Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: The DCCT/EDIC Research Group. Frequency of evidence-based screening for retinopathy in type 1 diabetes. N Engl J Med 2017;376:1507-16. DOI: 10.1056/NEJMoa1612836

03/20/2017

Supplementary Materials

Evidence-based Screening Frequency for Retinopathy in Type 1 Diabetes

The Diabetes Control and Complications Trial (DCCT)-Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group*

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2. Schedule of Retinal Examinations

During EDIC, each participant had a retinal examination every 4th year, based on the year of enrollment into the DCCT. For example, a patient randomized in 1987 had subsequent retinal examinations in EDIC (starting in 1994) during 1995 (8th anniversary), 1999 (12th anniversary) etc. In addition, the exam was performed in the entire cohort in 1997 (EDIC year 4) and 2003 (EDIC year 10).

3. Description of Models

Supplemental Table S1 shows the number of transitions from one visit (given by the row state) to the next one (given by the column state). State 1 is no retinopathy and no CSME and 5 is PDR or CSME. For example, there were 4898 visits where the participant had no retinopathy and no CSME (state 1) and remained in state 1 at the next visit, and 1823 cases where a participant in state 1 developed Mild NPDR (moved to state 2) at the next visit. There were 56 cases where a participant in state 3 progressed to state 4 at the next visit (3rd row and 4th column entry). Similarly, there were 36 cases where a participant in state 4 (SNPDR and no CSME) developed either PDR or CSME by the next visit.

Table S2 presents the model-estimated conditional probability of the next transition, if and when a subject does move from the current state at an examination. By definition, a subject in state 1 (no retinopathy) has probability 1 that the retinopathy status will worsen to state 2 if and when a transition from state 1 occurs. A subject in state 2 who does transition then has a probability of 0.599 of improving back to state 1 or 0.401 of worsening to state 3. At state 3, if the subject does transition there is a 59% chance of improving, 19% chance of moving to state 4 and 22% chance of reaching PDR/CSME. A subject with SNPDR but no CSME is more likely to improve (71% chance) than developing either PDR or CSME (29%).

Note that the model only attempts to estimate the probability of the 8 transitions for which there are adequate numbers of observed transitions in Table S1. These are 1 to 2, 2 to 1 or 3, 3 to 2, 4 or 5 and 4 to 3 or 5.

On average subjects remained in state 1 for 1.87 years before transitioning to a higher state (the sojourn time). Subjects remained in state 2 for 4.07 years, in state 3 for 1.63 years and state 4 for only 0.39 years. These times are per occasion within a state, not the total time in that state. For example, the average time a patient stayed in the mild state (2) was 4.07 years before transitioning to a different state, and a given subject could have spent time in state 2 multiple times (i.e. after multiple "moves"). For state 4, the mean sojourn time is only 0.39 years, in large part because patients at that level soon

receive pan-retinal laser therapy that transitions the subject to the absorbing state 5 (PDR or laser or CSME).

From these estimates, the model then provides an estimate of the probability of the set of 20 possible transitions over a given time period, such as a 3 year period (Table S3). For example, starting with no DR and no CSME, there is 31% chance the subject will be in state 1 after 3 years, 60% chance in state 2, 7% chance in state 3, 0.3% in state 4 and 1.6% in state 5. Confidence intervals can also be computed.

Such a table of transition probabilities can then be computed for any time period of interest. For illustration, Table S3 shows the probabilities of the 20 possible transitions over a 1 and over a 2 year period. From a set of such tables, for example at each year, a table with the specific transition probabilities of interest can be obtained. For example, Table 1 of the manuscript presents the probabilities of transition from lesser states to the most severe state (PDR/CSME) that in turn can guide decisions on the frequency of future examinations. Those probabilities at years 1, 2 and 3 in Table 1 come directly from the last column of the transitions probability table at years 1, 2 and 3 in Table S3.

We can also incorporate covariate effects in the model. Table 2 in the manuscript shows the hazard ratio for each transition per unit increase in HbA1c %. Table S4 herein presents the effect of other important covariates on these transitions with no adjustment for other factors. Increasing current age was associated with a reduced risk of transition among the lesser states (1-3) but with no significant effect on the probabilities of transition to PDR/CSME. Increasing current BMI was associated with decreased risk of both progression and regression from states 2 and 3 and with decreased risk of progressing from 4 to 5. However, these effects are confounded by mean HbA1c values, and all associations disappeared after adjustment except for transitions from 2 to 1 and 3 to 2. Increasing current duration of diabetes was associated with a decreased probability of transitioning from 1 to 2, 2 to 1 and 3, 3 to 5 and 2. However, these associations are confounded by age. After adjustment, only transitions from 3 to 5, 2 to 1 and 3 to 2 remained significant, while higher duration became positively correlated with transitions from mild to moderate NPDR. Current hypertension was associated with some transitions among the lesser states but not transitions to PDR/CSME. Some of these hypertension hazard ratios were very large owing to the sparseness of transitions among those with hypertension. Current hyperlipidemia was also associated with transitions among the lesser states but not to PDR/CSME.

Table S5 then presents covariate effects on these transitions from a multivariate model in which mean HbA1c, current age and current duration had significant effects, with the other covariates having no to minimal effect. The strong effect of glycemia is confirmed in the multivariate model, where higher HbA1c values are positively associated with higher risk of all progressions except from state 3 to state 5, and with lower chance of regression from state 2 to 1 and 3 to 2. Older age is associated with lower rates of progression from state 1 to 2 and 2 to 3 and regression from 2 to 1 and 3 to 2. Longer duration of diabetes is correlated with higher risk of progression from state 2 to 3 and 3 to 4, and with lower improvement from 2 to 1 and 3 to 2.

4. Cost-Benefit Analyses

A detailed description of the statistical methods employed in the cost-benefit analysis is provided in a separate manuscript published in *Biostatistics* that is available at:

https://doi.org/10.1093/biostatistics/kxx009

The supplemental appendix for this *Biostatistics* paper also includes the *R* code used to conduct the cost-effectiveness computations in that paper.

A technical report on which the *Biostatistics* paper is based, and the *R* code, are also available at

http://www.bsc.gwu.edu/bsc/webpage.php?no=6&rnd=288

A brief description follows.

For the 4, 3, 1, 1 year and other schedules we consider the properties over a period of 20 years into the future. Consider the progression from no-retinopathy (state 1) to PDR/CSME (state 5) using the (4, 3, 1, 1) year schedule. Since the participant is in state 1 at the initial (current) visit (visit 1), the next examination (visit 2) is scheduled after 4 years. At visit 2, the participant can be in any one of the 5 states. If the participant is in state 1 (or state 2) at that time, then visit number 3 is scheduled after an additional 4 (or 3) years, for a total of 8 (or 7) years since the first visit. However, if the participant is either in state 3 or 4 at the second visit, then the next examination is scheduled after 1 year, for a total of 5 years since the first visit. The procedure continues in the same fashion until either the subject reaches PDR/CSME, or the time since the first visit exceeds the 20 year time horizon.

For a given schedule, the **Undetected Time (T_U)**, refers to the elapsed time from the actual onset of progression to PDR/CSME (assumed to occur in continuous time, i.e. on a specific day) and the next examination. The less frequent the visits the longer the progression to PDR/CSME would go undetected.

Given that a subject reached PDR/CSME, Bayes' formula shows there is a 5.7% chance the previous state was no-retinopathy, 7.2% chance mild NPDR, 23.8% moderate NPDR and 63.3% severe NPDR. The cumulative incidence function of PDR/CSME is not linear (Figure 1) so that the average time to the PDR/CSME event is not in the middle of the interval between consecutive examinations. Taking this into account yields an average undetected time of 1.24 years if PDR/CSME event occurred after a no-retinopathy visit, 1.15 years after a mild NPDR visit, 0.53 years after a moderate NPDR and 0.64 years after a severe NPDR visit. This leads to an overall average of undetected time of 0.69 (=0.057*1.24+0.072*1.15+0.238*0.53+0.633*0.64) years,

The **Number of Prior Visits (N_V)** refers to the number of visits (exams) prior to the detection of progression to PDR/CSME at an exam. The more frequent the visits, the greater the number of negative prior visits before progression is detected. Over a 20-year follow-up, approximately 31% of the subjects starting in state 1 will reach PDR/CSME (Figure 1). The expected number of visits for a given screening frequency is obtained using a Monte Carlo approach. Further details are provided in the technical report.

Let N denote the size of the population of type 1 diabetes (N=10^6), c_v denote the cost of a visit, and let π_i be the proportion of population in state i ($i=1,2,3,4$). Let n_{ij} denote the number of visits before reaching the PDR/CSME state or exceeding the time horizon L ($L=20$) when starting from state i under the screening schedule j, where $i=1,2,3,4$ and $j=1,2$ corresponding to annual screening ($j=1$) and to the (4, 3, 0.5, 0.25) screening ($j=2$). Then the average cost of the visits under screening schedule j is given by

$$C_j = c_v \cdot N \cdot (1 - \pi_5) \cdot \sum_{i=1}^{4} \pi_i \cdot n_{ij} \,,$$

so that the difference in cost between the two screening schedules is

$$\Delta C = c_v \cdot N \cdot (1 - \pi_5) \cdot \sum_{i=1}^{4} \pi_i \cdot (n_{i1} - n_{i2}) \,.$$

The expected number of visits separately by schedule and starting state is provided below.

Schedule	State 1	State 2	State 3	State 4
(1,1,1,1)	18.3808	17.8150	13.6478	10.3944
(4,3,0.5,0.25)	7.6558	7.9444	9.8120	8.8383

Assume 10% of the type 1 diabetes population has already reached the PDR/CSME state, and of the remaining 90%, 25% are in the no retinopathy state, 25% in MiNPDR, 30% in MoNPDR, and 20% in SNPDR. The average cost per subject with a time horizon of $L=20$ years is \$2739.991under the (1,1,1,1) schedule, and \$1550.036 under the (4,3,0.5,0.25) schedule, for a 43.4% reduction in costs. Notice that the % reduction does not depend on the cost of a visit c_v. Considering the US T1D population is ~ 1 million, the annual screening schedule requires approximately \$2.46B over 20 years, while the (4,3,0.5,0.25) schedule requires \$1.39B, for a saving of \$1.07B.

5. An Online Application

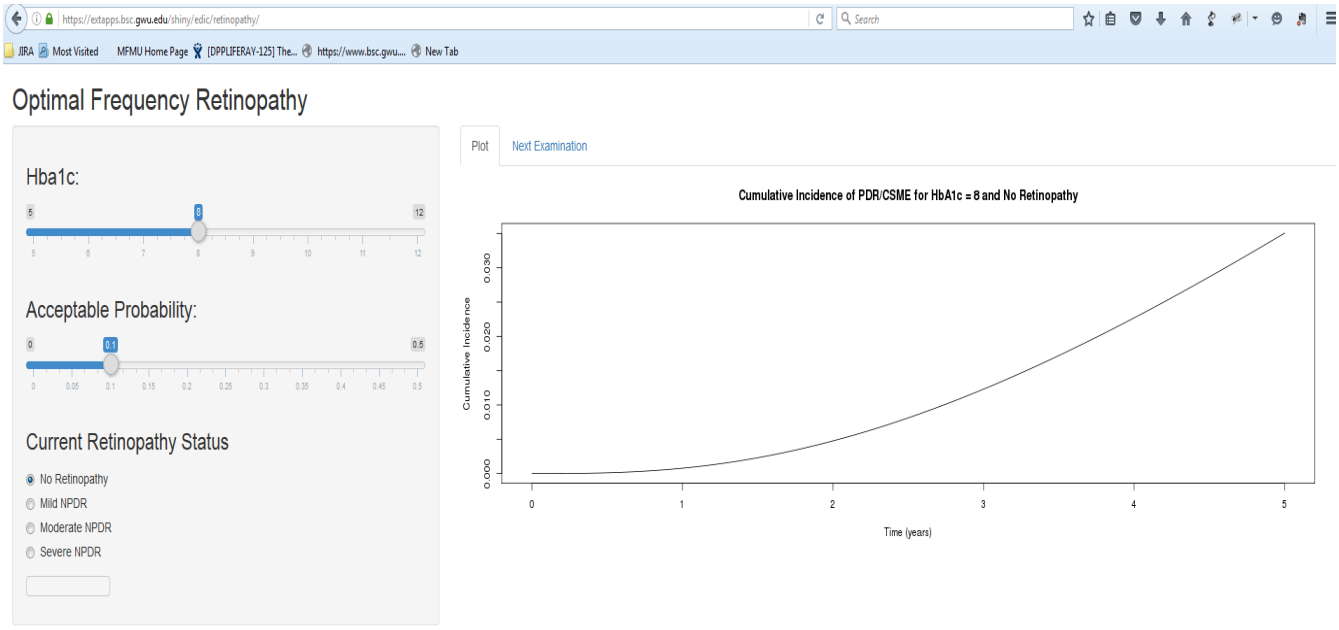
A Shiny application within R was developed to implement the methods described herein and to facilitate the application of our findings in clinical practice. It can be accessed at https://extapps.bsc.gwu.edu/shinypub/edic/retinopathy/.

Briefly, given patient level data, the goals are to:

1. describe the cumulative incidence of PDR/CSME based on a patient's current retinopathy status and historical mean HbA1c level; and
2. determine the time to the next examination such that the risk of reaching PDR/CSME before that time is below a specified value.

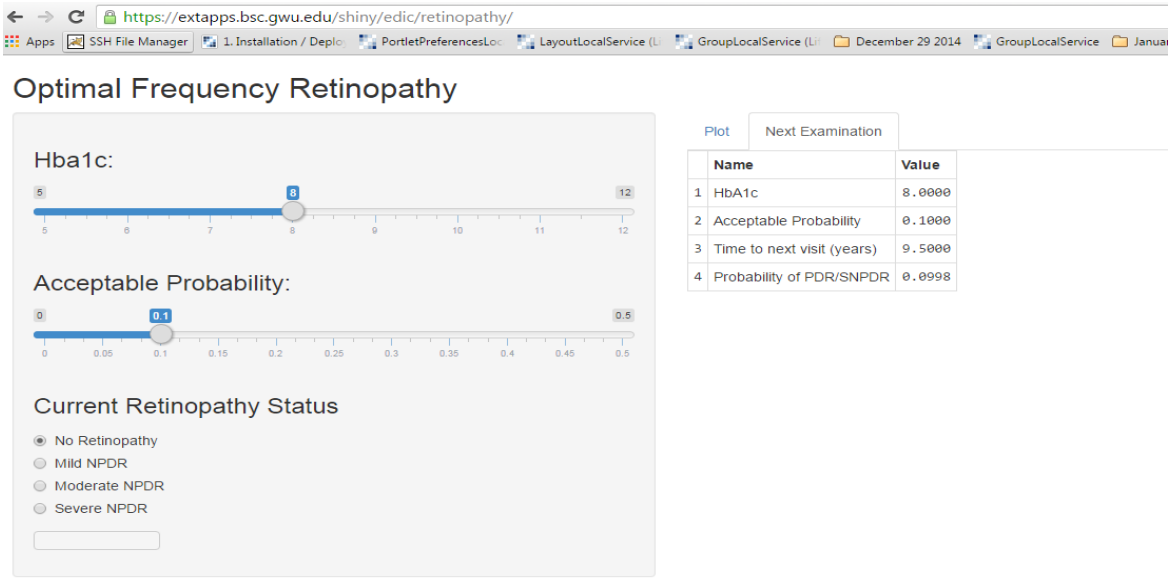
The interface (called dashboard) contains two panels.

The left panel is used to capture the input data, namely the patient's current retinopathy status and mean HbA1c (*HbA1c*), and the cut-off value for the risk of developing PDR/CSME before the next visit (*Acceptable Probability*). Once these input values are selected, the estimated cumulative incidence of reaching PDR/CSME for that patient is reported in the right panel.



To obtain the cumulative incidence of PDR/CSME, only the HbA1c value and the current retinopathy status are required, and, for illustration, the right panel in the screenshot presents the cumulative incidence of PDR/CSME for a subject with an HbA1c value of 8% and *no retinopathy* at the current visit.

The time to the next evaluation requires specifying the *Acceptable Probability* in addition to the HbA1c and the current retinopathy status, and the results are obtained by clicking on the *Next Examination* tab. The screenshot below reports the results for a patient with an HbA1c value of 8% and *no retinopathy* at the current visit, and with a 10% acceptable risk of reaching PDR/CSME before the next visit. The next visit can be scheduled in 9.5 years, with a 9.98% chance of reaching PDR/CSME within that time.



6. Model Fit Assessment

The proposed screening schedules are obtained using the distribution of the length of time until reaching the PDR/CSME condition which requires an intervention. These cumulative incidence functions are obtained by fitting a Markov model to the transitions among the retinopathy states. Therefore checking the Markov model assumptions and the model fit is important, and two approaches were investigated. The first approach compared the non-parametric (model-free) estimates and the Markov model estimates of the time to reaching the (absorbing) PDR/CSME state, while the second approach considered whether a more general semi-Markov model provides a better fit than the Markov model assuming exponentially distributed transition times.

It is important to note that in our application, subjects can move up and down among the states (i.e. progress and regress), and that the retinopathy state for a patient is only known at the time of a visit (i.e., panel data). In other words, the exact time when a patient transitions from one retinopathy state to another is unknown, and more important, not all transitions may have actually been observed.

For example, suppose a patient is in the no retinopathy state 1 at the first visit, and, one year later, at the second visit, the patient is in the mild NPDR state 2. It follows that the transition occurred within the first year, so that the sojourn time (i.e., the length of time spent in one state before moving to a different state) for the no retinopathy state is interval censored (all we know is that it is between 0 and 1 years). Now further assume the same subject is in the moderate NPDR state 3 at the third visit, after an additional 3 years, i.e. at 4 years. The question is what is a reasonable estimate for the sojourn time for the mild retinopathy state using this information? It seems that the upper bound is 4 years, and the lower bound is 1 year. However, it is not that simple. Consider the case when the subject was in the mild NPDR state at visit 3, the same as the state at visit 2. It might have happened that the patient remained in state 2 between visits 2 and 3, or that the patient moved from state 2 to state 3 (or state 1) and then back to state 2. Thus, it is not feasible to model sojourn times per-se.

Therefore, it is not possible to estimate non-parametrically the distribution of the transition times among transient states. However, estimation of the time to reaching the absorbing state (PDR/CSME) is feasible. To assess the Markov model fit, we compared the non-parametric estimates of the time to PDR/CSME to the cumulative incidence functions obtained using the Markov model fit.

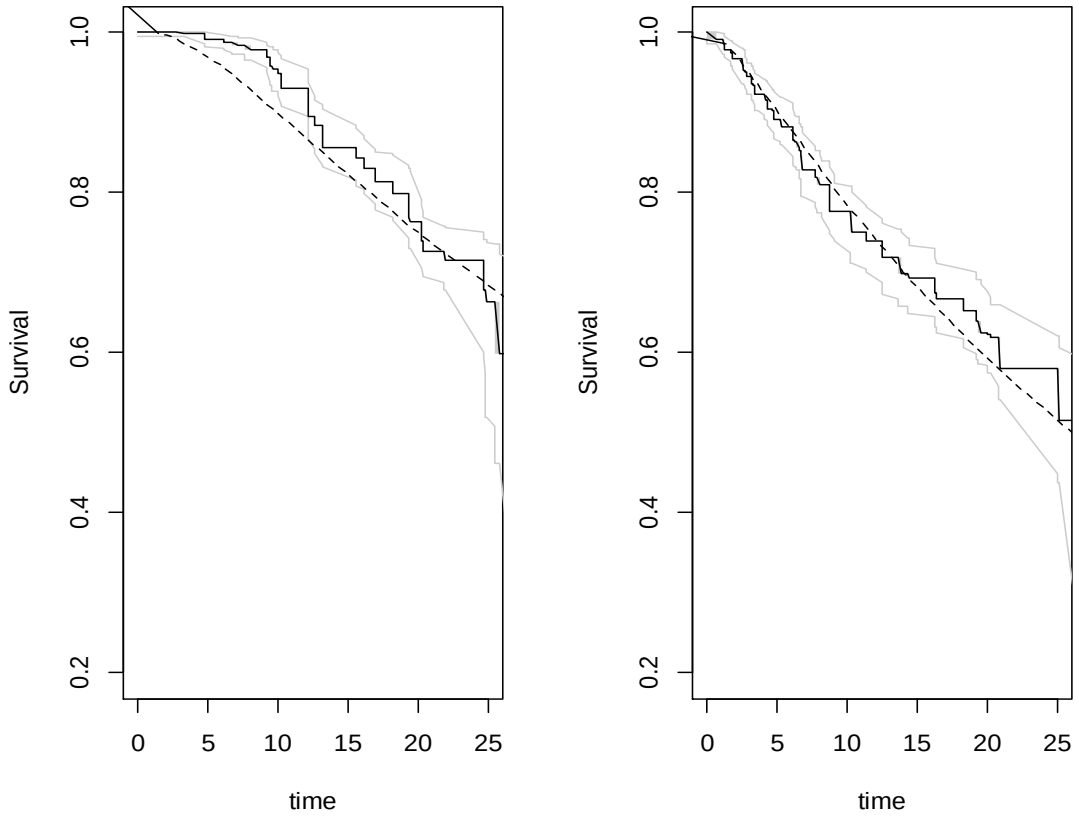
More specifically, we considered the subjects who started in the no retinopathy state at baseline, and estimated the time to reaching the PDR/CSME absorbing state. Since time from no retinopathy to PDR/CSME is a mixture of exponentially distributed transition times, it does not have a simple exponential distribution. However, this time (no retinopathy to PDR/CSME) will be interval-censored for a subject who reached the absorbing state during the follow-up and right-censored for a subject who did not. Therefore the Turnbull non-parametric MLE of the cumulative incidence function for interval censored data can be constructed for the time to reaching the absorbing state when starting from the no retinopathy state.

The same approach can be used to calculate the Turnbull NPMLE for the time from Mild retinopathy at baseline to PDR/CSME.

An important remark is in order. As explained in the Methods section, DCCT enrolled subjects in two cohorts: the primary prevention cohort and the secondary intervention

cohort. Inclusion criteria included no retinopathy for patients in the primary prevention cohort and very mild to moderate NPDR in the secondary intervention cohort. Therefore, at least initially, the estimated cumulative incidence in the combined DCCT cohort may underestimate the incidence of PDR/CSME, and potentially more so in the primary prevention cohort. Moreover, since one of the inclusion criteria for the primary prevention cohort was no retinopathy at baseline, the results are presented separately by cohort (primary vs. secondary).

The figure below depicts the Turnbull estimates (black solid line) and 95% pointwise confidence intervals (grey solid lines) and the model based survival curves (dashed lines) for time from no retinopathy to PDR/CSME in the primary prevention cohort (left panel) and for the time from Mild retinopathy to PDR/CSME in the secondary intervention cohort (right panel).



There is good agreement between the model estimates and the Turnbull estimates, and if anything, the model based predictions yield conservative guidelines.

We then investigated whether a semi-Markov model would provide a better fit. Semi-Markov models allow the transition time to depend on the time since entry in the current state. With the exception of some simpler models, such as progressive models when a subject can only move to a more severe state, the computation of the likelihood becomes very difficult. This applies to our case since subjects are allowed to transition to both

more and less severe retinopathy states, and we deal with a relatively large number of states (K=5).

In this situation it is more feasible to consider phase-type distributions for the sojourn times. Briefly, each state is assumed to be governed by several latent progressive states (i.e., no returns are allowed among the latent states). This approach can be modeled using a hidden Markov model, please see Titman and Sharples (*Biometrics*, 2010, 66(3), 742-752) for details.

We investigated this approach for our data. We were only able to fit a model with a phase-type distribution with two latent states for the sojourn time distribution for the no retinopathy state. The other models did not converge, which might suggest there was not enough information to support the semi-Markov assumption.

The Markov model and the semi-Markov model provided virtually identical results. The Akaike information criterion was 30119.94 (with 8 df) for the Markov model and 30118 (with 10 df) for the semi-Markov model. The cumulative incidence functions for the time to the PDR/CSME state when starting from the no retinopathy state for the two models are presented below (the cumulative incidence functions when starting from the other states are the same in the two models), and they are virtually identical.

Time (years)	**Markov Model**	**Semi-Markov Model**	
		Phase 1	**Phase 2**
1	0.00096 (0.00084,0.00109)	0.00086 (0.00073,0.00112)	0.00096 (0.00085,0.00110)
2	0.00594 (0.00531,0.00667)	0.00568 (0.00505,0.00678)	0.00599 (0.00538,0.00674)
3	0.01556 (0.01416,0.01724)	0.01517 (0.01364,0.01743)	0.01566 (0.01417,0.01745)
4	0.02892 (0.02635,0.03189)	0.02844 (0.02579,0.03187)	0.02907 (0.02642,0.03219)
5	0.04486 (0.04089,0.04923)	0.04434 (0.04048,0.04894)	0.04506 (0.04112,0.04933)

To summarize, the proposed screening schedules are based on estimates of the cumulative incidence functions for the time to reaching the PDR/CSME retinopathy state, which requires intervention. These incidence functions were obtained by fitting a Markov model to the observed transitions over time among the retinopathy states (panel data). The model-based cumulative incidence functions were found to adequately reflect the observed data by directly comparing them to their non-parametric estimates. Moreover, the Markov model assumption proved robust with respect to an alternative, more general, semi-Markov model.

7. Supplemental Tables and Figures

Table S1. Observed number of transitions of the retinopathy status from one visit to the next visit*.

From \To	None	MiNPDR	MoNPDR	SNPDR	PDR/CSME
1 No DR	4898	1823	9	1	3
2 Mild NPDR	1216	11510	854	17	227
3 Mod. NPDR	3	505	1076	56	238
4 Severe NPDR	0	4	33	11	36

*There were 23961 retinopathy assessment visits in the 1441 patients over the period 1983 – 2011. No further transitions were possible for the 504 subjects who reached PDR/CSME.

Table S2. Model estimated probability of the next transition if and when a subject transitions from the current state at an examination, and the estimated sojourn time while in each state (other than the final absorbing state PDR/CSME).

From \ To	None	MiNPDR	MoNPDR	SNPDR	PDR/CSME
1 No DR	--	1.0	--	--	--
2 Mild NPDR	0.599	--	0.401	--	--
3 Mod. NPDR	--	0.589	--	0.188	0.223
4 Severe NPDR	--	--	0.710	--	0.290
5 PDR/CSME	NA	NA	NA	NA	0
Sojourn Time (years)	1.867	4.066	1.629	0.389	--

Table S3. Model-estimated transition probabilities over a 1, 2 or 3 year period.

1 Year

From \ To:	None	MiNPDR	MoNPDR	SNPDR	PDR/CSME
1 No DR	0.611	0.371	0.017	0.0004	0.001
2 Mild NPDR	0.102	0.823	0.067	0.002	0.006
3 Mod. NPDR	0.017	0.246	0.586	0.029	0.123
4 Severe NPDR	0.007	0.122	0.453	0.094	0.325
5 PDR/CSME	NA	NA	NA	NA	1

2 Years

From \ To:	None	MiNPDR	MoNPDR	SNPDR	PDR/CSME
1 No DR	0.411	0.536	0.045	0.002	0.006
2 Mild NPDR	0.147	0.732	0.097	0.004	0.020
3 Mod. NPDR	0.046	0.357	0.373	0.020	0.205
4 Severe NPDR	0.025	0.225	0.316	0.022	0.412
5 PDR/CSME	NA	NA	NA	NA	1

3 Years

From \ To:	None	MiNPDR	MoNPDR	SNPDR	PDR/CSME
1 No DR	0.307	0.605	0.070	0.003	0.016
2 Mild NPDR	0.166	0.681	0.110	0.005	0.037
3 Mod. NPDR	0.071	0.405	0.252	0.013	0.259
4 Severe NPDR	0.044	0.275	0.211	0.012	0.459
5 PDR/CSME	NA	NA	NA	NA	1

Table S4. Unadjusted univariate models to assess each covariate effect individually on the risk of transitions. Time-dependent covariates included current smoking, hypertension and hyperlipidemia status (yes versus no), and current age, diabetes duration and BMI.

Current HbA1c

	HR	L	U
State 1 - State 2	1.1145	1.0841	1.1458
State 2 - State 3	1.3020	1.2538	1.3522
State 3 - State 4	1.3536	1.1137	1.6451
State 3 - State 5	1.1724	1.0142	1.3553
State 4 - State 5	1.3276	0.9362	1.8825
State 2 - State 1	0.9569	0.9167	0.9989
State 3 - State 2	0.8837	0.8267	0.9447
State 4 - State 3	0.8444	0.6670	1.0690

Treatment Group (Conventional versus Intensive)

	HR	L	U
State 1 - State 2	1.1909	1.0779	1.3158
State 2 - State 3	1.7203	1.4925	1.9829
State 3 - State 4	1.5987	0.5165	4.9480
State 3 - State 5	0.7381	0.5515	0.9880
State 4 - State 5	1.4543	0.2664	7.9369
State 2 - State 1	0.8196	0.7209	0.9319
State 3 - State 2	0.8550	0.6999	1.0445
State 4 - State 3	0.6599	0.1546	2.8162

Current Age (years)

	HR	L	U
State 1 - State 2	0.9716	0.9665	0.9767
State 2 - State 3	0.9651	0.9583	0.9719
State 3 - State 4	0.9852	0.9338	1.0394
State 3 - State 5	1.0015	0.9854	1.0179
State 4 - State 5	1.0294	0.9388	1.1289
State 2 - State 1	0.9377	0.9312	0.9443
State 3 - State 2	0.9296	0.9189	0.9405
State 4 - State 3	1.0785	1.0105	1.1511

Gender (Male versus Female)

	HR	L	U
State 1 - State 2	0.9793	0.8860	1.0825
State 2 - State 3	1.0433	0.9053	1.2022
State 3 - State 4	0.6670	0.3312	1.3430
State 3 - State 5	0.8034	0.6048	1.0671
State 4 - State 5	1.0226	0.3745	2.7923
State 2 - State 1	0.8678	0.7642	0.9854
State 3 - State 2	0.5995	0.4911	0.7319
State 4 - State 3	0.6576	0.2850	1.5173

Current Smoking (yes versus no)

	HR	L	U
State 1 - State 2	1.0791	0.9266	1.2566
State 2 - State 3	1.0912	0.9165	1.2993
State 3 - State 4	1.0385	0.4313	2.5004
State 3 - State 5	1.1066	0.8453	1.4486
State 4 - State 5	0.7039	0.2224	2.2276
State 2 - State 1	0.8498	0.6795	1.0627
State 3 - State 2	0.8122	0.5919	1.1144
State 4 - State 3	0.5642	0.1856	1.7152

Current BMI (kg/m^2)

	HR	L	U
State 1 - State 2	1.0028	0.9883	1.0174
State 2 - State 3	0.9693	0.9537	0.9851
State 3 - State 4	0.8523	0.7788	0.9326
State 3 - State 5	1.0103	0.9707	1.0514
State 4 - State 5	0.8589	0.7583	0.9728
State 2 - State 1	0.9065	0.8890	0.9244
State 3 - State 2	0.8940	0.8706	0.9180
State 4 - State 3	0.9304	0.8483	1.0203

Duration of diabetes at baseline (per 1 month)

	HR	L	U
State 1 - State 2	1.0074	1.0055	1.0094
State 2 - State 3	1.0099	1.0086	1.0113
State 3 - State 4	1.0033	0.9960	1.0106
State 3 - State 5	0.9982	0.9955	1.0009
State 4 - State 5	1.0030	0.9927	1.0134
State 2 - State 1	0.9864	0.9844	0.9885
State 3 - State 2	1.0101	1.0082	1.0120
State 4 - State 3	1.0035	0.9947	1.0124

Current duration of diabetes (per 1 year)

	HR	L	U
State 1 - State 2	0.9628	0.9544	0.9714
State 2 - State 3	0.9791	0.9692	0.9891
State 3 - State 4	0.9619	0.8897	1.0400
State 3 - State 5	0.9599	0.9364	0.9840
State 4 - State 5	0.9386	0.8164	1.0791
State 2 - State 1	0.7760	0.7645	0.7876
State 3 - State 2	0.8774	0.8603	0.8948
State 4 - State 3	1.0521	0.9271	1.1939

Current Hypertension (≥140/90 mmHg or medication use) versus not

	HR	L	U
State 1 - State 2	0.4884	0.3813	0.6256
State 2 - State 3	0.7540	0.6238	0.9114
State 3 - State 4	1.4769	0.0001	17424.48
State 3 - State 5	0.9236	0.3101	2.7507
State 4 - State 5	0.7343	0.0111	48.6097
State 2 - State 1	0.2798	0.2176	0.3598
State 3 - State 2	0.4110	0.3211	0.5262
State 4 - State 3	2.0245	0	119849.6

Current Hyperlipidemia (≥130 mg/dL or medication) versus not

	HR	L	U
State 1 - State 2	0.7834	0.6799	0.9027
State 2 - State 3	0.9826	0.8420	1.1466
State 3 - State 4	0.6776	0.2755	1.6669
State 3 - State 5	1.1539	0.8707	1.5292
State 4 - State 5	1.0752	0.2901	3.9851
State 2 - State 1	0.6009	0.5053	0.7145
State 3 - State 2	0.5733	0.4533	0.7249
State 4 - State 3	1.1839	0.4233	3.3109

Table S5. Cumulative incidence of PDR/CSME (PDR) as a function of the initial (current) level of retinopathy: none, mild NPDR (MINPDR), moderate NPDR (MONPDR) and severe NPDR (SNPDR) in the overall cohort and then stratified by other covariates.

Overall (as in Table 1 of the manuscript)

Time (years)	None to PDR	MINPDR to PDR	MONPDR to PDR	SNPDR to PDR
0.0833	0	0	0.0114	0.0566
0.1667	0	0.0002	0.0228	0.1039
0.25	0	0.0004	0.0340	0.1436
0.50	0.0001	0.0016	0.0661	0.2302
0.75	0.0004	0.0035	0.0957	0.2862
1	0.0010	0.0059	0.1225	0.3251
2	0.0059	0.0197	0.2049	0.4119
3	0.0156	0.0374	0.2592	0.4591
4	0.0289	0.0566	0.2969	0.4903
5	0.0448	0.0764	0.3248	0.5127

Mean HbA1c

HbA1c	Time (years)	None to PDR	MINPDR to PDR	MONPDR to PDR	SNPDR to PDR
6%	0.0833	0	0	0.0083	0.0122
	0.1667	0	0.0001	0.0162	0.0230
	0.25	0	0.0001	0.0235	0.0327
	0.50	0	0.0005	0.0432	0.0569
	0.75	0.0001	0.0011	0.0595	0.0762
	1	0.0002	0.0019	0.0733	0.0920
	2	0.0014	0.0057	0.1097	0.1333
	3	0.0037	0.0102	0.1290	0.1547
	4	0.0067	0.0148	0.1403	0.1669
	5	0.0102	0.0194	0.1477	0.1748
8%	0.0833	0	0	0.0102	0.0307
	0.1667	0	0.0002	0.0202	0.0564
	0.25	0	0.0003	0.0298	0.0782
	0.50	0.0001	0.0013	0.0567	0.1274
	0.75	0.0004	0.0028	0.0807	0.1618
	1	0.0008	0.0047	0.1022	0.1882
	2	0.0048	0.0155	0.1670	0.2580
	3	0.0123	0.0291	0.2094	0.3008
	4	0.0227	0.0439	0.2390	0.3298
	5	0.0351	0.0591	0.2611	0.3509

10%	0.0833	0	0.0001	0.0129	0.0784
	0.1667	0	0.0004	0.0263	0.1429
	0.25	0	0.0009	0.0401	0.1962
	0.50	0.0004	0.0034	0.0815	0.3094
	0.75	0.0012	0.0075	0.1216	0.3798
	1	0.0027	0.0131	0.1590	0.4274
	2	0.0168	0.0454	0.2800	0.5335
	3	0.0434	0.0872	0.3652	0.5946
	4	0.0791	0.1328	0.4279	0.6378
	5	0.1202	0.1792	0.4766	0.6705

Current HbA1c

Current HbA1c	Time (years)	None to PDR	MINPDR to PDR	MONPDR to PDR	SNPDR to PDR
6%	0.0833	0	0	0.0071	0.0252
	0.1667	0	0.0001	0.0140	0.0459
	0.25	0	0.0001	0.0206	0.0633
	0.50	0	0.0005	0.0389	0.1014
	0.75	0.0001	0.0011	0.0550	0.1269
	1	0.0002	0.0018	0.0693	0.1459
	2	0.0015	0.0060	0.1113	0.1936
	3	0.0040	0.0111	0.1375	0.2212
	4	0.0075	0.0168	0.1545	0.2388
	5	0.0117	0.0226	0.1665	0.2508
8%	0.0833	0	0	0.0099	0.0448
	0.1667	0	0.0001	0.0196	0.0822
	0.25	0	0.0003	0.0291	0.1139
	0.50	0.0001	0.0012	0.0563	0.1835
	0.75	0.0003	0.0026	0.0812	0.2294
	1	0.0007	0.0045	0.1037	0.2621
	2	0.0045	0.0151	0.1736	0.3385
	3	0.0118	0.0288	0.2204	0.3821
	4	0.0220	0.0438	0.2532	0.4116
	5	0.0344	0.0594	0.2778	0.4330

10%	0.0833	0	0.0001	0.0139	0.0787
	0.1667	0	0.0003	0.0280	0.1443
	0.25	0	0.0008	0.0423	0.1991
	0.50	0.0003	0.0030	0.0846	0.3177
	0.75	0.0010	0.0067	0.1247	0.3926
	1	0.0022	0.0115	0.1618	0.4432
	2	0.0135	0.0392	0.2792	0.5509
	3	0.0350	0.0746	0.3591	0.6081
	4	0.0641	0.1130	0.4159	0.6467
	5	0.0979	0.1521	0.459	0.6749

DCCT Treatment Group

Group	Time (years)	None to PDR	MINPDR to PDR	MONPDR to PDR	SNPDR to PDR
Standard	0.0833	0	0.0001	0.0081	0.0920
	0.1667	0	0.0003	0.0174	0.1682
	0.25	0	0.0007	0.0274	0.2316
	0.5	0.0003	0.0030	0.0603	0.3664
	0.75	0.0010	0.0069	0.0942	0.4482
	1	0.0024	0.0123	0.1270	0.5008
	2	0.0160	0.0450	0.2370	0.6006
	3	0.0426	0.0880	0.3164	0.6491
	4	0.0787	0.1347	0.3763	0.6826
	5	0.1204	0.1820	0.4242	0.7085
Intensive	0.0833	0	0.0001	0.0102	0.0631
	0.1667	0	0.0002	0.0205	0.1154
	0.25	0	0.0005	0.0309	0.1588
	0.5	0.0002	0.0019	0.0615	0.2519
	0.75	0.0006	0.0042	0.0904	0.3102
	1	0.0013	0.0072	0.1169	0.3496
	2	0.0079	0.0245	0.2008	0.4351
	3	0.0207	0.0468	0.2582	0.482
	4	0.0383	0.0713	0.2996	0.5142
	5	0.0592	0.0965	0.3315	0.5382

Sex

Sex	Time (years)	None to PDR	MINPDR to PDR	MONPDR to PDR	SNPDR to PDR
Male	0.0833	0	0	0.0105	0.0569
	0.1667	0	0.0002	0.0210	0.1055
	0.25	0	0.0004	0.0314	0.1471
	0.50	0.0001	0.0015	0.0616	0.2407
	0.75	0.0004	0.0033	0.0899	0.3029
	1	0.0009	0.0057	0.1162	0.3465
	2	0.0058	0.0197	0.2006	0.4410
	3	0.0155	0.0380	0.2597	0.4909
	4	0.0293	0.0584	0.3024	0.5244
	5	0.0461	0.0797	0.3348	0.5491
Female	0.0833	0	0.0001	0.0130	0.0547
	0.1667	0	0.0002	0.0257	0.0995
	0.25	0	0.0005	0.0380	0.1367
	0.50	0.0002	0.0018	0.0727	0.2165
	0.75	0.0005	0.0038	0.1034	0.2675
	1	0.0011	0.0064	0.1302	0.3032
	2	0.0063	0.0204	0.2067	0.3837
	3	0.0160	0.0374	0.2522	0.4257
	4	0.0291	0.0554	0.2820	0.4518
	5	0.0442	0.0734	0.3038	0.4701

Age (current)

Age	Time (years)	None to PDR	MINPDR to PDR	MONPDR to PDR	SNPDR to PDR
20 y	0.0833	0	0.0001	0.0111	0.0390
	0.1667	0	0.0003	0.0216	0.0751
	0.25	0	0.0006	0.0315	0.1084
	0.5	0.0002	0.0022	0.0579	0.1937
	0.75	0.0007	0.0046	0.0803	0.2607
	1	0.0015	0.0075	0.0994	0.3133
	2	0.0083	0.0222	0.1525	0.4344
	3	0.0194	0.0390	0.1850	0.4840
	4	0.0334	0.0564	0.2081	0.5084
	5	0.0491	0.0740	0.2267	0.5238
40 y	0.0833	0	0	0.0119	0.0632
	0.1667	0	0.0002	0.0238	0.1113
	0.25	0	0.0003	0.0357	0.1484
	0.5	0.0001	0.0013	0.0700	0.2203
	0.75	0.0003	0.0029	0.1021	0.2625
	1	0.0006	0.0049	0.1317	0.2929
	2	0.0038	0.0171	0.2282	0.3780
	3	0.0103	0.0333	0.2994	0.4389
	4	0.0199	0.0518	0.3542	0.4856
	5	0.0320	0.0715	0.3976	0.5226
60 y	0.0833	0	0	0.0124	0.0776
	0.1667	0	0.0001	0.0247	0.1069
	0.25	0	0.0002	0.0370	0.1228
	0.5	0	0.0007	0.0726	0.1570
	0.75	0.0001	0.0015	0.1064	0.1879
	1	0.0002	0.0026	0.1386	0.2173
	2	0.0013	0.0095	0.2524	0.3215
	3	0.0036	0.0194	0.3466	0.4079
	4	0.0075	0.0315	0.4250	0.4800
	5	0.0127	0.0450	0.4907	0.5408

Hypertension

Status	Time (years)	None to PDR	MINPDR to PDR	MONPDR to PDR	SNPDR to PDR
Yes	0.0833	0	0	0.0115	0.0277
	0.1667	0	0.0001	0.0228	0.0532
	0.25	0	0.0003	0.0339	0.0768
	0.50	0	0.0013	0.0660	0.1376
	0.75	0.0002	0.0028	0.0962	0.1869
	1	0.0004	0.0049	0.1246	0.2279
	2	0.0025	0.0175	0.2220	0.3433
	3	0.0075	0.0353	0.2978	0.4190
	4	0.0154	0.0564	0.3573	0.4748
	5	0.0264	0.0796	0.4049	0.5182
No	0.0833	0	0	0.0116	0.0622
	0.1667	0	0.0002	0.0231	0.1140
	0.25	0	0.0004	0.0344	0.1572
	0.50	0.0001	0.0017	0.0666	0.2503
	0.75	0.0005	0.0036	0.0957	0.3091
	1	0.0010	0.0061	0.1216	0.3487
	2	0.0062	0.0201	0.1979	0.4315
	3	0.0160	0.0373	0.2451	0.4723
	4	0.0291	0.0556	0.2766	0.4979
	5	0.0445	0.0742	0.2998	0.5158

Hyperlipidemia

Status	Time (years)	None to PDR	MINPDR to PDR	MONPDR to PDR	SNPDR to PDR
Yes	0.0833	0	0.0001	0.0127	0.0555
	0.1667	0	0.0002	0.0253	0.1017
	0.25	0	0.0005	0.0376	0.1405
	0.50	0.0001	0.0017	0.0732	0.2253
	0.75	0.0004	0.0038	0.1061	0.2808
	1	0.0009	0.0065	0.1364	0.3204
	2	0.0056	0.0223	0.2339	0.4159
	3	0.0153	0.0432	0.3028	0.4744
	4	0.0294	0.0666	0.3530	0.5159
	5	0.0471	0.0912	0.3912	0.5468
No	0.0833	0	0	0.0110	0.0522
	0.1667	0	0.0002	0.0219	0.0965
	0.25	0	0.0004	0.0326	0.1343
	0.50	0.0001	0.0015	0.0632	0.2193
	0.75	0.0004	0.0033	0.0911	0.2758
	1	0.0009	0.0056	0.1161	0.3156
	2	0.0057	0.0185	0.1919	0.4027
	3	0.0148	0.0347	0.2403	0.4471
	4	0.0273	0.0522	0.2733	0.4752
	5	0.0420	0.0701	0.2975	0.4950

Duration of Diabetes

Duration	Time (years)	None to PDR	MINPDR to PDR	MONPDR to PDR	SNPDR to PDR
5 years	0.0833	0	0.0001	0.0190	0.1198
	0.1667	0	0.0004	0.0362	0.2180
	0.25	0	0.0008	0.0520	0.2987
	0.50	0.0003	0.0027	0.0906	0.4657
	0.75	0.0008	0.0053	0.1189	0.5609
	1	0.0016	0.0084	0.1398	0.6165
	2	0.0076	0.0214	0.1824	0.6919
	3	0.0172	0.0353	0.2027	0.7092
	4	0.0291	0.0499	0.2177	0.7180
	5	0.0430	0.0654	0.2315	0.7253

Duration	Time (years)	None to PDR	MINPDR to PDR	MONPDR to PDR	SNPDR to PDR
10 years	0.0833	0	0.0001	0.0158	0.0881
	0.1667	0	0.0003	0.0310	0.1618
	0.25	0	0.0006	0.0454	0.2236
	0.50	0.0002	0.0023	0.0843	0.3571
	0.75	0.0006	0.0049	0.1168	0.4391
	1	0.0012	0.0081	0.1438	0.4915
	2	0.0069	0.0244	0.2132	0.5816
	3	0.0171	0.0437	0.2527	0.6151
	4	0.0306	0.0642	0.2806	0.6357
	5	0.0467	0.0854	0.3036	0.6519
20 years	0.0833	0	0	0.0107	0.0468
	0.1667	0	0.0002	0.0213	0.0859
	0.25	0	0.0004	0.0317	0.1189
	0.50	0.0001	0.0014	0.0619	0.1922
	0.75	0.0002	0.0030	0.0901	0.2406
	1	0.0005	0.0052	0.1161	0.2755
	2	0.0035	0.0181	0.2025	0.3633
	3	0.0096	0.0356	0.2677	0.4219
	4	0.0186	0.0557	0.3198	0.4683
	5	0.0301	0.0774	0.3634	0.5073
30 years	0.0833	0	0	0.0071	0.0243
	0.1667	0	0.0001	0.0142	0.0439
	0.25	0	0.0002	0.0212	0.0601
	0.50	0	0.0008	0.0419	0.0957
	0.75	0.0001	0.0017	0.0618	0.1208
	1	0.0002	0.0029	0.0809	0.1414
	2	0.0014	0.0106	0.1507	0.2092
	3	0.0041	0.0217	0.2104	0.2664
	4	0.0084	0.0352	0.2626	0.3165
	5	0.0141	0.0503	0.3089	0.3611