Development of a cost-effectiveness model for optimisation of the screening interval in diabetic retinopathy screening

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Scientific summary

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Background

Diabetes mellitus affects over 3 million people in the UK, with over 2.6 million people in England alone. Diabetic retinopathy (DR) is a common microvascular complication of type 1 and type 2 diabetes and remains a major cause of vision loss and blindness in those of working age.

A national screening programme for diabetic eye disease was initiated in England during 2003 with coverage across the country by 2008. The NHS Diabetic Eye Screening Programme is delivered by over 80 local screening programmes from both NHS and private providers.

The National Institute for Health and Care Excellence recommendations are for annual screening using digital retinal photography for all patients with diabetes aged 12 years and over until such time as specialist surveillance or referral to Hospital Eye Services (HES) is required. Going forward, this may be unsustainable in light of a 5% annual increase in the number of people with diabetes and increasingly constrained budgets. Although previous studies have assessed the cost-effectiveness of differing intervals for DR screening, the evidence is mixed. Adapting screening intervals to reflect personalised risk profiles could produce more cost-effective screening protocols.

During the screening episode (SE), best distance visual acuity is measured and digital photographs of the retina are taken after pharmacological dilatation of the pupils. The retinal images are then assessed or 'graded' to identify all the features of DR in a multistage, quality-assured process. Eyes with retinopathy are classified into one of three retinopathy grades or levels (R1 to R3 in increasing severity) depending on the presence and severity of retinopathy features, combined with one of two categories depending on whether the retinopathy is also affecting the patient's macula (M1 cases) or not (M0 cases). Eyes without any features of DR are classified as R0M0 (no retinopathy and hence no maculopathy). Seven categories from R0M0 to R3M1 are therefore possible for each eye, as R0M1 (maculopathy without retinopathy) is a disallowed category. The outcome for and subsequent management of the patient depends on the severity of the more affected eye.

The four more severe categories (R2M0, R2M1, R3M0 and R3M1) are considered as having potentially sight-threatening diabetic retinopathy (STDR) and require referral to HES as the primary outcome from screening. Cases that are classified as R1M1 in one or both eyes are also classified as having STDR but are sometimes offered interim review appointments in surveillance clinics or are referred directly to HES, depending on severity and circumstances. Patients classified as having only 'low-risk' DR (R1M0) in one or both eyes or no retinopathy (R0M0) in both eyes are offered an annual appointment for rescreening. The R1M0 cases in one or both eyes, along with the bilateral R0M0 cases, represent the vast majority of screened patients in each annual screening round.

Grading is subjective and is not an exact science, although all staff working in the national programme are appropriately qualified and are quality assured. There is variation between graders and between the same grader on a different day, as well as differences between programmes. Quality assurance procedures are in place to minimise variation as much as possible. The sensitivity and specificity (or misclassification rates) of the screening programme relies on accurate grading of photographs, but direct estimation of misclassification is not always possible. In this project we have, however, estimated and incorporated allowance for grading error using longitudinal data from an established screening programme with good quality assurance and quality-control procedures and a stable well-trained workforce. We have modelled the progression of DR from low-risk categories of bilateral R0M0, R1M0 in one eye or bilateral R1M0 to the various states whereby referral to HES was required and/or laser treatment was indicated.

Objectives

- To use eye screening, demographic and routinely collected clinical information from Gloucestershire to develop a risk score for each patient and to identify patient groups whose risk of retinopathy progression is low and whose screening interval can be safely extended.
- To extend our results to multiethnic populations using data sets from Nottinghamshire and South London and a large data set of predominantly white Caucasian patients from East Anglia. We required grading results from these data sets for at least a 3-year period. The risk score and algorithm was tested against retinopathy grades in these sets where follow-up data were available.
- To model what the influence of the grading classification error is on over-referrals and under-referrals and how that influence changes over time, taking into account sequential grading results and hospital outcome results, comparing screening intervals that vary according to risk score against current standard practice (annual screening for all patients) and other fixed-interval approaches.
- To determine whether assigning diabetic patients to differing DR screening intervals using a risk estimation model is cost-effective when compared with the current English NHS Diabetic Eye Screening Programme (i.e. annual screening for all people with diabetes).

Methods

An initial cohort of patients with at least two SEs was assembled from the Gloucestershire screening programme and clinical data were collected from primary care electronic records. The cohort ($n = 12,790$) was partitioned into derivation and validation sets using district council areas of primary care practice. Proportional hazards were used to identify variables influencing time to progression to STDR in the derivation set. The validation set was used to assess model fit by examining deciles of estimated risk.

Patients with no evidence of STDR were categorised into three groups or states: those with no DR (R0M0/R0M0), those with mild non-proliferative DR (NPDR) in just one eye (R1M0/R0M0) and those with mild NPDR in both eyes (R1M0/R1M0). Using the risk estimation algorithm the risk score in those with no evidence of STDR was estimated and the risk for subsequent progression to STDR was calculated by quintile.

The model needed to be tested in other data sets, including those with more ethnic variation than the predominantly white Caucasian patients that are found in the Gloucestershire population. Data were obtained from three other English screening programmes and, for a subset of these patients, clinical data were extracted from primary care.

We used a homogeneous hidden Markov model with seven states to estimate the probability of true progression or regression and the conditional probability of an observed grade given the true grade (misclassification). The stage or severity of retinopathy was assumed to progress as a function of duration of diabetes and transitions were adjusted for baseline glycated haemoglobin (HbA_{1c}) and type of diabetes.

A probabilistic decision analytic model, in the form of a hidden Markov model was developed to estimate the costs and quality-adjusted life-years for each DR screening strategy over the lifetime of the patient. Using data from the Gloucestershire screening programme, we obtained disease progression data and associated changes in visual acuity; screening, referral, assessment and treatment uptake rates; and secondary health-care costs. Other model parameters were obtained from the published literature.

Results

The Gloucestershire derivation data set contained 7012 patients [56% male; 4.4% type 1 diabetes, 95.6% type 2 diabetes; mean diabetes duration 1.9 years; mean age 65 years; HbA_{1c} median 50 mmol/mol (25–75th centile 43 to 60 mmol/mol), total cholesterol median 4.3 mmol/l (25–75th centile 3.7 to 5.1 mmol/l)] of whom 606 progressed to STDR by 5 years. The validation set comprised 5778 patients, with 490 progressing to STDR.

Variables included were R1M0 in both eyes [hazard ratio (HR) 7.13, 95% confidence interval (CI) 5.84 to 8.70]; R1M0 in one eye only [HR 2.56 (95% CI 2.05 to 3.20)]; HbA_{1c} [HR 1.28 (95% CI 1.3 to 1.34)] per 10 mmol/mol; duration of diabetes [HR 1.20 (1.16 to 1.24)] per 5 years since diagnosis and total cholesterol [HR 1.08 (95% CI 1.05 to 1.19)] per mmol/l.

The risk estimates from the derivation set were applied to the validation set. The rate of progression to STDR was 5 per 1000 person-years (PYs) in the lowest decile of risk and 75 per 1000 PYs in the highest decile.

In the cohort of 10,942 patients with at least three SEs and clinical information, in whom 1012 progressed to STDR, the area under the receiver operating characteristic (ROC) curve for one screening plus clinical information was 0.78 (95% CI from bootstrapping 0.75 to 0.80), for two screenings alone was 0.76 (95% CI 0.73 to 0.79) and for two screenings plus clinical information was 0.79 (95% CI 0.76 to 0.81).

The three English Programmes (East Anglia, South London and Nottinghamshire) used for further validation of the model had 17,634, 1223 and 1083 people, respectively, in whom a baseline and one further screening result and clinical risk factor data were available. There were few non-white patients in East Anglia, but 31% and 18% of patients in South London and Nottinghamshire were of African or African-Caribbean ethnicity, and 11% of patients in South London were of South Asian (predominantly Indian) ethnicity.

In the three groups, the median duration of diabetes was 4.5 years (25–75th centile 1 to 8.7 years), 3.5 years (25–75th centile 1.3 to 6.7 years) and 2.9 years (25–75th centile 0.6 to 6.6 years), respectively; median HbA_{1c} was 55 mmol/mol (25–75th centile 49 to 66 mmol/mol), 52 (25–75th centile 45 to 64 mmol/mol) and 53 (25–75th centile 46 to 63 mmol/mol), respectively; and median follow-up from date of index screening was 2.7 years (25–75th centile 2.0 to 3.0 years), 3.8 years (25–75th centile 2.0 to 6.8 years) and 4.2 years (25–75th centile 2.2 to 5.3 years), respectively.

The rate of detection of referable DR is elevated in those who were not screened promptly after diagnosis of type 2 diabetes.

In the absence of personalised, risk-based screening intervals, screening every 3 years instead of annually was found to be the most cost-effective strategy.

Using a risk-based strategy, the most cost-effective options were to screen those at low risk every 5 years and those at medium and high risk of developing STDR every 3 and every 2 years, respectively.

With annual screening, the average discounted screening cost per patient was £273 with annual screening, £144, £101 and £67 with screening every 2, 3 and 5 years. Mean costs associated with assessment of referral at HES was also higher when screening annually (£114) than at 2, 3 and 5 years (£70, £52 and £36, respectively). Combining all health and social care costs in the model, mean discounted costs are £20,672 for annual screening, £20,490 for 2-yearly screening, £20,433 for 3-yearly screening and £20,391 for 5-yearly screening.

From a total of 14,810 people, 68,992 examinations results were extracted from the screening service database. The modelling data set consisted of 65,839 grades from 14,187 people. Observations were

excluded if retinopathy or maculopathy grade were missing from either eye or were obviously duplicate entries, and people were excluded if they only had one useable observation or did not have a baseline HbA_{1c}, serum cholesterol or duration of diabetes recorded. The median number [interquartile range (IQR)] of examinations was 5 (3–6) and the median (IQR) interval between examinations was 1.04 years (0.99–1.17 years).

When the prevalence of STDR is 7%, as per the baseline prevalence in the data, the false-positive (FP) rate is estimated to be 1.6% and false-negative (FN) rate is 12.8%. When the prevalence of STDR is 15%, the FP rate is 2.4% and FN 12.4%, and for a prevalence of 20%, the FP rate is 2.8% and FN rate 11.4%.

In East Anglia the rate of progression to STDR in the lowest risk quintile was 3 per 1000 PYs and in the highest quintile was 74 per 1000 PYs; in South London the rate of progression to STDR was 1 in the lowest risk quintile and 55 in the highest risk quintile; and in Nottinghamshire the rate of progression to STDR was 2 in the lowest risk quintile and 79 in the highest risk quintile. The area under the ROC curve was 0.84, 0.79 and 0.87, respectively, for the three groups.

Conclusions

In the absence of personalised, risk-based screening intervals, screening every 3 years is cost-effective.

Using a risk-based strategy, the most cost-effective options using Gloucestershire data were to screen those at low risk every 5 years and those at medium and high risk of developing STDR/maculopathy every 3 and every 2 years, respectively.

However, there is uncertainty in the evidence informing cost-effectiveness models, particularly in terms of the natural history of disease progression, association between utility scores and visual acuity and the effectiveness of treatment for diabetic maculopathy. There is also uncertainty concerning the annual marginal costs attributable to treatment and assessments in the HES. Further research is required to confirm these results.

Risk estimation using either one SE plus clinical information or data from two SEs in this quality-assured eye screening programme are equally powerful for categorising risk of subsequent development of STDR requiring referral to a HES. These results were validated in other programmes.

Within each of the three programmes examined, the risk model discriminates well between those with very low and those with high risk of progression to STDR. The algorithm would be suitable for calculation of personalised screening intervals. Further validation in other screening programmes and ethnic groups is required.

Overall, misclassification of a photograph to a more advanced stage of any level of DR (including background DR) is more common than misclassification into a lower grade. A modelling approach to estimating misclassification rates is feasible using data from a screening programme but may be limited to progression up to and no further than referral.

Study registration

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