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A Markov model of Diabetic Retinopathy Progression for the Economic Evaluation of a novel DR prognostic device

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Abstract

The initial diagnosis of Diabetic Retinopathy (DR) is often in the advance stages of the condition, as patients are only promoted for an examination when sight has been affected. An innovative prognostic technique has recently been made available which can non-invasively detect the damaging effects of high blood glucose before the development of clinical symptoms. This innovation offers the opportunity to patients to make the necessary behavioural and medicinal modification to prevent further progress of the disease. This paper reports the development of a Markov model which emulates the natural progression of Diabetic Retinopathy based on data from clinical trials. The purpose of such a model is to estimate the chronic cost and health outcomes of DR, and it may be modified to reflect the potential changes in current practice or condition changes, hence allowing for an economic evaluation of the DR prognostic test. The implications and limitations of the model were also discussed in the paper.

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Keywords: Diabetic Retinopathy, Markov Model

Introduction

Diabetic Retinopathy (DR) is a debilitating complication of diabetes, where the micro-vascular network of the retina becomes damaged, unable to control blood flow, and, as the condition worsens, start to proliferate. It is also one of the leading causes of blindness in the western world both for people of working age and those aged over 65 (Bamashmus, Matlhaga et al. 2004).

There is evidence that both Diabetes Mellitus (DM) and DR may be prevented or at least their progression slowed. Results from the Da Qing Impaired Glucose Tolerance (IGT) study (Pan, Li et al. 1997), the Malmo Feasibility Study (Eriksson and Lindgarde 1991) and the Finnish Diabetes Prevention Study (Tuomilehto, Lindstrom et al. 2001), indicate that progression from pre-DM, a condition of impaired fasting glucose and or impaired glucose tolerance, to DM may be slowed by weight reduction, sufficient exercise and/or appropriate diet. The UKPDS (UK Prospective Diabetes Study Group 1998; Kohner, Stratton et al. 2001; Stratton, Kohner et al. 2001) and WESDR (Batchelder and Barricks 1995) studies also provide evidence that strict control of blood glucose, blood pressure and weight can slow the progression of DR.

Currently, a diagnosis of DR is undertaken using dilated fundus microscopies performed by optometrists or ophthalmologists. However, DR and DM are often not diagnosed until the disease is advanced when sight is likely to have already been affected. Although laser treatment may be used to slow the progression to blindness in these advanced stages, these treatments also permanently damage the retina. Thus it seems logical that preventing the development of DR or identifying it early will increase the likelihood that an individual will retain sight, maintain a good quality of life and avoid the discomfort and cost of treatment (Javitt, Aiello et al. 1994).

Our laboratory has developed a novel, non-invasive prognostic device aimed at identifying the earliest stages of DR (Martin and Markhotina 2003). This innovation (prog-DR) can detect the damaging effects of high blood glucose on the retinal microvasculature, before the development of clinical symptoms. It is expected that this test will be able to identify pre-diabetics as well as undiagnosed diabetics who have not developed DR.

Despite the intrinsic appeal of this technology, it is important to systematically assess the associated outcomes and costs. Although a randomised controlled trial, including an economic evaluation would be the most powerful means of determining the value of the test, such trials require large amounts of time and infrastructure and are expensive. To circumvent these limitations and to study the feasibility of the test before committing to a randomised clinical trial, models are often used to simulate real-world conditions, to forecast future outcomes, as well as predict outcomes when conditions such as prevalence rates, compliance to medications, costs are so on are variable, especially in chronic diseases such as diabetes (Eastman, Javitt et al. 1997; Lamotte, Annemans et al. 2002; The CDC Diabetes Cost-effectiveness Group 2002; Clarke, Gray et al. 2004; Zhou, Isaman et al. 2005). Although there are various models of interventions for DM (Eastman, Javitt et al. 1997; Lamotte, Annemans et al. 2002; The CDC Diabetes Cost-effectiveness Group 2002; Clarke, Gray et al. 2004; Zhou, Isaman et al. 2005) and or DR(Dasbach, Fryback et al. 1991; Vijan, Hofer et al. 2000; Sharma, Hollands et al. 2001; Davies, Roderick et al. 2002; Harper, Sayyad et al. 2003), these often fail to include patient behaviour such as diet, exercise patterns and response to treatment and screening recommendations (i.e. compliance) nor do they include pre-DM as a state in the model.

Economic evaluations are used to assess the costs and consequences of alternative interventions, in this case, comparing a prognostic test for DR with no test. Such evaluations fall into four categories: cost minimisation, cost utility, cost benefit or cost effectiveness analyses. The aim of this paper is to describe the development of a Markov model designed to estimate the costs and consequences of pre-DR screening.

Methods

The Markov model was built in Microsoft Excel 2003 Professional edition on an IBM Intel Celeron computer. Markov models are used to describe random processes that evolve over time. The most common application of Markov models in health is to characterize all the possible prognoses for a given group of patients. This entails modeling the progress over time of a notional group of patients through a finite number of health states. Patients are initially placed into one of the health states, and the probabilities of transition to the other states in the model are defined within a given time period, known as a Markov cycle.

Markov Progression Model

The natural progression of DR is shown in Figure 1. The ideal scenario would be to prevent DM and DR, which would involve diagnosis at the pre-DM and pre-DR stage, before the development of symptomatic damage to sight associated with DM and/or DR. The aim of early diagnosis is to enable patients to modify their lifestyle and/or undergo medical interventions earlier, thus increasing the probability of preventing or slowing the progression to DM and DR. Although there have been reports of cases of regression of DR as a result of interventions, the reported incidence is low(Kawasaki, Hasegawa et al. 2006); hence the model assumes a uni-directional flow of progression, and the transition of the disease is only to more advanced stages. However, subjects may skip one or more stages and move into more advanced stages.

Although this pre-symptomatic screening test can also identify non-diagnosed DM and hence may have implications for the development of other complications of diabetes such as renal failure and cardiovascular disease (CVD), these were not included in the model. This is because the primary aim of the screening test is the prevention of DR. There is a positive association between the severity of DR and other co-morbidities of diabetes such as cardiovascular disease (Klein, Klein et al. 1999; van Hecke, Dekker et al. 2005) ; however, these associations are not always straightforward. For example, the probability of individuals with diabetes developing cardiovascular disease is better explained by the presence of factors such as hypertension (van Hecke, Dekker et al. 2005), and nephropathy (Torffvit, Lovestam-Adrian et al. 2005) whereas the severity of retinopathy has been shown to be associated with a decreased probability of developing CVD(Lovestam-Adrian, Hansson-Lundblad et al. in press). Diabetic nephropathy, which is also a micro-vascular complication of diabetes, shows more consistent association with the severity of DR (Villar, Garcia et al. 1999; Rossing, Hougaard et al. 2002) however, glycemic (Powrie, Watts et al. 1994; Villar, Garcia et al. 1999) and blood pressure control (Stephenson, Fuller et al. 1995; Schrier, Estacio et al. 2002) are still important predictors (in conjunction with the presence of retinopathy) of nephropathy.

As a Markov model uses transition probabilities and most clinical studies present the data as hazard rates of progression, these were converted to transitional probabilities

for this model by using the formula below, where r is the hazard rate and t is time:

$$P_{transition} = 1 - e^{\left(\frac{-r}{t}\right)}$$

The Hypothetical Population

As the diagnostic test is intended to be performed by optometrists or ophthalmologists, the cohort of interest was created by using the number of people who attended an optometrist or ophthalmologist for a comprehensive or brief initial consultation (Medicare Benefit Schedule (MBS) codes 10900 or 10916 respectively) in 2005 (3,017,424 people) (Medicare Australia 2005). The cohort was divided into two groups based on eligibility for the pre-DR test.

To be eligible, an individual must not have already been diagnosed with DM or DR. Undiagnosed diabetics with DR can be identified by dilated fundus microscopy, a procedure recommended by the Optometrists Association Australia (OAA) (Optometrists Association Australia 2005) for those suspected of DR or DM. The OAA also recommends that those with DR are referred to general practitioners for further investigation. Therefore, those eligible for the pre-DR test include normal subjects, undiagnosed diabetics without DR and pre-diabetics. The latter two groups progress through the model.

Using Australian epidemiological data, the percentage of the hypothetical population who are eligible and progress through the model are shown in Table 1 and 2.

Pre-diabetic progressions and lifestyle characteristics

Studies have found that pre-diabetics have a very high probability of developing DM. The Da Qing IGT study (1997) as well as other clinical studies have shown that increases in weight or Body Mass Index (BMI) accelerate the progression to diabetes, whilst adhering to a healthy diet and undertaking regular exercise can slow the progression (Edelstein, Knowler et al. 1997; Tuomilehto, Lindstrom et al. 2001).

This model takes into account some of these real-life decisions or characteristics of pre-diabetics; one such decision is their choice of diet and exercise patterns which are assumed to be related to their body mass index (BMI). According to the Diabesity Study, 59.6% of the diabetic population in Australia is overweight (BMI above 25); therefore 40.4% can be considered lean.

It was assumed that lean subjects have similar diet and exercise patterns to respondents to the 2003 NSW Health Survey, where sufficient exercise for a non-over weight person was defined as 2.5 hours of physical activity per week and a "healthy" diet was defined as one which includes sufficient consumption of fibre (Centre for Epidemiology and Research and NSW Department of Health 2004). For overweight subjects, it was assumed that four hours of physical activity per week is sufficient, and an appropriate diet include a reduced intake of fat, saturated fat and an increased intake of fibre(2001). However, as subjects are currently not diagnosed with pre-DM, it is assumed that they will undertake a pattern of "healthy" diet and exercise at the same rate as lean subjects because they do not receive any information which would predispose them to attempt a more challenging diet and exercise pattern. Based on these data, the lifestyle characteristics of the cohort were estimated and are summarized in Table 3.

The transitional probabilities to DM are based on the Da Qing IGT study (1997) (Pan, Li et al. 1997); the probabilities are dependent on the BMI and lifestyle characteristics of individuals, so that for the same lifestyle characteristic, lean subjects have a reduced probability of progression. For example, lean subjects with an appropriate diet, sufficient exercise or both, have progression probabilities of 0.0770, 0.0496 and 0.0688, whereas the progression probabilities for overweight subjects are 0.1033, 0.1127 and 0.1167.

Diabetic progressions and lifestyle characteristics

For diabetics, the progression to more severe stages is dependent on two factors. The first is the choice of blood glucose control method, which is usually based on the severity of abnormal blood glucose levels. According to the DiabCo$t study (Colagiuri, Colagiuri et al. 2003) 1% of diabetics do not actively attempt to control their blood glucose; 32.7% control their glucose levels through diet and exercise, 59.6% use hypoglycemic tablets and 6.7% use insulin alone or in combination with other hypoglycemic medications.

The second factor influencing progression is compliance with the chosen blood glucose control method; it is assumed that those who comply achieve strict control of blood glucose levels, whereas those who do not comply achieve conventional control. According to a study by Rubin(Rubin 2005) compliance is lowest for behavioral types

of control (diet and exercise) at 5.7%, highest for simple tablet consumption at 61-85% and moderate for insulin injections (62-64%).

Individuals who are either a non-diagnosed pre-diabetic or non-diagnosed diabetic do not have the information which would enable them to manage their blood glucose levels. The model assumes that their management regime consists of diet and exercise. However, under the current screening protocol, around 10.58% of non-diagnosed diabetics will be identified each year(Dunstan, Zimmet et al. 2001). This information is incorporated into the model.

Non-sight threatening DR (nSTDR)

The transitional probabilities for the stages of DR - defined as microaneurysm (MA), mild non-proliferative DR (nPDR) and moderate nPDR - were derived from the UKPDS (UK Prospective Diabetes Study Group 1998). Despite the availability of many other excellent studies on DR progression, the UKPDS was chosen as it was based on the more common type of DM (Type 2), involved a large number of participants (over 3800) and was conducted over a long period of time (up to 10yrs).

The UKPDS showed that progression from the early stages of DR was influenced by the level of blood glucose control achieved. That is, a strict blood glucose control regime (aimed at achieving an FPG of less than 6 mmol/L), slowed the rate of progression compared with conventional blood glucose control methods. These rates of progression were converted to annual transition probabilities and distributed among the stages of diabetic retinopathy. The distribution was based on the assumption that progression to the next stage of severity is twice that to the stage after and so on. The transition probabilities are summarized in Table 4.

For progression to macular oedema, the transition probabilities were based on the WESDR (Klein, Klein et al. 1995) as the UKPDS does not include these data. The WESDR cohort was similar to the conventional control group in the UKPDS, as the majority of the cohort had a glycosylated hemoglobin (HbA) percentage above 7%. As the incidence of macular oedema (maculopathy) was 6.7 times more frequent for those with higher (HbA) (Klein, Klein et al. 1995), the transitional probabilities for the intensive blood glucose control were divided by this amount.

Sight-threatening DR (STDR)

As DR progresses, more of the retina becomes damaged and the risk of sight being affected increases. The stages at which sight is most likely to be threatened include severe nPDR, PDR and macular edema. The transitional probabilities for severe nPDR and PDR were derived from the UKPDS (UK Prospective Diabetes Study Group 1998), and the progression to macular oedema was based on the WESDR. A summary of the transitional probabilities is shown in Table 4.

For these sight threatening stages, the progression to more advanced stages is influenced by more than the control of blood glucose. It may also be affected by the need for laser treatment and compliance with monitoring and treatment recommendations.

Panretinal and focal laser photocoagulation can be used to restore some eyesight and slow the deterioration of the retina. As the laser treatment also causes irreversible damage to the retina, due to laser burns, the procedure is not always recommended. Identification of the need for treatment is facilitated by compliance with the recommendations for monitoring compiled by the National Health and Medical Research Council (NHMRC) (National Health and Medical Research Council 1997). For example, if the need for laser treatment was not identified (eg if diabetes was not diagnosed) or the intervention not carried out, the transitional probability of remaining in the current stage (no progression) is reduced to zero and the probability of transition to more advanced stages is increased; conversely, identified need and a high level of compliance with the intervention would result in a zero rate of deterioration and/or probability of progression (if the treatment was successful).

The probability that laser treatment is needed was based on the UKPDS (UK Prospective Diabetes Study Group 1998) which showed the number of people who received laser treatment. It is likely that a person will have both eyes treated. Australian hospital data (Yi, Bamroongsuk et al. 2003) was used to estimate the average number of eyes treated per patient, which was found to be 1.586 eyes per patient. The adjusted annual probability for treatment was then distributed across different stages of STDR based on the utilization proportion for each stage (Kohner, Stratton et al. 2001). The annual probabilities for laser treatment for intensive control are 0.0001, 0.0025 and 0.0172 for severe nPDR, PDR and ME; and 0.0002, 0.0034 and 0.0232 for conventional control respectively.

The likelihood of individuals complying with these recommendations was based on the study by Schoenfeld, Greene, Wu, et al., (2001), which showed that 64.8% of the diabetic population fully complied with the diabetes vision care guidelines for eye examinations (Aiello, Gardner et al. 2000); 11.1% per cent attended examinations but did not undertake all recommended tests (partial compliance), and the remaining 24.1% did not attend an eye examination at all (zero compliance).

The probability of treatment is zero for individuals who do not comply with the NHMRC recommendations for eye examinations- such an individual would not be identified as needing treatment in the first place. Conversely, the probability of treatment is one for those who fully complied with the recommendations. As the NHMRC (National Health and Medical Research Council 1997) recommends three to twelve eye examinations per year for maculopathy and four to six eye examinations per year for severe nDR and PDR, it is assumed that a minimum of three or four examinations per year is sufficient to decide whether laser treatment is required. As partial compliance means that individuals have at least one examination per year, it is estimated that there is at least a one in four chance (or one in three for maculopathy) that the need for laser treatment will be identified and the same chance that an individual will comply with treatment recommendations. The effects of additional eye examinations were tested in the sensitivity analysis.

The success rate for laser treatments was derived from Australian hospital data(Bamroongsuk, Yi et al. 2002), based on the assumption that the laser treatment was deemed successful if no further treatment was required. It should be noted however that further treatment may not be required or provided due to other reasons such as no observed improvement with the treatment regime or non-compliance of patients. As no data about these possibilities were available, the sensitivity of the incremental cost-effectiveness ratio (ICER) to variations of the success rate was tested. In the model, base-case success rates for laser treatments are set at 64.9% for severe nPDR and PDR and 48.8% for macular edema.

Blindness and Death

The transitional probabilities of progressing to blindness were based on studies by Janghorbani, Jones and Allison (2000), Lawson, Hunt and Kohner (1985) and the UKPDS (UK Prospective Diabetes Study Group 1998). The UKPDS (UK Prospective

Diabetes Study Group 1998) shows that the transitional probability of progressing to blindness is 1.16 times higher for those with conventional blood glucose control than for those who achieve strict control. As the subjects in the blindness studies are similar to the conventional blood glucose control group with blood glucose levels above 6 mmol/L and HbA above 7% (Lawson, Hunt et al. 1985; Janghorbani, Jones et al. 2000), the transitional probabilities to blindness were divided by 1.16 to yield the intensive transition probabilities. These are summarized in Table 5.

The transitional probabilities of progressing to death were based on a study by Cusick, Meleth, Agron, et al., (2005) for Type 2 diabetics. As the ratio of deaths due to diabetes and other causes is 1:1.53 (UK Prospective Diabetes Study Group 1998), the transitional probabilities of dying were divided by this ratio to differentiate between the two types of mortality.

In the UKPDS, it was shown that the mortality rate associated with conventional blood glucose control is 1.085 time higher than for intensive control (UK Prospective Diabetes Study Group 1998). As the subjects in the study by Cusick, Meleth, Agron, et al. (2005) were similar to the conventional blood glucose control group in the UKPDS, the transition probabilities were divided by 1.085 to yield the transition probabilities for those with intensive blood glucose control. The transition probabilities to death are summarized in Table 6.

It should be noted that it is these transitions probabilities that are likely to ultimately affect the outcomes of life years and sight years estimated in the model.

Health utility measurement (determining QALY scores)

Quality-adjusted life years (QALYs) and other measures of utility have been developed as a means of valuing the trade-off between length of life and health-related quality of life. A number of approaches such as standard gamble, time trade-off or rating scales can be used to produce scores which represent the valuation attached to a number of health states. The health states cover dimensions such as mobility, pain/discomfort, self-care, psychological state and ability to perform usual activities. Scores are assigned to different health states so that full health has a score of one and death a score of zero.

In this study, results from a study by Brown, Brown, Sharma, et al., (1999) provided utility values for a range of visual acuities associated with DR. A study by Fong, Sharza, Chen, et al., (2002) provided information on the range of visual acuity for different stages of DR and data from the worst eye was used. The weighted average utility scores were derived using a combination of information from these two studies and are shown in Table 7.

Cost data

Type 2 Diabetes Mellitus is a costly disease. Not only do individuals and society incur direct and non-direct health care costs, patients and their carers may also lose income and society productivity (Colagiuri, Colagiuri et al. 2003). In this model, a range of health care costs was considered. These were discounted at 3% per annum (Murray and Lopez 1996; Mathers, Vos et al. 1999) and varied between 5% and 7% in the sensitivity analysis.

Blood glucose management

The 2005 Pharmaceutical Benefits Schedule (PBS) (Department of Health and Ageing 2005) report lists the blood glucose indicators, insulin and other hypoglycemic medication available in Australia, including the prices paid by consumers. It is assumed that individuals purchase 53 weeks' worth of medications and medical consumables each year (one for each week of the year and one week's worth of back-up). The intake of hypoglycemic medications recommended by the Australian medicines handbook (AMH 2004) was used in the model and it is assumed that blood glucose was measured once per day.

The Australian government collects pharmaceutical usage information via Medicare Australia, and this information is available online: (http://www.medicareaustralia.gov.au). The Australian government also funds a National Diabetes Services Scheme (NDSS) which subsidizes syringes and insulin pens which registered diabetics can access. Based on these data, the weighted average annual cost for insulin alone or in combinations with other hypoglycemic medications was estimated to be $5,329.72 – $6,793.82 per year, $81.92 - $169.91 per year for hypoglycaemic tablets and $342.40 per year for blood glucose indicators.

In order to use these pharmaceutical products, prescriptions and re-assessment of dosage are needed. The Medicare Benefit Schedule (MBS) (Department of Health

and Ageing 2004), recommends that diabetics visit a general practitioner twice a year; it was assumed that one standard (MBS 2620) and one long consultation (MBS 22622) would be needed (Department of Health and Ageing 2004). This adds $59 to the cost of blood glucose management.

Eye examinations

The MBS price for an eye examination is $60.25 (MBS 10914) (Department of Health and Ageing 2004), and the frequencies of eye examinations were based on NHMRC recommendations for diabetics (National Health and Medical Research Council 1997). For those with PDR and ME, fluorescein angiography in one or both eyes is recommended by the NHMRC. The costs of retinal photography, multiple exposures of 1 or both eyes with intravenous dye injection (MBS code 11215 or 11218) are $104.35 and $128.90 respectively (Department of Health and Ageing 2004); the weighted average cost per person of $127, based on usage of these services in the year beginning June 2004 (published on the Medicare website), was used.

The likelihood of compliance with the Australian NHMRC recommendations was based on the study by Schoenfeld, Greene, Wu, et al., (2001), which shows that 65% of the diabetic population fully comply with the diabetes vision care guidelines for eye examinations in America (Aiello, Gardner et al. 2000). Eleven per cent attended examinations but did not undertake all recommended tests (partial compliance), and the remaining 24% did not attend an eye examination at all (zero compliance).

As the NHMRC recommends one eye examination every two years for nSTDR, and the model cycles annually, partial compliance for these stages was taken as being equal to full compliance.

Laser treatment cost

Retinal photocoagulation or laser treatment for DR (MBS 42809) costs $382.80 per session of treatment (Department of Health and Ageing 2004); however, multiple sessions and follow-up treatment are often needed. Based on Australian hospital data (Bamroongsuk, Yi et al. 2002), individuals with either severe nPDR or PDR undergo panretinal laser treatment; 99.973% require multiple laser sessions and 35% require follow up treatment. As the median waiting and follow-up assessment time indicate that no more than 5 treatments sessions are possible each year, the proportion of eyes which underwent 1 – 5 laser sessions were estimated. The weighted average cost of

laser treatment per eye was also estimated (including the cost for the excess eye consultations above the NHMRC recommendations) and multiplied by the average number of eyes treated per patient (Yi, Bamroongsuk et al. 2003). This yielded an annual cost per patient of $1959.13.

Similar estimates were made for macular edema, but since both focal and panretinal photocoagulations were used, the weighted average of these treatments of $1604.43 were used in the calculation of the annual cost per patient.

Non-health cost of blindness

The direct non-health costs associated with blindness vary between countries as well as states within countries, as different infrastructure and support mechanisms are available. Expert opinion from Mr. M. Simpson from the Royal Blind Society (NSW) was used to estimate the costs of blindness (see Table 8).

Sensitivity Analysis

The influence of 11 parameters on life years, sight years, QALYs gained and the cost were evaluated. Univariate sensitivity analysis was performed by varying the parameters upwards and downwards by 10% (Table 9). An elasticity test (the percentage change in outcome divided by the percentage change in parameter) of 0.8 or more was considered to be elastic.

Discussion

The aim of this paper was to describe a model built to estimate the cost and health outcomes of screening for DR. Once constructed, such a model can be modified to predict and/or take account of changes in costs and health outcomes associated with alterations to policies, practices and/or the health profile of the population. A Markov model was built using information from a combination of sources including clinical trials and epidemiology data. This type of model is a cohort or population based model; it does not take into consideration individual progression pathways, but rather the progression of the cohort. It is relatively simple type of model, but appropriate for the modelling problem at hand (Barton, Bryan et al. 2004).

It is intended that the model will be modified and estimated assuming that the prog-DR test is used as a standard prognostic procedure, thereby determining the value of this test. In reality, the prog-DR test will need to be further assessed to ensure its

safety and efficacy. Once this has been established, a randomised clinical trial would provide the most accurate estimates of the effectiveness and cost-effectiveness of the test. At this stage, these steps are neither possible nor practical; thus a model is useful in predicting and forecasting possible costs and consequences.

Although models have been previously developed to evaluate interventions for DM(Eastman, Javitt et al. 1997; The CDC Diabetes Cost-effectiveness Group 2002; Clarke, Gray et al. 2004; Zhou, Isaman et al. 2005) and DR (Vijan, Hofer et al. 2000), these were not ideal for this situation for various reasons. Firstly, the DM models include the progression of a wide range of complications such as CVD, nephropathy, neuropathy and the portion on DR are often simplified to 3-4 stages(Eastman, Javitt et al. 1997; The CDC Diabetes Cost-effectiveness Group 2002; Zhou, Isaman et al. 2005), considered only as a blindness endpoint (Clarke, Gray et al. 2004; Tilden, Mariz et al. 2007) or clustered as a microvascular complication (Lamotte, Annemans et al. 2002). Although this is reasonable for a broad view of DM, it is not sufficient for an in-depth study on DR progression. Also, as previously mentioned, DR is not the best predictor of the macrovascular and microvascular complications of DM and the association of DR with these complications is not always straight forward. In this study, a conservative approach has been taken and the potential beneficial effects of early DR and pre-DM diagnosis on these complications were not included in our model.

Several in depth models on DR progression have been published (Dasbach, Fryback et al. 1991; Vijan, Hofer et al. 2000; Sharma, Hollands et al. 2001; Davies, Roderick et al. 2002; Harper, Sayyad et al. 2003) and these are well equipped to examine the effects of early DR diagnosis. However, the differentiating ability of the intervention to be investigated in this study is its usefulness as a prognostic device for DM and DR; hence it is essential to also examine the pre-DR and pre-DM stages of DR progression.

Many reports have shown that patient response to and participation in screening and treatment regime are of paramount importance for most diabetic interventions (Schoenfeld, Greene et al. 2001; Polak, Crijns et al. 2003) as reviewed by Lerman(Lerman 2005), yet these are not often addressed in DM and DR intervention models. For example, studies have shown that compliance to behaviour oriented glycemic control is much lower than for simple medications (Rubin 2005); only 16%

of diabetic patient received the recommended annual screening in two consecutive years (Mukamel, Bresnick et al. 1999) and more than one third of patients do not follow screening guidelines (Schoenfeld, Greene et al. 2001). Therefore, patient behaviour such as compliance to screening and treatment recommendations and diet and exercise pattern during the pre-DM phase were included in this model as it seemed likely that this would have major impact on the cost effectiveness of the prog-DR test.

Detailed results of the economic evaluation will be described in a separate paper. However, in summary, the base case model predicts that a majority of the 599,393 individuals with undiagnosed diabetes and pre-diabetes who visit optometrists in a one year period, would progress to more severe stages of DR as shown in Figure 2 and that, on average, an individual would lose 0.03 QALYs (the average QALY score per person would decrease from 0.840 to 0.810) over a 10 year period. The model also predicts that a total cost of over $4,090 million would be incurred by the health and welfare systems with the cost of blindness being the most costly component (more than $3,296 million) followed by the cost for blood glucose management (more than $627 million).

Limitations of the model

Markov models lack memory such that the transition probability is only dependent on the current state and not any previous states. This may not always be the case in "real life" situations; for example a patient who has been compliant with blood glucose management over a number of years is more likely to remain compliant, whereas a patient who has been erratic or non-compliant is less likely to comply in the new cycle. This issue may have been overcome by introducing new states in the model which are dependent on previous actions; however this would complicate the model and is not practical as there are not sufficient data on compliance probabilities of DM and DR patients, based on previous compliance.

An inherent weakness of any model is that it assumes ceteris paribus, that is everything remains the same, when this is not always the case. For example, some of the data used in this model originated in the 1990s, and since then the management of DM, DR and blood glucose levels has improved due to better understanding of the disease process and development of improved medications. Patient behaviour, such

as compliance to blood glucose management and eye examinations, which is important in determining the success of a diagnostic test, may also change over time. Therefore, a model is only as good as the assumptions made, and as reliable as the data it was built on.

An assumption which may not be realistic is that success in blood glucose management, (and therefore the reduced probability of progression), is dependent on the method used and rate of compliance. It implicitly assumes that patients will use the appropriate management method and that compliance automatically translates to success. Unfortunately, this is not always the case, as trial and error may be required to find the appropriate blood glucose management method or medication for a patient and depending on the severity of the disease, some patients may find it more or less difficult to successfully manage their blood glucose levels.

As mentioned, the model combines the results of research undertaken on populations living in UK (UK Prospective Diabetes Study Group 1998), China (Pan, Li et al. 1997) and US (Klein, Klein et al. 1995) and include subjects mostly over 30 years of age (Klein, Klein et al. 1995) whereas the hypothetical population is Australian and includes patients from all ages. The assumption is that these data are comparable whereas they are in fact the best data available.

The health utility values are also limited to the data available. The model requires utility values specific to different states of DR; however most authors report utility values based on visual acuity (Brown, Brown et al. 1999; Sharma, Oliver-Fernandez et al. 2003). Tung et al reported utility values for different stages of DR (Tung, Chen et al. 2005), however the sample size is relatively small (373), the response rate is only 44% and the sample population had all been diagnosed with DM for over 10 years ; in contrast, many members of the hypothetical population would be newly diagnosed.

Therefore, the study by Fong Sharza et al. (2002) on the visual acuity of DR patients at different stages was used to translate the utility values for different visual acuity levels of DR patients in the study by Brown et al [41]. It should be noted however, that the sample population in the Brown et al study had poor visual acuity (20/40 or worse) as the authors found that patients with good vision were unwilling to trade-off life years for perfect vision, making it difficult to use the time trade-off method to find

the utility values. Also, as the authors suggested, patients with poor visual acuity may have already adapted to living with this handicap and hence may not consider a fall in visual acuity as having a major impact on their quality of life. Despite these two issues, the study by Brown et al provided the best available data showing that loss of vision has a detrimental effect on quality of life.

In summary, this Markov model for DR progression was able to estimate the DR states of a hypothetical cohort, including quality adjusted life years and costs, and can be used as to predict potential changes to these outcomes if health policies and practices are modified. The model will be used to estimate the cost effectiveness and cost utility of the prog-DR screening test.

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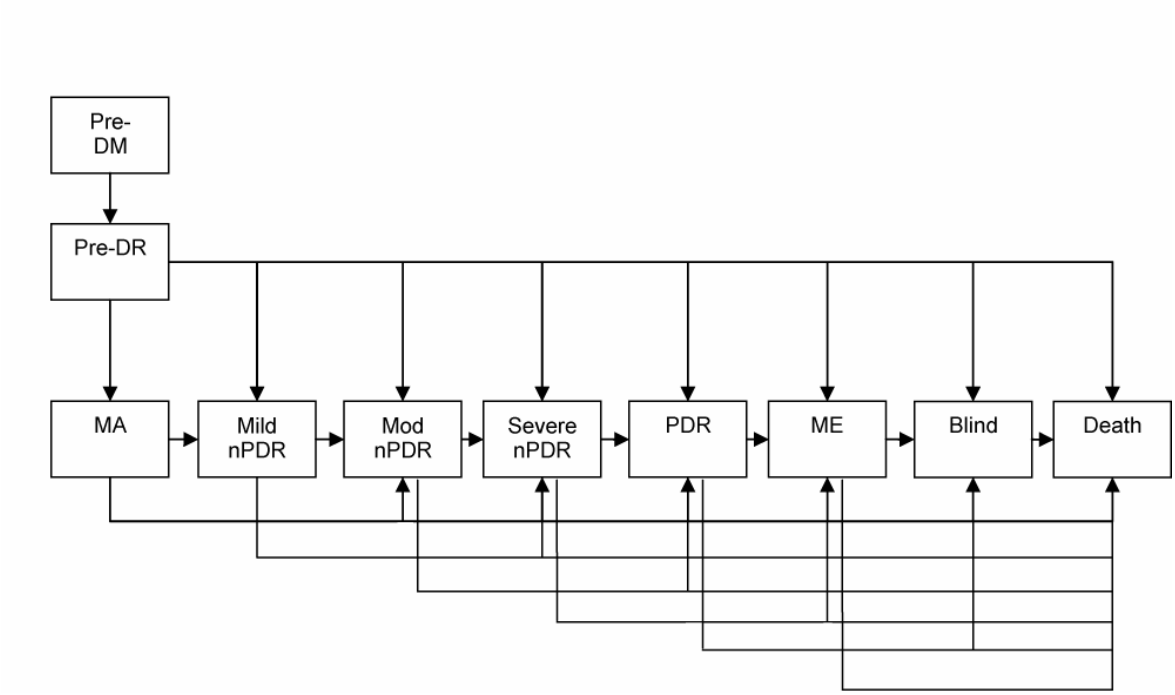
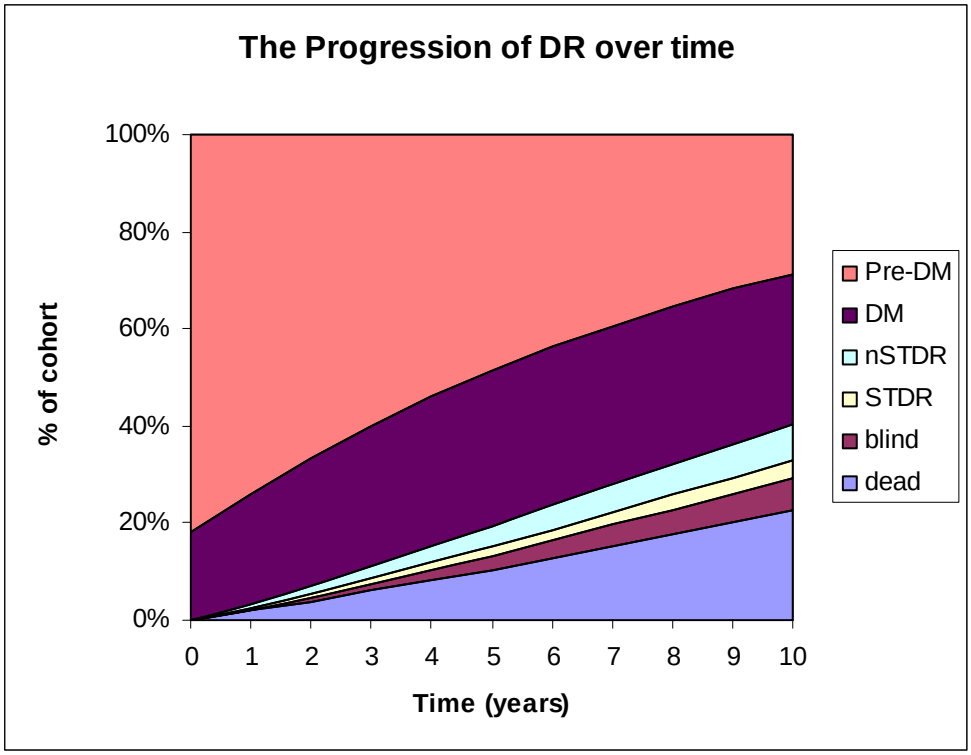
Figure 1: The progression of DR: Pre-DM is pre-diabetes



Pre-DR is pre diabetic retinopathy that is a diabetic stage without DR; MA is micro-aneurysm, nPDR is non-proliferative DR; PDR is proliferative DR and ME is macular edema. The severity of the stages increases from left to right.

Figure 2: The progression of DR over time



Pre-DM is pre-diabetes; DM is Diabetes Mellitus without clinical signs of DR; nSTDR is non-sight threatening Diabetic Retinopathy, and STDR is sight threatening Diabetic Retinopathy.

Table 1: The percentage of diagnosed and undiagnosed Diabetics with and without DR

	Undiagnosed Diabetics	Diagnosed Diabetics
With DR	= 3.8%* x 6.2%†	= 3.8%* x 21.9%†
	= 0.2356%	= 0.8322%
Without DR	= 3.8% - 0.2356%	= 3.8 % - 0.8322
	= 3.5644%	= 2.9688%

*** The prevalence rate of diagnosed and undiagnosed Diabetes were based on the Diabesity study (Dunstan, Zimmet et al. 2001). † The prevalence rate for diabetic retinopathy were based on the study by Tapp, Shaw, Harper, et al (2003) (Tapp, Shaw et al. 2003). Numbers are rounded to four decimal places.**

Table 2: The number of subjects eligible for the DR prognostic test

Cohort attending an optometrist	3,017,424
- Normal	2,296,260
- DM [*]	114,662
- Undiagnosed DM with DR [†]	7,109
- Undiagnosed DM with no DR [§]	107,553
- Pre-DM [‡]	491,840

*** the prevalence of diabetes (Dunstan, Zimmet et al. 2001); [†] and [§]: details shown in table 1; [‡] the prevalence of pre-DM was 16.3%(Dunstan, Zimmet et al. 2001). The cohort which progresses through the model includes pre-diabetics and undiagnosed diabetics without DR.**

Table 3: The lifestyle charactertics of the cohort

Lifestyle / Health	None [‡]	Diet [§]	Exercise [‖]	Diet & exercise [#]
Lean [*]	44.3043%	= 19.3–8.704%	= 45-8.704%	=19.3 x 45%
		= 10.5957%	= 36.3957%	= 8.7043%
Over-weight[†]	25.5200%	= 12-8.52%	= 71-8.52%	=12 x 71%
		= 3.4800%	= 62.4800%	=8.5200%

***Data based on the NSW Health Survey (2003) (NSW Health Department 2003); [†] Data based on the study by Tuomilehto, Lindstrom, et al., (2001) (Tuomilehto, Lindstrom et al. 2001). [‡] the residual percentage; [§] calculated by subtracting the achievement rate for both diet and exercise from that of diet; [‖] calculated by subtracting the achievement rate for both diet and exercise from that of exercise; [#] calculated by multiplying the achievement of diet by that of exercise. Numbers are rounded to four decimal places.**

Table 4: The transition probabilities for non-sight threatening DR with intensive control and conventional blood glucose control

	Pre-DR	MA only	mild nPDR	mod nPDR	severe nPDR	PDR	ME
Pre-DR	#	0.0194	0.0097	0.0049	0.0024	0.0012	0.0020
		(0.0234)	(0.0117)	(0.0058)	(0.0029)	(0.0015)	(0.0131)
MA only	0	#	0.0200	0.0100	0.0050	0.0025	0.0034
			(0.0242)	(0.0121)	(0.0061)	(0.0030)	(0.0230)
mild nPDR	0	0	#	0.0215	0.0107	0.0054	0.0043
				(0.0259)	(0.0130)	(0.0065)	(0.0288)
mod nPDR	0	0	0	#	0.0251	0.0125	0.0074
					(0.0302)	(0.0151)	(0.0496)
severe nPDR					#	0.0376	0.0030
						(0.0453)	(0.0198)
PDR						#	0.0033
							(0.0220)

The transition probabilities for non-sight threatening DR with intensive control and conventional blood glucose control represented in brackets. # represents the residual probability and numbers are rounded to four decimal places

Table 5: The transition probabilities to blindness from different stage of DR.

	Intensive control	Conventional control
Pre-DR (no DR)	0.0171	0.0199
MA only	0.0171	0.0199
mild nPDR	0.0427	0.0497
mod nPDR	0.0427	0.0497
severe nPDR	0.0427	0.0497
PDR	0.0544	0.0633
ME	0.0783	0.0908

Numbers are rounded to four decimal places.

Table 6: Transitional probabilities to death by diabetes-related complications and other causes.

	Intensive control		Conventional control	
	DM related	Others	DM related	Others
Pre-DR	0.0207	0.0148	0.0224	0.0146
MA only	0.0207	0.0148	0.0224	0.0146
mild nPDR	0.0207	0.0148	0.0224	0.0146
mod nPDR	0.0284	0.0204	0.0309	0.0201
severe nPDR	0.0320	0.0229	0.0347	0.0226
PDR	0.0332	0.0238	0.0360	0.0235
ME	0.0332	0.0238	0.0360	0.0235
Blind	0.0332	0.0238	0.0360	0.0235

Numbers are rounded to four decimal places.

Table 7: The Quality of Life Scores for different stages of Diabetic Retinopathy.

	QoL score
Pre-DR (no DR)	0.8402
MA only	0.8402
mild nPDR	0.8360
moderate nPDR	0.8182
severe nPDR	0.8182
PDR	0.8137
Maculo	0.7800
Blind	0.6400

Numbers are rounded to four decimal places.

Table 8: Cost of Blindness

Cost Type	Employed person	Unemployed
CSTDA support *		
Employment	$479.94	
Advocacy, info, & print disability	$21.28	$21.28
Admin	$153.91	$153.91
Centrelink Welfare support †		
Disability Pension Payment	$10,847.20 - &12,922.20	$10,847.20 - &12,922.20
Pharmaceutical Supplement	$75.40 - $150.80	$75.40 - $150.80
Rent Assistance	$2,470.00 - $2615.60	$2,470.00 - $2615.60
Employment Entry Payment	$9633.00	
Energy/Household concession	$657.80	$657.80
Travel Concessions	$1,470.56 - $21,840.00	$1,470.56
Mobility Allowance	$1,856.40	
Others		
Occupational Therapy ‡	$3,354.62	$3,354.62
Work-related writing equip §	$1,583.00	
Total	$22,940.11 - $55,338.55	$19,050.77 - $21,416.77
Weighted Average ‖	$20,226.57 - $31,593.30	

The average annual cost per user in each support category under the Commonwealth State/Territory Disability Agreement (CSTDA) in New South Wales (NSW) (Australian Institute of Health and Welfare 2004); † Centrelink welfare support for single and coupled residents (Department of Human Services 2005); ‡ assume a visit to the therapist once a week at standard cost per visit (NSW Health Department 2003); § cost of equipment such as Braille, talking watches and so on (Vision Australia 2005); ‖ according to expert opinion, 70% of the blind are unemployed or underemployed. Note that the prices were inflated to 2005 levels, based on weighted average inflation rate (Australian Bureau of Statistics 2006).

Table 9: Univariate Sensitivity Analysis on health outcomes and costs.

	LY	**SY**	**QALY**	**Cost**
Prevalence				
Pre-DM	-8.33 (8.33) *	-8.44 (8.44) *	-8.38 (8.38) *	-4.04 (4.04)
DM	-1.67 (1.67)	-1.56 (1.56)	-1.62 (1.62)	-4.19 (5.88)
Obesity	0.03 (-0.03)	0.06 (-0.06)	0.04 (-0.04)	0.15 (-1.55)
Rate for				
Laser treatment need	-0.00 (0.00)	0.01 (-0.01)	-0.00 (0.00)	-0.10 (0.14)
Laser treatment success	0.00 (0.00)	-0.00 (0.00)	0.00 (0.00)	0.86 (0.83)
DM diagnosis	-0.00 (0.00)	-0.01 (0.01)	-0.03 (0.03)	-0.28 (2.0)
Costs				
Blood glucose management				-1.57 (1.63)
Eye examination				0.45 (1.23)
Laser Treatment				0.84 (0.85)
Blindness				-7.15 (8.84) *
Total costs				-9.96 (10.02) *

Table shows the percentage change in health outcomes or costs, with a 10% increase or decrease (in brackets) in parameters. * indicates elasticity.