Diabetic retinopathy is no longer the leading cause of blindness among people of working age – thanks, at least in part, to retinal screening. But there are still lessons to be learned, and changes are planned to national retinal screening programmes. Three new papers look at the timing, accuracy and economics of this important element in diabetes care.
of, retinopathy and maculopathy, with referral to a specialist eye clinic being triggered by the higher grades indicating significant diabetic eye disease.

The Four Nations Diabetic Retinopathy Screening Intervals Project was established by the National Screening Committee in May 2012 to determine whether the evidence supports the introduction of extended intervals between screening, for those who show no signs of retinopathy at two successive screening appointments. This would improve the cost-effectiveness of the retinal screening model, allowing resources to be devoted to those individuals at higher risk. The issue of screening intervals is also of interest in the context of those who do not attend for screening. Since diabetic eye disease can progress without symptoms, missing out on appointments may put an individual’s vision at risk. A further issue of concern is the accuracy of grading, given that undergrading may lead to missing referable cases of retinopathy and maculopathy.

Three new papers highlight these issues. One shows that longer time intervals between diagnosis and screening increases the risk of retinopathy, the second looks at the cost-effectiveness of extending the screening interval and the third reports on the accuracy of grading.

Delay is dangerous

The first study, from Professor Peter Scanlon of the Gloucester Retinal Research Group and colleagues, looks at how age and time to first screening affect the risk of retinopathy. According to a recent report from one of the English screening programmes, rates of referable diabetic retinopathy are higher among those not screened promptly after a diagnosis of Type 2 diabetes. The analyses in this new study look at the relationship between time from diagnosis to first screen and the presence of retinopathy at that first screen. They also look at time from registration to screening by age group.

The data on which the study is based come from national screening programmes in Wales, Scotland and Northern Ireland and from four local English programmes (Brighton, Derbyshire, Leeds and Staffordshire). There were a total of 689,025 people on the register, of whom 74.4 per cent had a date of diabetes diagnosis recorded. The median age of those with Type 1 diabetes (9.4 per cent) was 22 years and of those with Type 2 diabetes (90.6 per cent) it was 59 years.

For people screened for the first time in 2011, of those who had a type and time of diagnosis recorded, the proportion with any retinopathy and with referable (including ‘fast track’) retinopathy, increased with time from diagnosis to screening. For people diagnosed in 2010 or 2011, the proportion with any kind of retinopathy at screening was 18 per cent, while for those diagnosed before 1990 it was 67 per cent. The figures for ‘fast track’ referable retinopathy were 0.1 per cent and 8.7 per cent, respectively. Those individuals diagnosed before 1990 and not screened until 2010 or 2011 were 19 times more likely to have referable retinopathy and 69 times more likely to have ‘fast track’ referable retinopathy.

Age, programme factors

The researchers also carried out an analysis of the influence of age of the individual upon the interval between registration and attendance at first retinal screening. Data was available for 3,958 people aged 12–17 years, 19,058 aged 18–34 years, 15,549 aged 35–59 years and 215,797 aged 60 years and above. Those in the 18–34 years age group were the least likely to attend for screening in the first three years after registration. At two years, one in seven of those aged below 18 years or above 35 years had not attended screening. For the 18–34 year age group, the figure was one in four.

There was also some variability between the different programmes in the analysis. The proportions screened at 12 months from registration ranged from 63 per cent to 85 per cent and, at 36 months, from 81 per cent to 91 per cent.
This study is the first to reveal that the 18–34 year age group is more likely than other age groups to have a longer interval between registration and attendance.

Take-home messages

It is already known that age, socio-economic deprivation, poor glycaemic control, hypertension, smoking and primary care/screening team factors all influence attendance at retinal screening. Particularly concerning is that there is a link between non-attendance, poor diabetes control and blindness registration. Indeed, one missed attendance is associated with a three times higher risk of needing laser photocoagulation treatment subsequently.

This study is the first to reveal that the 18–34 year age group is more likely than other age groups to have a longer interval between registration and attendance at first screening, with a consequent greater risk of referable diabetic retinopathy being present at that first screen. This finding likely reflects the known propensity for non-attendance in this age group and that younger people are more likely to have Type 1 diabetes. It is particularly important that these young adults are screened. There are long-term quality of life issues involved for them, as well as broader economic implications for society from lost productivity.

Another significant finding is that the risk of referable, including ‘fast track’, retinopathy increases among those who are not screened promptly following registration, independent of the duration of diabetes. Delaying screening for three years or more after registration increases the risk of proliferative retinopathy four-fold. The authors believe this indicates that there is a difference between those who delay and those who attend promptly. Further research is needed to understand the reasons for delay and whether screening programmes might be adapted to address these.

The findings suggest that the screening programmes should collect data on those who do and do not attend over a 1, 2, 3, 4 and 5-year period. In addition to the date of registration, the date of diagnosis should also be routinely recorded. Without these data, the high-risk group who have never attended cannot be identified for follow-up. Finally, it was noted that some screening programmes seem better at attracting young people than others. Programmes have different approaches to delivery. It could be that those programmes with lower attendance could learn from those with higher attendance and make some changes.

COST-EFFECTIVENESS OF EXTENDED SCREENING

Retinal screening is currently recommended annually for all people with diabetes in the national screening programmes. However, as the numbers with diabetes continue to increase, screening costs are set to rise accordingly. It is time for efficiency gains to be considered. Many of those who attend screening actually have no, or minimal, signs of retinopathy. Research has shown that these individuals have a low risk of developing referable disease within the following year. Thus, the efficiency gains needed may be achieved by offering extended screening to this lower risk group.

The NHS National Screening Committee has recently recommended extending the screening interval to two years for those who fall into this group. However, before such an approach is adopted, it is important to balance the financial gains to the health service against the potential risk of missing referable disease by extending the screening interval. Previous research on this issue has produced mixed results. Therefore, researchers in Scotland have carried out a study of the cost-effectiveness of adopting a risk-stratified approach to extended screening.

Modelling extended intervals

In this study, researchers used data from screening outcomes from the Scottish Care Information Diabetes Collaboration (SCI-DC), which captures more than 99 per cent of the diabetes population. From this, they derived transition probabilities between non-referable and referable retinopathy. They used this to simulate the progression of a synthetic cohort through the screening pathway. Risks of visual loss associated with referable disease, health and social care costs associated with treatment and visual loss were incorporated into the model.

The SCI-DC provided data for screening visits for 255,712 individuals who had had at least one screening exam between October 2005 and November 2011. This revealed 11,201 cases of referable background retinopathy (R3) or proliferative retinopathy (R4) and 25,333 cases of referable maculopathy (M2).

The study suggests that two-yearly screening would have little impact upon those with no diabetic retinopathy. For those who had no retinopathy on two consecutive screening occasions, there would be around 36 additional cases of moderate to severe loss of vision per 100,000 population over 30 years. Many of these would improve with treatment. The cost saving was estimated at £8.1m per year. The findings broadly support a move to biennial screening. The main caveat is that younger people with Type 1 diabetes exposed to longer periods of extended screening could be more at risk of diabetic eye disease. It may therefore be wiser to adopt a ‘safer’ screening strategy in this group.
HOW ACCURATE IS SCREENING?

It is known that there is variation in screening both between and within graders. Under-grading occurs when tiny abnormalities are missed and over-grading occurs if harmless dust spots, for instance, are recorded as abnormalities or when a minor abnormality is classed as something more serious. Both can lead to misclassification of the true level of retinopathy. Moreover, such grading variation can give an impression of progression of retinopathy over time when the condition is actually stable. This could have implications if screening intervals are extended. What if an individual has their interval extended after apparently negative results when, in fact, they need to keep on with annual screening because of retinopathy that has been missed? Or, conversely, over-grading might mean annual screens are being carried out on those who could otherwise move to extended screening.

Precision and accuracy of the grading of retinal screening photographs is key to the effectiveness of screening programmes. However, a direct estimation of misclassification rates has never been done before; screening accuracy is usually reported in terms of referable disease. Thus Jason Oke, and co-workers at the University of Oxford, carried out a study to quantify the level of misclassification in a screening programme and what impact this might have upon the proposed plan to extend screening intervals.

Modelling misclassification

The researchers used longitudinal data on retinal photographs from 2005 to 2012 from the Gloucestershire Diabetic Eye Screening programme and also risk factor data, such as HbA1c and duration of diabetes. The photos were all graded centrally by trained assessors. Where retinopathy of any level was detected, they were graded by a second assessor. There is no gold standard to represent the true state of retinopathy on each screening occasion, so statistical models were used to estimate this, using risk factor data and observed sequences of screening grade. The model relied on considering data across the whole cohort over the whole time period. The more inconsistent the readings – for instance, high retinopathy at one visit, none at the next – the higher the estimated misclassification rate. The model defined five levels of retinopathy/maculopathy, ranging in severity from none observed, to proliferative disease. These were treated as states in a hidden Markov model – an approach that has previously been used extensively to model disease progression and applied to cancer screening strategies.

A hidden Markov model can account for the fact that the true state of disease might not always be reflected by the test – in other words, it accounts for misclassification. The modelling cohort consisted of 65,839 observations on 14,187 people, amounting to 59,949 person-years. The model was used to estimate the true state for each observed grade in the data to assess the overall accuracy of the screening programme.

Erring on the safe side

This study showed that misclassification is not uncommon, at 21.6 per cent of screening episodes, but occurs most often between no detectable retinopathy and background retinopathy in one or both eyes. The screening programme tended to err on the side of caution – over-grading and over-referring rather than under-grading and under-referring.

It is true that under-grading could lead to a few individuals getting their screening interval extended and going on to develop referable retinopathy. But, overall, the study suggests that extended intervals will not harm the majority of those attending screening. The modelling approach described here could be applied to any retinal screening programme as a kind of safety check and would save on the costs of re-grading images.

The screening programme tended to err on the side of caution – over-grading and over-referring rather than under-grading and under-referring.