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CONTINUOUS COMPUTER SIMULATION ANALYSIS OF THE COST-EFFECTIVENESS OF SCREENING AND TREATING DIABETIC RETINOPATHY

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Abstract

This paper analyzes the cost-effectiveness of screening and treating diabetic retinopathy (DR) by simulating the disease progress continuously with existing data. A new computer simulation based on Monte Carlo techniques and logistic transformation follows cohorts from diabetes onset until death in five care scenarios. For younger-onset patients, ophthalmic care reduces the prevalence of blindness by 52% or greater while savings in disability facilities and production losses surpass direct costs. For older-onset patients, less favorable results appear. Financial benefits surpass costs for juvenile-onset patients. For other patients, the net costs of ophthalmic care seem lower than in other health care programs.

Keywords: Computer Simulation, Cost-effectiveness Analysis, Diabetic Retinopathy, Screening

Photocoagulation is an effective treatment for diabetic retinopathy (DR) and macular edema (ME). Studies in the United States in the 1970s and 1980s have proved that photocoagulation reduces the incidence of blindness resulting from DR by more than 50% (5;7;9). Although DR usually progresses slowly and rather predictably, patients experience the first symptoms long after the appropriate time for treatment has passed (27). Therefore, regular eye examinations are necessary to provide ophthalmologists with adequate information for timely treatment. The question arises of which intervals should be chosen in screening for DR. Shorter intervals increase the likelihood of timely discovery of the progression toward high-risk states. Longer intervals, however, may be required because of the scarcity of human resources and financial means. A cost-effectiveness analysis is needed to determine the optimal frequency of screening for DR with subsequent photocoagulation. This is all the more important because the number of diabetic patients is forecasted to grow considerably during the next decades (29).

Since the effectiveness of photocoagulation has been demonstrated definitively, ethical arguments forbid founding a cost-effectiveness study on a randomized controlled trial. Several researchers have developed computer simulations to avoid ethical problems (4;12;13;14;15;16). These simulations use Markov processes to model the progression of DR in a small number of discrete steps, usually five to seven health states. Consequently, they cannot relate the sensitivity and specificity of screening or the effectiveness of photocoagulation to the stage of DR. For this study, a new computer simulation was created to overcome this limitation by imitating the progression of DR in an indefinite number of health states on the basis of existing empirical data.

METHODS

The simulation follows cohorts that initially consist of 10,000 female and 10,000 male patients. Each cohort is homogeneous regarding the age of onset of DM. In the insulin-dependent diabetes mellitus (IDDM) cohort, patients face IDDM from the age of 15. Both for non–insulin dependent diabetes mellitus-a (NIDDM-a) (insulin taking) and for NIDDM-b (non–insulin taking), there are three cohorts for three ages of onset: 35, 55, and 75 years. For each cohort, the disease progression is assessed in five screening scenarios. Scenario 0 is no ophthalmic care. In the scenarios 1 to 4, the first eye examination is performed immediately after DM is diagnosed. The date of the next eye examination is determined by the retinal diagnosis in the weakest eye. In scenario 4, patients without DR are screened once a year, patients with DR but excluding ME and proliferative diabetic retinopathy (PDR) twice a year, and patients with ME and/or PDR four times a year. In the other scenarios, the screening frequencies are halved as compared to the next more intensive scenario.

Once every 3 months, the simulation computes the state of the macula and the peripheral retina, the central acuity, and the peripheral vision of each eye separately beginning at the onset of DM until the last cohort member dies. This computation produces real numbers in the interval (0, 1), ranging from the worst to the best possible condition. Although the simulation can accommodate any period, a term of 3 months was chosen, because this is the shortest interval between subsequent examinations in scenario 4 for patients suffering from ME and/or PDR in either eye. Epidemiological studies of DR usually present prevalence rates for some characteristic moments in the disease progression. Therefore, the individual value allocation to various aspects of the retina is based on approximations (Table 1). These few rates suffice to construct logistic functions that specify the prevalence

Table 1. Maximum Prevalence of Retinal Disorders and Visual Impairment

	IDDM	NIDDM-a	NIDDM-b
DR	98%	95%	72%
ME	33%	38%	28%
PDR	67%	32%	15%
⩽20/40	35%	14%	14%
Blindness	12%	6%	6%

Definitions: NIDDM-a, insulin taking; NIDDM, non–insulin dependent diabetes mellitus; NIDDM-b, non–insulin-taking NIDDM; IDDM = insulin-dependent diabetes mellitus; DR = diabetic retinopathy; ME = macular edema; PDR = proliferative diabetic retinopathy.

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of retinal disorders and visual impairment at any moment after the onset of IDDM or NIDDM.

The disease progression in the macula illustrates this process. The simulation expresses the state of the macula by means of a real number in the interval (0, 1). The border between absence and presence of DR is arbitrarily fixed at 2/3 and the upper border of ME at 1/3. Experiments were made to test the effects of shifts up to /0.1 in these borders. They did not affect the outcomes of the simulation. Through logistic transformation, the data of each patient are converted from the interval (0, 1) to the interval $(-\infty, +\infty)$. The prevalence rates of ME and DR are considered as probability densities of a normal distribution to the left of the logistic transformation of 1/3 and 2/3, respectively: 0.6934 and 0.6934. The mean and the standard deviation are then determined of the normal distribution corresponding to the two prevalence rates and the logistic transformation of the border value of DR and ME. With the logit transformation, this normal distribution is converted to a logistic-normal distribution in the interval (0, 1). The same technique is applied to the peripheral retina and the two acuity categories: central acuity and peripheral vision. The latter refers to the visual quality of the retina excluding the macula.

These logistic-normal distributions can be constructed, provided two prevalence rates are known. As this condition is fulfilled, these distributions are available at any moment during the simulation. The three-monthly round of individual value allocations starts by drawing random numbers from these normal distributions. The numbe of random numbers totals eight times the number of living patients, as four aspects are investigated per eye. After a logit-transformation of these numbers, they provide a set of new values that should be allocated to the various eyes. The allocation is based on the rank in the cohort in the previous period and on the condition of the other aspects in the same and the other eye of the patient. A more detailed description of this technique is presented elsewhere (3). On the basis of these detailed individual data, every patient can easily be assigned to at least one of the following categories: no DR; DR excluding both ME and PDR; ME; PDR; adequate vision ($<$ 20/40); poor central and/or peripheral vision (20/40 or worse, but at least 20/200); and blindness ($\leqslant$ 20/200 in the better eye with the best correction).

Eye examinations consist of ophthalmoscopy in mydriasis by an experienced ophthalmologist. If ME or PDR is discovered, the patient receives focal, grid, or panretinal laser treatment, occasionally preceded and followed by fluorescein angiography according to national consensus guidelines (11). Although many diabetic patients in the Netherlands and the United States disregard screening guidelines, full patient participation is assumed (4;30). This assumption may restrict the applicability of the simulation. However, one can easily compose numerous weighted mixes of the results in different scenarios, including scenario 0. This implies that any rate of noncompliance can be included in these mixes. Thus, the outcomes of the simulation may apply to a spectrum of compliance rates. Data on the incidence and prevalence of DR, ME, PDR, and visual impairment were borrowed from international publications (6;17;18;19;20;21;22;24;25;26). Table 1 presents some key data of the simulation.

Data on the sensitivity and specificity of eye examinations and on the effectiveness of photocoagulation have a similar basis (1;4;5;7;9;14;28;31). However, the simulation does not apply these data directly, because it is plausible that these variables depend on the state of the retina. The diagnosis of the retina, for instance, tends to become less reliable as the state of the retina approaches the border value of background DR and PDR. By lack of data on variations in sensitivity and

specificity, hypothetical functions were constructed to relate the sensitivity and specificity to the state of the retina. Near the border value of two categories of health states, for example, background DR and PDR, the sensitivity and specificity equal the "average" values of the studies that were consulted. The more the state of the retina differs from the border value, the more sensitivity and specificity approximate 100%.

The simulation follows a similar line regarding the effectiveness of photocoagulation. Down to a certain retinal state, the damage caused by photocoagulation outweighs treatment benefits. Above that state, no treatment is given. Below that state, the likelihood of successful treatment decreases as the condition of the retina deteriorates. We could not find data on this rather self-evident relationship. Therefore, a hypothetical function was constructed. The likelihood of success attains its maximum when the deteriorating retina first reaches the state where the benefits of photocoagulation surpass the harmful effects. While the retina deteriorates further, the success function yields lower values. The maximum of the function surpasses the success rates found in empirical investigations. Consequently, the function can provide an average success rate for all retinal states where photocoagulation is justified that approximately equals the empirically found success rates.

No proof of consensus on market prices for ophthalmic care was found. Alternatively, the simulation resorts to the official medical charges that were operative in the Netherlands in 1992 (3, 134). Time costs are comparatively insignificant and widely spread. Consequently, they should not have a significant impact on policy decisions and are left out of consideration. Losses of earnings or production caused by disease or disablement were determined on the basis of the friction costs technique (23). It only considers those losses that occur during the friction period, which is needed to replace sick or disabled workers. The more widely used human capital approach calculates losses over a much longer period. Consequently, the friction costs technique leads to far more conservative estimates of the financial benefits of laser treatment, which comprise the decrease in earnings and production losses following the reduction in visual impairment.

RESULTS

IDDM

The outcomes of the simulation show that few patients ($< 3\%$) suffer from any visual impairment before the age of 25. In the absence of ophthalmic treatment, the prevalence of poor vision then rises steadily. Some 10 years later, this is followed by a rise in the prevalence of blindness. After the age of 50, both prevalence rates stabilize near their maxima: 35% and 12% respectively (Table 1). In the absence of ophthalmic care (s0), a female patient is blind in an average of 2.5 years, a male patient in 2.0 years. Ophthalmic care reduces the prevalence of blindness substantially, maximally by 51.65% for female patients in s4 as compared with s0 (Table 2). From s0 to s1, the reduction of blindness is clearly larger than from s1 to s2, while the transition from s0 to s1 involves the same increase in the volume of ophthalmic care as the transition from s1 to s2. Consequently, ophthalmic care has diminishing marginal returns. This is most obvious from s3 to s4.

The maximum annual number of eye tests in s4 is nearly four times as high as in s1 (Table 3). The cumulative number of laser treatments is 39% larger in s4 as compared with s1. Consequently, the increase in the number of laser treatments is disproportionate to the rise in the intensity of ophthalmic care, measured by the

Table 2. IDDM: Cumulative Prevalence of Blindness (Years and % of s0) in a Cohort of 10,000 Female and a Cohort of 10,000 Male Patients from the onset of IDDM until Death

	Females		Males	
s0	24,529	100.00%	20,100	100.00%
s1	19,341	78.85%	15,653	77.87%
s2	14,852	60.55%	12,472	62.05%
s3	12,788	52.13%	10,873	54.09%
s4	11,860	48.35%	10,191	50.70%

frequency of ophthalmic examinations. Laser treatments are performed a few years earlier in scenarios with more intensive ophthalmic care: in s1 on average at the age of 45.04 years (10.43) and in s4 on average at the age of 42.00 years (9.82) (t test: $p < .001$). Apparently, this time difference contributes to a considerably higher effectiveness of laser treatments.

Although the results in Table 4 are based on the more conservative friction costs technique, all the average results are negative. This implies that savings in disability facilities and production losses surpass direct costs. Ophthalmic care generates positive macroeconomic returns. The first marginal amount is also negative.

NIDDM

Among patients who are confronted with NIDDM from the age of 75, the reduction of blindness is comparatively insignificant in all the four scenarios with ophthalmic care (Table 5). For the ages of onset of 35 and 55 years, the reduction of blindness is situated roughly midway between that for the IDDM cohort and the oldest onset NIDDM cohorts.

As shown in Table 4, the cost-effectiveness analysis does not lead to any negative results for NIDDM cohorts. This implies that the financial benefits of ophthalmic care for NIDDM patients are always inferior to the costs.

DISCUSSION

This simulation is based on data that give conservative estimates of the balance of effects, benefits, and costs. Nevertheless, the average analysis demonstrates that the financial benefits of ophthalmic care for IDDM patients surpass the direct costs in the four scenarios with eye care. The marginal analysis (Table 4) shows quite an unfavorable result for scenario 4. Therefore, it seems advisable to follow scenario 3, which corresponds to the guidelines on which Organisations of Medical Specialists

Table 3. IDDM: Cumulative Number of Panretinal Laser Treatments in a Cohort of 10,000 Female plus 10,000 Male Patients from the Onset of IDDM until Death

Age	s1	s2	s3	s4	s2/s1	s3/s1	s4/s1
25	125	270	414	527	216%	331%	422%
35	2,737	4,764	6,038	7,482	174%	221%	273%
45	13,128	17,732	19,541	21,606	135%	149%	165%
55	18,282	22,727	24,702	27,254	124%	135%	149%
65	20,532	24,640	26,870	29,392	120%	131%	143%
75	21,445	25,621	27,716	30,086	119%	129%	140%
109	21,758	25,885	27,914	30,241	119%	128%	139%

Table 4. IDDM and NIDDM: Balance of Direct Costs and Benefits per Year Realized Sight Gain; Approximation by Friction Cost Technique (Discount Rate 5% per Year)

	IDDM	NIDDM-a			NIDDM-b		
Age of Onset	15 years	35 years	55 years	75 years	15 years	55 years	75 years
Average analysis							
From s0 to s1	−*f*437	*f*10,635	*f*11,342	—	*f*10,800	*f*25,716	—
From s0 to s2	−*f*1,791	*f*9,577	*f*37,062	*f*9,285	*f*5,922	*f*13,444	—
From s0 to s3	−*f*1,166	*f*11,580	*f*26,471	*f*326,914	*f*6,458	*f*19,517	—
From s0 to s4	−*f*468	*f*12,694	*f*18,933	—	*f*11,368	*f*12,298	*f*20,617
Marginal analysis							
From s1 to s2	−*f*3,847	*f*7,880	—	*f*2,957	*f*3,081	*f*8,067	*f*4,587
From s2 to s3	*f*2,287	*f*19,294	*f*16,753	—	*f*7,698	*f*95,342	—
From s3 to s4	*f*92,154	*f*17,824	*f*9,025	—	—	*f*4,612	*f*3,848

Missing values refer to cases where more intensive eye care leads to a lower discounted value of realized sight gain.

in the Netherlands reached agreement. It is remarkable, then, that the rather small increase in the number of laser treatments from scenario 1 to scenario 2, 3, and 4 results in a comparatively much larger reduction of blindness. In other words, by intensifying eye care, the effectiveness of photocoagulation increases because patients are treated in a more timely manner. For NIDDM patients, a purely financial approach never shows a surplus. However, the net costs of ophthalmic care seem low as compared with programs in other medical fields (12).

Starting from comparable data, the simulations by Javitt et al. (12;13;14;15;16) and by Dasbach et al. (4) lead to similar outcomes, although they follow quite different modeling techniques. Those simulations are characterized by (a) seven (Javitt) and four (Dasbach) health states including death; (b) fixed transition probabilities; (c) a small set of fixed incidence rates; (d) the absence of disease regression;

Table 5. NIDDM: Cumulative Prevalence of Blindness (Years and % of s0) in Two Cohorts of 10,000 Female and Two Cohorts of 10,000 Male Patients from the Onset of NIDDM until Death

		NIDDM-a				NIDDM-b			
		Females		Males		Females		Males	
Age of	s0	8,953	100%	6,489	100%	9,642	100%	7,173	100%
onset	s1	8,539	95%	6,184	95%	8,710	90%	6,491	90%
35 yrs	s2	7,701	86%	5,674	87%	7,985	83%	5,975	83%
	s3	7,154	80%	4,975	77%	7,087	73%	5,261	73%
	s4	6,534	73%	4,821	74%	6,796	70%	5,164	72%
Age of	s0	4,077	100%	2,469	100%	4,313	100%	2,655	100%
onset	s1	3,783	93%	2,302	93%	3,969	92%	2,442	92%
55 yrs	s2	3,412	84%	2,161	88%	3,827	89%	2,228	84%
	s3	3,255	80%	1,859	75%	3,394	79%	2,186	82%
	s4	2,844	70%	1,801	73%	3,115	72%	1,907	72%
Age of	s0	1,012	100%	631	100%	1,053	100%	692	100%
onset	s1	1,046	103%	612	97%	1,034	98%	645	93%
75 yrs	s2	943	93%	591	94%	1,009	96%	655	95%
	s3	855	84%	564	89%	925	88%	624	90%
	s4	801	79%	526	83%	959	91%	603	87%

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(e) fixed values for the sensitivity and specificity of ophthalmic examinations; and (f) fixed success rates for laser treatment. Moreover, Dasbach et al. (4) compute the disease progression by means of matrices with a Markov technique that prohibits following patients individually. Thus, the information of the disease progression is at any time confined to the total number of persons in each of the four health states.

Because of the expanse of each step, both simulations classify large numbers of patients in a homogeneous group, for instance, sight-threatening PDR in Javitt's simulation. In this model, all the patients in this group have reached one particular grade of PDR. Actually, however, sight-threatening PDR comprises a wide spectrum of grades. Generally speaking, photocoagulation in earlier stages of PDR has a much higher success rate than in the most severe stages. This implies that the effectiveness of photocoagulation directly depends upon the composition of the sight-threatening PDR group. When eye care becomes more intensive and patients are screened more frequently, the average interval between the first appearance of PDR and its detection decreases. Thus, patients can receive photocoagulation in an earlier stage of PDR when treatment is likely to be more successful. An analysis of the effectiveness of photocoagulation in different scenarios of eye care is only valid if the simulation model can imitate the disease progression in much smaller steps. Therefore, we developed this new simulation where the number of steps can be increased at one's own discretion. As a result, the disease progression is imitated virtually continuously. This also enables one to relate the sensitivity and specificity of eye tests to the state of the retina. This enables creation of a more valid picture of the effectiveness of screening.

The 1996 version of Javitt's simulation uses quality-adjusted life yeas (QALYs) to evaluate effects (12). As there is insufficient evidence of consensus on QALYs regarding visual impairment among diabetic patients, we decided to focus this simulation on savings in production losses and facilities provided for disabilities. The latter seem more open to straightforward empirical testing. As far as we know, no other simulation resorts to the more conservative friction costs technique. The generally used capital approach may well lead to exaggerated estimates of production losses, since the number of unemployed workers is quite considerable in nearly all Western countries, so that most visually impaired workers can be replaced rather easily.

Nevertheless, this simulation needs further refinement. Some sources on the effectiveness of laser treatment are more than a decade old. Meanwhile, this treatment has become more common and sophisticated, so that the above results may underestimate today's effectiveness of ophthalmic care for diabetic patients. As the open structure of our simulation implies broad applicability, the existing computer program can be used with any new set of data to update the results.

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