Cost-Utility Analysis of Screening Intervals for Diabetic Retinopathy in Patients With Type 2 Diabetes Mellitus

Sandeep Vijan, MD, MS
Timothy P. Hofer, MD, MS
Rodney A. Hayward, MD

Context Annual eye screening for patients with diabetes mellitus is frequently proposed as a measure of quality of care. However, the benefit of annual vs less frequent screening intervals has not been well evaluated, especially for low-risk patients.

Objective To examine the marginal cost-effectiveness of various screening intervals for eye disease in patients with type 2 diabetes, stratified by age and level of glycemic control.

Design Markov cost-effectiveness model.

Setting and Participants Hypothetical patients based on the US population of diabetic patients older than 40 years from the Third National Health and Nutrition Examination Survey.

Main Outcome Measures Patient time spent blind, quality-adjusted life-years (QALYs), and costs of annual vs less frequent screening compared by age and level of hemoglobin A_{1c}.

Results Retinal screening in patients with type 2 diabetes is an effective intervention; however, the risk reduction varies dramatically by age and level of glycemic control. On average, a high-risk patient who is aged 45 years and has a hemoglobin A_{1c} level of 11% gains 21 days of sight when screened annually as opposed to every third year, while a low-risk patient who is aged 65 years and has a hemoglobin A_{1c} level of 7% gains an average of 3 days of sight. The marginal cost-effectiveness of screening annually vs every other year also varies; patients in the high-risk group cost an additional $40 530 per QALY gained, while those in the low-risk group cost an additional $211 570 per QALY gained. In the US population, retinal screening annually vs every other year for patients with type 2 diabetes costs $107 510 per QALY gained, while screening every other year vs every third year costs $49 760 per QALY gained.

Conclusions Annual retinal screening for all patients with type 2 diabetes without previously detected retinopathy may not be warranted on the basis of cost-effectiveness, and tailoring recommendations to individual circumstances may be preferable. Organizations evaluating quality of care should consider costs and benefits carefully before setting universal standards.

JAMA. 2000;283:889-896 www.jama.com

DIABETES MELLITUS IS A LEADING cause of blindness in the United States.[1] Randomized trials have clearly demonstrated that the risk of developing severe visual loss from proliferative diabetic retinopathy (PDR) and macular edema can be significantly reduced through the use of laser photocoagulation.[2-5] Thus, screening, detection, and appropriate treatment of PDR and macular edema have the potential to significantly reduce the incidence of visual loss in patients with diabetes.

Screening is vital to preventing visual loss from diabetes because retinopathy is often asymptomatic early in the course of the disease.[6,7] While no randomized trials have demonstrated that screening directly reduces rates of blindness, simulation models predict a reduction in visual loss with retinal screening. A number of previous cost-effectiveness analyses have demonstrated that, from a societal or governmental viewpoint, annual screening and treatment for PDR and macular edema are cost-effective interventions.[8-10] As a result of these studies, provision of annual screening is being used as a measure of quality of care, with inclusion in Health Employer Data and Information Set (HEDIS) measures and other guidelines for diabetes care.[11-14] While these guidelines have been widely disseminated, compliance has been disappointing, with annual screening rates generally ranging from 18% to 65% and broad-based population surveys suggesting rates of approximately 50%.[15-18]

See also Patient Page.

Author Affiliations: Veterans Affairs Health Services Research and Development Quality Enhancement Research Initiative and the Michigan Diabetes Research and Training Center, University of Michigan, Ann Arbor.
Corresponding Author and Reprints: Sandeep Vijan, MD, MS, Veterans Affairs Health Services Research and Development, PO Box 130170, Ann Arbor, MI 48113-0170 (e-mail: svijan@umich.edu).

Previous analyses of screening for diabetic eye disease have not adequately examined the marginal benefits of increased screening frequency or specific methods of targeting patients. For example, it has been suggested that all patients with type 2 diabetes be screened at diagnosis and, if the result is negative, further screening be deferred for 3 to 4 years.[14] Clinical predictors of diabetic retinopathy can also be used to effectively stratify the frequency of diabetic eye screening. For example, risk of retinopathy and eventual blindness can be stratified by level of glycemic control.[12,19-21] Thus, we sought to evaluate whether hemoglobin A_{1c} level can be used to effectively stratify the frequency of diabetic retinal screening and improve the efficiency and cost-effectiveness of screening.

METHODS

We created a nonstationary Markov model[22,23] to simulate the progression of diabetic retinopathy and macular edema. Simulated patients were classified based on whether they had no retinopathy, nonproliferative retinopathy (based on the modified Airlie House classification),[24] proliferative retinopathy (levels greater than 53e), macular edema, or blindness (defined as visual acuity of less than 20/100 in the better eye). The simulated patients were further classified by whether they had been diagnosed as having retinopathy or macular edema. The key assumptions and estimates for the model are outlined in TABLE 1.

To provide a population base of patients with type 2 diabetes for the study, we used the characteristics of the diabetic population older than 40 years in the Third National Health and Nutrition Examination Survey (NHANES III),[37] a nationally representative sample of the US population. Patients were grouped into initial levels of eye disease in the model based on the prevalence of various levels of diabetic eye disease reported in NHANES III. We used ordinal logistic regression to smooth the predictions of levels of eye disease based on age and glycemic control. These estimates are outlined in TABLE 2.

The model structure is outlined in the FIGURE. The incidence of developing and progressing through the stages of nonproliferative retinopathy was assumed to be related to level of glycemic control, as outlined in Table 1. The relationship was derived from the UK Prospective Diabetes Study (UKPDS), which showed that a decrease of 0.9% in hemoglobin A_{1c} (from 7.9% to 7.0%) was related to a 21% decrease in risk of retinopathy progression over 12 years.[21] Progression beyond nonproliferative retinopathy to PDR, macular edema, and

Table 1. Baseline Case Parameter Estimates and Assumptions*

Parameter	Baseline Case	Sensitivity Analysis Range
Annual Disease Progression Rates		
Retinopathy (state 3) to high-risk PDR[2,3]	0.08	0.06-0.10
Retinopathy (state 1 or 2) to macular edema[2,3]	0.006	0.001-0.01
Retinopathy (state 3) to macular edema[2,3]	0.03	0.01-0.05
High-risk PDR to blindness with photocoagulation[8,25]	0.02	0.002-0.03
High-risk PDR to blindness without photocoagulation[8,25]	0.09	0.07-0.11
Macular edema to blindness with photocoagulation[8,25]	0.03	0.01-0.05
Macular edema to blindness without photocoagulation[8,25]	0.05	0.03-0.07
Mortality Multipliers		
Diabetes mellitus[26-30]	1.80	1.60-2.00
Retinopathy levels <35[31]	1.23	1.09-1.35
Retinopathy levels 43-53e[31]	1.49	1.37-1.61
PDR[31]	1.76	1.64-1.88
Macular edema[31]	1.76	1.64-1.88
Blindness[31]	2.34	2.22-2.46
Characteristics of Retinopathy Screening Test		
No retinopathy called nonproliferative retinopathy[32,33]	0.05	0.04-0.06
No retinopathy called PDR[32,33]	0.003	0.0002-0.006
Nonproliferative retinopathy called no retinopathy[32,33]	0.22	0.21-0.23
Nonproliferative retinopathy called PDR[32,33]	0.02	0.01-0.03
PDR called no retinopathy[32,33]	0.02	0.01-0.03
PDR called nonproliferative retinopathy[32,33]	0.03	0.02-0.04
Sensitivity for macular edema[14,34,35]	0.82	0.70-0.94
Specificity for macular edema[14,34,35]	0.79	0.67-0.91
Costs, $		
Visit cost for dilated eye examination[36]	53	28-78
Fluorescein angiogram[36]	163	113-213
Focal photocoagulation[36]	1490	1290-1690
Scatter photocoagulation[36]	1740	1540-1940

*PDR indicates proliferative diabetic retinopathy. Annual progression from no retinopathy to retinopathy state 1, state 1 to state 2, and state 2 to state 3 (see Figure) was determined from the UK Prospective Diabetes Study.[21] For patients with hemoglobin A_{1c} of 7%, the annual progression rate was 0.0406; for 9%, 0.0761; for 11%, 0.1425; and for 13%, 0.2669.

Table 2. Estimates of Type 2 Diabetes Distribution by Age and Level of Glycemic Control*

Age, y	Hemoglobin A_{1c}, % 7	9	11	13
Proportion of Population With Early Retinopathy† at Entry to Simulation				
40-49	0.085	0.133	0.166	0.203
50-59	0.097	0.14	0.18	0.237
60-69	0.11	0.152	0.193	0.245
70-79	0.122	0.167	0.208	0.251
Proportion of Population With Different Levels of Glycemic Control				
40-49	0.063	0.041	0.040	0.018
50-59	0.096	0.097	0.037	0.016
60-69	0.188	0.107	0.036	0.007
70-79	0.141	0.067	0.039	0.005

*Estimates are based on smoothed estimates from the Third National Health and Nutrition Examination Survey.
†Early retinopathy is defined as level ≤35 in the Airlie House classification scheme.[24]

blindness was assumed to be independent of level of glycemic control.[38,39] Rates of such progression were taken from the Diabetic Retinopathy Study (DRS) and the Early Treatment of Diabetic Retinopathy Study (ETDRS).[2,3]

Mortality rates were based on life tables published by the US government.[37] These were modified to reflect the increased mortality rates observed in patients with diabetes in general[26-30] and were further adjusted for disease state based on observed mortality risks in observational studies.[31] The mortality multipliers are outlined in Table 1.

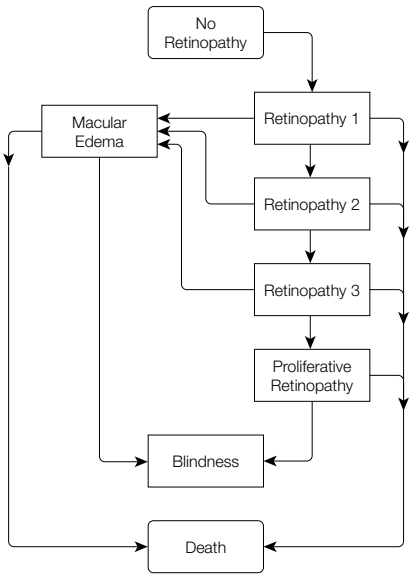
The effects of screening were estimated by interposing an eye examination at annual to every fifth year intervals. We assumed that retinal screening was done by ophthalmologists, because primary care physicians typically have low screening accuracy.[14] Screening characteristics were derived from epidemiologic studies (Table 1)[32-35,40,41]; these numbers reflect the proportion of patients who are misdiagnosed at examination (for example, in the baseline case, the case in which the simulation is run with the "baseline" estimates in Table 1, 4.6% of patients without retinopathy are diagnosed as having nonproliferative retinopathy, but only 0.32% of patients without retinopathy are diagnosed as having PDR). Patients who were diagnosed, correctly or incorrectly, as having retinopathy were subsequently screened annually. Patients who were diagnosed as having high-risk PDR or confirmed high-risk macular edema were treated with scatter and focal photocoagulation, respectively. Therapy for macular edema was guided by fluorescein angiography.[13] Photocoagulation was assumed to reduce the rate of progression to blindness as shown in reanalysis of the data from the DRS and ETDRS[2,3,25] (Table 1). Patients who developed macular edema were assigned the risk of blindness from macular edema, even if they developed PDR. This assumption was made because photocoagulation is less effective in preventing visual loss from macular edema than PDR.

Quality-adjusted life-years (QALYs) were used as the primary model outcome measure. The model predictions for overall life expectancy were adjusted for time spent blind based on a utility for blindness of 0.69 in the baseline case.[42-44] Because screening for eye disease can appear to improve survival as a result of the increased observed mortality rates seen in patients with more advanced eye disease, we standardized life expectancy to that of annual screening and calculated the total QALYs for each screening interval by using the time spent blind and the utility of blindness. Total effectiveness was then calculated by comparing the total QALYs with each screening interval. All costs and years of life were discounted at 3%.

Costs were standardized by using average Medicare reimbursement for an ophthalmology visit with dilated eye examination, laser photocoagulation (focal and scatter), and fluorescein angiogram. In the baseline case, no direct costs were attributed to blindness, although the impact of attributing medical and societal costs to blindness was explored in sensitivity analyses. In these sensitivity analyses, we used costs of blindness from prior cost-effectiveness analyses[9,10,45] to allow comparison between studies. Thus, in the baseline case, we used the perspective of a third-party payer, while governmental and societal perspectives were explored in sensitivity analyses.

We evaluated the costs and effectiveness of screening the US population of patients with known type 2 diabetes using data from NHANES III (Table 2). The proportions and total numbers of patients with diabetes in the US population were calculated using the survey weights from NHANES III. We assumed that, at baseline, none of the patients had been previously screened, so that at entry, all patients were screened at the intervals defined in the model. On diagnosis of retinopathy, patients were screened annually. The predictions of the model (costs and QALYs) were then applied to the US patient population, stratified by age and level of glycemic control. By summing total QALYs and costs across age and hemoglobin A_{1c} strata and comparing these between screening intervals, we were able to calculate the marginal cost-effectiveness of increasing screening frequency for the population of patients with type 2 diabetes in the United States.

Figure. Model Schematic of Progression of Diabetic Retinopathy and Macular Edema



One-way sensitivity analyses were conducted on individual estimates to assess their impact on the costs and effectiveness of screening. The ranges of estimates encompass the ranges reported in the literature. Because only single studies were available in some cases (eg, ETDRS and DRS), a range of possible effectiveness was estimated for the purposes of sensitivity analyses. These ranges are outlined in Table 1. Multivariate sensitivity analyses were conducted using a simulation approach to estimate the variance and distribution of the cost-effectiveness estimates. This approach uses Monte Carlo simulation and repeatedly samples from the multivariate distribution of ranges of the estimates, calculating costs and effectiveness at each sampling. This allows estimation of the distribution of the cost-effectiveness estimate. The technique is more fully described elsewhere.[46,47] For the purposes of this simulation, we assumed that the estimates were normally distributed, with the baseline case representing the mean and the ranges in Table 1 encompassing 4 SDs. Each vari-

Table 3. Model Predictions for Various Health States in High-, Moderate-, and Low-Risk Groups

Risk Group	Risk of Any Retinopathy, %	Risk of Blindness, %		Average Time Spent Blind in Those Who Become Blind, y*	
		No Screening	Annual Screening	No Screening	Annual Screening
High (age, 45 y; hemoglobin A_{1c}, 11%)	86.1	22.4	10.1	8.1	7.7
Moderate (age, 65 y; hemoglobin A_{1c}, 9%)	49.4	2.7	1.2	4.3	4.2
Low (age, 75 y; hemoglobin A_{1c}, 7%)	35.6	0.8	0.3	3.0	2.7

*Average time was not discounted.

Table 4. Average Predicted Time Spent Blind at Varying Screening Intervals*

Hemoglobin A_{1c}, %	No Screening	Every Fifth Year	Every Third Year	Every Year
Ages 40-49 y				
7	101	63	55	48
9	199	116	101	88
11	358	194	170	149
13	600	309	271	239
Ages 50-59 y				
7	51	34	28	23
9	91	57	44	39
11	160	94	73	66
13	294	166	127	116
Ages 60-69 y				
7	20	15	12	9
9	32	23	19	14
11	50	35	29	21
13	91	61	50	37
Ages 70-79 y				
7	6	6	5	3
9	10	9	7	5
11	14	13	10	7
13	22	19	16	10

*Blindness is defined as visual acuity of 20/100 or worse in the better eye[3]; time was discounted at 3% per year. Values reflect the average time spent blind for each patient (patients with and without blindness) in the stratum. All data are presented as days.

able in the model was included in the multivariate sensitivity analysis. This approach avoids the extreme variations that can be seen in typical multivariate sensitivity analyses and assumes that error in the estimates is random rather than skewed in any direction. For these sensitivity analyses, 10 000 Monte Carlo simulation runs were conducted for each stratum.

RESULTS

Table 3 shows model predictions for various health states for 3 selected groups (high, moderate, and low risk) of patients. Results for average predicted time spent blind, using the baseline case assumptions, are presented in Table 4. As expected, risk of blindness varies by age and hemoglobin A_{1c} level. For example, in the absence of a screening program, a 45-year-old patient who maintains an average hemoglobin A_{1c} level of 11% would be predicted to spend, on average, 358 days blind during his or her lifetime, while a 65-year-old patient who maintains a hemoglobin A_{1c} level of 7% would be predicted to spend, on average, 20 days blind. The estimates of risk in Table 4 clearly show that screening is effective and that more frequent screening is more effective. For our prototypical high-risk case (aged 45 years; average hemoglobin A_{1c}, 11%), screening every 5 years decreases estimated average time spent blind by 164 days per patient (from 358 to 194 days spent blind), increasing the screening interval to every 3 years reduces time spent blind by 24 days, and annual screening further reduces time spent blind by 21 days. For most groups, however, the marginal return on increasing screening frequency is small; for example, screening every 3 years vs no screening for a 65-year-old patient with hemoglobin A_{1c} of 7% reduces time spent blind from 20 to 12 days, while screening annually further reduces time spent blind to 9 days, but at more than twice the cost ($380 per patient vs $810 per patient, data not shown).

The marginal cost-effectiveness of increasing screening frequency, stratified by age and hemoglobin A_{1c} levels, is presented in Table 5. Given the diminishing returns accrued by greater screening frequency, it is not surprising to find that annual screening usually costs more per QALY gained than less frequent screening intervals. For example, for a 65-year-old patient with an average hemoglobin A_{1c} level of 9%, an annual screening program compared with an every other year screening program would result in spending an additional $123 580 for every additional QALY gained. In this same group, every other year vs every third year screening, costs an additional $62 610 per QALY gained. For many patients, annual screening costs are substantially more, with little marginal benefit, when compared with screening every other or even every third year. The patients who benefit the most, and for whom screening is most cost-effective, are those who have particularly poor glycemic control.

We examined the accuracy of the model by comparing the predictions of the model for clinical end points with those observed in the UKPDS. The cumulative incidence of retinopathy progression in the model was similar at all times to those observed in the UK study (eg, for patients with a hemoglobin A_{1c} level of 7%, the 12-year incidence was 38.6% in the UKPDS and 37.5% in our model). Examination of stages beyond initial retinopathy suggest that the model is highly predictive of the UKPDS results as well. For example, our model predicts that UKPDS patients with an average hemoglobin A_{1c} level of 7% will have a 10-year risk of photocoagulation of 7.6% (also 7.6% in the UKPDS), and those with an average hemoglobin A_{1c} level of 8% will have a 10-year risk of photocoagulation of 10.0% (vs 10.3% in the UKPDS).

Costs and Effectiveness in the US Population

We used data from NHANES III, a representative population-based sample of the United States, to provide estimates of the levels of glycemic control and age of the population

of patients with known type 2 diabetes in the United States. Based on the survey weights from NHANES III, we estimate that approximately 5.3 million people have been diagnosed as having type 2 diabetes (this sample was limited to subjects for whom both age and hemoglobin A_{1c} values were reported). As shown in TABLE 6, the model predicts that the current population of patients with type 2 diabetes will accumulate 50 081 384 QALYs without any retinopathy screening. Screening at 5-year intervals increases this to 50 216 915 QALYs at a cost of approximately $2.3 billion, for a cost-effectiveness of about $16 790 per QALY gained. However, the marginal cost-effectiveness of increasing screening frequency from every other year to every year costs more than $107 000 per QALY gained.

Sensitivity Analyses

We conducted extensive sensitivity analyses to examine the factors that had the greatest impact on our estimates of cost-effectiveness. While there are few data suggesting that blindness has a direct consequence on medical care costs, blindness has potential costs such as government provision of disability compensation and Medicare.[48] One prior analysis estimated values of the social cost of blindness ranging from $32 per year for those who become blind at age 65 years or older to $14 296 per year for those who become blind prior to age 65 years,[45] while another estimated $5100 per year of blindness.[9] These numbers have a fairly substantial effect on the overall cost-effectiveness of the intervention; in fact, for high-risk populations (those with young onset or poor glycemic control), annual screening appears to save money compared with no screening. However, inclusion of these costs has minimal impact on the marginal cost-effectiveness of increasing screening frequency, with changes of less than $5000 per additional QALY gained (compared with the baseline case results) being typical. The effect of adding societal costs is small because increasing screening intervals have only a small impact on time spent blind for most patients with type 2 diabetes.

The single most important variable in determining overall costs is the cost of the screening examination. When the cost is decreased to $28, approximately half of current Medicare reimbursement for an eye examination, the marginal cost-effectiveness of annual screening vs every other year screening improves, but still remains more than $50 000 per QALY for many subgroups. When the results are applied to the US population, a 50% reduction of the cost of a dilated eye examination leads to a marginal cost-effectiveness of $86 500 per QALY for annual vs every other year screening. Thus, even if the cost of an examination is cut in half, it does not substantially affect the baseline case conclusion that annual screening is not cost-effective when compared with screening every other year.

The variable that had the largest impact on the effectiveness of screening was the utility placed on a year of blindness. In the baseline case, we used a utility of 0.69.[43,44] One prior analysis used much lower utility values for blind-

Table 5. Marginal Cost-effectiveness of Increased Screening Frequency*

Hemoglobin A_{1c}, %	Every 5 y vs None	Every 3 y vs Every 5 y	Every 2 y vs Every 3 y	Every Year vs Every Other Year
		Ages 40-49 y		
7	21 430	38 320	73 200	181 510
9	13 100	22 000	36 760	80 060
11	8 380	14 140	21 350	40 530
13	5550	9 220	12 870	20 860
		Ages 50-59, y		
7	30 830	44 750	81 290	198 980
9	21 250	28 980	46 600	99 790
11	14 240	19 560	28 200	51 150
13	9050	11 990	15 510	23 310
		Ages 60-69 y		
7	54 230	57 870	94 710	211 570
9	41 830	41 790	62 610	123 580
11	31 320	31 850	42 460	72 410
13	20 770	21 410	25 700	35 840
		Ages 70-79 y		
7	168 750	95 830	130 250	255 820
9	128 190	69 670	86 970	151 010
11	102 120	56 510	63 270	98 100
13	74 210	44 720	46 710	59 400

*All costs and benefits were discounted at an annual rate of 3%. All data are presented as dollars and indicate marginal cost per quality-adjusted life-year gained.

Table 6. Marginal Cost-effectiveness of Increased Screening Frequency in the US Population*

Screening Frequency	Total Costs, $†	Total Quality-Adjusted Life-Years†	Marginal Cost-effectiveness, $‡
None	0	50 081 384	Not applicable
Every 5 y	2 275 623 500	50 216 915	16 790
Every 3 y	3 199 261 100	50 247 544	30 160
Every 2 y	3 979 841 300	50 263 233	49 760
Annual	5 543 143 200	50 277 774	107 510

*Population of patients recently diagnosed as having type 2 diabetes (within 5 years) in Third National Health and Nutrition Examination Survey.
†Total costs represent total over the projected lifetime of the cohort; costs are rounded to nearest $100, life-years to nearest whole year, and all costs and life-years are discounted at 3%.
‡Marginal cost-effectiveness vs the preceding screening frequency; eg, annual compared with every other year screening.

Table 7. Multivariate Sensitivity Analyses: Estimated Benefit Across Range of Parameter Estimates*

Group Characteristics	Ranges of Outcomes	Range† of Marginal Value of Screening: Every 2 vs Every 3 y	Range† of Marginal Value of Screening: Annual vs Every 2 y
High-risk patients: aged 45 y; hemoglobin A_{1c}, 11%	Range of reduction in time spent blind	8.9-18.4 d	7.9-15.5 d
	Cost-effectiveness range	$10 990-$28 850	$23 210-$58 920
Moderate-risk patients: aged 65 y; hemoglobin A_{1c}, 9%	Range of reduction in time spent blind	2.1-3.4 d	1.8-3.2 d
	Cost-effectiveness range	$41 420-$90 030	$89 740-$205 300
Low-risk patients: aged 75 y, hemoglobin A_{1c}, 7%	Range of reduction in time spent blind	0.6-1.1 d	0.5-1.0 d
	Cost-effectiveness range	$82 190-$193 150	$169 630-$366 490

*Sensitivity analyses were conducted by repeated random sampling across the ranges of parameter estimates listed in Table 1.
†Ranges encompass 95% of all outcomes.

ness: 0.48 for the majority of blind individuals, with a subset who had even lower utility values.[8] When a value of 0.48 is used for the utility of blindness, annual screening in the US population appears more cost-effective, with values of approximately $60 000 per QALY gained compared with every other year screening. Other variables affected the effectiveness of screening, but the influence of these variables was not large across a reasonable range of values.

Multivariate sensitivity analyses were conducted by creating distributions of the estimates based on the ranges outlined in Table 1 and running repeated iterations of the model, randomly sampling from these ranges.[46,47] This produces a distribution of the cost-effectiveness values. The 95% range of cost-effectiveness for 3 groups is outlined in TABLE 7. The distribution shows only a 17.3% chance that the marginal cost-effectiveness of annual vs every other year screening is greater than $50 000 per QALY for the high-risk group. In contrast, none of the 10 000 simulations performed for the medium- and low-risk groups demonstrated that annual screening is cost-effective compared with every other year screening.

COMMENT

Diabetic eye disease remains a major cause of blindness in the United States. Randomized trials have shown that laser photocoagulation can significantly reduce the risk of blindness in patients with advanced eye complications.[2,3] However, optimal screening intervals have not been adequately evaluated, particularly with regard to variability in eye disease risk in those at low risk. Despite this, many organizations, including the National Committee for Quality Assurance, through HEDIS measures,[11] recommend that annual eye examinations be used not only as a general guideline, but as a quality standard in all patients with diabetes.

Our study suggests that such recommendations may be overzealous. The baseline case analysis shows that in many groups of patients, annual screening offers very little marginal benefit over every other year screening. For some low-risk groups (eg, those with good glycemic control, older age, and no retinopathy on prior examination), every third year screening may be almost as good as annual screening and is a more cost-effective approach. In addition to health care costs, unnecessary patient burden must be considered. Patients with diabetes average 8 to 12 outpatient visits annually,[49] and visits that have little expected benefit can compete with other recommended care, both in terms of health care resources and patient time and energy.

Using NHANES III to estimate the distribution of age and glycemic control in the United States, we have shown that if a single screening strategy were to be recommended for the entire US population, every other year screening would seem to be the optimal choice, if the commonly suggested guideline of $50 000 per QALY gained is used as the definition of a cost-effective intervention.[50] However, recommendations better tailored to individual patient circumstances would seem preferable. A number of potential screening strategies could be proposed. For example, annual screening could be recommended for all patients with hemoglobin A_{1c} values over 10% (<20% of patients with diabetes in the US population according to NHANES III), while the remainder of the population could undergo screening every 2 to 3 years, with the least frequent screening interval being reserved for those with excellent glycemic control. Monitoring and feedback systems would be needed to ensure that this less frequent screening interval did not lead to patients not being screened at all. The most aggressive approach supportable by our results would be to recommend that annual screening is the safest strategy, but that if patients achieve good glycemic control and have normal results of baseline examination, every second or third year screening is almost as good at preventing visual loss. Under this scenario, professional recommendations do not change, but performance and quality measures, particularly those associated with incentive and disincentive payments, must recognize that patients and physicians might choose less frequent screening intervals.

We conducted extensive sensitivity analyses to test the robustness of our conclusions. In general, the largest uncertainty is not how little benefit the low-risk patients receive, but precisely how large the benefit is to the higher risk, and thus higher benefit, patients. Inclusion of a direct cost of blindness into the model had minimal impact on the marginal cost-effectiveness of annual screening, although it dramatically improves the overall cost-effectiveness of any screening com-

pared with no screening. Sensitivity analyses also show that the cost of the screening examination is an important component of the overall cost-effectiveness of a screening program. However, even when costs are cut in half, the marginal cost-effectiveness of annual vs every other year screening is more than $50 000 per QALY gained. We should also note that, given recent data, hypertension control may further reduce the efficacy of screening since aggressive treatment of hypertension appears to reduce risk of retinopathy substantially.[51,52] Therefore, we may have overestimated the benefits of screening for those with excellent blood pressure control.

One weakness of our study is our inability to firmly define the utility of blindness (visual acuity <20/100) and lesser levels of visual impairment. Sensitivity analyses demonstrate that the utility of blindness is an important predictor of the cost-effectiveness of a screening program, and estimates of average utility vary widely.[43,45] In addition, we were unable to adequately assess the impact of states of visual impairment less than blindness because of limited information on the risks and utilities of these states. Because utility is likely to vary dramatically from patient to patient, a shared decision-making approach to retinal screening intervals may be best when formulating a plan of care for patients with diabetes. Whether we recommend annual or every second to third year screening, patients should know that the lowest risk will accrue with annual screening; however, as long as glycemic control is good, and screening occurs every 2 to 3 years, the risk of developing blindness is still low. Another potential weakness is that an annual screening program could allow other conditions, such as glaucoma and cataracts, to come to earlier medical attention. However, the impact of screening for these conditions in a diabetic population has not been studied.

This study is also limited in its ability to address potential variations in retinopathy risk in minority populations. While the risk of retinopathy appears to be higher in certain ethnic groups, there continue to be conflicting data on level of risk,[53-55] and some or all of the increased risk may be due to hypertension and level of glycemic control.[56-58] In particular, it should be noted that there are conflicting data on the risks of retinopathy in the Hispanic population; recent analyses suggest that elevated risk may persist after adjustment for glycemic control and hypertension.[58] It should also be noted that the risk estimates used in this analysis were based on the UKPDS study population, which included minorities, but not Hispanic Americans. Thus, the aggregate estimates may reflect reasonable population, but not patient-specific, risks, and certain groups, most notably Hispanics and Native Americans, may not be adequately represented in the analysis.

It is clear that we can improve the efficiency of screening by targeting patients based on commonly measured clinical indicators. Ironically, those who will benefit most from eye screening are the patients whom providers often find the most frustrating to treat; namely, those with poor glycemic control. However, these are the patients who need to be the most aggressively screened. This may run counter to a common impulse to give up on other interventions when patients are noncompliant or are unsuccessful with treatments to improve glycemic control. However, setting a standard of having 80% of a diabetes population receiving annual eye examinations will not be productive if the high-risk patients are the ones not being regularly screened.

Our study suggests that annual retinal screening for most patients with type 2 diabetes produces little benefit that is not achieved with every second to third year screening. Although our conclusions would be stronger if there were empirical data on the efficacy of varying screening frequencies, the results of this analysis suggest that the often-cited policy of annual eye screening for all patients with type 2 diabetes should be reevaluated. Furthermore, groups involved in dissemination of quality-of-care standards need to reconsider the marginal benefit of frequent eye examinations when setting their quality and performance standards. If not, we run the risk of encouraging, or even demanding, inefficiency and requiring care that would not be wanted by many well-informed persons with type 2 diabetes.

Funding/Support: This study was supported in part by Veterans Affairs Health Services Research Service and National Institutes of Health grant P60-DK20572. Dr Hofer is a Veterans Affairs Services Research and Development Career Development Awardee.

REFERENCES

1. *Diabetes in America*. 2nd ed. Bethesda, Md: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 1995.
2. Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy: clinical application of Diabetic Retinopathy Study (DRS) findings, DRS report number 8. *Ophthalmology*. 1981;88:583-600.
3. Early Treatment of Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy: ETDRS report number 9. *Ophthalmology*. 1991;98(suppl 5):766-785.
4. Early Treatment of Diabetic Retinopathy Study Research Group. Early Treatment of Diabetic Retinopathy Study design and baseline patient characteristics: ETDRS report number 7. *Ophthalmology*. 1991;98 (suppl 5):741-756.
5. Early Treatment of Diabetic Retinopathy Study Research Group. Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema: ETDRS report number 2. *Ophthalmology*. 1987;94: 761-774.
6. Klein R, Klein BE, Moss SE, DeMets DL. The validity of a survey question to study diabetic retinopathy. *Am J Epidemiol*. 1986;124:104-110.
7. Klein R, Moss SE, Klein BE. New management concepts for timely diagnosis of diabetic retinopathy treatable by photocoagulation. *Diabetes Care*. 1987;10: 633-638.
8. Javitt JC, Aiello L. Cost-effectiveness of detecting and treating diabetic retinopathy. *Ann Intern Med*. 1996;124:164-169.
9. Dasbach EJ, Fryback DG, Newcomb PA, et al. Cost-effectiveness of strategies for detecting diabetic retinopathy. *Med Care*. 1991;29:20-39.
10. Javitt JC, Aiello LP, Chiang Y, et al. Preventive eye care in people with diabetes is cost-saving to the federal government: implications for health-care reform. *Diabetes Care*. 1994;17:909-917.
11. *Health Employer Data and Information Set*. Version 3.0. Washington, DC: National Committee for Quality Assurance; 1997:2.
12. Vijan S, Hofer TP, Hayward RA. Estimated benefits of glycemic control in microvascular complications in type 2 diabetes. *Ann Intern Med*. 1997;127: 788-795.
13. Aiello LP, Gardner TW, King GL, Blankenship G. Diabetic retinopathy. *Diabetes Care*. 1998;21:143-156.
14. Singer DE, Nathan DM, Fogel HA, Schachat AP. Screening for diabetic retinopathy. *Ann Intern Med*. 1992;116:660-671.
15. Martin TL, Selby JV, Zhang D. Physician and patient prevention practices in NIDDM in a large urban

managed-care organization. *Diabetes Care*. 1995;18: 1124-1132.
16. Wylie-Rosett J, Basch C, Walker EA, et al. Ophthalmic referral rates for patients with diabetes in primary-care clinics located in disadvantaged urban communities. *J Diabetes Complications*. 1995;9:49-54.
17. Mayfield JA, Rith-Najarian SJ, Acton KJ, et al. Assessment of diabetes care by medical record review: the Indian Health Service model. *Diabetes Care*. 1994; 17:918-923.
18. Brechner RJ, Cowie CC, Howie LJ, Herman WH, Will JC, Harris MI. Ophthalmic examination among adults with diagnosed diabetes mellitus. *JAMA*. 1993; 270:1714-1718.
19. Eastman RC, Javitt JC, Herman WH, et al. Model of complications of NIDDM, II: analysis of the health benefits and cost-effectiveness of treating NIDDM with the goal of normoglycemia. *Diabetes Care*. 1997;20: 735-744.
20. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329:977-986.
21. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352:837-853.
22. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Med Decis Making*. 1993;13:322-338.
23. Medhi J. *Stochastic Processes*. 2nd ed. New Delhi, India: John Wiley & Sons; 1994.
24. Early Treatment of Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie House classification: ETDRS report number 10. *Ophthalmology*. 1991;98(suppl 5): 786-806.
25. Frederick FL. How effective are treatments for diabetic retinopathy [letter]? *JAMA*. 1993;269: 1290-1291.
26. Morrish NJ, Stevens LK, Head J, Fuller JH, Jarrett RJ, Keen H. A prospective study of mortality among middle-aged diabetic patients (the London Cohort of the WHO Multinational Study of Vascular Disease in Diabetics), I: causes and death rates. *Diabetologia*. 1990;33:538-541.
27. Panzram G. Mortality and survival in type 2 (non-insulin-dependent) diabetes mellitus [published correction appears in *Diabetologia*. 1987;30:364]. *Diabetologia*. 1987;30:123-131.
28. Muggeo M, Verlato G, Bonora E, et al. The Verona diabetes study: a population-based survey on known diabetes mellitus prevalence and 5-year all-cause mortality. *Diabetologia*. 1995;38:318-325.
29. Panzram G, Zabel-Langhennig R. Prognosis of diabetes mellitus in a geographically defined population. *Diabetologia*. 1981;20:587-591.
30. Krolewski AS, Czyczyk A, Janeczko D, et al. Mortality from cardiovascular diseases among diabetics. *Diabetologia*. 1977;13:345-350.
31. Klein R, Moss SE, Klein BE, DeMets DL. Relation of ocular and systemic factors to survival in diabetes. *Arch Intern Med*. 1989;149:266-272.
32. Moss SE, Klein R, Kessler SD, Richie KA. Comparison between ophthalmoscopy and fundus photography in determining severity of diabetic retinopathy. *Ophthalmology*. 1985;92:62-67.
33. Klein R, Klein BE, Neider MW, et al. Diabetic retinopathy as detected using ophthalmoscopy, a nonmydriatic camera and a standard fundus camera. *Ophthalmology*. 1985;92:485-491.
34. Sussman EF, Tsiaris WG, Soper KA. Diganosis of diabetic eye disease. *JAMA*. 1982;247:3231-3234.
35. Kinyoun J, et al, for the Early Treatment of Diabetic Retinopathy Study Research Group. Detection of diabetic macular edema: ophthalmoscopy versus photography: ETDRS report number 5. *Ophthalmology*. 1989;96:746-750.
36. Medicare program: revisions to payment policies and five-year review of and adjustments to the relative value units under the physician fee schedule for calendar year 1997 and physician volume performance standard rates of increase for federal fiscal year 1997, notice. 61 *Federal Register* 59489-716 (1996).
37. Plan and operation of the Third National Health and Nutrition Examination Survey, 1988-94, series 1: programs and collection procedures. *Vital Health Stat 1*. 1994;32:1-407.
38. Nathan DM. The pathophysiology of diabetic complications: how much does the glucose hypothesis explain? *Ann Intern Med*. 1996;124:86-89.
39. Aiello LP, Avery RL, Arrigg PG, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. *N Engl J Med*. 1994;331:1480-1487.
40. Jones D, Dolben J, Owens DR, Vora JP, Young S, Creagh FM. Non-mydriatic Polaroid photography in screening for diabetic retinopathy: evaluation in a clinical setting. *BMJ*. 1988;296:1029-1030.
41. Nathan DM, Fogel HA, Godine JE, et al. Role of diabetologist in evaluating diabetic retinopathy. *Diabetes Care*. 1991;14:26-33.
42. Dasbach EJ, Fryback DG, Thornbury JR. Medical decision making: health utility preference differences [abstract]. *Med Decis Making*. 1992;12:4.
43. Fryback DG, Dasbach EJ, Klein R, et al. The Beaver Dam Health Outcomes Study: initial catalog of health-state quality factors. *Med Decis Making*. 1993; 13:89-102.
44. Eastman RC, Javitt JC, Herman WH, et al. Model of complications of NIDDM, I: model construction and assumptions. *Diabetes Care*. 1997;20:725-734.
45. Javitt JC, Aiello L. Cost-effectiveness of detecting and treating diabetic retinopathy. *Ann Intern Med*. 1996;124:164-169.
46. Mullahy J, Manning W. Valuing health care: costs, benefits, and effectiveness of pharmaceuticals and other medical technologies. In: Sloan FA, ed. *Statistical Issues in Cost-Effectiveness Analyses*. New York, NY: Cambridge University Press; 1995:149-184.
47. Manning WG, Fryback DG, Weinstein MC. Reflecting uncertainty in cost-effectiveness analysis. In: Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. *Cost-Effectiveness in Health and Medicine*. New York, NY: Oxford University Press; 1996.
48. Chiang Y, Bassi LJ, Javitt JC. Federal budgetary costs of blindness. *Milbank Q*. 1992;70:319-341.
49. Hayward RA, Manning WG, Kaplan SH, Wagner EH, Greenfield S. Starting insulin therapy in patients with type 2 diabetes: effectiveness, complications, and resource utilization. *JAMA*. 1997;278:1663-1669.
50. Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization. *CMAJ*. 1992;146:473-481.
51. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ*. 1998;317:703-713.
52. UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. *BMJ*. 1998;317:713-720.
53. Haffner SM, Fong D, Stern MP, et al. Diabetic retinopathy in Mexican Americans and non-Hispanic whites. *Diabetes*. 1988;37:878-884.
54. Hamman RF, Mayer EJ, Moo-Young JA, Hildebrandt W, Marshall JA, Baxter J. Prevalence and risk factors of diabetic retinopathy in non-Hispanic whites and Hispanics with NIDDM: San Luis Valley Diabetes Study. *Diabetes*. 1989;38:1231-1237.
55. Tudor SM, Hamman RF, Baron A, Johnson DW, Shetterly SM. Incidence and progression of diabetic retinopathy in Hispanics and non-Hispanic whites with type 2 diabetes: San Luis Diabetes Study, Colorado. *Diabetes Care*. 1997;21:53-61.
56. Harris EL, Feldman S, Robinson CR, Sherman S, Georgopolous A. Racial difference in the relationship between blood pressure and risk of retinopathy among individuals with NIDDM. *Diabetes Care*. 1993;16: 748-754.
57. Harris EL, Sherman SH, Georgopoulos A. Black-white differences in risk of developing retinopathy among individuals with type 2 diabetes. *Diabetes Care*. 1999;22:779-783.
58. Harris MI, Klein R, Cowie CC, Rowland M, Byrd-Holt DD. Is the risk of diabetic retinopathy greater in non-Hispanic blacks and Mexican Americans than in non-Hispanic whites with type 2 diabetes? a U.S. population study. *Diabetes Care*. 1998;21:1230-1235.