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Appendix A. HbA_{1c} Transition Probability Matrix Estimation

To estimate the 3-month HbA_{1c} transition probabilities, we selected all pairs of HbA_{1c} records from the 37,501 eligible patients such that the period between tests was between 2.5 and 3.5 months and the patient was not on insulin during that time period. This resulted in 30,249 pairs (multiple pairs permitted per patient). Using the observed HbA_{1c} value, $h_{i,t}$, of patient i at time epoch t, the corresponding natural HbA_{1c} value (without medication), $h^n_{i,t}$, was estimated as:

$$h^n_{i,t} = h_{i,t}\frac{1}{1-\omega(m_{i,t})}, \quad \forall i,t$$

Where $m_{i,t}$ denotes patient i's current treatment regimen and $\omega(m_{i,t})$ is the estimated relative reduction in HbA_{1c} when patient i is using treatment regimen $m_{i,t}$ at time period t (**Table 1**). We discretized all natural HbA_{1c} values into 10 HbA_{1c} states as defined in **Supplement Table s1** and **Supplement Table s2**. For any two HbA_{1c} states, a and b, we denoted the total number of transitions from state a to state b as n_{ab}. The maximum likelihood estimate of the transition probability from state a to state b was estimated as:

$$q_a(b) = \frac{n_{ab}}{\sum_{b\in\mathcal{L}} n_{ab}}, \quad \forall a \in \mathcal{L}$$

where $\mathcal{L}$ is the set of HbA_{1c} states.

Appendix B. Treatment Effect Estimation

Five classes of glucose-lowering medications were considered: metformin, sulfonylurea, DPP-IV inhibitor, GLP-1 agonist, and insulin. We assumed that once insulin was initiated, HbA_{1c} would be maintained at a predefined level (it is set to be 7% in our numerical experiments). We also assumed that medications other than insulin had additive effect in reducing HbA_{1c} (1); therefore, each medication effect was estimated independently.

For each medication other than insulin, we selected patients who had at least one HbA_{1c} record within 3 months before and after its initiation, and who were treated with this medication for at least 3 consecutive months. For each selected patient, we calculated the pre-treatment HbA_{1c} and the post-treatment HbA_{1c} by taking the mean of his/her HbA_{1c} records during the 3-month intervals before and after the date of initiation, respectively. The medication effect shown in **Table 1** was then calculated as the overall mean relative change between the pre-treatment HbA_{1c} and the post-treatment HbA_{1c} of all the selected patients.

Appendix C. Model Calibration and Validation

To calibrate and validate the model we used all HbA_{1c} pairs of the eligible 37,501 patients such that the period between HbA_{1c} tests was greater than or equal to 3.5 months (in order to have at least one 3-month transition) and the patient was not on insulin during that time period. This resulted in 97,667 pairs.

For each value of the linear trend factor, β, between 0 and 0.25, and for each initial test result in each pair, we simulated the second test result in the pair 100 times using the 3-month HbA_{1c} transition probability matrix (**Supplement Table s1** and **Supplement Table s2**) and the number of transitions, t_k, determined by the time interval between the two HbA_{1c} tests of each pair k. Using the model-generated natural HbA_{1c} state, $\theta^k(t_k)$, for each pair k, we calculated the model-generated HbA_{1c} value, $h_{k,t_k}(\theta^k(t_k))$ with medications initiated during the time interval as follows:

$$h_{k,t_k}(\theta^k(t_k)) = h^n\left(\theta^k(t_k)\right) + \beta \times t_k - \omega(m_{k,t_k}) \times h^n\left(\theta^k(t_k)\right),$$

where $h^n\left(\theta^k(t_k)\right)$ is the mean natural HbA_{1c} value of being in the HbA_{1c} state $\theta^k(t_k) \in \mathcal{L}$ at diagnosis (**Supplement Table s1** and **Supplement Table s2**) and $\omega(m_{k,t_k})$ is the medication effect of using medications

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m_{k,e_R}. Finally, we determined the model-generated HbA_{1c} state for that pair based on the model-generated HbA_{1c} value.

Given the 100 model-generated 97,667 HbA_{1c} pairs, we calculated the mean of the sum of the squared errors (SSE) between the model-generated HbA_{1c} state distribution and the observed HbA_{1c} state distribution as:

$$F(\beta) = \frac{\sum_{i=1}^{n} (\pi - p^i(\beta))^T (\pi - p^i(\beta))}{n}$$

where $\pi = (\pi(e_1), \pi(e_2), \ldots, \pi(e_{10}))$ represents the observed HbA_{1c} state probability distribution (based on the second HbA_{1c} values in all pairs) and the vector $p^i(\beta)$ represents the model-generated HbA_{1c} state probability distribution for the i^{th} simulation with a fixed linear trend value β. The best linear trend was selected as the one that minimizes the mean of the SSE.

We found that the optimal trend factor was 0.1075 for men (mean SSE of 0.0022) and 0.105 for women (mean SSE of 0.0015) with the median difference between the observed HbA_{1c} distribution and the simulated HbA_{1c} distribution of 0.0096 (minimum: 0.0027, maximum 0.0271) for men and 0.0055 (minimum: 0.0000, maximum: 0.0197) for women.

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Supplementary Table 1. Glycosylated hemoglobin (HbA_{1c}) used in the Markov model for women. HbA_{1c} range definition at diagnosis, the mean natural HbA_{1c} values for each HbA_{1c} state at diagnosis (prior to initiating medication), the initial HbA_{1c} distributions at diagnosis, and 3-month HbA_{1c} transition probability matrices for men and women.

		HbA_{1c} State									
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
HbA_{1c} Range		<6	[6,6.5)	[6.5,7)	[7,7.5)	[7.5,8)	[8,8.5)	[8.5,9)	[9,9.5)	[9.5,10)	≥10
Mean HbA_{1c} value (%)		5.70	6.25	6.74	7.24	7.73	8.23	8.73	9.22	9.72	11.73
Initial HbA_{1c} Distribution		0.0771	0.1543	0.2125	0.1800	0.1105	0.0848	0.0502	0.0350	0.0273	0.0683
Transition Probability Matrix	**HbA_{1c} state 1**	0.6379	0.3042	0.0481	0.0088	0.0010	0.0000	0.0000	0.0000	0.0000	0.0000
	HbA_{1c} state 2	0.1717	0.5086	0.2692	0.0412	0.0064	0.0020	0.0000	0.0000	0.0000	0.0010
	HbA_{1c} state 3	0.0299	0.1731	0.5214	0.2258	0.0374	0.0085	0.0018	0.0004	0.0011	0.0007
	HbA_{1c} state 4	0.0114	0.0538	0.2830	0.4167	0.1716	0.0446	0.0114	0.0029	0.0021	0.0025
	HbA_{1c} state 5	0.0048	0.0240	0.1055	0.2740	0.3329	0.1678	0.0568	0.0199	0.0055	0.0089
	HbA_{1c} state 6	0.0045	0.0116	0.0491	0.1438	0.2482	0.2768	0.1598	0.0661	0.0268	0.0134
	HbA_{1c} state 7	0.0015	0.0120	0.0316	0.0648	0.1687	0.2364	0.2184	0.1370	0.0768	0.0527
	HbA_{1c} state 8	0.0043	0.0065	0.0281	0.0562	0.0864	0.1533	0.1879	0.1965	0.1555	0.1253
	HbA_{1c} state 9	0.0000	0.0166	0.0194	0.0332	0.0831	0.1357	0.1662	0.1717	0.1828	0.1911
	HbA_{1c} state 10	0.0078	0.0111	0.0277	0.0532	0.0831	0.0920	0.0854	0.0976	0.1042	0.4379

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Supplementary Table 2. Glycosylated hemoglobin (HbA_{1c}) used in the Markov model for men. HbA_{1c} range definition at diagnosis, the mean natural HbA_{1c} values for each HbA_{1c} state at diagnosis (prior to initiating medication), the initial HbA_{1c} distributions at diagnosis, and 3-month HbA_{1c} transition probability matrices for men and women.

		HbA_{1c} State									
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
HbA_{1c} Range		<6	[6,6.5)	[6.5,7)	[7,7.5)	[7.5,8)	[8,8.5)	[8.5,9)	[9,9.5)	[9.5,10)	≥10
Mean HbA_{1c} value (%)		5.69	6.25	6.73	7.24	7.74	8.24	8.74	9.21	9.73	11.59
Initial HbA_{1c} Distribution		0.0694	0.1388	0.1968	0.1626	0.1138	0.0919	0.0619	0.0424	0.0328	0.0896
Transition Probability Matrix	**HbA_{1c} state 1**	0.6244	0.2885	0.0685	0.0093	0.0034	0.0025	0.0008	0.0008	0.0000	0.0017
	HbA_{1c} state 2	0.1574	0.4949	0.2953	0.0402	0.0072	0.0038	0.0004	0.0000	0.0004	0.0004
	HbA_{1c} state 3	0.0349	0.2061	0.4715	0.2279	0.0441	0.0078	0.0024	0.0012	0.0024	0.0018
	HbA_{1c} state 4	0.0130	0.0592	0.2462	0.4014	0.1971	0.0549	0.0166	0.0043	0.0029	0.0043
	HbA_{1c} state 5	0.0098	0.0237	0.1058	0.2606	0.3029	0.1852	0.0686	0.0243	0.0083	0.0108
	HbA_{1c} state 6	0.0058	0.0134	0.0645	0.1335	0.2313	0.2888	0.1514	0.0550	0.0294	0.0268
	HbA_{1c} state 7	0.0104	0.0142	0.0455	0.0796	0.1308	0.2284	0.2351	0.1422	0.0645	0.0493
	HbA_{1c} state 8	0.0111	0.0249	0.0456	0.0526	0.0982	0.1674	0.1840	0.1646	0.1328	0.1189
	HbA_{1c} state 9	0.0125	0.0233	0.0412	0.0376	0.0789	0.1057	0.1595	0.1792	0.1344	0.2276
	HbA_{1c} state 10	0.0098	0.0249	0.0537	0.0688	0.0629	0.0799	0.0911	0.0996	0.1134	0.3958

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