Age at initiation and frequency of screening to detect type 2 diabetes: a cost-effectiveness analysis

Richard Kahn, Peter Alperin, David Eddy, Knut Borch-Johnsen, John Buse, Justin Feigelman, Edward Gregg, Rury R Holman, M Sue Kirkman, Michael Stern, Jaakko Tuomilehto, Nick J Wareham

Summary

Background No clinical trials have assessed the effects or cost-effectiveness of sequential screening strategies to detect new cases of type 2 diabetes. We used a mathematical model to estimate the cost-effectiveness of several screening strategies.

Methods We used person-specific data from a representative sample of the US population to create a simulated population of 325 000 people aged 30 years without diabetes. We used the Archimedes model to compare eight simulated screening strategies for type 2 diabetes with a no-screening control strategy. Strategies differed in terms of age at initiation and frequency of screening. Once diagnosed, diabetes treatment was simulated in a standard manner. We calculated the effects of each strategy on the incidence of type 2 diabetes, myocardial infarction, stroke, and microvascular complications in addition to quality of life, costs, and cost per quality-adjusted life-year (QALY).

Findings Compared with no screening, all simulated screening strategies reduced the incidence of myocardial infarction (3–9 events prevented per 1000 people screened) and diabetes-related microvascular complications (3–9 events prevented per 1000 people), and increased the number of QALYs (93–194 undiscounted QALYs) added over 50 years. Most strategies prevented a significant number of simulated deaths (2–5 events per 1000 people). There was little or no effect of screening on incidence of stroke (0–1 event prevented per 1000 people). Five screening strategies had costs per QALY of about US$10 500 or less, whereas costs were much higher for screening started at 45 years of age and repeated every year ($15 509), screening started at 60 years of age and repeated every 3 years ($25 738), or a maximum screening strategy (screening started at 30 years of age and repeated every 6 months; $40 778). Several strategies differed substantially in the number of QALYs gained. Costs per QALY were sensitive to the disutility assigned to the state of having diabetes diagnosed with or without symptoms.

Interpretation In the US population, screening for type 2 diabetes is cost effective when started between the ages of 30 years and 45 years, with screening repeated every 3–5 years.

Funding Novo Nordisk, Bayer HealthCare, and Pfizer.

Introduction

The worldwide incidence, prevalence, and economic effect of type 2 diabetes are substantial. Since the disease is usually asymptomatic in its earliest stages, many cases remain undiagnosed for long periods. Upon diagnosis, many individuals already have diabetes-related complications. Several organisations have recommended screening algorithms to identify individuals with undiagnosed type 2 diabetes to help reduce the burden of the disease.

Since no clinical trials have compared the benefits of starting screening at various ages and with different intervals to detect new cases of type 2 diabetes, most recommendations for screening have been based on mathematical models. Our review of these analyses shows that the models used have not been extensively validated to determine their accuracy, do not address repetitive screening with defined intervals, compare a very limited number of screening algorithms, and do not compare the effects of screening asymptomatic individuals with screening symptomatic individuals.

To address these issues, we have calculated the cost-effectiveness of a range of simulated screening strategies to detect new cases of type 2 diabetes compared with testing simulated people only after symptoms develop.

Methods

Mathematical model

For this cost-effectiveness analysis, we used the Archimedes model, a detailed, person-by-person, large-scale simulation model of physiology, disease, and healthcare systems. This model uses many ordinary and differential equations to represent normal physiology, and a wide range of diseases and disorders related to diabetes and its complications, tests, treatments, care processes, health outcomes, visits and hospital admissions, procedures, and related costs. All conditions pertinent to an analysis are included in a single integrated model, which enables the model to address comorbidities in a physiologically realistic way. To undertake simulations, we use person-specific data to create simulated people that match real people with respect to factors such as demographics (eg, age, sex).
In the simulation of the CARDS trial, the model accurately predicted the rates of myocardial infarction and stroke in people with diabetes and the effect of atorvastatin on cardiovascular disease; however, the model underestimated the effect of atorvastatin on stroke. This result probably occurred because of the absence of any information about the effect of atorvastatin on stroke versus that of other statins, which the model had previously simulated accurately. The model has since been modified to account for the drug-specific effect of atorvastatin on stroke.

There are no clinical trials of screening for type 2 diabetes against which to validate the model. However, the model has been validated for simulating the aspects of physiology that determine the effect of atorvastatin on stroke versus that of other drugs, and the Collaborative Atorvastatin Diabetes Study (CARDS) study. For these validations, only a description of the trial design and the aggregated population characteristics were known before the validation exercise. The model was accurate in predicting the incidence of diabetes in the control group and the effects of metformin and lifestyle modification in the DPP study. In the simulation of the CARDS trial, the model accurately predicted the incidence at which people develop type 2 diabetes as a function of age, sex, and ethnic origin; and the rate at which hyperglycaemia progresses in those who are at risk of type 2 diabetes and in those who are newly diagnosed with the disease. More

Panel: Nine simulated screening strategies

- No screening (control)
- Screen the entire population for type 2 diabetes starting at age 30 years. For those not diagnosed, repeat screening every 3 years up to age 75 years (30 years, every 3 years)
- Start screening at age 45 years and repeat every 3 years up to age 75 years (45 years, every year)
- Start screening at age 45 years and repeat every 3 years up to age 75 years (45 years, every 3 years)
- Start screening at age 45 years and repeat every 5 years up to age 75 years (45 years, every 5 years)
- Start screening at age 60 years and repeat every 3 years up to age 75 years (60 years, every 3 years)
- Screen only when the person’s blood pressure is greater than 140/90 mm Hg. Repeat screening every year at the corresponding visit for blood pressure monitoring, up to age 75 years (hypertension diagnosis, every year)
- Screen only when the person’s blood pressure is greater than 135/80 mm Hg. Repeat screening every 5 years at the corresponding visit for blood pressure monitoring, up to age 75 years (hypertension diagnosis, every 5 years)
- Start screening at age 30 years and repeat every 6 months until age 75 years (maximum screening)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Cost (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure measurement</td>
<td>0.00</td>
</tr>
<tr>
<td>Fasting plasma glucose test</td>
<td>4.40</td>
</tr>
<tr>
<td>Lipid panel</td>
<td>14.24</td>
</tr>
<tr>
<td>Type 2 diabetes screening visit</td>
<td>52.24</td>
</tr>
<tr>
<td>Cholesterol screening visit</td>
<td>52.24</td>
</tr>
<tr>
<td>Hypertension screening visit</td>
<td>52.24</td>
</tr>
<tr>
<td>Type 2 diabetes screening visit at time of hypertension management visit</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Costs derived from 2006 Medicare costs. Medication costs derived from Drugstore.com on April 24, 2009.

Table 1: Base case assumptions for the costs of tests and visits relating to type 2 diabetes, hypertension, and cholesterol

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Disutility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disorders with type 2 diabetes</td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td>-0.180</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>-0.200</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>-0.200</td>
</tr>
<tr>
<td>Foot amputation</td>
<td>-0.105</td>
</tr>
<tr>
<td>Partial foot amputation</td>
<td>-0.105</td>
</tr>
<tr>
<td>Foot ulcer</td>
<td>-0.170</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>-0.180</td>
</tr>
<tr>
<td>Serious eye disease (blindness)</td>
<td>-0.160</td>
</tr>
<tr>
<td>Stroke</td>
<td>-0.167</td>
</tr>
<tr>
<td>Type 2 diabetes with no major complications (diagnosis by symptoms)</td>
<td>-0.035</td>
</tr>
<tr>
<td>Type 2 diabetes with no major complications (diagnosis by screening)</td>
<td>0</td>
</tr>
</tbody>
</table>

Disutilities assigned to various states relating to type 2 diabetes and its complications

- No screening (control)
- Screen the entire population for type 2 diabetes starting at age 30 years. For those not diagnosed, repeat screening every 3 years up to age 75 years (30 years, every 3 years)
- Start screening at age 45 years and repeat every 3 years up to age 75 years (45 years, every year)
- Start screening at age 45 years and repeat every 3 years up to age 75 years (45 years, every 3 years)
- Start screening at age 45 years and repeat every 5 years up to age 75 years (45 years, every 5 years)
- Start screening at age 60 years and repeat every 3 years up to age 75 years (60 years, every 3 years)
- Screen only when the person’s blood pressure is greater than 140/90 mm Hg. Repeat screening every year at the corresponding visit for blood pressure monitoring, up to age 75 years (hypertension diagnosis, every year)
- Screen only when the person’s blood pressure is greater than 135/80 mm Hg. Repeat screening every 5 years at the corresponding visit for blood pressure monitoring, up to age 75 years (hypertension diagnosis, every 5 years)
- Start screening at age 30 years and repeat every 6 months until age 75 years (maximum screening)
details about the model, such as how simulated people are created, how diabetes develops, and how outcomes are calculated can be found in several publications\textsuperscript{14–21} and a technical report.\textsuperscript{22}

**Study design**

In this analysis, we created a simulated population of 325 000 non-diabetic individuals aged 30 years who had the demographic characteristics of people without diabetes in the National Health and Nutrition Examination Surveys 1999–2004.\textsuperscript{23} The methods for creating simulated people preserved the distributions and correlations of all the important variables, making the simulated population representative of the US population at that age. The simulated individuals were each subjected to nine different screening strategies in sequence (see panel for list of strategies). In the control (no screening) strategy, simulated individuals were tested for type 2 diabetes only if they developed symptoms of the disease (which occurred in the model at a mean fasting plasma glucose concentration of 11.4 mmol/L [SD 1.4]\textsuperscript{c} or if they were diagnosed with cardiovascular disease, in which case they were tested every year for type 2 diabetes during follow-up visits. Cardiovascular disease was defined as stroke, myocardial infarction, percutaneous transluminal coronary angioplasty, or a coronary artery bypass graft. Type 2 diabetes was defined as a plasma glucose concentration after overnight fasting of 7 mmol/L or more, confirmed with a second test. A maximum screening strategy (panel) was created to obtain an upper bound on the benefit of simulated screening and was not intended to be a feasible alternative.

All simulated individuals in the nine simulated screening strategies were screened in the model for hyperlipidaemia and hypertension at frequencies derived from the National Ambulatory Medical Care Survey\textsuperscript{24} and Medicare Expenditure Panel Survey.\textsuperscript{25} Specifically, simulated people were screened for hypertension every 2 years from age 30 years to 44 years, every 1.5 years from age 45 years to 64 years, and every year from age 65 years to 75 years. They were screened for raised LDL cholesterol concentration according to the Adult Treatment Panel (ATP) III\textsuperscript{c} every 5 years from age 45 years to 75 years. Individuals with type 2 diabetes were screened for hypertension at each office visit for diabetes, and were screened for hyperlipidaemia every year.

Simulated individuals diagnosed with type 2 diabetes were treated in the model in accordance with a recent consensus algorithm.\textsuperscript{26} Briefly, metformin treatment and lifestyle modification were started at the time of diagnosis, irrespective of initial haemoglobin A\textsubscript{1c} (HbA\textsubscript{1c}) percentage. Treatment was intensified with a sulphonylurea then insulin, as needed, to attempt to achieve an HbA\textsubscript{1c} percentage of less than 7%. Hyperlipidaemia and hypertension were treated in accordance with guidelines from the ATP III\textsuperscript{c} and the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure,\textsuperscript{27} respectively. Performance and compliance related to glucose concentrations, blood pressure, and lipid concentrations were based on the levels seen in patients with diabetes in the National Health and Nutrition Examination Survey.\textsuperscript{22}

**Study outcomes and statistical analysis**

Simulated individuals in all groups were followed up for 50 years or until they died. All simulated outcomes were recorded as they occurred and reported yearly. Here we report the simulated incidence of type 2 diabetes, myocardial infarction, stroke, and microvascular complications (the sum of foot amputations, blindness, and end-stage renal disease). Blindness was defined as legal blindness (worse than 20/400) in the better eye, and end-stage renal disease was defined as dialysis, kidney transplant, or glomerular filtration rate (GFR) less than 15 mL/min. Costs of screening, diagnosis, treatment, and monitoring were calculated for the following disorders: type 2 diabetes and all its complications,

![Figure 1: Proportion of simulated people diagnosed with type 2 diabetes over 50 years of follow-up, by screening strategy](https://www.thelancet.com/vol375/issue1367/fig1)

See panel for definitions of screening strategies.

<table>
<thead>
<tr>
<th>Screening Strategy</th>
<th>Years gained (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 years, every 3 years</td>
<td>6.30 (0.079)</td>
</tr>
<tr>
<td>45 years, every year</td>
<td>5.98 (0.061)</td>
</tr>
<tr>
<td>45 years, every 3 years</td>
<td>5.33 (0.072)</td>
</tr>
<tr>
<td>45 years, every 5 years</td>
<td>4.72 (0.073)</td>
</tr>
<tr>
<td>60 years, every 3 years</td>
<td>1.83 (0.048)</td>
</tr>
<tr>
<td>Hypertension diagnosis, every year</td>
<td>2.84 (0.109)</td>
</tr>
<tr>
<td>Hypertension diagnosis, every 5 years</td>
<td>2.43 (0.083)</td>
</tr>
<tr>
<td>Maximum screening</td>
<td>7.84 (0.079)</td>
</tr>
</tbody>
</table>

See panel for definitions of screening strategies.
Figure 2: Expected number of events prevented by each screening strategy compared with control after 50 years of follow-up

Error bars represent 95% CIs. Microvascular outcomes defined as legal blindness, end-stage renal disease, and amputations. In the control group, there were 235 myocardial infarctions, 105 strokes, 137 microvascular events, and 474 deaths per 1000 people after 50 years of follow-up. Number needed to treat to prevent one event, at 50 years, is listed below each column in the figure. See panel for definitions of screening strategies. NA=not applicable.
coronary artery disease, stroke, hypertension, hyperlipidaemia, and congestive heart failure. Medication costs were obtained from Drugstore.com as of April, 2009. All other costs (eg, emergency visits, office visits and admissions, and procedures) were based on 2006 Medicare costs.

Quality-adjusted life-years (QALYs) were calculated on the basis of the time individuals spent with different disorders, such as having a foot ulcer, and estimated disutilities for these same disorders. We used disutilities published by Sullivan and Ghushchyan for all disorders apart from amputation, for which we had to use other data. Costs and QALYs were discounted at a rate of 3%. Table 1 shows the costs of tests and visits, and table 2 shows the disutilities. Variations and uncertainty about costs, disutilities, and discount rates were studied through sensitivity analysis. The analysis was done from the perspective of a health service or delivery system that is responsible for all medical costs. Dichotomous outcomes were compared by use of the χ² test. Continuous outcomes were compared by use of the t test. Results were considered significant if p<0.05. Analyses were done with the Ubuntu Linux version of R 2.8.1 (version release Dec 22, 2008).

Role of the funding source
The sponsors of the study had no role in design of the final protocol, data collection, data analysis, data interpretation, writing of the report, or in the decision to submit the paper for publication. All authors had full
access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the cumulative proportion of simulated people diagnosed with type 2 diabetes over 50 years of follow-up for each screening strategy. With each age that screening started, there was a rapid rise in the cumulative proportion of simulated people with type 2 diabetes that gradually approximated the incidence obtained with maximum screening. The cumulative proportion of simulated people diagnosed with type 2 diabetes was much lower for the strategies in which screening started upon the diagnosis of hypertension than for the strategies in which screening started at age.

Table 3 shows the mean number of years earlier that type 2 diabetes was diagnosed in the eight screening strategies than it was with control. All screening strategies reduced the time spent undiagnosed with type 2 diabetes before the development of symptoms. Age at which screening started had a proportional effect on lead time.

Figure 2 show the effects of the screening strategies over 50 years of follow-up on simulated myocardial infarction, stroke, microvascular outcomes, and death. All strategies resulted in reduced simulated rates of myocardial infarction (3–9 events prevented per 1000 people screened) and microvascular complications (3–9 events prevented per 1000 people), but they had no effect on incidence of stroke (0–1 events prevented per 1000 people). Most strategies prevented a significant number of simulated deaths (2–5 events per 1000 people), apart from the two strategies associated with the development of hypertension. At most, as seen in the maximum screening strategy, the absolute event rate reduction was small (eg, 3–6%, 1·4%, 6–6%, and 1·1% for myocardial infarction, stroke, microvascular outcomes, and death, respectively). In general, simulated screening beginning at 30 years or 45 years of age showed the greatest reduction in simulated events apart from stroke, whereas screening starting with the diagnosis of hypertension was least effective at reducing all events. All strategies were associated with similar reductions in the number of cases of blindness and amputations, but there was no effect on end-stage renal disease (data not shown).

Screening added a significant number of QALYs compared with no screening (figure 3; p<0·0001 for all strategies), with initiation of screening being most effective at younger ages. The cost-effectiveness of screening is shown in figure 4. Five of the strategies had a cost per QALY of about US$10 500 per year or less, whereas costs were much higher for screening started at 45 years of age and repeated every year ($15 509), screening started at 60 years of age and repeated every 3 years ($25 738), and the maximum screening strategy ($40 778). The two strategies in which diabetes screening coincided with management of hypertension had the lowest cost per QALY because the cost of the office visit was attributed to hypertension management. Similarly, if the strategy of screening starting at age 45 years with follow-up every 5 years coincided with the general recommendations for lipid screening,27 then the cost per QALY would decline from $9786 to $6106. Figure 5 shows discounted QALYs and discounted costs of the eight screening strategies compared with no screening. Incremental cost-effectiveness ratios were $62 287 for screening started with diagnosis of hypertension and repeated every year compared with no screening, $129 611 for screening started at 30 years of age and repeated every 3 years compared with screening started with diagnosis of hypertension and repeated every year, and $301 285 for maximum screening compared with screening started at 30 years of age and repeated every 3 years.

Table 4 shows the sensitivity of the cost per QALY to 20% increases or decreases in the main assumptions (cost of screening, treatment of type 2 diabetes, disutilities associated with diabetes-related disorders), and the effects on cost per QALY of various discount rates. Our results were fairly insensitive to all these assumptions. Conversely, table 5 shows that our results were sensitive to the quality of life disutility assigned to detection of type 2 diabetes because of the onset of symptoms such as polyuria or polydipsia, but before the development of any complications related to type 2 diabetes. On the basis of Sullivan and Ghushchyan’s26 survey of people with uncomplicated type 2 diabetes, we assumed a disutility of 0–035 for this state (table 1). People with and without symptoms were included in that survey. If the disutility on quality of life for people without symptoms is less than 0·035, every strategy will have a much greater cost per QALY (table 5).

Figure 1: Cost per quality-adjusted life-year (QALY) of eight screening strategies compared with no screening. See panel for definitions of screening strategies.
Our analysis assumed that there is no loss in quality of life caused by living with type 2 diabetes detected by screening (ie, before any symptoms) up until the occurrence of complications (table 1). If, in fact, there is an adverse effect on quality of life during this period, the cost per QALY of the screening strategies will also be higher, because screening increases the time that people spend in this state.

**Discussion**

Our study shows that a range of simulated screening strategies could reduce the rate of myocardial infarction, microvascular events, and deaths in people with type 2 diabetes compared with no screening. For example, if screening is started at 30 years of age and repeated every 3 years, about seven myocardial infarctions per 1000 people aged 30 years could be prevented over 50 years. The same screening strategy can be expected to spend in this state.

The small beneficial effect of screening on myocardial infarction is consistent with the results of recent clinical trials that studied the effect of glucose lowering on cardiovascular disease.\(^{17-40}\) The effect might also be a result of the effective management of hypertension and hyperlipidaemia in our simulation. The absence of any significant effect on stroke and end-stage renal disease is consistent with the results of clinical studies.\(^{17-40}\)

The magnitude of the simulated outcomes affected by screening was small compared with the natural variability in outcomes seen in simulated populations even as large as 325 000 individuals. Consequently, there was a wide range of uncertainty (95% CIs) around the mean values for each of the outcomes, and in a simulation of 325 000 people there was no significant difference between most of the screening strategies for most of the clinical outcomes. However, screening at the time of visits for management of hypertension had a smaller effect on microvascular outcomes than did strategies in which screening was initiated on the basis of age. This finding is attributable to the fairly small number of cases of type 2 diabetes detected in the hypertension-based strategies.

Five of the strategies had costs per QALY of around $10 500 or less. Strategies in which screening was done opportunistically at the time of visits for management of hypertension, or was scheduled to coincide with general recommendations for lipid testing,\(^27\) had the lowest costs per QALY. In these circumstances there was no office visit cost attributable to diabetes screening. All other screening strategies involved the cost of an office visit.

The five most cost-effective simulated screening strategies varied in their expected degree of benefit. Initiation of screening at 30 years or 45 years of age provided the most benefit. The appropriate choice of strategy would deliver the greatest benefit, while having a low cost per QALY. We therefore recommend starting screening between the ages of 30 years and 45 years, with screening repeated every 3–5 years. The cost per QALY would be further improved if screening were combined with screening events for other disorders, such as screening for hypertension. Similarly, initiation of screening at 45 years with follow-up every 5 years would have the best cost per QALY if screening were done at the time of a visit for lipid testing.

The costs per QALY were not very sensitive to 20% changes in the reference assumptions about costs of screening, treatments, or disutilities associated with amputation from a base case assumption (1.20). Our study shows that a range of simulated screening strategies could reduce the rate of myocardial infarction, microvascular events, and deaths in people with type 2 diabetes compared with no screening. For example, if screening is started at 30 years of age and repeated every 3 years, about seven myocardial infarctions per 1000 people aged 30 years could be prevented over 50 years. The same screening strategy can be expected to spend in this state.

The small beneficial effect of screening on myocardial infarction is consistent with the results of recent clinical trials that studied the effect of glucose lowering on cardiovascular disease.\(^{17-40}\) The effect might also be a result of the effective management of hypertension and hyperlipidaemia in our simulation. The absence of any significant effect on stroke and end-stage renal disease is consistent with the results of clinical studies.\(^{17-40}\)

The magnitude of the simulated outcomes affected by screening was small compared with the natural variability in outcomes seen in simulated populations even as large as 325 000 individuals. Consequently, there was a wide range of uncertainty (95% CIs) around the mean values for each of the outcomes, and in a simulation of 325 000 people there was no significant difference between most of the screening strategies for most of the clinical outcomes. However, screening at the time of visits for management of hypertension had a smaller effect on microvascular outcomes than did strategies in which screening was initiated on the basis of age. This finding is attributable to the fairly small number of cases of type 2 diabetes detected in the hypertension-based strategies.

Five of the strategies had costs per QALY of around $10 500 or less. Strategies in which screening was done opportunistically at the time of visits for management of hypertension, or was scheduled to coincide with general recommendations for lipid testing,\(^27\) had the lowest costs per QALY. In these circumstances there was no office visit cost attributable to diabetes screening. All other screening strategies involved the cost of an office visit.

The five most cost-effective simulated screening strategies varied in their expected degree of benefit. Initiation of screening at 30 years or 45 years of age provided the most benefit. The appropriate choice of strategy would deliver the greatest benefit, while having a low cost per QALY. We therefore recommend starting screening between the ages of 30 years and 45 years, with screening repeated every 3–5 years. The cost per QALY would be further improved if screening were combined with screening events for other disorders, such as screening for hypertension. Similarly, initiation of screening at 45 years with follow-up every 5 years would have the best cost per QALY if screening were done at the time of a visit for lipid testing.

The costs per QALY were not very sensitive to 20% changes in the reference assumptions about costs of screening, treatments, or disutilities associated with the complications of type 2 diabetes. However, our results were sensitive to the disutility of type 2 diabetes detected because of onset of symptoms, and to the assumption that there is no harmful effect on quality of life if type 2 diabetes is diagnosed through screening, up to the occurrence of complications. In our analysis, one of the main benefits of screening was detection of

<table>
<thead>
<tr>
<th>Reference</th>
<th>Costs of screening*</th>
<th>Treatment costs†</th>
<th>Disutility associated with diabetes-related disorders‡</th>
<th>Disutility associated with amputation§</th>
<th>Discount rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-20%</td>
<td>+20%</td>
<td>-20%</td>
<td>+20%</td>
<td>-20%</td>
</tr>
<tr>
<td>30 years, every 3 years</td>
<td>10 512</td>
<td>9 017</td>
<td>12 006</td>
<td>9 904</td>
<td>11 119</td>
</tr>
<tr>
<td>45 years, every year</td>
<td>15 509</td>
<td>13 095</td>
<td>17 923</td>
<td>14 821</td>
<td>16 196</td>
</tr>
<tr>
<td>45 years, every 3 years</td>
<td>9 721</td>
<td>8 710</td>
<td>10 752</td>
<td>8 806</td>
<td>10 656</td>
</tr>
<tr>
<td>45 years, every 5 years</td>
<td>9 786</td>
<td>8 994</td>
<td>10 579</td>
<td>8 622</td>
<td>10 951</td>
</tr>
<tr>
<td>60 years, every 3 years</td>
<td>25 378</td>
<td>23 022</td>
<td>28 455</td>
<td>23 307</td>
<td>28 170</td>
</tr>
<tr>
<td>Hypertension diagnosis, every year</td>
<td>6 287</td>
<td>6 180</td>
<td>6 394</td>
<td>5 137</td>
<td>7 438</td>
</tr>
<tr>
<td>Hypertension diagnosis, every 5 years</td>
<td>6 490</td>
<td>6 450</td>
<td>6 503</td>
<td>5 232</td>
<td>7 747</td>
</tr>
<tr>
<td>Maximum screening</td>
<td>40 778</td>
<td>33 276</td>
<td>48 180</td>
<td>40 025</td>
<td>41 532</td>
</tr>
</tbody>
</table>

Data are US$. See panel for definitions of screening strategies. *All screening costs decreased (−) or increased (+) by 20%. †All treatment costs decreased or increased by 20%. ‡All disutility weights decreased or increased by 20%. §Disutility weight associated with amputation from a base case assumption (−0.105).
type 2 diabetes before symptoms appeared and therefore avoidance of any reduction in quality of life that occurred after the onset of symptoms. Although there is evidence for this assumption,\textsuperscript{16,17} the sensitivity of our results to it suggests that more research is needed to establish the effects of early-stage type 2 diabetes on quality of life.

A widely held belief is that the earlier type 2 diabetes is detected, the greater the likelihood that complications will be prevented.\textsuperscript{21} This theory can be assessed in our analysis by comparing the three strategies in which screening was started at 45 years, with screening repeated every 1 year, 3 years, and 5 years, respectively. Compared with no screening, these three strategies detected type 2 diabetes a mean 6·0 years, 5·3 years, and 4·7 years earlier, respectively. All three strategies showed a decrease in rates of myocardial infarction and microvascular complications compared with no screening, but there were no significant differences in health outcomes between the three strategies, even in a population of 325,000 people followed up for 50 years. One additional factor that is likely to contribute to the lack of a difference in health outcomes in this simulation is that in our analysis the proportion of people achieving the goals of therapy after diagnosis is the same in each strategy. Thus, the time spent with poor control of glucose, lipids, and blood pressure in these strategies varied by a maximum of 1·3 years. Also, mild type 2 diabetes in the initial years of the disease might have less of an effect on complications than does hyperglycaemia because the disease worsens over many more years.

Our analysis differs from other cost-effectiveness analyses in several ways.\textsuperscript{18–20} The most important difference is that previous modelling studies addressed only one-off, not sequential, screening. Second, our analysis was based on a representative sample of the US population, and took into account all pertinent demographic, behavioural, and biomarker risk factors. It also included realistic levels of screening and management of related disorders such as hypertension and hyperlipidaemia. Third, we included the most recent treatment recommendations for type 2 diabetes that call for more aggressive use of glucose-lowering drugs.\textsuperscript{20}

Fourth, we compared a range of screening strategies that started at different ages and were repeated at different frequencies and included the option of repeated opportunistic screening at visits for the management of hypertension. Fifth, unlike state-transition models, the Archimedes model preserves the continuous nature of biological variables, the interactions between these variables, and the continuous nature of time. These factors are particularly important for the analysis of sequential screening, the essence of which is shifting the time the disorder is detected and the effect of earlier detection and treatment on outcomes. Finally, to our knowledge, Archimedes is the only model that has been validated against epidemiological studies of the incidence of type 2 diabetes in different populations, and against the rate of progression of hyperglycaemia in clinical trials of high-risk patients and newly diagnosed patients.

Our analysis has several limitations. As is true of any analysis or clinical study, our results apply to a particular setting (ie, the USA). To facilitate application of our results to other settings we included sensitivity analyses that could be used to modify particular variables to see how the results were affected.

In our analysis, we assumed 100% performance and compliance with testing. Our objective was to establish benefits and costs of various screening strategies if people followed the recommendations. Outcomes that will occur in real settings will be different because of incomplete performance and compliance. The costs we report here will also be different in settings in which the costs of visits, drugs, laboratory tests, and other cost-generating events differ.

We analysed screening by the fasting plasma glucose test. In the Archimedes model, this test delivers a value on a continuous scale and, as in real settings, the reported value has a range of error around the true value. Our results were not sensitive to a range of assumptions about the accuracy of the fasting plasma glucose test. We did not analyse screening using either the oral glucose tolerance test (2 h after a glucose dose) or HbA\textsubscript{1c} test. Screening with either of those tests is unlikely, however, to appreciably change our results, since the threshold for detection of type 2 diabetes corresponds closely for all three tests.\textsuperscript{16} However, use of a paper risk assessment method before glucose testing might improve the cost-effectiveness of the screening strategies by removing a portion of the population from further testing.

Although the Archimedes model has been validated against most of the important clinical trials related to the treatment of type 2 diabetes and its complications, as well as against trials in people without diabetes, there have been no trials assessing any of the screening strategies we analysed, nor any assessing the behaviours

<table>
<thead>
<tr>
<th>Hypertension diagnosis, every year</th>
<th>-100% (0)</th>
<th>-50% (0·0175)</th>
<th>Reference (0·055)</th>
<th>+50% (0·0525)</th>
<th>+100% (0·07)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 years, every 3 years</td>
<td>33 432</td>
<td>15 994</td>
<td>10 512</td>
<td>7 828</td>
<td>4 644</td>
</tr>
<tr>
<td>45 years, every year</td>
<td>22 282</td>
<td>13 551</td>
<td>9 731</td>
<td>7 593</td>
<td>4 858</td>
</tr>
<tr>
<td>45 years, every 3 years</td>
<td>67 297</td>
<td>38 723</td>
<td>25 738</td>
<td>19 829</td>
<td>12 423</td>
</tr>
<tr>
<td>45 years, every 5 years</td>
<td>29 870</td>
<td>20 410</td>
<td>15 509</td>
<td>12 502</td>
<td>8 441</td>
</tr>
<tr>
<td>60 years, every 3 years</td>
<td>30 314</td>
<td>14 876</td>
<td>9 886</td>
<td>7 317</td>
<td>4 369</td>
</tr>
<tr>
<td>Hypertension diagnosis, every year</td>
<td>16 899</td>
<td>9 218</td>
<td>6 287</td>
<td>4 790</td>
<td>2 948</td>
</tr>
<tr>
<td>Maximum screening</td>
<td>21 927</td>
<td>10 100</td>
<td>6 490</td>
<td>4 806</td>
<td>2 826</td>
</tr>
</tbody>
</table>

Data are cost per QALY (US$). Value of disutility for type 2 diabetes diagnosed because of symptoms but before the onset of complications decreased (-) or increased (+) by 50% or 100%. See panel for definitions of screening strategies.

Table 5: Sensitivity of cost per quality-adjusted life-year (QALY) to assumptions about the disutility of type 2 diabetes diagnosed because of symptoms but before the onset of complications.
of patients and clinicians that result from screening. Thus, there is no way to validate our results until a real trial is done on all points of interest.

Despite these limitations, we believe our results are applicable to real-life settings. The Archimedes model has been constructed to be as realistic as possible and the scenarios we studied were realistic, although some simplifications were necessary. The model has also been validated for the incidence of type 2 diabetes in different ethnic populations and the rate at which hyperglycaemia progresses in people at high risk or in people with type 2 diabetes. Furthermore, the model reproduces the effects of the interventions studied here. These validations promote confidence in, but do not prove, the accuracy of the model.

Our analysis suggests that a randomised clinical trial to compare different screening strategies for type 2 diabetes would not be feasible. Even a trial with 325 000 people in each group followed for 50 years with perfect follow-up and ideal performance and compliance to screening would probably not show significant differences between strategies. Thus, the only formal way to analyse screening for type 2 diabetes is through a mathematical model.

Thus, five simulated screening strategies for type 2 diabetes had costs per QALY of around $10 500 or less, but the differences in cost-effectiveness between those strategies were not significant. The strategies did, however, differ in the amount of benefit they provided, with those in which screening is initiated at specified ages providing more than twice the benefit of those that relied on visits for the management of hypertension, as has been recommended.4 These conclusions are insensitive to a wide range of assumptions; however, our results were sensitive to the quality of life disutility assigned to detection of type 2 diabetes because of the onset of symptoms. Our analyses suggest that screening for type 2 diabetes is cost effective when started between the ages of 30 years and 45 years, with screening repeated every 3–5 years.

Contributors
All authors contributed to the design of the study. RK, PA, DE, and JF participated in data collection. All authors contributed to data analysis and the writing of the report, and approved the final version of the report.

Conflicts of interest
We declare that we have no conflicts of interest.

Acknowledgments
The study was supported by an educational grant to the American Diabetes Association from Novo Nordisk, Bayer HealthCare and Pfizer. We thank Gerardo Soto-Campos, Barbara Peskin, and Helene Grossman for their invaluable help with this study. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the institutions in which they work.

References


44 UK Prospective Diabetes Study Group. Quality of life in type 2 diabetic patients is affected by complications but not by intensive policies to improve blood glucose or blood pressure control (UKPDS 37). Diabetes Care 1999; 22: 1125–36.