N)	0.14	0.34	
Male (Y/N)	0.43	0.50	
Previously treated (Y/N)	0.36	0.48	
MD at conversion	−2.94	2.67	
Life expectancy	Various		UK interim life *Tables 2018–20* (gender average)[19]

Source
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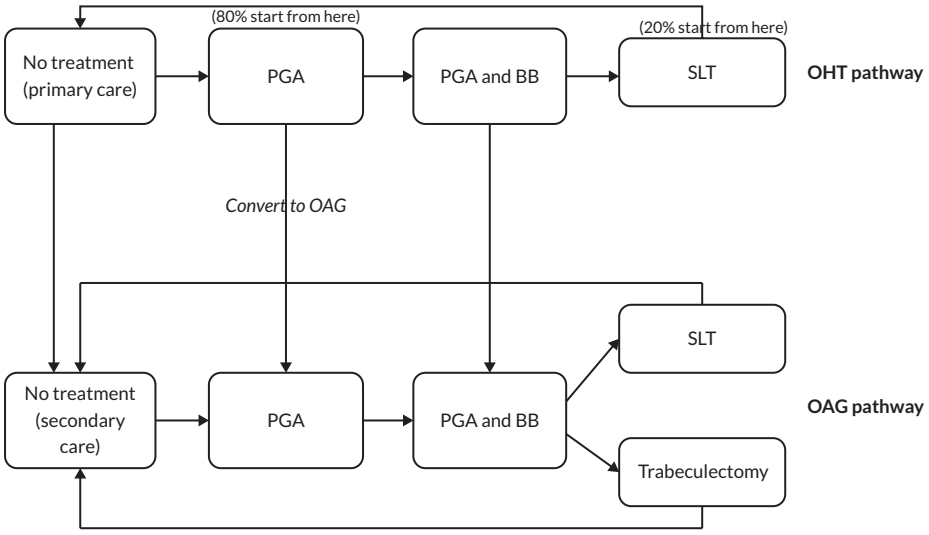

FIGURE 3 Treatment sequence for the OHT and OAG pathway.

treatment sequence was assumed for patients converting to glaucoma. However, trabeculectomy was considered as another option if a patient did not meet the condition of SLT treatment.

Clinical visits

The frequency of clinical visits was informed by the NICE guidelines and further calibrated using experts' views. To reflect imperfect diagnostic accuracy of conversion from OHT to mild OAG in the community optometrists setting sensitivity and specificity were assumed to be < 1 (0.76 and 0.93 for sensitivity and specificity).[22] Perfect information for the diagnosis of glaucoma as well as the detection of disease progression was assumed in the HES setting (sensitivity and specificity of both conversion and progression equal to 1). It was further assumed that

community optometrists would detect conversion to OAG if the patient progressed to moderate, severe glaucoma, or visual impairment.

Costs of monitoring and treatment and health utilities

The unit cost for a visit to the NHS ophthalmology services was obtained from the NHS reference cost. Following Burr *et al.*[17] this unit cost was assumed to include the IOP test only, while the unit cost for both the IOP and VF tests was assumed to be twice the cost of an IOP test given the time needed to complete the visit. The unit cost for IOP and VF tests under community optometrist settings was assumed to equal an NHS sight test fee.[17] Following the same logic, the fee for the IOP-only test was halved.

The cost for latanoprost and timolol was used to cost the PGAs and BB medical treatment, respectively. These unit costs were obtained from the *British National Formulary* (BNF),[23] assuming one bottle of the eyedrops per month per patient. Unit cost for the trabeculotomy was obtained from the NHS reference costs.[24] The unit cost for the SLT was obtained from the LiGHT trial.[25]

We used the EuroQol-5 Dimensions to value quality of life for each disease state in the model (i.e. OHT, mild, moderate, severe glaucoma and visual impairment) based on a valuation study of an OAG population from the UK.[26] Given small differences in visual damage between OHT and mild OAG, the utility scores for these two states were assumed to be the same.[17] We assumed no quality-of-life reductions due to treatment side effects based on the notion that side effects would either be mild, for a very short period of time, or would trigger a treatment change. Clinical effectiveness input data, costs and utilities are reported in *Table 2*.

TABLE 2 Parameters and sources for the treatment effectiveness, costs and utilities

Treatment	Data input	Distribution	Data source
PGAs (Latanoprost). IOP proportion reduction	Mean: 0.295 SD: 0.08	Beta (alpha: 22; beta: 9)	Valk *et al.*[27] and van Gestel[28]
PGAs and BB (Latanoprost and Timolol) as second-line treatment (additional effectiveness compared with Latanoprost)	Mean: 0.14 SD: 0.08	Beta (alpha: 2; beta: 15)	Webers *et al.*[29] and van Gestel[28]
SLT	Mean: 0.312 SD: 0.08	Beta (alpha: 9.2; beta: 20.2)	Mean estimate: Chi *et al.*;[30] SD: assumption
Trabeculotomy	Mean: 0.447 SD: 0.189	PERT	Crabb *et al.*[31] and Kirwan *et al.*[32]
Costs for monitoring			
HES: IOP only	£147		NHS reference costs (2021–2);[19] ophthalmology outpatient attendance (service code: 130)
HES: IOP and VF	£294		Assumption
Primary care: NHS sight test fee: IOP only	£11.57		Assumption
Primary care: NHS sight test fee: IOP and VF	£23.14		Department of Health (General Ophthalmic Services: NHS sight test fee, updated in April 2023)[33]
Costs for treatments			
Latanoprost	£149.76 per year (2.5 ml = £12.48)		BNF 2023; Xalatan
Latanoprost and Timolol	£171.84 per year (2.5 ml = £14.32)		BNF 2023; Xalacom
SLT	£151 (per patient)		Gazzard *et al.*[25]
Trabeculotomy	£1694 (per patient)		NHS reference costs (2021–2);[19] glaucoma surgical procedures (HRGs code: BZ92B; average of total cases)

TABLE 2 Parameters and sources for the treatment effectiveness, costs and utilities (*continued*)

Treatment	Data input	Distribution	Data source
Disease states			
Patients with OHT	0.8015		Assumption
Patients with mild OAG	0.8015		Burr, Kilonzo, *et al.* (2007)[26]
Patients with moderate OAG	0.7471		Burr, Kilonzo, *et al.* (2007)[26]
Patients with severe OAG	0.7133		Burr, Kilonzo, *et al.* (2007)[26]
Visually impaired OAG patients	0.535		Burr, Mowatt, Hernández, *et al.* (2007)[34]

HRG, Healthcare Resource Group; PERT, project evaluation and review technique.

Data analysis

A cohort of 50,000 patients with diagnosed OHT were used in the simulation using TreeAge (2023 R2.0) (TreeAge Software, Inc., Williamstown, MA, USA) for the base-case analysis. All the analyses were based on the NHS perspective with all costs expressed in Great British pounds and 2021–2 prices. The adjustment was conducted using a web-based tool.[35] The time horizon of the model was lifetime with cost and utilities discounted at an annual rate of 3.5%.

To identify the key drivers of uncertainty around the costs and effectiveness, one-way and probabilistic sensitivity analyses (PSA) were used after the base-case analysis. One-way sensitivity analyses were conducted for: (1) the threshold of treatment decision regarding the RP strategy; (2) medication and monitoring costs; (3) adherence rate to medication. Cohorts of 10,000 patients were used for all sensitivity analyses. Higher numbers of simulated patients (e.g. 50,000) significantly increased the model running time but, on visual inspection, produced similar results. Finally, 10,000 simulated patients with 1000 replications (second order uncertainty) were used for the PSA. Further details for the PSA including probability distributions used are provided in Wu *et al.*,[3] online supplemental material.

Model validation and calibration

The model has been carefully validated based on the internal data set used and several external data sources, and several calibrations have been made. Further details for the validation and calibration process are provided in Wu *et al.*,[3] online supplemental material.

Methods objective 3: to determine the clinical and cost-effectiveness of treating people with ocular hypertension who have intraocular pressure of 22 or 23 mmHg

To assess the clinical and CE of treating people with OHT who have IOP of 22 or 23 mmHg, we refitted the OHTS-EGPS model using just those patients in this subgroup (23.5% of the entire cohort). The estimated hazard ratios (HRs) for this model were compared with one fitted using the entire cohort.

To assess the CE of treating people with OHT with IOP of 22 or 23 mmHg, a DES model was used to perform the CE analysis. This model was similar to the one used for assessing the CE of the risk prediction tool, except that all participants in the standard care strategy (the comparator) were maintained in community optometry without treatment, while all participants in the treat-all strategy (the intervention) were initially treated in HES.

The main outcome measures were costs, quality-adjusted life-years (QALYs) and incremental cost-effectiveness ratio (ICER) per additional QALY.

Methods objective 4: to elicit the preferences of patients with ocular hypertension for eye monitoring services in the United Kingdom

Study sample

The multicentre study included four (UK) NHS sites (Belfast Health and Social Care Trust, Nottingham University Hospitals Trust, Manchester University NHS Foundation Trust, and London Moorfields Eye Hospital

NHS Foundation Trust). OHT patients who had been under active hospital review within the past year were identified by clinicians or research nurses from medical records. The inclusion criteria were a diagnosis of OHT by a health professional and aged 18 years or above. Based on recommended sample sizes for discrete choice experiment (DCE) studies,[36] our target sample size was 375 respondents. The study was approved by NHS Research Ethics Board (23/EM/0060) and received local research and development approval from each site.

Data collection

Between June and September 2023, the study pack was posted to potential study participants. The study pack included a personalised invitation letter, participant information sheet, the DCE survey for self-completion and a pre-paid return envelope. Postcard reminders were sent to all potential respondents 1 week after the initial mail-out. One thousand two hundred and fifty potential respondents were identified across the sites based on an assumed response rate of 30%.[37] Implied consent was assumed if a participant completed and returned the survey. The survey asked respondents to complete 10 DCE choice tasks and describe their current OHT monitoring and socioeconomic status.

The discrete choice experiment

Following best practice recommendations for the development of DCEs, the attributes and levels included in the DCE were chosen following a literature review and qualitative research with OHT patients.[36,38] Six attributes were included to describe alternative OHT monitoring services (*Table 3*): how OHT monitoring is organised, visit frequency (every 6–24 months), travel time from home (15–60 minutes), clinicians use of a risk calculator to inform the monitoring plan (no, yes), risk of developing glaucoma in 10 years (5–20%) and monitoring cost (£50–300).

Based on the attributes and levels, a D-efficient fractional-factorial design was used to construct 20 choice tasks using the Ngene software (version 1.3.0) (ChoiceMetrics, Sydney, NSW, Australia).[39] A D-efficient design minimises the error variance of the estimator used for analysis. This means that the analysis model and any prior estimates must be specified at the design stage. The analysis model was specified as main effects only and given the lack of

TABLE 3 Discrete choice experiment attributes and levels

Attributes	Levels				
Where you go to have your tests tested and who carries out the tests (ORGANISATION)[a]	Face-to-face service: Your eyes will be tested by an eye doctor at the hospital. The eye doctor will talk with you about your tests, current situation and follow-up plans on the day of the test.	Hospital-based virtual clinic: Your eyes will be tested by a technician at the hospital. After the tests, an eye doctor will review your test results. You will receive a letter about your tests, current situation and follow-up plans another day.	Community optometrist: Your eyes will be tested by a local optometrist. The optometrist will talk with you about your tests, current situation and follow-up plans on the day of the test.		
How often your eyes are tested (FREQUENCY)	Once every 6 months	Once every 12 months	Once every 18 months	Once every 24 months	
Travel time from home (TRAVEL)	15 minutes	30 minutes	45 minutes	60 minutes	
This eye service plan is based on (CALCULATOR)	Eye doctor's experience	Eye doctor's experience and the results of a risk calculator			
Out of 100 people with ocular hypertension how many will convert to glaucoma in the next 10 years (RISK)	5	10	15	20	25 (no further visits)
Your cost of attending eye care services over the next 2 years (COST) (£)	50	100	200	300	0 (no further visits)

a Corresponding variable names used in the statistical analysis.

strong evidence regarding the direction of the parameters, all the parameter priors were assumed to be zero. The design aimed to select 20 choice tasks, which were split into 2 blocks of 10 tasks to reduce the burden to respondents. This design meant that there were 2 versions of the survey each with 10 choice tasks. Respondents were asked to imagine that they were offered a chance to change their OHT monitoring service. In each choice, task respondents were asked to 'choose' the monitoring service that they would prefer from two alternative services A or B, or 'no further visits' (*Figure 4*). The survey was tested in a series of four 'Think Aloud' interviews with patient representatives to ensure the survey was clear and readily understood and minor wording changes were made.

Data analysis

The DCE data were modelled using a random utility framework. This framework assumes that the utility *U* a respondent *n* receives from monitoring service *i* in choice task *t* can be represented by a deterministic and a random part:[40]

$$U_{itn} = \beta X_{itn} + \varepsilon_{itn} \quad (1)$$

Xitn is a vector representing the DCE attributes presented in alternative *i*, *β* is the marginal utilities, and *εitn* is the error term following a Gumbel distribution. We assume that respondents choose the monitoring plan that brings them the highest utility in each choice set. Equation 1 can be rewritten as:

$$U_{itn} = ASC_0 + \beta_1 FACETOFACE + \beta_1 VIRTUAL + \beta_3 FREQUENCY\_6 + \beta_4 FREQUENCY\_12 + \beta_5 FREQUENCY\_18 + \beta_6 TRAVEL + \beta_7 CALCULATOR + \beta_8 RISK + \beta_9 COST + \gamma_n + \varepsilon_{itn} \quad (2)$$

$$\gamma_n \sim N(0, \sigma)$$

where ASC_0 represents an alternative specific constant for the monitoring alternatives and captures respondents' preferences to be monitored or not. The *β* coefficients represent the mean marginal utility of each attribute on the utility of a monitoring service. The interpretation of the mean marginal utilities depends on the unit of measurement. *FACETOFACE* and *VIRTUAL* represent the organisation attribute and were coded as dummy variables that measure the mean marginal utility of a face-to-face hospital service and a hospital-based virtual clinic relative to a community optometrist. The *FREQUENCY* of testing was coded as dummy variables to allow for non-linearities in respondents' preferences for monitoring frequency and these measured the mean marginal utility of a 6- (*FREQUENCY_6*), 12- (*FREQUENCY_12*) and 18- (*FREQUENCY_18*) month monitoring interval relative to a 24-month interval. *TRAVEL* was a linear variable and

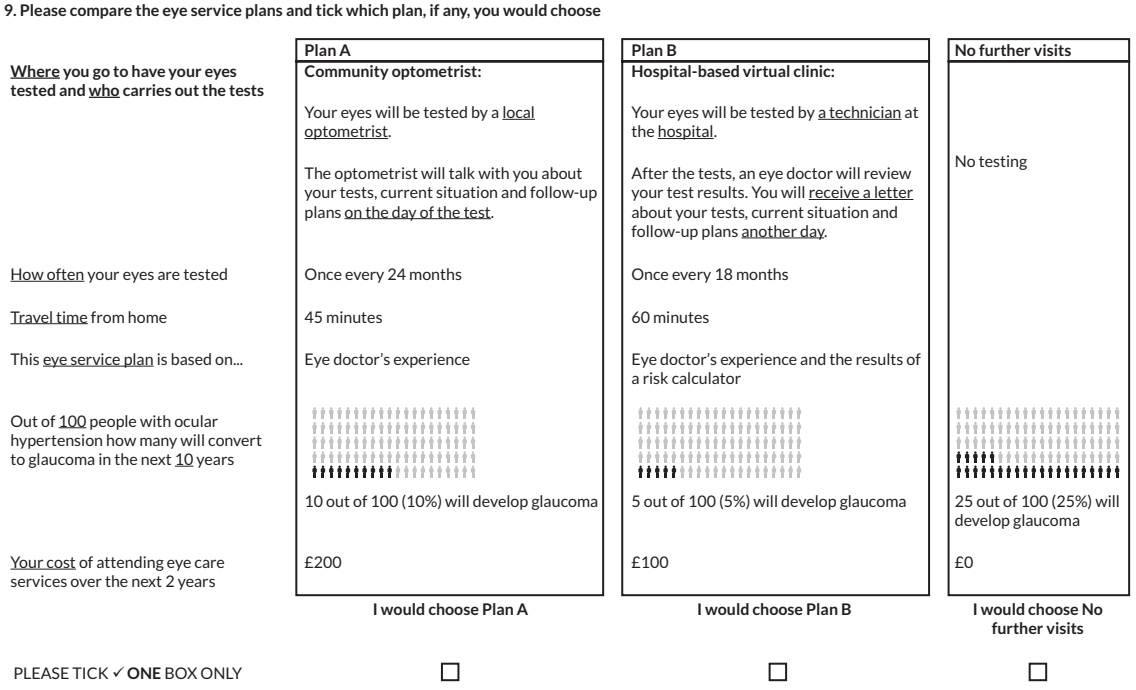

FIGURE 4 Example of choice cards. Reproduced with permission from Wu *et al.*[2] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure above includes minor additions and formatting changes to the original text.

represented the mean marginal utility of a 1-hour increase in travel time. *CALCULATOR* was a dummy variable that measured the mean marginal utility of the monitoring interval being based on the 'eye doctor's experience and the results of a risk calculator' compared to 'eye doctor's experience' alone. *COST* was a linear and continuous variable that represented the effect of a £1 increase in the cost of attending eye care services over the next 2 years [Nonlinear specification for the travel and cost attributes has been tested by adding a quadratic term for each regression. The results did not support the use of nonlinear specification (i.e. the quadratic terms were not significant at a 5% level) and a linear specification was adopted]. We expected that respondents would prefer shorter travel times and lower monitoring service cost but had no a-priori preference expectations for the remaining attributes. We also calculated respondents' mean marginal willingness-to-pay (WTP) for change in OHT monitoring service)[36,38] which allowed us to compare respondents' values across the attributes. The marginal WTP for a service attribute X is given by the ratio of the coefficient of the service attribute to the coefficient of the cost attribute:

$$WTP_X = -\frac{\beta_X}{\beta_9} \quad (3)$$

We used the delta method to construct 95% confidence intervals (CIs) for the estimated WTP.[41]

We explored observed preference heterogeneity by interacting selected respondent characteristics with the DCE attributes. First, we tested the effect of previous OHT monitoring experience on preferences for monitoring attributes. We explored interactions between respondents' previous and recently experienced OHT monitoring organisation and the DCE attributes. We also explored interactions between selected socioeconomic variables such as age and sex with DCE attributes.

All data analyses were performed using Stata version 17.0 (StataCorp LP, College Station, TX, USA). The DCE data were analysed using an error component logit (ECL) model to account for potential correlation across respondents' choice tasks.[42] Therefore, the additional error term (γn) captured any patient-specific error and was specified to follow a standard normal distribution. The model was estimated using simulated maximum likelihood estimation with 1000 Halton draws.[43]

Results

Results Objective 1: to validate and update the OHTS-EGPS risk prediction model in a large population of UK adults with OHT

Validation of the OHTS-EGPS model

A total of 1530/9030 (16.9%) patients converted to glaucoma during follow-up. Patients who converted were 4 years older on average than those that did not and had slightly higher PSD (*Table 4*). Proportions converted ranged from 11.7% (hospital 9) to 20.7% (hospital 1). Distributions of other predictors were similar across groups. Proportions treated at baseline ranged from 22.0% (hospital 8) to 48.1% (hospital 10).

TABLE 4 Characteristics of participants with glaucoma within 5 years and those with no glaucoma within 5 years (not restricted based upon 5 years of follow-up)

		Entire cohort	
Variable	**Category**	**No glaucoma**	**Glaucoma**
N		7500	1530
Age: mean (SD)		61.5 (10.5)	65.6 (10.4)
Age (years)	40–49	1249 (17%)	132 (9%)
	50–59	2070 (28%)	321 (21%)
	60–69	2488 (33%)	505 (33%)
	70–79	1421 (19%)	468 (31%)
	≥ 80	272 (4%)	104 (7%)
Male		4084 (54%)	840 (55%)

TABLE 4 Characteristics of participants with glaucoma within 5 years and those with no glaucoma within 5 years (not restricted based upon 5 years of follow-up) (*continued*)

		Entire cohort	
Variable	**Category**	**No glaucoma**	**Glaucoma**
Hospital ID	1	447 (6%)	117 (8%)
	2	366 (5%)	64 (4%)
	3	537 (7%)	91 (6%)
	4	337 (4%)	111 (7%)
	5	996 (13%)	159 (10%)
	6	2165 (29%)	512 (33%)
	7	1084 (14%)	251 (16%)
	8	758 (10%)	118 (8%)
	9	621 (8%)	82 (5%)
	10	189 (3%)	25 (2%)
IOP: mean (SD)		25.0 (2.6)	25.1 (2.7)
IOP (mmHg)	< 22.5	1302 (17%)	289 (19%)
	22.5–25	2588 (35%)	474 (31%)
	25–27.5	2099 (28%)	453 (30%)
	27.5–30	988 (13%)	193 (13%)
	≥ 30	523 (7%)	121 (8%)
CCT: mean (SD)		560.3 (35.6)	553.0 (35.1)
CCT (μm)	< 500	278 (4%)	74 (5%)
	500–549	2214 (30%)	511 (33%)
	550–599	2953 (39%)	538 (35%)
	≥ 600	869 (12%)	112 (7%)
	Missing	1186 (16%)	295 (19%)
PSD: mean (SD)		1.6 (0.3)	1.8 (0.4)
PSD (dB)	< 1.5	2186 (29%)	215 (14%)
	1.5–2	2268 (30%)	497 (32%)
	2–2.5	485 (6%)	178 (12%)
	≥ 2.5	97 (1%)	44 (3%)
	Missing	2464 (33%)	596 (39%)
VCDR: mean (SD)		0.5 (0.2)	0.5 (0.2)
VCDR	< 0.2	169 (2%)	23 (2%)
	0.2–0.4	1286 (17%)	179 (12%)
	0.4–0.6	1873 (25%)	313 (20%)
	0.6–0.8	1248 (17%)	301 (20%)
	≥ 0.8	103 (1%)	40 (3%)
	Missing	2821 (38%)	674 (44%)

continued

TABLE 4 Characteristics of participants with glaucoma within 5 years and those with no glaucoma within 5 years (not restricted based upon 5 years of follow-up) (*continued*)

		Entire cohort	
Variable	**Category**	**No glaucoma**	**Glaucoma**
Ethnicity	White	4796 (64%)	1076 (70%)
	Non-White	487 (6%)	118 (8%)
	Not stated	2217 (30%)	336 (22%)
FH glaucoma		2002 (27%)	368 (24%)
Diabetes		973 (13%)	265 (17%)
Hypertension		1059 (14%)	173 (11%)
Treatment		2220 (30%)	502 (33%)

Source
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The discriminant power of the OHTS-EGPS model (model A) was suboptimal, ranging from 0.55 to 0.67 between hospitals, with a pooled c-index (95% CI) of 0.61 (0.60 to 0.63) (*Table 5*). Calibration was also poor, ranging from 0.25 to 0.64 between hospitals (slope of 1.00 indicates perfect calibration), with a pooled calibration slope of 0.45 (0.38 to 0.51). These estimates indicate that predictions are more extreme than observed risk, that is the model systematically underestimated risk across all but the highest risk quintile (see *Figure 4*; the majority of points are above the perfect calibration line). Model performance showed no substantial differences when restricted to complete cases.

Updating the OHTS-EGPS model

The overall re-estimated model (model B) performed better than the OHTS-EGPS model (model A), with a pooled c-index of 0.67 (0.65, 0.69) indicating better discrimination (*Table 6*). Calibration of the re-estimated model was good, with a pooled calibration slope of 0.96 (0.84 to 1.09) and good calibration across all hospitals except hospital number 9 (*Figure 5*).

In both the overall and hospital-specific models (model B), re-estimated coefficients for age, VCDR and PSD were similar to those in the original OHTS-EGPS model. In contrast, the first measurement of IOP in OHT patients was not associated with conversion risk in our data set [HR 0.99 (0.98 to 1.01) vs. 1.09 in OHTS-EGPS]. The coefficient for CCT was substantially lower in our cohort [HRs in re-estimated model 1.06 (0.99 to 1.14) vs. 2.04 in OHTS-EGPS], indicating that a low CCT was not associated with increased glaucoma risk in our cohort.

Varying the choice of predictors in the risk prediction model had little influence on model performance, with measures of both discrimination and calibration almost identical across the five model variants. Model coefficients for each predictor varied little among the model variants, indicating that they were largely unaffected by the addition or removal of other predictors. However, the coefficients in each model variant provide additional insight into the factors associated with conversion from OHT to glaucoma. Removing VCDR had little impact, indicating that measurement variability is not an issue in this data set. Gender and FH of glaucoma were not associated with conversion risk whereas hypertension was associated with reduced risk of conversion [HR 0.81 (95% CI 0.69 to 0.96)] and diabetes was associated with increased risk [1.27 (95% CI 1.11 to 1.45)]. These two variables were included in the backward selected model but IOP and CCT were dropped, reinforcing our finding that these two variables have minimal predictive value in our data set. Averaging IOP measurements across eyes in the main model had no influence on model performance; estimates were the same when worse eye IOP was used instead. Restricting analysis to only those with IOP ≤ 23 had similarly little influence.

The OHTS-EGPS model was refitted using just those not treated at VF baseline (n = 6308 using the entire cohort, n = 2904 in complete-case analysis). The estimated HRs for each predictor and the overall model performance were almost identical to the main model fitted using both those treated and those untreated at VF baseline. A similar pattern was observed when we refitted the model using just those that never received treatment (n = 2712 using the entire cohort, n = 1658 in complete-case analysis).

TABLE 5 Performance of OHTS-EGPS model with original coefficients (model A) by hospital

	OHTS-EGPS (model A)	Hospital 1	Hospital 2	Hospital 3	Hospital 4	Hospital 5
n		117/564	64/430	91/628	111/448	159/1155
Baseline predictor, HR (95% CI)						
Age (decade)	1.26	1.44 (1.19 to 1.75)	1.46 (1.13 to 1.87)	1.18 (0.89 to 1.55)	1.20 (0.99 to 1.46)	1.31 (1.09 to 1.56)
IOP (mmHg)	1.09	1.00 (0.93 to 1.07)	1.03 (0.94 to 1.13)	0.94 (0.86 to 1.04)	1.04 (0.96 to 1.12)	1.04 (0.98 to 1.10)
CCT (per 40 µm thinner)	2.04	0.83 (0.67 to 1.02)	1.12 (0.84 to 1.50)	1.20 (0.90 to 1.60)	1.11 (0.89 to 1.39)	1.11 (0.84 to 1.48)
VCDR (per 0.1 larger)	1.19	1.03 (0.92 to 1.15)	1.07 (0.92 to 1.25)	1.05 (0.89 to 1.23)	1.17 (1.04 to 1.33)	1.17 (1.02 to 1.35)
PSD ratio (per 0.2 dB greater)	1.13	1.26 (1.13 to 1.39)	1.11 (0.93 to 1.32)	1.38 (1.08 to 1.76)	1.25 (1.08 to 1.44)	1.19 (1.05 to 1.34)
Performance measure						
c-index		0.55 (0.50 to 0.61)	0.63 (0.56 to 0.71)	0.64 (0.58 to 0.71)	0.62 (0.56 to 0.68)	0.64 (0.58 to 0.69)
Calibration slope		0.25 (0.05 to 0.46)	0.45 (0.16 to 0.73)	0.55 (0.28 to 0.81)	0.52 (0.30 to 0.74)	0.49 (0.28 to 0.70)
	OHTS-EGPS (model A)	**Hospital 6**	**Hospital 7**	**Hospital 8**	**Hospital 9**	**Hospital 10**
n		512/2677	251/1335	118/876	82/703	25/214
Baseline predictor, HR (95% CI)						
Age (decade)	1.26	1.40 (1.28 to 1.54)	1.23 (1.07 to 1.42)	1.32 (1.09 to 1.61)	1.35 (1.04 to 1.75)	1.16 (0.72 to 1.88)
IOP (mmHg)	1.09	0.99 (0.96 to 1.03)	0.99 (0.94 to 1.04)	1.03 (0.97 to 1.10)	0.95 (0.86 to 1.05)	0.94 (0.81 to 1.10)
CCT (per 40 µm thinner)	2.04	1.10 (0.97 to 1.25)	0.91 (0.75 to 1.10)	0.99 (0.81 to 1.22)	1.17 (0.89 to 1.55)	1.37 (0.82 to 2.27)
VCDR (per 0.1 larger)	1.19	1.04 (0.97 to 1.12)	1.22 (1.07 to 1.38)	1.00 (0.88 to 1.13)	1.07 (0.63 to 1.84)	1.24 (0.90 to 1.71)
PSD ratio (per 0.2 dB greater)	1.13	1.19 (1.13 to 1.26)	1.30 (1.19 to 1.42)	1.30 (1.16 to 1.46)	1.63 (1.42 to 1.87)	1.16 (0.73 to 1.84)
Performance measure						
c-index		0.61 (0.58 to 0.63)	0.62 (0.58 to 0.66)	0.59 (0.54 to 0.64)	0.64 (0.57 to 0.70)	0.67 (0.54 to 0.79)
Calibration slope		0.45 (0.34 to 0.57)	0.47 (0.29 to 0.65)	0.36 (0.16 to 0.57)	0.64 (0.29 to 0.98)	0.59 (0.05 to 1.13)
Pooled c-index[a] = 0.61 (0.60 to 0.63)						
Pooled calibration slope[a] = 0.45 (0.38 to 0.51)						

a Pooled using meta-analysis.

Note
Multiple Imputation. Re-estimated coefficients for each hospital given.

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This synopsis should be referenced as follows: Wright D, Wu H, King A, Montesano G, Higgins B, Gazzard G, *et al.* Validating and updating the OHTS-EGPS model predicting 5-year glaucoma risk among patients with ocular hypertension using electronic medical records: a cohort study. *Health Technol Assess* 2026;**30**(25). https://doi.org/10.3310/GJAA0514

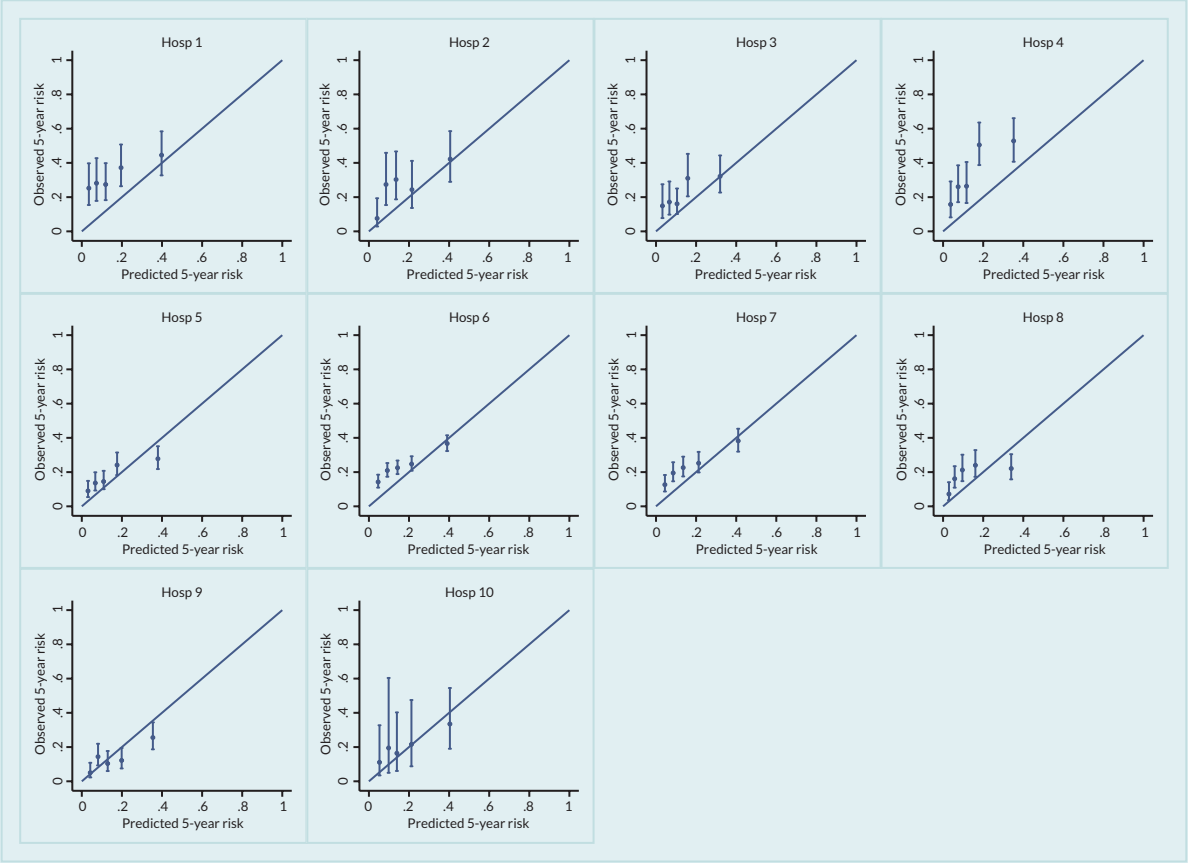

FIGURE 5 Calibration plots of OHTS-EGPS model with original coefficients (model A) by hospital (multiple imputation, based upon first imputed data set). Reproduced with permission from Wright *et al.*[1] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure above includes minor additions and formatting changes to the original text.

TABLE 6 Internal/external validation of OHTS-EGPS model with re-estimated coefficients (model B) and risk at 5 years, by hospital – model fitted in nine hospitals and evaluated separately in the 10th hospital

	n	c-index	Calibration slope
Imputed data set[a]			
Hospital			
1	117/564	0.68 (0.62 to 0.74)	0.91 (0.63 to 1.19)
2	64/430	0.66 (0.59 to 0.74)	0.75 (0.31 to 1.19)
3	91/628	0.69 (0.61 to 0.76)	1.12 (0.64 to 1.60)
4	111/448	0.65 (0.59 to 0.71)	0.91 (0.55 to 1.26)
5	159/1155	0.66 (0.61 to 0.71)	0.94 (0.66 to 1.22)
6	512/2677	0.66 (0.63 to 0.68)	0.83 (0.69 to 0.97)
7	251/1335	0.69 (0.65 to 0.73)	1.08 (0.84 to 1.31)
8	118/876	0.68 (0.62 to 0.74)	0.94 (0.62 to 1.26)
9	82/703	0.75 (0.68 to 0.81)	1.76 (1.22 to 2.31)
10	25/214	0.67 (0.51 to 0.84)	0.91 (−0.03 to 1.85)

TABLE 6 Internal/external validation of OHTS-EGPS model with re-estimated coefficients (model B) and risk at 5 years, by hospital – model fitted in nine hospitals and evaluated separately in the 10th hospital (*continued*)

n	c-index	Calibration slope
Pooled[b]		
	0.67 (0.65 to 0.69)	0.96 (0.84 to 1.09)

a Model = 1 − 0.786^exp((0.272 × (agedecade − 6.262)) + (−0.006 × (IOP − 24.731)) + (0.059 × (T_CCT + 14.098)) + (0.233 × (T_PSD − 8.379)) + (0.100 × (T_VCDR − 4.782)); where T_CCT = −CCT/40 and T_PSD = PSD/0.2 and T_VCDR = VCDR/0.1.
b Pooled using meta-analysis.

The overall risk in this group was much smaller (7.3% converted in complete case-analysis) but HRs and model performance were similar and the 95% CIs overlapped the estimates from the main model. These results indicate that model performance was largely unaffected by IOP-lowering treatment at baseline.

There were no substantial differences between the multiple imputation and the complete-case analyses for the different model variants.

Influence of baseline variables on treatment

Age and FH of glaucoma were not associated with treatment at VF baseline. There was a positive association between IOP and treatment probability and those with thinner CCT had increased probability of receiving treatment.

Results Objective 2: to assess the relative efficiency of alternative monitoring pathways for people with ocular hypertension according to glaucoma risk compared with standard practice

Base case analysis

The simulated results for the base-case scenarios are shown in *Table 7*. Almost all (99%) patients were treated in the RP strategy, while about 47% of patients were treated in the SC strategy. However, 89% of the patients in SC were treated in the lifetime. For the SC and RP strategies, 43% and 47% of the patients were estimated to have converted to glaucoma, respectively. In the SC strategy, more patients progressed to moderate (24%) and severe (11%) glaucoma and visual impairment (5%), which implies significant QALY losses due to VF defects. This is not surprising as more patients received treatment in the RP strategy. Regarding CE results, the RP strategy incurred higher costs but gained higher QALYs than the SC strategy. The difference in QALYs between strategies is relatively small as the strategies differ mainly in the decision to treat determined at the start of the model. The RP strategy is more CE than the SC strategy with an ICER (£11,522) which is below the cost per QALY threshold of £20,000 used by NICE.

One-way sensitivity analysis

Overall, the RP remains CE until the adherence rate decreases down to 75%, cost of medication increases by up to 50%, cost of monitoring increases by up to 50%. However, the change of risk threshold for the risk prediction tool has the largest impact on the ICER – the RP strategy becomes less cost-effective when the threshold increases, and ICER exceeds the CE threshold of £20,000 when the risk threshold is more than 12%.

Probabilistic sensitivity analysis

The RP strategy has a 98% probability of being CE at the £20,000 per QALY threshold, which is consistent with the base-case results.

Results Objective 3: to determine the clinical and cost-effectiveness of treating people with ocular hypertension who have intraocular pressure of 22 or 23 mmHg

The estimated HRs for this model compared with one fitted using the entire cohort are shown in *Table 8*. The risk of conversion was similar in both groups (16.9% converted in the entire cohort vs. 17.0% in the 22–23 subgroup). In both models, age, PSD ratio and VCDR were associated with increased risk of conversion and the magnitude of these associations was very similar across both models. The 95% CI for each of these variables overlapped across models. Model performance was also similar across models with c-indexes of 0.67 and 0.68 in the entire cohort and the 22–23 subgroup respectively.

TABLE 7 Cost-effectiveness results for the base-case analysis. Lifetime time horizon

	Proportion of treated (%)		Proportion of patients in each state (%)				
Pathway	**Initial**	**Final**	**OHT**	**OAG mild**	**OAG moderate**	**OAG severe**	**Visual impairment**
Standard practice strategy (%)	47	89	43	17	24	11	5
Risk prediction strategy (%)	99	100	47	17	22	10	4
	Average total cost (£)	**Incremental cost (£)**	**Average total QALYs**	**Incremental QALYs**	**ICER (£)**		
Standard practice strategy	£4662		10.89				
Risk prediction strategy	£4925	£262	10.92	0.023	£11,522		

Source
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TABLE 8 Performance of risk prediction models. Multiple imputation

	Main model (entire cohort)	Main model (Only IOP ≤ 23)
Conversions/*n*	1530/9030	362/2127
Baseline predictor, HR (95% CI)		
Age (decade)	1.31 (1.24 to 1.38)	1.28 (1.15 to 1.42)
IOP (mmHg)	0.99 (0.98 to 1.01)	0.88 (0.74 to 1.04)
CCT (per 40 µm thinner)	1.06 (0.99 to 1.14)	1.12 (0.97 to 1.28)
PSD ratio (per 0.2 dB greater)	1.26 (1.22 to 1.30)	1.27 (1.20 to 1.35)
VCDR (per 0.1 larger)	1.10 (1.07 to 1.14)	1.13 (1.05 to 1.21)
Performance measure		
c-index[a]	0.67 (0.66 to 0.69)	0.68 (0.65 to 0.71)

a Calculated within each hospital and pooled using meta-analysis models across hospitals.

Source
Reproduced with permission from Wright *et al.*[1] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The table above includes minor additions and formatting changes to the original text.

The results of the CE analysis are presented in *Table 9*. The treat-all strategy produced higher costs (£4781) but also higher QALYs (10.81) than the SC strategy in the base-case analysis. The ICER value is £25,539 in the base-case analysis, suggesting that the treat-all strategy is not CE compared with standard care under the £20,000 WTP threshold suggested by NICE.

Results Objective 4: to elicit the preferences of patients with ocular hypertension for eye monitoring services in the United Kingdom

Sample characteristics

Three hundred and sixty surveys were returned (response rate = 29%); of which 99.2% fully or partially completed

TABLE 9 Cost-effectiveness results for the base-case analysis of treating IOP of 22 and 23 mmHg. Lifetime time horizon

	Proportion of patients in each state (%)				
Pathway	**OHT**	**OAG mild**	**OAG moderate**	**OAG severe**	**Visual impairment**
Standard practice strategy (%)	39	24	29	8	1
The treat-all strategy (%)	53	20	21	5	1
	Average total cost (£)	**Incremental cost (£)**	**Average total QALYs**	**Incremental QALYs**	**ICER (£)**
Standard practice strategy	£3680		10.77		
The treat-all strategy	£4781	£1102	10.81	0.04	£25,539

TABLE 10 Summary of patient characteristics

Variables	*N*	Statistic
Age (years), mean ± SD	343	68.6 ± 11.2
Male, *n* (%)	343	186 (54.2)
Retired, *n* (%)	342	217 (63.5)
Diagnosed with OHT in more than 5 years, *n* (%)	352	203 (57.7)
Experience of eye care services, n (%)		
Face-to-face hospital visit	353	323 (91.5)
Hospital-based virtual clinic	353	150 (42.5)
Community optometrist	353	167 (47.3)
Eye tests frequency equal or longer than annually, *n* (%)	341	203 (59.5)

N, number in sample.

the DCE choice tasks (i.e. 357; 3 did not complete the DCE section at all). Respondents who failed to complete any of the choice tasks were excluded from the analysis.

Table 10 summarises the respondents' characteristics. The mean age was 68.6 years (SD= 11.2), with 54.2% male, and 63.5% retired. Most respondents were diagnosed with OHT more than 5 years ago (57.7%). Almost all respondents had experience of a face-to-face hospital service (91.5%). Fewer respondents had experience of hospital-based virtual clinics (42.5%) or community optometrist monitoring (47.3%). The frequency of monitoring varied across respondents with 59.5% of respondents having a 12-month or longer monitoring interval and 40.5% having a 6-month or shorter interval.

Patient preferences

Table 11 presents the results of the ECL model. The positive and significant alternative specific constant [14.497; CI = (0.169 to 28.825)] suggests that respondents prefer to have their OHT monitored. Respondents preferred face-to-face hospital service [β = 0.538; CI = (0.377 to 0.699)] and hospital-based virtual clinic monitoring [β = 0.241; CI = (0.089 to 0.393)] compared to monitoring by a community optometrist. Respondents preferred more frequent monitoring with the monitoring intervals of 6, 12 or 18 months compared to 24 months [β = 0.685; CI = (0.516 to 0.854), β = 0.892; CI = (0.710 to 1.074), β =0.299; CI = (0.163 to 0.435), respectively]. The most popular monitoring interval was 12 months. Respondents preferred shorter travel times to the monitoring location [β = −0.257; CI = (−0.437 to −0.076)]. Respondents had no preference for a monitoring plan based on the results of the risk calculator to be used in addition to the eye doctor's experience. As expected, respondents preferred a lower risk of developing glaucoma in the next 10 years [β = −0.992; CI = (−1.140 to −0.844)] and that the cost of the monitoring service was lower [β = −0.001; CI = (−0.002 to −0.001)].

TABLE 11 Patients' preferences for the attributes of eye monitoring services

Attribute	Coefficient	(95% CI)	*p*-value
Estimated preferences			
Alternative specific constant (mean)	14.497	(0.169 to 28.825)	0.047
Alternative specific constant (SD)	6.948	(−1.140 to 15.036)	0.092
How monitoring is organised			
Community optometrist	Reference		
Face-to-face hospital service	0.538	(0.377 to 0.699)	< 0.01
Hospital-based virtual clinic	0.241	(0.089 to 0.393)	< 0.01
Frequency of eye tests			
Every 24 months	Reference		
Every 18 months	0.299	(0.163 to 0.435)	< 0.01
Every 12 months	0.892	(0.710 to 1.074)	< 0.01
Every 6 months	0.685	(0.516 to 0.854)	< 0.01
Travel time from home	−0.257	(−0.437 to −0.076)	< 0.01
Risk calculator			
Eye doctor's experience only	Reference		
Eye doctor's experience and a risk calculator	0.034	−0.038 to 0.106	0.358
Risk of developing glaucoma	−0.992	(−1.140 to −0.844)	< 0.01
Cost of attending eye care services	−0.001	(−0.002 to −0.001)	< 0.01
Model information			
Log likelihood	−2099		
AIC	4220		
Number of participants	357		
Number of parameters	11		
Number of observations/choices	3264		

AIC, Akaike Information criterion.

Note
Risk of developing glaucoma is rescaled by 0.1.

Figure 6 presents the mean WTP estimates and 95% CIs for unit changes in the DCE attributes. Respondents most strongly supported monitoring services that cost more but that reduced their risk of conversion to glaucoma more. Respondents are willing to pay £767 [95% CI = (£433 to £1101)] over the next 2 years for a monitoring service that reduces their risk of conversion by 10%. Respondents were willing to pay £690 [95% CI = (£382 to £998)] more over the next 2 years for a monitoring service with tests every 12 months compared to every 24 months. Respondents preferred face-to-face hospital monitoring by an eye doctor or a hospital-based virtual clinic rather than community optometrist [£416; 95% CI = (£206 to £625) vs. £186; 95% CI = (£51 to £322) over 2 years, respectively].

The results of the observed preference heterogeneity analysis are summarised in *Figure 7*, which reports the attributes for which we found statistically significant

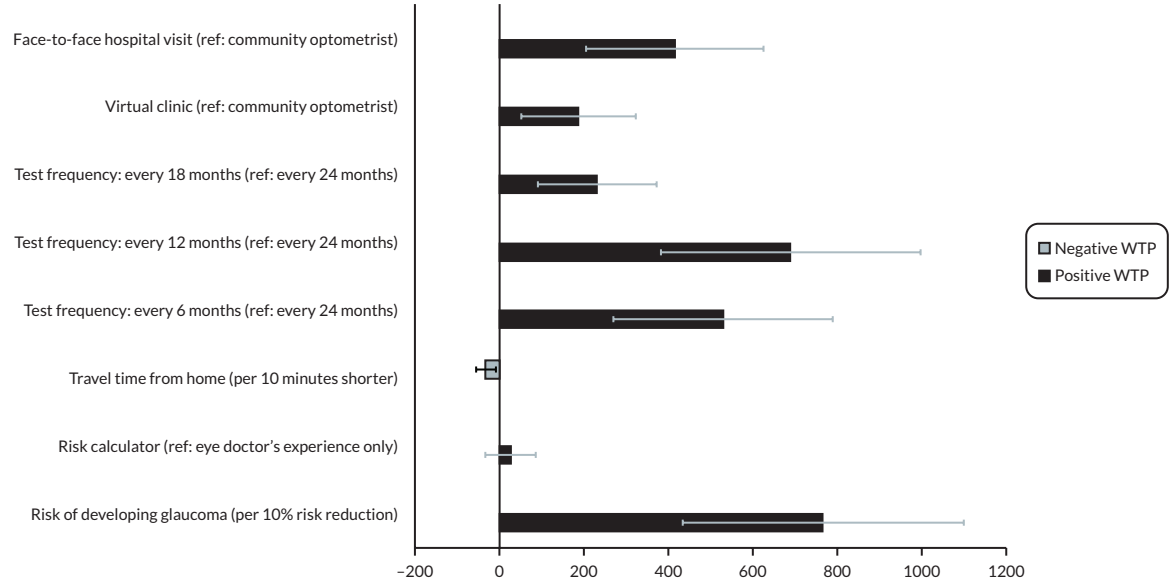

FIGURE 6 Mean WTP estimates for the eye care service attributes (£ in next 2 years). Reproduced with permission from Wu *et al.*[2] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure above includes minor additions and formatting changes to the original text.

Prefer virtual clinic	**Prefer face-to-face hospital service**
• Male • No prior experience of using community optometrist service • Have recent experience of using virtual clinic eye service	• Male • No experience of using community optometrist service
Prefer community optometrist	**Prefer more frequent tests**
• Have recent experience of using community optometrist service	• Age > 65

Age > 65 is a dummy variable which equals to 1 if a patient's age is over 65 and equals to 0 otherwise; Male is a dummy variable which equals to 1 if a patient is male and equals to 0 if female; Prior/recent experience of using community optometrist service (virtual clinic eye service) is a dummy variable which equals to 1 if patients self-reported that they had used community optometrist service (virtual clinic eye service) before, or during the last eyecare visit, and equals to 0 otherwise. The frequency attribute is coded as linear to facilitate interpretation.

FIGURE 7 High-level summary of the findings from the preference heterogeneity analysis. Reproduced with permission from Wu *et al.*[2] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure above includes minor additions and formatting changes to the original text.

interactions. We found that male respondents preferred hospital-based virtual clinics more than female respondents. Respondents' prior experience of monitoring impacts on their preferences. Respondents who had never experienced monitoring by a community optometrist preferred hospital-based services (face-to-face hospital monitoring by an eye doctor or a hospital-based virtual clinic) compared with those who had experienced monitoring by a community optometrist. Furthermore, those who previously experienced monitoring by a community optometrist prefer this to either hospital-based service.

Discussion

Discussion Objective 1: to validate and update the OHTS-EGPS risk prediction model in a large population of UK adults with OHT

In this study we validated the OHTS-EGPS risk prediction model (model A) using a real-world data set seven times larger than the US–European data set used for model development and 30–50 times larger than four cohorts previously used to validate the model. The principal finding is that, when applied in its original form, the prediction model performed poorly. Discrimination was lower in this clinical data set (c-index = 0.61) than reported when the OHTS-EGPS model was developed (c-index = 0.74) and in earlier validations (c-index = 0.70 to 0.83). In calibration terms, the model underestimated risk in all but the highest risk quintile. Reduced performance during validation is common among risk prediction models and may reflect overfitting during model development or measurement error.[44,45] However, the model itself is relatively simple, a linear combination of relevant variables and their coefficients and so overfitting is unlikely. In this study, measurement error is most likely to stem from missing data but our results varied little when complete-case analysis was performed.

The suboptimal performance of the risk predictor found in our cohort limits the potential impact of our study. Although the discrimination of our risk predictor improves marginally compared with the OHTS-EGPS model, clinicians should be cautious with the use of a risk predictor in people with OHT.

A more likely explanation for the suboptimal model performance is differences in patient characteristics, disease incidence and patient management between the populations of the original OHTS-EGPS trials and our study. As randomised clinical trials, OHTS and EGPS scheduled study visits every 6 months for 5 years,[18] whereas in our clinical data intervals between assessment were longer and more variable. Other differences in study design were in the definition of glaucoma conversion; OHTS-EGPS used assessment of both optic disc deterioration (two sets of photographs) and VF changes (three consecutive abnormal tests interpreted by a reading centre) to indicate conversion, whereas we used the GHT only (two tests) without investigators confirmation.

Across our entire data set, the cumulative risk of conversion from OHT to glaucoma at 5 years (16.9%) was higher than the OHTS cohort but similar to the risks reported in the original EGPS study (16.8% in placebo group)[18] and in a more recent but smaller real-world study drawing data from five hospitals in England (17.5%).[10] OHTS may underestimate the risk of conversion due to survivorship bias (38% of participants were not newly diagnosed and had treatment washout before enrolment). We noted a considerable variation in conversion risk among hospitals which may reflect differences in populations or treatment approach among different ophthalmologists, and both discrimination and calibration were worse in hospitals with particularly high risk, highlighting the sensitivity of these models to disease incidence. Conversion rate among patients with baseline IOP of 22–23 mmHg was similar to the overall cohort.

Our second aim was to improve prediction by updating the model (model B), achieving modest improvements in discrimination (c-index increased to 0.67) and approaching the performance of the OHTS-EGPS model across the populations in which it was developed. This level of discrimination is similar to that reported for validation of risk prediction tools used in other clinical areas: c-indexes of stroke risk prediction tools among women ranged from 0.61 to 0.65 for the widely used CHADS and QStroke scores, respectively (0.63–0.71 among men).[46] Hepatocellular carcinoma risk models produced c-indexes ranging from 0.56 to 0.77, also displaying substantial variation in performance depending on the validation set used.[47]

Calibration of the updated model was also improved but this is largely a function of the refitting process. The overall structure of the updated model was similar to OHTS-EGPS with the notable exceptions that IOP and CCT at OHT start were not associated with glaucoma conversion risk in our data set. Furthermore, risk factor estimates for IOP and CCT were unchanged when the model was restricted to those that were not treated at baseline, or those that were never treated. It is likely that in our study, these associations were absent because these two measurements strongly influence the decision whether and when to start treatment which may in turn influence conversion risk. This hypothesis is supported by our finding that higher IOP and lower CCT were associated with higher probability of receiving treatment at baseline. Our finding that IOP was not associated with risk has been observed in similar studies using UK EMRs[10] and clinical trial cohorts.[17]

It was notable that model performance was largely unaffected by treatment. Excluding those treated at baseline did not affect the model. Rate of progression was slower among those never treated (7.3%). Not treated at baseline 13.7%. Main model 14.5% complete case.

We found a strong association between diabetes diagnosis and increased risk of glaucoma conversion. This may be due to VF defects induced by diabetic retinopathy. Proliferative retinopathy or diabetic macular oedema would likely result in abnormal GHT, triggering a conversion event. This explanation appears likely given a recent review and meta-analysis that suggested diabetes is associated with elevated IOP but not necessarily with glaucoma.[48] People with systemic hypertension were less likely to convert from OHT to glaucoma. The reduction in risk may be attributable in part to treatment of hypertension with oral BBs.[48,49]

Our current model uses only information of baseline data. A possible extension would be to use measurements from the first two or three clinic visits to capture initial responses to treatment and improve model performance. Given the variability among patients in monitoring intervals and likely responses, more flexible models fitted using machine learning should be considered. Finally, this data set is a valuable resource to investigate prediction models for glaucoma progression, including both those that converted from OHT used in this analysis and those with pre-existing glaucoma.

Strengths and limitations of the risk prediction model

The main strength of this study was availability of a large data set representative of the OHT/glaucoma population in England managed in HESs, capturing substantial variability across the ten sites in patient demographics, case-mix and management pathways. The main limitation is associated with the retrospective nature of data collection. There was a substantial amount of missing data in some clinical measurements, although model performance was largely unaffected with similar estimates in the multiply imputed and complete-case analyses. Another limitation is that measurement intervals for IOP and VF was irregular. IOP is prone to both high short-term variability and measurement error, and for some patients there was a delay between the baseline IOP measurement and the first VF assessment. We did not assess the influence of significant ocular comorbidities, for example, retinal disorders that required treatment (these eyes were excluded) and that may affect vision on glaucoma conversion risk.

Conclusions of the risk prediction model

We validated the OHTS-EGPS risk prediction model for conversion from OHT to glaucoma using electronic data from a large cohort. By refitting the model, we achieved modest improvements in model performance warranting further research on how these predictions might be incorporated into clinical practice.

Discussion Objectives 2 and 3: to determine the clinical and cost-effectiveness of treating people with ocular hypertension

This study aimed to investigate the CE of a risk prediction tool used in making clinical decisions in OHT monitoring. Costs and effectiveness of a risk prediction tool used by health professionals were examined against the SC pathway using a DES model. Our results demonstrate that making treatment decisions based on our risk prediction tool used in a secondary care (HES) setting is likely to be cost-effective. Results remain qualitatively unchanged against different scenarios and sensitivity analyses, except for a change in the risk threshold used to decide treatment initiation. For a 5-year risk of conversion to glaucoma threshold of 12% or above the RP strategy stopped being CE.

A similar study concerning OHT monitoring was conducted by Burr *et al.* in which the CE of two risk prediction strategies were compared against a 'treat all' strategy in which all patients were offered medication with no active monitoring of conversion.[17] The risk prediction strategies in their study were more costly and effective, yet they were not considered cost-effective using a £30,000 per QALY threshold. The discrepancy in findings is not surprising, as the model settings in our study have been tailored to reflect the current NICE guidelines and updated knowledge on modelling time to conversion and progression. We also had access to a comprehensive patient-level data set extracted from EMRs, which allows us to perform individual patient sampling. In our study, the cohort had a higher 5-year risk of conversion compared with the simulated cohort in Burr *et al.* (i.e. 17% vs. 10% patients converted to glaucoma in 5 years). The construction of the risk prediction strategy in our study differs from that of Burr *et al.* (2012). We incorporate monitoring in both community optometry and HES into the risk prediction strategy, while patients in Burr *et al.* (2012) were monitored in either community optometry or hospital in two separate pathways. Another notable difference lies in the use of a calibrated risk prediction tool based on patients' records of UK OHT patients (see results of Objective 1). Other similar studies investigated the CE of more intensive glaucoma monitoring pathways (compared with usual care) and found mixed results.[31,50]

The strategies compared differ only in the decision algorithm used to determine whether to offer treatment with the risk prediction strategy under the current risk threshold indicating a very high proportion of patients being initially treated with medications or SLT. The findings imply that medications and SLT are inexpensive treatment options, safe, and are effective in delaying conversion and

progression. However, the message cannot be interpreted simply as 'treating all OHT diagnosed individuals is always cost effective', as several factors need to be considered in clinical practice: (a) The NICE guidelines suggest effective identification of patients who have risk of visual impairment to offer them treatment.[16] In other words, providing treatment to those who have low risk of visual loss in their lifetime while failing to treat high-risk patients can reduce quality of life – either situation reflects an inefficient use of resources and would decrease the CE of the monitoring strategy. (b) Our sample includes a large proportion of patients with high-risk profiles; in reality, cohorts with an increased proportion of low-risk patients are expected and these patients would be discharged to community optometry. (c) Patient-centred care has been an important part of clinical decision-making of OHT and glaucoma treatment in the UK and internationally.[33,51,52] Treatment decisions must be tailored based on individual patient needs and consider factors such as eyedrop tolerance and adverse effects.[53,54] Therefore, patients with no immediate risk of conversion to glaucoma may not be offered treatment. Finally, given the high-risk nature of our sample our results are consistent with findings from a large trial study in which high-risk OHT patients benefited the most from treatment,[55] and also with a model-based economic evaluation study suggesting that treating high-risk patients is more likely to be cost-effective.[56]

Limitations of the economic evaluation

This study has several limitations. First, the risk prediction tool has several limitations: (a) The predictive power of the tool is suboptimal.[6] In a recent validation study using UK OHT patients, the c-index is 0.69, while c-index= 1 represents a perfect prediction. (b) The risk stratification threshold is based on one study (i.e. Kass *et al.*[55]) and may be subject to revision. (c) For the specific risk prediction tool used in this study, the algorithm was generated based on a full sample of OHT patients with IOP from 21 to 32 mmHg, yet the parameter inputs in the algorithm should be slightly different as we used a partial sample of patients with IOP from 24 to 32 mmHg in modelling due to the use of standard referral criteria of OHT patients to the HES. These imperfections may explain the relatively large divergence in the proportion of patients being initially treated between the RP and SC strategies. In addition, we attached a zero research and development and production cost to the risk prediction tool based on the assumption that these costs would be flattened out in the long run. However, little is known about the operating costs of using the risk calculator in clinical practice. Studies that investigate monitoring of chronic conditions using digital technology suggest that operating costs such as integration and training costs may be non-negligible.[57] Our results suggest that further studies are needed to confirm the observed CE analyses of monitoring strategies based on a more advanced risk prediction algorithm, and the economic evaluation should incorporate fixed and running costs of applying the risk prediction tool.

Regarding the subgroup of patients with IOP of 22–23 mmHg, the treat-all strategy produced higher costs (£4781) but also higher QALYs (10.81) than the standard care strategy in the base-case analysis. The ICER value is £25,539 in the base-case analysis, suggesting that the treat-all strategy is not cost-effective compared with standard care. It is unlikely the subgroup of patients with IOP of 22–23 mmHg that remained under HES is representative of the overall population as most people with perceived low risk would have been discharged to community optometrist care.

Conclusion of the economic evaluation

In conclusion, the use of a risk prediction tool is likely to be cost-effective, although subject to several limitations regarding the characteristics of the sample used and the discriminatory power of the risk tool. Future research can extend the analysis to tools with higher discrimination and populations with lower risk of conversion to glaucoma.

Discussion Objective 4: to elicit the preferences of patients with ocular hypertension for eye monitoring services in the United Kingdom

The use of a risk prediction tool can result in service redesign and the potential changes in service delivery should be informed by patients' preferences. To our knowledge, this work is the first to estimate OHT patients' preferences for monitoring services in the UK. We used a DCE to understand patients' preferences for attributes of monitoring. Previous studies in this area sought the views of glaucoma patients or the general population. The results indicate that the organisation of the review process, the type of health professional involved in testing, test frequency, travel time, risk of developing glaucoma and cost of service all influenced patients' choices of OHT monitoring. Our results also showed that patients were willing to trade-off different service attributes and cost of the services, which allowed us to calculate their WTP for different attributes of these services.

The latest NICE (UK) guidelines recommend variable risk-based monitoring intervals, between every 1 and 24 months depending on a patient's risk profile, certainty of test results and control of IOP.[16] Our results reveal that patients' preferred monitoring interval is 12 months

compared with 6-monthly intervals or greater. Similar to Burr *et al.*,[17] we found that the aspect of monitoring most valued was the reduction in the risk of converting to glaucoma. However, our results suggest that the organisation of the monitoring process is also important to patients, in contrast to Burr *et al.*'s observation that this attribute was not important to a general population sample. In this study, the organisation attribute combines the monitoring location and health professionals involved. Our results suggest that patients preferred monitoring by more senior health professionals (an ophthalmologist in the hospital compared to an optometrist in community) which is consistent with similar studies investigating patient preferences for glaucoma monitoring.[58,59] Shorter travel times were preferred by respondents – similar to findings reported by Bhargava[58] and Muth *et al.*[60] in studies of glaucoma patients.

However, patients with prior experience of community optometrist monitoring preferred this to hospital-based monitoring. The existence of preference heterogeneity based on respondents' experience suggests that patients who are unfamiliar with community optometry services will probably need additional support to accept monitoring in this setting. In addition, it indicates that once patients have experienced community-based monitoring they are generally comfortable with it and prefer it, this is an important consideration in future development of OHT monitoring pathways.

Limitations of patient preference evaluation

Our analysis has three limitations. First, in the DCE the monitoring frequency ranges from every 6 to every 24 months. These options represent the suggested intervals for patients with low to medium risk of developing glaucoma. Some high-risk patients may have shorter intervals (e.g. every 3 months) and as such, some respondents may find the longer intervals unrealistic. However, these patients accounted for a small percentage of the OHT population. Second, in the survey design stage, we combined several features (e.g. healthcare professional, place of testing and testing environment) into one attribute – the organisation; this reflects current service organisation in the UK NHS and the realistic constraints of staffing availability and location and reflects how participants in the qualitative research discuss their monitoring. However, the integrated attribute means that we cannot separate preferences for location and staffing. Future research would be required to disentangle these elements to better understand patients' preferences for these aspects of care. Third, WTP values for some attributes of services are higher than the highest level of cost [i.e. $249 (£300)] presented in the DCE. This result can be attributed to the issue of WTP overshooting or cost non-attendance.[61] One reason could be that respondents were willing to pay more for monitoring services than the highest cost presented in the DCE.

Conclusions of patient preference evaluation

In conclusion, this preference elicitation study contributes to the understanding of OHT patients' preferences for service attributes of regular eye monitoring. Reducing the risk of conversion to glaucoma is the most important factor influencing respondents' choice of monitoring service. Although the hospital setting is favoured by the majority of respondents, those with previous experience prefer community optometry monitoring.

Patient and public involvement

Two patients were co-applicants and part of the research team and helped design the study protocol. We were supported by Glaucoma UK (patient charity). We had patient and public involvement (PPI) representation in the Project Management Group, Study Steering Committee meetings and at the Knowledge Transfer event at the end of the study. PPI involvement was particularly helpful in the pilot stage and focus group discussion designing the DCE.

A knowledge transfer event held in London in November 2023 had PPI input. Patients helped identify further research priorities (see below).

Glaucoma UK will publish the *Plain language summary* to facilitate dissemination to patients and the public.

Equality, diversity and inclusion

Glaucoma can affect anyone but people with certain characteristics (i.e. disadvantaged socioeconomic background) have a higher risk of suffering severe visual loss from glaucoma. Participating centres involved large and diverse populations (e.g. London, Nottingham). We had data from 10 different hospitals across England, including district general hospitals and academic units. NHS routine data of chronic eye diseases such as glaucoma is likely to be representative of the diversity of the UK population.

We explored the influence of non-White ethnicity in the risk of conversion to glaucoma.

Our research team was diverse regarding demographics and academic expertise.

Impact and learning

Areas for further consideration on OHT, risk prediction and glaucoma care suggested in discussions at the GRIP knowledge transfer event held at City, University of London, 21 November 2023 were as follows:

Patients were interested in alternative models of care and, in particular, in home tonometry. For example, they asked if equipment could be made available to patients to prevent anxiety over unknown IOP levels in the period between appointments.

There was an interest among patients and clinicians in exploring a broader range of risk factors than those included in GRIP. Possibly including genetic information but also more detailed clinical information where available, for example, regarding the anatomy of the eye (axial length), retinal layers, and the optic nerve (e.g. OCT).

An exploration of the influence of glaucoma treatment on the performance of the risk prediction model was recommended. Hospitals with a smaller proportion of patients treated at baseline may have risk over-predicted if these patients are in fact at lower risk.

Consideration should be given on how the output of the risk prediction model might be communicated with clinicians and how it might be used when discussing treatment decisions with patients. The suboptimal performance of the risk predictor limits the potential impact of our work.

Research into the effectiveness, efficiency and acceptability of community-based service delivery should be considered. Investigating ways to standardise glaucoma care that can be given in community optometry to ensure equality of care nationwide by the development of national care pathway standards. One example is the glaucoma training award (NESGAT) for independent prescribing community optometrists.

Educating the public about the safety and effectiveness of alternative models of service delivery, such as virtual care, over traditional clinics would be useful.

Three articles have been published in professional journals expanding the information included in this synopsis.[1–3]

Implications for decision-makers

The risk predictor validated in our study had a moderate performance, below the c-index value of 0.7 that represents good discriminatory ability. Further research is advisable before implementing its use. Regarding the burden of glaucoma, it was acknowledged that glaucoma blindness is mostly preventable and late presentation is the most important factor associated with glaucoma blindness. Population screening for glaucoma is not recommended at the moment. Alternative approaches should be explored. It was proposed it would be useful to have an estimate of the costs to the NHS due to late presentation at glaucoma clinics. Analysis of the severity of disease at presentation (e.g. originated by the GRIP study), combined with estimates of subsequent treatment costs would enable a national figure to be generated. This could be used to justify an increased support for community optometry (probably via General Ophthalmic Services) or other community-led support services to identify people with glaucoma and refer at an earlier stage.

Research recommendations

These research questions and recommendations were identified at the Knowledge Transfer event held at London, City University, on the 21 November 2023. The event was attended by clinicians, researchers, patients and Glaucoma-UK (charity supporting people with glaucoma).

- Are there other important risk factors than those included in EMRs, for example, genetic information or data regarding the anatomy of the eye (axial length), retinal layers, and the optic nerve (e.g. OCT)?
- What can be done to avoid late presentation of glaucoma? How can we best detect undiagnosed patients with significant glaucoma disease? At present screening would not be CE but are there other approaches for case detection that could be explored.
- Evaluation of the effectiveness and CE of community-based OHT and glaucoma care.
- Modelling of risk prediction on a prospective cohort of patients using modern VF and imaging technologies.

Although a prospective randomised comparison of risk prediction versus standard care would answer the question about the effectiveness of a risk predictor, the study would not represent good value for research money due to the large size and long duration of follow required.

Conclusion of the glaucoma risk prediction project

We validated and updated the OHTS-EGPS predictor model in a large population with OHT, achieving modest

improvements. The use of a risk prediction tool is likely to be cost-effective, but there is still uncertainty about the implementation in clinical practice due to the sub-optimal performance. A risk predictor with a c-index value above 0.7 in a UK population would be needed to be able to make a strong recommendation and facilitate its implementation.

Reducing the risk of conversion was the most important preference for patients with OHT. While a majority of patients preferred monitoring at HES, those with previous experience with community optometry preferred this option.

Future work should address the influence of genetic or other ocular factors in disease progression, evaluation of effectiveness and CE of different models of eye care, and on how to avoid late glaucoma presentation.

Additional information

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Patient data statement

This work uses data collected by the NHS as part of routine patient care. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it is important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Ethics statement

The risk prediction work was approved by the East of England – Essex Research Ethics Committee, REC reference: 21/EE/0109. The patient preference work was approved by East Midlands – Nottingham 2 Research Ethics Committee, REC reference: 23/EM/0060.

Information governance statement

Queen's University Belfast (Queen's) is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, Queen's is the Data Controller, and you can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for our Data Protection Officer here: www.qub.ac.uk/privacynotice

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/GJAA0514.

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This synopsis was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Study registration

This study is registered as researchregistry6647, researchregistry8734; www.researchregistry.com/.

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Award publications

This synopsis provided an overview of the research award *Glaucoma Risk Prediction in ocular hypertension (GRIP): a cohort study using electronic medical records to validate a risk predictor and determine the cost-effectiveness of different monitoring schemes according to risk of conversion to glaucoma*. Other articles published as part of this thread are:

Wright DM, Azuara-Blanco A, Cardwell C, Montesano G, Crabb DP, Gazzard G, *et al*.; GRIP Study Group. Validating and updating the OHTS-EGPS model predicting 5-year glaucoma risk among ocular hypertension patients using electronic records. *Ophthalmol Glaucoma* 2025;**8**:143–51. https://doi.org/10.1016/j.ogla.2024.10.009

Wu H, Gazzard G, King A, Morgan J, Wright D, Crabb DP, *et al*. Cost-effectiveness of monitoring ocular hypertension based on a risk prediction tool. *BMJ Open Ophthalmol* 2024;**9**:e001741. https://doi.org/10.1136/bmjophth-2024-001741

Wu H, Hernández R, Crabb DP, Gazzard G, Harper RA, King A, *et al*. Patient preferences for ocular hypertension monitoring: a discrete choice experiment. *BMJ Open Ophthalmol* 2024;**9**:e001639. https://doi.org/10.1136/bmjophth-2024-001639

For other articles from this thread and for more information about this research, please view the award page (www.fundingawards.nihr.ac.uk/award/NIHR131808).

Additional outputs

Glaucoma risk prediction presentations to professional conferences

European Glaucoma Society, https://egs2022.org/, Athens, 4–8 June 2022. Poster. 'Glaucoma Risk Prediction in ocular hypertension (GRIP). A cohort study using electronic medical records to validate a risk predictor for conversion to glaucoma'.

World Glaucoma Congress, https://worldglaucomacongress.org/, Rome, 28 June–1 July 2023. Rapid fire presentation. 'Glaucoma Risk Prediction in ocular hypertension (GRIP). A cohort study using electronic medical records to validate a risk predictor'.

UK and Eire Glaucoma Society, https://glaucoma.uk/ukegs/2023-ukegs-conference/. London, 22–23 November 2023. Invited talk (20 minutes). Title: 'Getting to GRIPs with Ocular Hypertension – what's the real risk?'

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List of abbreviations

BB	beta-blocker
BNF	*British National Formulary*
CCT	central corneal thickness
CE	cost-effectiveness
DCE	discrete choice experiment
DES	discrete event simulation
ECL	error component logit
EGPS	European Glaucoma Prevention Study
EMRs	electronic medical records
FH	family history
GHT	Glaucoma Hemifield Test
GRIP	glaucoma risk prediction
HES	hospital eye service
ICER	incremental cost-effectiveness ratio
IOP	intraocular pressure
NICE	National Institute for Health and Care Excellence
OAG	open-angle glaucoma
OHT	ocular hypertension
OHTS	Ocular Hypertension Study
PGA	prostaglandin analogue
PPI	patient and public involvement
PSD	pattern standard deviation
QALY	quality-adjusted life-year
SC	standard care
SLT	selective laser trabeculoplasty
VCDR	vertical cup to disc ratio
VF	visual fields
WTP	willingness to pay

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