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Modelling the cost-effectiveness of adopting risk-stratified approaches to extended screening intervals in the national diabetic retinopathy screening programme in Scotland

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What's new?

- A microsimulation model of the diabetic retinopathy screening and treatment pathways in Scotland was developed; incorporating risks of progression estimated from contemporary, longitudinal, population-based screening outcome data.
- The adoption of biennial screening intervals for those with diabetes and no diabetic retinopathy is likely to be cost-effective.
- There is greater uncertainty surrounding the long-term cost-effectiveness of biennial screening in younger people with Type 1 diabetes and no retinopathy, due to the higher long-term cumulative risk of developing interval referable disease, and a lower competing risk of death from all causes.

Abstract

Aims To assess the cost-effectiveness of adopting risk-stratified approaches to extended screening intervals in the national diabetic retinopathy screening programme in Scotland.

Methods A continuous-time hidden Markov model was fitted to national longitudinal screening data to derive transition probabilities between observed non-referable and referable retinopathy states. These were incorporated in a decision model simulating progression, costs and visual acuity outcomes for a synthetic cohort with a covariate distribution matching that of the Scottish diabetic screening population. The cost-effectiveness of adopting extended (2-year) screening for groups identified as low risk was then assessed over a 30-year time horizon.

Results Individuals with a current grade of no retinopathy on two consecutive screening episodes face the lowest risk of progressing to referable disease. For the cohort as a whole, the incremental cost per quality-adjusted life year gained for annual vs. biennial screening ranged from approximately £74 000 (for those with no retinopathy and a prior observed

grade of mild or observable background retinopathy) to approximately £232 000 per quality-adjusted life year gained (for those with no retinopathy on two consecutive screening episodes). The corresponding incremental cost-effectiveness ratios in the subgroup with Type 1 diabetes were substantially lower; approximately £22 000 to £85 000 per quality-adjusted life year gained, respectively.

Conclusions Biennial screening for individuals with diabetes who have no retinopathy is likely to deliver significant savings for a very small increase in the risk of adverse visual acuity and quality of life outcomes. There is greater uncertainty regarding the long-term cost-effectiveness of adopting biennial screening in younger people with Type 1 diabetes.

Introduction

The Scottish diabetic retinopathy screening programme was established in late 2005, based on a system of annual screening of all those with diabetes (aged ≥ 12 years) using digital retinal photography. The programme screened 199 268 (80.7%) eligible people in 2013/2014 [1]. With the prevalence of diabetes increasing by 4% annually in Scotland [2], costs of screening are set to rise unless efficiency gains can be realized.

Although the early identification and treatment of people at risk of sight loss from proliferative diabetic retinopathy is clearly beneficial, many people currently screened annually have no visible signs of retinopathy (or evidence of only mild disease). A number of cohort studies have demonstrated that such people face a low risk of developing referable disease within 1 year [3,4], suggesting efficiency gains could be achieved with the selective application of extended screening intervals. Consequently, the National Health Service (NHS) National Screening Committee has recently recommended that screening intervals might be extended to 2-yearly in those at low risk based on the results of two screening episodes [5,6].

Several modelling studies have assessed the cost-effectiveness of adopting extended intervals for individuals at low risk of progression to referable disease, but these have produced mixed findings, due in part to differences in the estimated underlying risks of progression [7]. The aim of this study was to assess the cost-effectiveness of adopting a risk-stratified approach to extended screening intervals using contemporary data from the national screening programme in Scotland.

Patients and methods

Screening and grading protocol

People eligible for screening in Scotland are identified via the National Diabetes Registry—the Scottish Care Information-Diabetes Collaboration (SCI-DC) database—which automatically captures data on people with a diagnosis code for diabetes. It has an estimated coverage of > 99% of the diagnosed population. The screening examination involves single central 45° field digital photographs with mydriasis if required, which are graded centrally using a quality-assured grading system [8].

The grading system provides a retinopathy (R) grade and a maculopathy (M) grade [9]. Action is determined by the most severe finding in the worst eye with grades of R3 (referable background retinopathy), R4 (proliferative retinopathy) and M2 (referable maculopathy) triggering referral to a specialist eye clinic. Individuals with no (R0) or mild (R1) background retinopathy are currently recalled to screening at 1 year, whereas those with observable disease (R2 and/or M1) are recalled at 6 months.

Overview of the modelling approach

In this study, we used observed data on screening outcomes to derive transition probabilities between non-referable and referable retinopathy states. A decision analytic model was then used to simulate the progression of a synthetic cohort with a covariate distribution matching that of the Scottish diabetic screening population. Downstream risks of visual loss associated with referable disease, health and social care costs, and health state utility data were incorporated in the model based on the existing literature. The cost-effectiveness of adopting alternative risk-stratified approaches to extended screening intervals was then assessed.

Derivation of transition probabilities

The methods for deriving transition probabilities from the longitudinal screening data are described in detail elsewhere [4]. The dataset held by SCI-DC provided outcome data from sequential screening visits for 255 712 individuals who had at least one screening exam between October 2005 and November 2011. The median [interquartile range (IQR)] number of screening visits was 4 (2–5) and the median (IQR) interval between visits was 54 (51–59) weeks. In total, 11 201 cases of referable background (R3) or proliferative retinopathy (R4), and 25 333 cases of referable maculopathy (M2) were observed over follow-up. As well as information on screening outcomes, the dataset contains clinical and demographic variables, including type of diabetes, diagnosis date, sex and age.

To allow for misclassification, a continuous-time hidden Markov model was fitted to the screening data using the MSM package for R [10], and then used to examine the effect of individual level covariates on the transitions between four discrete observed states: (1) no visible retinopathy (R0); (2) mild background retinopathy (R1); (3) observable background retinopathy or maculopathy (R2/M1); and (4) referable retinopathy or maculopathy (R3, R4, M2). The model specified four hidden states corresponding to these four observed states,

each with a vector of emission probabilities. The Q matrix of transition rates was constrained to allow transitions only between adjacent hidden states, and the emission probabilities were constrained to allow misclassification only to observed states adjacent to the hidden state. State 4 was modelled as an absorbing state—no transition to a less severe state can occur. Two covariates—sex and duration of diabetes—were included in the model as effects on the transition rates between hidden states. Using this approach, the model-based probabilities of observing a transition to referable disease (R3, R4 or M2) over ensuing time intervals (up to 3 years) were calculated by type of diabetes, sex, diabetes duration and current/prior observed retinal photographic screening grade.

Economic modelling

The characteristics of the simulated cohort were based on a random sample (n = 7349) of the Scottish screening cohort (Table 1). The decision model (Fig. 1) was used to simulate progression on a 3-monthly cycle for those with non-referable disease (state 1, 2 or 3), no history of referable disease and complete descriptive data (n = 6348; 86.4%). Details of the model and the input parameter values are provided in Appendix S1 (Tables S1–S3). An overview is provided below.

The transition probabilities between observed retinopathy states were incorporated and referenced by the characteristics of simulated individuals in the economic model. Because there are currently insufficient rounds of screening to assess observed transitions in the longer term, duration of diabetes and the expected current and prior screening grades of simulated individuals were updated every 12 months, and the onward 1- and 2-year probabilities of progression to referable disease were reset every 24 months based on these updated characteristics. Probabilities of developing referable disease were expressed as 3-monthly probabilities, in keeping with model cycle length.

Incident referable disease was disaggregated to M2, R3 and R4 based on observed screening data.

For referable maculopathy (M2) with diabetic macular oedema (DMO) left untreated [11], a 30% risk of moderate visual loss [≥ 15 Early Treatment of Diabetic Retinopathy Study (ETDRS) letters] was modelled over 3 years [12]. Focal laser treatment was assumed for identified asymptomatic DMO not involving the centre of the macula, reducing the risk of vision loss by 50% [12,13]. Intravitreal ranibizumab injections [14] were modelled for symptomatic DMO (visual acuity ≤ 75 ETDRS letter), with visual acuity outcomes matching those observed at 2 years in the Diabetic Retinopathy Clinical Research Network Protocol I trial [15]. Following this, a simple natural history model was applied reflecting the tendency for vision to decline slowly over time [16,17].

The untreated risks of progression from R3 to R4 (11.5% per year) and from R4 to severe visual loss (8.8% per year) were identified from the published literature [18–20]. Treatment with pan-retinal photocoagulation was modelled to confer an 80% relative risk reduction for severe visual loss [19,21]. Individuals suffering severe visual loss (visual acuity ≤ 25 ETDRS letters) were modelled to undergo early vitrectomy, with 66% achieving visual acuity > 35 (mean 50) ETDRS letters [22]. For those with binocular sight-threatening disease, the risk of visual loss in each eye was modelled independently. Mortality was modelled based on age/sex-specific UK life tables combined with standardized mortality ratios reflecting the increased risk of death associated with Type 1 and Type 2 diabetes [23,24].

Costs

Costs associated with photographic screening (£35.98 per visit), optical coherence tomography monitoring (£33.14 per visit) [11], referral and treatment [25–27], and long-term

health and social care [22,28] were incorporated in the model (Table S1). All costs were expressed in 2012–2013 pounds sterling [26].

Quality-adjusted life years

The survival time of simulated individuals was quality adjusted using health state utility weights reflecting the desirability of their modelled visual acuity status. This approach allowed quality-adjusted life years (QALYs) to be estimated. Uncertainty exists as to how vision loss in one or both eye(s) affects health-related quality of life. A conservative approach was adopted, whereby health state utilities associated with visual acuity in the worse-seeing eye [16] were referenced for those with two good eyes (visual acuity> 35 ETDRS letters) at baseline, with best-seeing eye utility values [29] applied if vision dropped to ≤ 35 letters in both eyes. Utility values associated with visual acuity in the best-seeing eye [29] were referenced for simulated individuals with only one good eye at baseline. We also report expected differences in the incidence of moderate visual loss and severe visual loss or vitrectomy. These estimates do not account for the fact that visual impairment is at least partly reversible in a significant proportion of cases.

Screening strategies

The analysis focused on the impact of adopting 2-year screening intervals in subgroups of individuals with no retinopathy and duration of diabetes ≤ 25 years. Screening programme sensitivity was estimated to be 0.857 based on the reported sensitivities of graders operating at different levels within the grading system in Scotland [8,30,31]. Screening uptake was set at 80% [1] and it was conservatively assumed that individuals do not present to ophthalmology services unless identified through the screening programme. The following strategies were compared:

1. Current practice—annual screening for those with no or mild retinopathy, 6-monthly screening for observable retinopathy/maculopathy;
2. Two-year intervals for those with no retinopathy;
3. Two-year intervals for those with no retinopathy at first screen or no retinopathy observed at two consecutive screening episodes; and
4. Two-year interval for those observed with no retinopathy at two consecutive screening episodes.

Individuals developing any retinopathy were returned to current practice once identified. It was also conservatively assumed that individuals missing an appointment would remain on their assigned interval until their next screen. Secondary analyses considered separately the subgroup with Type 1 diabetes.

Analysis

Monte Carlo simulation was used to propagate the passage of individuals through the model one at a time. Modelled costs and QALYs were discounted at a rate of 3.5% per annum [32]. Incremental cost-effectiveness ratios (ICERs), reflecting the difference in mean costs over the difference in mean QALYs between two strategies, were calculated for more effective strategies vs. the next less effective option. To help interpret the ICERs, a threshold willingness-to-pay ratio of £30 000 per QALY was applied [32]. Probabilistic sensitivity analysis was carried out by assigning a probability distribution (Table S1) to each model input parameter and analysing the model 1000 times, each time using a randomly selected value for each input parameter from its assigned distribution [33]. Deterministic sensitivity analysis assessed the impact of varying parameter values and structural assumptions individually and in combination. A further exploratory analysis assessed the 1-year

progression risk above which annual screening may become cost-effective compared with biennial screening.

Results

Model-based transition probabilities

The estimated risks of progression derived from the analysis of the national longitudinal screening data are tabulated in Tables S2 and S3.

Individuals with a current grade of no retinopathy and a prior grade of no retinopathy (or no prior screen) face the lowest risk of progressing to referable disease. As reported previously [4], prior screening grades improve the prediction of subsequent transition beyond the current state; for example, those with no retinopathy and a prior grade of observable or mild retinopathy face a higher risk of progression than those with no retinopathy previously observed.

Economic analysis

Table 2 summarizes the projected mean costs and outcomes at 3 years for the alternative screening strategies. The 2-year interval strategies result in health service cost savings for very small increases in the incidence of visual loss. For example, strategy 3 results in an expected saving of approximately £19 per patient, for an increase in the incidence of moderate and severe visual loss/vitrectomy of 1–2 per 100 000 screened. Economic cost savings at the population level would equate to approximately £3.3 million (£19 × 200 000 × 0.864) over 3 years.

Tables 3 and 4 present the results of applying the alternative interval strategies iteratively over 30 years. Over time the cumulative differences in costs and outcomes between the

strategies increase, with the biennial strategies leading to an increase in the cumulative incidence of moderate visual loss of 36–54 per 100 000, or severe visual loss/vitrectomy (in any eye) of 31–46 per 100 000. However, the ICERs for the more effective strategies remain very high. For example, current practice is estimated to cost an extra £232 290 per QALY gained compared with the strategy involving the targeted use of biennial screening for those with no retinopathy on two consecutive screening episodes.

Table S4 (Appendix S2) replicates the above analysis for those with Type 1 diabetes. In this subgroup, the ICER is £21 740 per QALY gained for annual vs. biennial screening for those with a current grade of no retinopathy and a prior grade of mild/observable retinopathy. The ICER for current practice is estimated to be £85 399 per QALY gained compared with the selective use of biennial intervals for those with no retinopathy on two consecutive screening episodes. The increases in cumulative incidence of moderate visual loss and severe visual loss/vitrectomy range from 24 to 36 per 100 000 and from 32 to 50 per 100 000, respectively—with the smaller increases being associated with the selective use of biennial intervals in those with no retinopathy on two consecutive screening episodes (Table S5).

Deterministic sensitivity analysis

Table S6 (Appendix S2) presents the results of deterministic sensitivity analyses. For the cohort as whole, the findings are generally robust to changes in key input parameters. If individuals on a biennial interval who miss a screening visit are recalled to annual screening, this greatly reduces the increased incidence of moderate visual loss and severe visual loss/vitrectomy associated with the biennial screening (by approximately 80–85%), and greatly increases the ICERs for annual screening. The ICERs for current practice were also found to be similarly high when applying the biennial interval strategies irrespective of

diabetes duration; £209 014 and £94 693 per QALY gained for the cohort as a whole and the Type 1 cohort, respectively (Table S6, scenarios 18 and 19).

Risk threshold analysis

Applying conservative assumptions, the risk threshold analysis suggests that the ICER for annual vs. biennial screening may fall below £30 000 when the 1-year risk of progression rises above ~ 4.3% for those with Type 2 diabetes, or above ~ 1.4% for those with Type 1 diabetes. When the risk of progression is below ~ 0.5% in those with Type 2 diabetes, the additional cost per QALY gained for annual vs. biennial screening rises above £100 000. However, for Type 1 diabetes, the ICER for annual screening only rises above £100 000 when the 1-year risk of progression drops below ~ 0.2%.

Probabilistic sensitivity analysis

The results of the probabilistic sensitivity analysis comparing the 2-year interval strategies are summarized in Fig. 2. These indicate that strategy 2 (2-year intervals for all those with no diabetic retinopathy) has the highest probability of being cost-effective at willingness to pay of £30 000 per QALY gained. Figure S1 presents the probabilistic results for those with Type 1 diabetes.

Discussion

This study suggests that the magnitude of any increase in the incidence of visual loss, with the adoption of biennial screening for those with no diabetic retinopathy, is likely to be very small. Biennial screening for those with no retinopathy on two consecutive screening episodes generated ~ 36 additional cases of moderate or severe visual loss per 100 000 over 30 years. However, a good proportion of these cases would be expected to improve following

appropriate treatment [22,34]. In addition, conservative assumptions were applied in the model to guard against underestimating the risk of interval referable disease progressing to proliferative retinopathy. It may, therefore, overestimate the long-term risks of visual loss and modelled cumulative differences between the strategies on this outcome. Furthermore, most of the additional cases of visual loss (80–85%) occurred in the second year following a missed screening episode, in individuals on a biennial interval who were modelled to go a further 2 years before being recalled. In reality, such individuals could be recalled earlier to annual screening, greatly reducing any increase in the risk of visual loss. Conversely, the corresponding cost savings with biennial screening are relatively large, equating to approximately £8.1 million (net present value) per 100 000 for the most conservative biennial screening strategy.

For the cohort as a whole, the base case ICERs for annual vs. biennial screening ranged from approximately £74 000 (for those with no retinopathy and a prior observed grade of mild or observable retinopathy) to approximately £232 000 per QALY gained (for those with no retinopathy on two consecutive screening episodes). The ICERs for annual screening in those with Type 1 diabetes were lower due to a lower competing risk of death and a slightly higher proportion of incident referable disease being R3/R4. However, the ICER for annual screening in those with no retinopathy on two consecutive screens remained well above £30 000 per QALY [32]. The model findings were generally found to be robust to changes in key parameters and assumptions, with the ICER for current practice remaining above £30 000 per QALY. The findings in the Type 1 subgroup were somewhat more sensitive. However, if individuals on a biennial interval who miss a screening visit are recalled to annual screening, this greatly increases the ICERs for annual vs. biennial screening in all cohorts.

Applying conservative modelling assumptions, the ICER for annual vs. biennial screening, in those with Type 2 diabetes, was found to fall below £30 000 when the 1-year risk of

progression was above ~ 4.3%. In those with Type 1, diabetes the corresponding risk threshold was ~ 1.4%. These thresholds may, in reality, be higher. For comparison, the observed one-year probabilities of progression among individuals with no diabetes on two consecutive screening episodes were recently reported to vary between 0.1% and 0.6% across seven UK based screening programmes [35].

Strengths and limitations

The risks of progression to referable disease, in the short term, were derived from longitudinal Scottish population-based screening data. In addition, care was taken to ensure the modelled screening and downstream monitoring/treatment pathways were consistent with current clinical practice. By using a microsimulation approach, we were also able incorporate heterogeneity in the simulated cohort and dynamically adjust intervals to the modelled screening history of simulated individuals.

The long-term analysis assumes that the estimated short-term transition probabilities between observed retinopathy states—referenced by sex, current/prior grade and type/duration of diabetes—are valid for predicting future progression based on modelled updating of the time-varying characteristics of the simulated cohort. Given that the longitudinal screening data cover a median of four screening visits, this is an uncertain assumption. Any decision to adopt wider intervals iteratively over time (based on these criteria) should be carefully monitored and reviewed. As more data become available on the ongoing risk of progression, more sophisticated ways of identifying those at low risk of progression may be identified. A further caveat of the analysis is that the progression risks were derived from screening data collected primarily before the introduction of automated grading in Scotland. However, because automated grading was found to have similar sensitivity to manual disease/no disease

grading (i.e. the task it replaces in the Scottish grading system) [30,31], we do not expect this to have a material impact on our findings.

Owing to a lack of contemporary data on the progression of untreated referable retinopathy in the Scottish context, the economic modelling relied on assumptions and older natural history data to inform this. Therefore, estimated visual loss and QALY losses associated with biennial screening may be overestimated if the contemporary post-referral disease progression rates are lower than in the 1970s/1980s due to changes in the management of risk factors. This seems plausible because glycaemic and blood pressure management is much more aggressive now compared with the 1970/1980s [36–38]. It would be beneficial to conduct further observational studies to better inform this area of uncertainty.

The model adopted a health and social care perspective in line with NICE guidelines for evaluating health technologies in the UK NHS [32]. However, it is acknowledged that visual impairment has a broader impact on costs to individuals and society as a whole, which have not been captured here. Furthermore, there is a paucity of data on the health and social care costs associated with legal blindness in the UK, and those included in the model were estimated for older people with age related macular degeneration [28]. Therefore, the model based results are likely more robust for older groups with Type 2 diabetes.

Comparison with other similar studies

The majority of cost-effectiveness studies that have assessed the use of extended screening intervals have concluded that similar clinical outcomes can be achieved at lower cost in those with no or mild retinopathy [7]. Although three prior modelling studies concluded that annual screening is more cost-effective [39–41], these studies applied higher aggregate risks of progression than those estimated for individuals with no retinopathy in the contemporary Scottish cohort.

Scanlon *et al*. recently conducted a comprehensive modelling study assessing the impact of adopting risk-stratified screening intervals in the national screening programme in England [42]. They similarly informed progression risks using multistate modelling of longitudinal screening data, and embedded these in a Markov decision model. For those with no retinopathy on two consecutive screening episodes, they estimated that the adoption of 2-year screening intervals would save on average £225 000 per QALY lost compared with annual screening. Our comparable estimate is £232 290 per QALY lost for a similar policy. Scanlon *et al*. also estimated a saving of £113 823 per QALY lost for 3-year vs. 2-year intervals in this low-risk group. Given the many uncertainties regarding the impact and risk of visual loss following the development of referable disease in the Scottish context, we focused on assessing the robustness of the cost-effectiveness findings for biennial intervals. However, it is entirely plausible that even wider intervals may be cost-effective against standard thresholds in low-risk groups.

Implications for policy

This study generally supports the adoption of extended 2-year screening intervals for individuals with diabetes who have no retinopathy. The adoption of explicit criteria for extended screening intervals would free up resources for reinvestment, allowing screening programmes to meet increasing demand within budget constraints, whilst guarding against the passive slippage of screening intervals due to capacity constraints. Furthermore, freed resources could be reinvested in potentially more cost-effective activities; such as efforts to improve screening uptake in higher risk non-attenders.

Conclusions

A shift to biennial screening for individuals with Type 2 diabetes who have no retinopathy is likely to deliver significant savings for a very small increase in the risk of adverse visual acuity and quality of life outcomes. Given uncertainty over the longer term risk of progression in those who would be exposed continually to an extended interval, the safer strategies which target only those with no history of observed retinopathy may be preferred. Although our results suggest these safer strategies are also likely to be cost-effective in those with Type 1 diabetes, there is currently greater uncertainty surrounding the longer term cost and quality of life impact of any visual loss in this younger cohort.

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Competing interests

None declared.

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Author contributions

GS, SP, PM, HL, HC, JO and GL and designed the study. PM, HL and HC were responsible for the management and analysis of the longitudinal screening data. PM developed and analysed the continuous-time hidden Markov model for deriving transition probabilities between observed retinopathy states. GS developed and analysed the economic model, with supporting contributions from MJ. SP conceived of the idea for the study and supported the development and analysis of the economic model. GL and JO provided clinical expertise on the screening and treatment pathways incorporated in the model. All authors reviewed drafts of the manuscript and contributed critically to the final paper.

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FIGURE 1 Schematic of the model structure.

FIGURE 2 Cost-effectiveness acceptability curves for the 2-year interval strategies, applied iteratively over a 30-year time horizon. DR, diabetic retinopathy.

Supporting Information

Additional Supporting Information may be found in the online version of this article.

Appendix S1. Additional information on the economic model inputs and assumptions.

Appendix S2. Additional analysis.

Table S1. Economic model parameter input values and assumptions.

Table S2. Fitted probabilities of progression to any referable retinopathy at 1 and 2 years, by duration of diabetes, sex, and current and prior photographic grade (Type 1 diabetes).

Table S3. Fitted probabilities of progression to any referable retinopathy at 1 and 2 years, by duration of diabetes, sex, and current and prior photographic grade (Type 2 diabetes).

Table S4. Estimated mean and incremental costs and QALYs for the alternative interval strategies in those with Type 1 diabetes, applied iteratively over 30 years.

Table S5. Costs and consequences of applying the alternative strategies iteratively over time in those with Type 1 diabetes (30-year time horizon).

Table S6. Deterministic sensitivity analysis surrounding the continuous use of the alternative 2-year interval strategies (over 30 years).

Figure S1. Cost-effectiveness acceptability curves for the 2-year interval strategies, applied iteratively over a 30-year time horizon (Type 1 diabetes only).

Table 1 Sample cohort characteristics based on data at last screen

	Whole cohort		Type 1 diabetes		Type 2 diabetes	
Variable	*N*	Mean (SD) or *n* (%)	*N*	Mean (SD) or *n* (%)	*N*	Mean (SD) or *n* (%)
Age, mean (SD)	7349	64.8 (15.1)	793	41.5 (16.3)	6523	67.7 (12.2)
Duration, mean (SD)	7349	8.7 (8.0)	793	18.3 (12.9)	6523	7.5 (6.3)
ETDRS letters (left), mean (SD)	7223	75.4 (16.2)	793	80.6 (12.5)	6523	74.8 (16.4)
ETDRS letters (right), mean (SD)	7222	75.3 (16.0)	793	80.3 (13.7)	6523	74.6 (16.2)
Type 2 diabetes; *n* (%)	7349	6523 (88.8)	–	–	–	–
Male, *n* (%)	7349	4034 (54.9)	793	433 (54.6)	6523	3587 (55.0)
Current state, *n* (%)	7349		793		6523	
1 (R0/M0)		4843 (65.9)		335 (42.2)		4484 (68.7)
2 (R1)		1662 (22.6)		263 (33.2)		1391 (21.3)
3 (M1, R2)		84 (1.1)		20 (2.5)		64 (1.0)
4 (R3, R4, M2)		478 (6.5)		160 (20.18)		317 (4.9)
Missing		282 (3.84)		15 (1.89)		267 (4.1)
Previous state, *n* (%)	7349		793		6523	
1 (R0/M0)		3893 (53.0)		275 (34.7)		3603 (55.2)
2 (R1)		1417 (19.3)		256 (32.3)		1155 (17.7)
3 (M1, R2)		88 (1.2)		22 (2.8)		66 (1.0)
4 (R3, R4, M2)		264 (3.59)		77 (9.7)		185 (2.8)
NA		1287 (17.5)		140 (17.7)		1139 (17.5)
Missing		400 (5.44)		23 (2.9)		375 (5.8)

ETDRS, Early Treatment of Diabetic Retinopathy Study; R0/M0, no retinopathy and no maculaopathy; R1, mild background retinopathy; R2 observable background retinopathy; M2, observable maculopathy; R3, referable background retinopathy; R4, proliferative retinopathy; M2, referable maculopathy; NA, not applicable.

Table 2 Costs and consequences of the alternative strategies at 3 years

	1. Current practice	2. Two-year interval for all with no DR	3. Two year interval for those with no DR and no DR previously observed	4. Two year interval for those with no DR at two consecutive screens
Total NHS costs (£)	213.88	192.79	195.18	199.67
Incidence of referable disease (%)	5.34	5.34	5.34	5.34
Incidence of detected referable (%)	3.00	2.96	2.98	2.99
Incidence of MVL (per 100 000)	256	259	257	257
Incidence of SVL or vitrectomy (per 100 000)	61	62	62	62
Years free of MVL	2.73811	2.73807	2.73809	2.73809
QALYs	2.25430	2.25430	2.25430	2.25430

DR, diabetic retinopathy; no DR, no diabetic retinopathy; MVL (moderate visual loss ≥ 15 ETDRS letters); SVL (severe visual loss ≤ 25 ETDRS letters); bold type highlights the strategy most favoured on each outcome.

Table 3 Costs and consequences of applying the alternative strategies iteratively over time (30-year time horizon)

	1. Current practice	2. Two-year interval for all with no DR	3. Two-year interval for those with no DR and no DR previously observed	4. Two-year interval for those with no DR at two consecutive screens
Total NHS costs (£)	2016.59	1921.00	1930.80	1935.76
Incidence of referable disease (%)	34.79	34.79	34.79	34.79
Incidence of detected referable (%)	32.59	32.39	32.45	32.46
Incidence of MVL (per 100 000)	13 012	13 066	13 048	13 048
Incidence of SVL or vitrectomy (per 100 000)	5 910	5 956	5 942	5 942
Years free of MVL	10.736	10.732	10.733	10.733
QALYs	9.1678	9.1673	9.1674	9.1675

DR, diabetic retinopathy; no DR, no diabetic retinopathy; MVL (moderate visual loss ≥ 15 ETDRS letters); SVL (severe visual loss ≤ 25 letters).

Table 4 Estimated mean and incremental costs and QALYs for the alternative interval strategies applied iteratively over 30 years

	Mean cost (£)	Incremental cost (£)	Mean QALYs	Incremental QALY	ICER/QALY (£)	Net monetary benefit (£)
2. Two-year interval for those with no DR	1 921.00		9.16731			£273 098
3. Two-year interval for those with no DR and no DR previously recorded	1 930.80	10	9.16744	0.000132	£73 960	£273 092
4. Two-year interval for those with no DR at two consecutive screens	1 935.76	5	9.16745	0.000010	£480 006	£273 088
1. Current practice	2 016.59	81	9.16780	0.000348	£232 290	£273 017

Strategies compared incrementally to the next less effective, non-dominated alternative. DR, diabetic retinopathy; ICER, incremental cost-effectiveness ratio.