Supplementary Appendices for Dynamic Monitoring and Control of Irreversible Chronic Diseases with Application to Glaucoma

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Appendix A Optimization of the Final Period Disease Control Action

The value function in the last period is given by

$$V_N(\wp_N) = \min_{\beta_N}\{E\left[(\alpha_N - \alpha_{N-1})' A_N (\alpha_N - \alpha_{N-1})\right] + \beta_N{}' B_N \beta_N \\ + E\left[(\alpha_{N+1} - \alpha_N)' A_{N+1} (\alpha_{N+1} - \alpha_N)\right]\}. \tag{42}$$

Replacing $E\left[(\alpha_N - \alpha_{N-1})' A_N (\alpha_N - \alpha_{N-1})\right]$ and $E\left[(\alpha_{N+1} - \alpha_N)' A_{N+1} (\alpha_{N+1} - \alpha_N)\right]$ by their values given by Lemmas 3 and 4 in Appendix B respectively, and combining terms results in

$$V_N(\wp_N) = \left(\hat{\alpha}_{N|N} - \hat{\alpha}_{N-1|N}\right)' A_N \left(\hat{\alpha}_{N|N} - \hat{\alpha}_{N-1|N}\right) + \hat{\alpha}'_{N|N}\left((T_N - I)' A_{N+1} (T_N - I)\right)\hat{\alpha}_{N|N} \\ + tr\left[A_N\left(\hat{\Sigma}_{N|N} + \hat{\Sigma}_{N-1|N} - T_{N-1}\hat{\Sigma}_{N-1|N} - \hat{\Sigma}_{N-1|N} T_{N-1}{}'\right)\right] \\ + tr\left[A_{N+1}\left((T_N - I)\hat{\Sigma}_{N|N}(T_N - I)' + Q_N\right)\right] \\ + \min_{\beta_N}\{\beta_N{}'(G_N{}' A_{N+1} G_N + B_N)\beta_N + \beta_N{}'(G_N{}' A_{N+1}(T_N - I)\hat{\alpha}_{N|N}) \\ + (\hat{\alpha}'_{N|N}(T_N - I)' A_{N+1} G_N)\beta_N\}, \tag{43}$$

where tr represents the trace of the matrix. Let the minimization term in Eq. 43 be denoted by $\tilde{J}_N$. That is, let

$$\tilde{J}_N = \min_{\beta_N}\{\beta_N{}'(G_N{}' A_{N+1} G_N + B_N)\beta_N + \beta_N{}'(G_N{}' A_{N+1}(T_N - I)\hat{\alpha}_{N|N}) \\ + (\hat{\alpha}'_{N|N}(T_N - I)' A_{N+1} G_N)\beta_N\}. \tag{44}$$

This minimization can be performed by completion of squares as described in Lemma 5 in Appendix B. Eq.'s 45 - 48 give the optimum disease control β^*_N and the result of minimization $\tilde{J}_N$. The optimum disease control at time N is given by

$$\beta^*_N = -U_N \hat{\alpha}_{N|N}, \tag{45}$$

where the control law of last time period, U_N, is given by

$$U_N = \left(G_N{}' A_{N+1} G_N + B_N\right)^{-1} G_N{}' A_{N+1}(T_N - I), \tag{46}$$

and the result of minimization over β_N is given by

$$\tilde{J}_N = -\hat{\alpha}'_{N|N}\tilde{P}_{N+1}\hat{\alpha}_{N|N}, \tag{47}$$

where

$$\tilde{P}_{N+1} = (T_N - I)' A_{N+1} G_N (G_N' A_{N+1} G_N + B_N)^{-1} G_N' A_{N+1} (T_N - I). \tag{48}$$

Substitution of Eq. 47 into Eq. 43 yields

$$\begin{aligned} V_N(\wp_N) = {} & \left(\hat{\alpha}_{N|N} - \hat{\alpha}_{N-1|N}\right)' A_N \left(\hat{\alpha}_{N|N} - \hat{\alpha}_{N-1|N}\right) + \hat{\alpha}_{N|N}' \left((T_N - I)' A_{N+1} (T_N - I) - \tilde{P}_{N+1}\right) \hat{\alpha}_{N|N} \\ & + tr\left[A_N \left(\hat{\Sigma}_{N|N} + \hat{\Sigma}_{N-1|N} - T_{N-1} \hat{\Sigma}_{N-1|N} - \hat{\Sigma}_{N-1|N} T_{N-1}{}'\right)\right] \\ & + tr\left[A_{N+1} \left((T_N - I) \hat{\Sigma}_{N|N} (T_N - I)'\right)\right] + tr\left[A_{N+1} Q_N\right]. \end{aligned} \tag{49}$$

Defining P_N as follows,

$$P_N = (T_N - I)' A_{N+1} (T_N - I) - \tilde{P}_{N+1}, \tag{50}$$

and also replacing $tr\left[A_{N+1}\left((T_N - I)\hat{\Sigma}_{N|N}(T_N - I)'\right)\right]$ by its simpler form as identified in Lemma 6 in Appendix B, we can further simplify Eq. 49 as follows.

$$\begin{aligned} V_N(\wp_N) = {} & \left(\hat{\alpha}_{N|N} - \hat{\alpha}_{N-1|N}\right)' A_N \left(\hat{\alpha}_{N|N} - \hat{\alpha}_{N-1|N}\right) + tr\left[A_N \hat{\Sigma}_{N|N}\right] \\ & + \hat{\alpha}_{N|N}' P_N \hat{\alpha}_{N|N} + tr\left[P_N \hat{\Sigma}_{N|N}\right] + tr\left[A_N \left(\hat{\Sigma}_{N-1|N} - T_{N-1} \hat{\Sigma}_{N-1|N} - \hat{\Sigma}_{N-1|N} T_{N-1}{}'\right)\right] \\ & + tr\left[\tilde{P}_{N+1} \hat{\Sigma}_{N|N}\right] + tr\left[A_{N+1} Q_N\right]. \end{aligned} \tag{51}$$

Appendix B Lemmas

In the derivation of optimal control the following lemmas are needed.

Lemma 1. *For any symmetric $n*n$ matrix A, the following holds.*

$$E\left[x'Ay\right] = \bar{x}'A\bar{y} + tr\left[AV_{x,y}\right]. \tag{52}$$

Where

$$\bar{x} = E[x], \tag{53}$$

$$\bar{y} = E[y], \tag{54}$$

$$V_{x,y} = E\left[(x-\bar{x})(y-\bar{y})'\right]. \tag{55}$$

Proof of Lemma 1:

Proof. By writing the matrix operations in terms of summations we will have

$$x'Ay = \sum_{i=1}^{n}\sum_{j=1}^{n} x_i A_{ij} y_j. \tag{56}$$

Hence

$$E\left[x'Ay\right] = \sum_{i=1}^{n}\sum_{j=1}^{n} A_{ij} E[x_i y_j], \tag{57}$$

but

$$E[x_i y_j] = E[x_i]E[y_j] + E\left[\left(x_i - E[x_i]\right)\left(y_j - E[y_j]\right)\right] = \bar{x}_i \bar{y}_j + V_{x_i,y_j}. \tag{58}$$

When Eq. 58 is substituted in Eq. 57:

$$E\left[x'Ay\right] = \bar{x}'A\bar{y} + \sum_{i=1}^{n}\sum_{j=1}^{n} A_{ij} V_{x_i,y_j} = \bar{x}'A\bar{y} + tr\left[AV_{x,y}\right], \tag{59}$$

where $tr\left[M\right]$ stands for trace of M (i.e., sum of diagonal terms).

□

Lemma 2. *With information up to time t, we have the following covariance relations.*

$$Cov(\alpha_t, \alpha_{t+1}|\wp_t) = \hat{\Sigma}_{t|t}\mathrm{T}_t{}', \tag{60}$$

$$Cov(\alpha_{t+1}, \alpha_t|\wp_t) = \mathrm{T}_t\hat{\Sigma}_{t|t}, \tag{61}$$

$$Cov(\alpha_t, \alpha_{t-1}|\wp_t) = \mathrm{T}_{t-1}\hat{\Sigma}_{t-1|t}, \tag{62}$$

$$Cov(\alpha_{t-1}, \alpha_t|\wp_t) = \hat{\Sigma}_{t-1|t}\mathrm{T}_{t-1}{}'. \tag{63}$$

Proof of Lemma 2:

Proof. Before we start proving these equations note that

$$Cov\left(\alpha_t, \alpha_t|\wp_t\right) = E\left[\alpha_t\alpha_t{}'\right] - E\left[\alpha_t\right]E[\alpha_t]' \rightarrow E\left[\alpha_t\alpha_t{}'\right] = \hat{\Sigma}_{t|t} + \hat{\alpha}_{t|t}\hat{\alpha}'_{t|t}. \tag{64}$$

Therefore,

$$\begin{aligned} Cov(\alpha_t, \alpha_{t+1}|\wp_t) &= E\left[\alpha_t\alpha_{t+1}{}'\right] - E\left[\alpha_t\right]E[\alpha_{t+1}]' \\ &= E\left[\alpha_t(\mathrm{T}_t\alpha_t + G_t\beta_t + \eta_t)'\right] - E\left[\alpha_t\right]E[\mathrm{T}_t\alpha_t + G_t\beta_t + \eta_t]' \\ &= E\left[\alpha_t\alpha_t{}'\right]\mathrm{T}_t{}' + \hat{\alpha}_{t|t}\beta_t{}'G_t{}' - \hat{\alpha}_{t|t}\left(\hat{\alpha}'_{t|t}\mathrm{T}_t{}' + \beta_t{}'G_t{}'\right) \\ &= \left(\hat{\Sigma}_{t|t} + \hat{\alpha}_{t|t}\hat{\alpha}'_{t|t}\right)\mathrm{T}_t{}' - \hat{\alpha}_{t|t}\hat{\alpha}'_{t|t}\mathrm{T}_t{}' \\ &= \hat{\Sigma}_{t|t}\mathrm{T}_t{}', \end{aligned} \tag{65}$$

and similarly

$$Cov(\alpha_{t+1}, \alpha_t|\wp_t) = \mathrm{T}_t\hat{\Sigma}_{t|t}. \tag{66}$$

Furthermore,

$$\begin{aligned} Cov(\alpha_t, \alpha_{t-1}|\wp_t) &= E\left[\alpha_t\alpha_{t-1}{}'\right] - E\left[\alpha_t\right]E[\alpha_{t-1}]' \\ &= E\left[\left(\mathrm{T}_{t-1}\alpha_{t-1} + G_{t-1}\beta_{t-1} + \eta_{t-1}\right)\alpha_{t-1}{}'\right] - E\left[\mathrm{T}_{t-1}\alpha_{t-1} + G_{t-1}\beta_{t-1} + \eta_{t-1}\right]E[\alpha_{t-1}]' \\ &= \mathrm{T}_{t-1}E\left[\alpha_{t-1}\alpha_{t-1}{}'\right] + G_{t-1}\beta_{t-1}\hat{\alpha}'_{t-1|t} - \mathrm{T}_{t-1}\hat{\alpha}_{t-1|t}\hat{\alpha}'_{t-1|t} - G_{t-1}\beta_{t-1}\hat{\alpha}'_{t-1|t} \\ &= \mathrm{T}_{t-1}\left(\hat{\Sigma}_{t-1|t} + \hat{\alpha}_{t-1|t}\hat{\alpha}'_{t-1|t}\right) - \mathrm{T}_{t-1}\hat{\alpha}_{t-1|t}\hat{\alpha}'_{t-1|t} \\ &= \mathrm{T}_{t-1}\hat{\Sigma}_{t-1|t}, \end{aligned} \tag{67}$$

and similarly

$$Cov(\alpha_{t-1}, \alpha_t|\wp_t) = \hat{\Sigma}_{t-1|t}\mathrm{T}_{t-1}{}'. \tag{68}$$

$\square$

Lemma 3. *With information up to time t, the expected quadratic penalty of disease progression from period $t-1$ to t can be calculated as follows.*

$$E\left[(\alpha_t-\alpha_{t-1})' A_t\left(\alpha_t-\alpha_{t-1}\right)|\wp_t\right]=\left(\hat{\alpha}_{t|t}-\hat{\alpha}_{t-1|t}\right)' A_t\left(\hat{\alpha}_{t|t}-\hat{\alpha}_{t-1|t}\right) + tr\left[A_t\left(\hat{\Sigma}_{t|t}+\hat{\Sigma}_{t-1|t}-T_{t-1}\hat{\Sigma}_{t-1|t}-\hat{\Sigma}_{t-1|t}{T_{t-1}}'\right)\right]. \quad (69)$$

Proof of Lemma 3:

Proof. Using Lemma 1 and Lemma 2,

$$\begin{aligned}
E\left[(\alpha_t-\alpha_{t-1})' A_t\left(\alpha_t-\alpha_{t-1}\right)|\wp_t\right] &= E\left[{\alpha_t}' A_t\alpha_t|\wp_t\right]+E\left[{\alpha_{t-1}}' A_t\alpha_{t-1}|\wp_t\right] \\
&- E\left[{\alpha_t}' A_t\alpha_{t-1}|\wp_t\right]-E\left[{\alpha_{t-1}}' A_t\alpha_t|\wp_t\right] \\
&= \hat{\alpha}'_{t|t}A_t\hat{\alpha}_{t|t}+tr[A_t\hat{\Sigma}_{t|t}]+\hat{\alpha}'_{t-1|t}A_t\hat{\alpha}_{t-1|t}+tr[A_t\hat{\Sigma}_{t-1|t}] \\
&- \hat{\alpha}'_{t|t}A_t\hat{\alpha}_{t-1|t}-tr[A_tT_{t-1}\hat{\Sigma}_{t-1|t}]-\hat{\alpha}'_{t-1|t}A_t\hat{\alpha}_{t|t}-tr[A_t\hat{\Sigma}_{t-1|t}{T_{t-1}}'] \\
&= \left(\hat{\alpha}_{t|t}-\hat{\alpha}_{t-1|t}\right)' A_t\left(\hat{\alpha}_{t|t}-\hat{\alpha}_{t-1|t}\right)+tr\left[A_t\left(\hat{\Sigma}_{t|t}+\hat{\Sigma}_{t-1|t}-T_{t-1}\hat{\Sigma}_{t-1|t}-\hat{\Sigma}_{t-1|t}{T_{t-1}}'\right)\right]. \quad (70)
\end{aligned}$$

$\square$

Lemma 4. *With information up to time t, the expected quadratic penalty of disease progression from period t to $t+1$ can be calculated as follows.*

$$\begin{aligned}
&E\left[(\alpha_{t+1}-\alpha_t)' A_{t+1}\left(\alpha_{t+1}-\alpha_t\right)|\wp_t\right] \\
&= \hat{\alpha}'_{t|t}\left((T_t-I)' A_{t+1}(T_t-I)\right)\hat{\alpha}_{t|t}+{\beta_t}'({G_t}' A_{t+1}G_t)\beta_t+{\beta_t}'({G_t}' A_{t+1}(T_t-I)\hat{\alpha}_{t|t}) \\
&+ (\hat{\alpha}'_{t|t}(T_t-I)' A_{t+1}G_t)\beta_t+tr\left[A_{t+1}\left((T_t-I)\hat{\Sigma}_{t|t}(T_t-I)'+Q_t\right)\right]. \quad (71)
\end{aligned}$$

Proof of Lemma 4:

Proof. Using Eq. 1, Lemma 1 and Lemma 2,

$$\begin{aligned}
E\left[(\alpha_{t+1}-\alpha_t)' A_{t+1}\left(\alpha_{t+1}-\alpha_t\right)|\wp_t\right] &= E\left[{\alpha_{t+1}}' A_{t+1}\alpha_{t+1}|\wp_t\right]+E\left[{\alpha_t}' A_{t+1}\alpha_t|\wp_t\right] \\
&- E\left[{\alpha_{t+1}}' A_{t+1}\alpha_t|\wp_t\right]-E\left[{\alpha_t}' A_{t+1}\alpha_{t+1}|\wp_t\right] \\
&= (T_t\hat{\alpha}_{t|t}+G_t\beta_t)' A_{t+1}(T_t\hat{\alpha}_{t|t}+G_t\beta_t)+tr\left[A_{t+1}(T_t\hat{\Sigma}_{t|t}{T_t}'+Q_t)\right]+\hat{\alpha}'_{t|t}A_{t+1}\hat{\alpha}_{t|t}+tr[A_{t+1}\hat{\Sigma}_{t|t}] \\
&- (T_t\hat{\alpha}_{t|t}+G_t\beta_t)' A_{t+1}\hat{\alpha}_{t|t}-tr\left[A_{t+1}T_t\hat{\Sigma}_{t|t}\right]-\hat{\alpha}'_{t|t}A_{t+1}(T_t\hat{\alpha}_{t|t}+G_t\beta_t)-tr\left[A_{t+1}\hat{\Sigma}_{t|t}{T_t}'\right] \\
&= \hat{\alpha}'_{t|t}\left((T_t-I)' A_{t+1}(T_t-I)\right)\hat{\alpha}_{t|t}+{\beta_t}'({G_t}' A_{t+1}G_t)\beta_t+{\beta_t}'({G_t}' A_{t+1}(T_t-I)\hat{\alpha}_{t|t}) \\
&+ (\hat{\alpha}'_{t|t}(T_t-I)' A_{t+1}G_t)\beta_t+tr\left[A_{t+1}\left((T_t-I)\hat{\Sigma}_{t|t}(T_t-I)'+Q_t\right)\right]. \quad (72)
\end{aligned}$$

□

Lemma 5.

$$\tilde{J}_N = \min_{\beta_N}\{\beta_N{}'(G_N{}'A_{N+1}G_N + B_N)\beta_N + \beta_N{}'(G_N{}'A_{N+1}(T_N - I)\hat{\alpha}_{N|N})$$
$$+ (\hat{\alpha}'_{N|N}(T_N - I)'A_{N+1}G_N)\beta_N\} = -\hat{\alpha}'_{N|N}\tilde{P}_{N+1}\hat{\alpha}_{N|N}. \tag{73}$$

Proof of Lemma 5:

Proof. The minimization over β_N can be performed by completion of squares. For a detailed discussion on how to take minimization by completion of squares please see Section 3.3 of Sayed (2011). In here, we provide a short proof.

$\tilde{J}_N$ can be expressed in matrix form as follows.

$$\tilde{J}_N = \min_{\beta_N}\left\{\begin{bmatrix} 1 & \beta_N{}' \end{bmatrix}\begin{bmatrix} 0 & \hat{\alpha}'_{N|N}(T_N - I)'A_{N+1}G_N \\ G_N{}'A_{N+1}(T_N - I)\hat{\alpha}_{N|N} & G_N{}'A_{N+1}G_N + B_N \end{bmatrix}\begin{bmatrix} 1 \\ \beta_N \end{bmatrix}\right\}. \tag{74}$$

The center matrix in 74 can be factored into a product of upper-triangular, diagonal, and lower-triangular matrices as follows.

$$\tilde{J}_N = \min_{\beta_N}\{\begin{bmatrix} 1 & \beta_N{}' \end{bmatrix}\begin{bmatrix} 1 & \omega_N{}' \\ 0 & I \end{bmatrix}\begin{bmatrix} -\hat{\alpha}'_{N|N}(T_N - I)'A_{N+1}G_N\omega_N & 0 \\ 0 & G_N{}'A_{N+1}G_N + B_N \end{bmatrix}$$
$$\begin{bmatrix} 1 & 0 \\ \omega_N & I \end{bmatrix}\begin{bmatrix} 1 \\ \beta_N \end{bmatrix}\}, \tag{75}$$

where

$$\omega_N = \left(G_N{}'A_{N+1}G_N + B_N\right)^{-1}G_N{}'A_{N+1}(T_N - I)\hat{\alpha}_{N|N}. \tag{76}$$

Expanding the right-hand-side of Eq. 75 yields

$$\tilde{J}_N = \min_{\beta_N}\left\{-\hat{\alpha}'_{N|N}(T_N - I)'A_{N+1}G_N\omega_N + (\beta_N + \omega_N)'\left(G_N{}'A_{N+1}G_N + B_N\right)(\beta_N + \omega_N)\right\}, \tag{77}$$

in which only the second term depends on the unknown β_N. Note that $(G_N{}'A_{N+1}G_N + B_N)$ is positive semidefinite. This is because A_{N+1} and B_N are diagonal cost matrices with only positive terms on the main diagonal. So, the second term in Eq. 77 is always nonnegative and will be minimized by choosing $\beta_N = -\omega_N$.

Therefore, the optimum disease control β^*_N and the result of minimization, i.e., $\tilde{J}_N$, are given by the following equations respectively.

$$\beta_N^* = -U_N \hat{\alpha}_{N|N}, \tag{78}$$

where

$$U_N = \left(G_N{}' A_{N+1} G_N + B_N\right)^{-1} G_N{}' A_{N+1}(T_N - I), \tag{79}$$

and

$$\tilde{J}_N = -\hat{\alpha}'_{N|N} \tilde{P}_{N+1} \hat{\alpha}_{N|N}, \tag{80}$$

where

$$\tilde{P}_{N+1} = (T_N - I)' A_{N+1} G_N (G'_N A_{N+1} G_N + B_N)^{-1} G'_N A_{N+1}(T_N - I). \tag{81}$$

□

Lemma 6.

$$tr\left[A_{N+1}\left((T_N - I)\hat{\Sigma}_{N|N}(T_N - I)'\right)\right] = tr\left[P_N \hat{\Sigma}_{N|N}\right] + tr\left[\tilde{P}_{N+1}\hat{\Sigma}_{N|N}\right] \tag{82}$$

Proof of Lemma 6:

Proof. We know $tr\,[XY] = tr\,[YX]$, $tr\,[X\,(YZ)] = tr\,[(XY)\,Z]$ and $tr\,[(X+Y)\,Z] = tr\,[XZ] + tr\,[YZ]$. Therefore,

$$tr\left[A_{N+1}\left((T_N - I)\hat{\Sigma}_{N|N}(T_N - I)'\right)\right] = tr\left[\left((T_N - I)' A_{N+1}(T_N - I)\right)\hat{\Sigma}_{N|N}\right] \tag{83}$$

From Eq. 50 we know $(T_N - I)' A_{N+1}(T_N - I) = P_N + \tilde{P}_{N+1}$. Hence,

$$\begin{aligned} tr\left[\left((T_N - I)' A_{N+1}(T_N - I)\right)\hat{\Sigma}_{N|N}\right] &= tr\left[\left(P_N + \tilde{P}_{N+1}\right)\hat{\Sigma}_{N|N}\right] \\ &= tr\left[P_N \hat{\Sigma}_{N|N}\right] + tr\left[\tilde{P}_{N+1}\hat{\Sigma}_{N|N}\right] \end{aligned} \tag{84}$$

□

Lemma 7.

$$\begin{aligned} \underset{z_{t+1}}{E}\left[\hat{\alpha}'_{t+1|t+1} P_{t+1} \hat{\alpha}_{t+1|t+1} | \wp_t\right] &= (T_t \hat{\alpha}_{t|t} + G_t \beta_t)' P_{t+1} (T_t \hat{\alpha}_{t|t} + G_t \beta_t) \\ &+ tr\left[P_{t+1}\left(T_t \hat{\Sigma}_{t|t} T_t{}' + Q_t - \hat{\Sigma}_{t+1|t+1}\right)\right]. \end{aligned} \tag{85}$$

Proof of Lemma 7:

Proof. From Lemma 1 and Eq. 4

$$\underset{z_{t+1}}{E}\left[\hat{\alpha}'_{t+1|t+1}P_{t+1}\hat{\alpha}_{t+1|t+1}|\wp_t\right] = \underset{z_{t+1}}{E}\left[\hat{\alpha}_{t+1|t+1}|\wp_t\right]'P_{t+1}\underset{z_{t+1}}{E}\left[\hat{\alpha}_{t+1|t+1}|\wp_t\right]$$
$$+ tr\left[P_{t+1}\underset{z_{t+1}}{E}\left[\left(\hat{\alpha}_{t+1|t+1} - \underset{z_{t+1}}{E}\left[\hat{\alpha}_{t+1|t+1}|\wp_t\right]\right)\left(\hat{\alpha}_{t+1|t+1} - \underset{z_{t+1}}{E}\left[\hat{\alpha}_{t+1|t+1}|\wp_t\right]\right)'\right]\right]$$
$$= (T_t\hat{\alpha}_{t|t} + G_t\beta_t)'P_{t+1}(T_t\hat{\alpha}_{t|t} + G_t\beta_t) + tr\left[P_{t+1}K_{t+1}\underset{z_{t+1}}{E}\left[\tilde{y}_{t+1}\tilde{y}'_{t+1}\right]K_{t+1}{}'\right], \tag{86}$$

in which

$$\underset{z_{t+1}}{E}\left[\tilde{y}_{t+1}\tilde{y}'_{t+1}\right] = \underset{z_{t+1}}{E}\left[\left(z_{t+1} - Z_{t+1}(T_t\hat{\alpha}_{t|t} + G_t\beta_t)\right)\left(z_{t+1} - Z_{t+1}(T_t\hat{\alpha}_{t|t} + G_t\beta_t)\right)'\right]. \tag{87}$$

Replacing z_{t+1} by its value given by Eq. 2 yields

$$\underset{z_{t+1}}{E}\left[\tilde{y}_{t+1}\tilde{y}'_{t+1}\right] = \underset{z_{t+1}}{E}\left[\left(\varepsilon_{t+1} + Z_{t+1}(\alpha_{t+1} - T_t\hat{\alpha}_{t|t} - G_t\beta_t)\right)\left(\varepsilon_{t+1} + Z_{t+1}(\alpha_{t+1} - T_t\hat{\alpha}_{t|t} - G_t\beta_t)\right)'\right]$$
$$= \underset{z_{t+1}}{E}\left[(\varepsilon_{t+1} + Z_{t+1}(\alpha_{t+1} - E[\alpha_{t+1}]))(\varepsilon_{t+1} + Z_{t+1}(\alpha_{t+1} - E[\alpha_{t+1}]))'\right]$$
$$= H_{t+1}^{(\theta_{t+1})} + Z_{t+1}\left(T_t{}'\hat{\Sigma}_{t|t}T_t + Q_t\right)Z'_{t+1}$$
$$= S_{t+1}. \tag{88}$$

Substitution of Eq. 88 into Eq. 86 results

$$\underset{z_{t+1}}{E}\left[\hat{\alpha}'_{t+1|t+1}P_{t+1}\hat{\alpha}_{t+1|t+1}|\wp_t\right] = (T_t\hat{\alpha}_{t|t} + G_t\beta_t)'P_{t+1}(T_t\hat{\alpha}_{t|t} + G_t\beta_t) + tr\left[P_{t+1}K_{t+1}S_{t+1}K_{t+1}{}'\right]. \tag{89}$$

Using Eq.'s 35, 7, 8, and 9 yields

$$\underset{z_{t+1}}{E}\left[\hat{\alpha}'_{t+1|t+1}P_{t+1}\hat{\alpha}_{t+1|t+1}|\wp_t\right] = (T_t\hat{\alpha}_{t|t} + G_t\beta_t)'P_{t+1}(T_t\hat{\alpha}_{t|t} + G_t\beta_t)$$
$$+ tr\left[P_{t+1}\left(T_t\hat{\Sigma}_{t|t}T_t{}' + Q_t - \hat{\Sigma}_{t+1|t+1}\right)\right]. \tag{90}$$

□

Lemma 8.

$$\underset{z_{t+1}}{E}\left[\left(\hat{\alpha}_{t+1|t+1}-\hat{\alpha}_{t|t+1}\right)'A_{t+1}\left(\hat{\alpha}_{t+1|t+1}-\hat{\alpha}_{t|t+1}\right)|\wp_t\right]$$
$$=\left((T_t-I)\hat{\alpha}_{t|t}+G_t\beta_t\right)'A_{t+1}\left((T_t-I)\hat{\alpha}_{t|t}+G_t\beta_t\right)$$
$$+\,tr\left[A_{t+1}\left(T_t\hat{\Sigma}_{t|t}T_t'+Q_t-\hat{\Sigma}_{t+1|t+1}-\hat{\Sigma}_{t+1|t+1}\hat{\Sigma}_t^{*\prime}-\hat{\Sigma}_t^{*}\hat{\Sigma}_{t+1|t+1}+\hat{\Sigma}_{t|t+1}\right)\right]. \tag{91}$$

Proof of Lemma 8:

Proof. This expectation can be divided into four parts as follows.

$$\underset{z_{t+1}}{E}\left[\left(\hat{\alpha}_{t+1|t+1}-\hat{\alpha}_{t|t+1}\right)'A_{t+1}\left(\hat{\alpha}_{t+1|t+1}-\hat{\alpha}_{t|t+1}\right)|\wp_t\right]=\underset{z_{t+1}}{E}\left[\hat{\alpha}'_{t+1|t+1}A_{t+1}\hat{\alpha}_{t+1|t+1}|\wp_t\right]$$
$$-\underset{z_{t+1}}{E}\left[\hat{\alpha}'_{t+1|t+1}A_{t+1}\hat{\alpha}_{t|t+1}|\wp_t\right]-\underset{z_{t+1}}{E}\left[\hat{\alpha}'_{t|t+1}A_{t+1}\hat{\alpha}_{t+1|t+1}|\wp_t\right]+\underset{z_{t+1}}{E}\left[\hat{\alpha}'_{t|t+1}A_{t+1}\hat{\alpha}_{t|t+1}|\wp_t\right]. \tag{92}$$

The first expectation in 92 is similar to the expectation of Lemma 7. Therefore,

$$\underset{z_{t+1}}{E}\left[\hat{\alpha}'_{t+1|t+1}A_{t+1}\hat{\alpha}_{t+1|t+1}|\wp_t\right]=(T_t\hat{\alpha}_{t|t}+G_t\beta_t)'A_{t+1}(T_t\hat{\alpha}_{t|t}+G_t\beta_t)$$
$$+\,tr\left[A_{t+1}\left(T_t\hat{\Sigma}_{t|t}T_t'+Q_t-\hat{\Sigma}_{t+1|t+1}\right)\right]. \tag{93}$$

The second expectation in 92 can be simplified as follows.

$$\underset{z_{t+1}}{E}\left[\hat{\alpha}'_{t+1|t+1}A_{t+1}\hat{\alpha}_{t|t+1}|\wp_t\right]=\underset{z_{t+1}}{E}\left[\hat{\alpha}_{t+1|t+1}|\wp_t\right]'A_{t+1}\underset{z_{t+1}}{E}\left[\hat{\alpha}_{t|t+1}|\wp_t\right]+tr\left[A_{t+1}Cov\left(\hat{\alpha}_{t+1|t+1},\hat{\alpha}_{t|t+1}\right)\right]$$
$$=(T_t\hat{\alpha}_{t|t}+G_t\beta_t)'A_{t+1}\hat{\alpha}_{t|t}+tr\left[A_{t+1}Cov\left(\hat{\alpha}_{t+1|t+1},\hat{\alpha}_{t|t+1}\right)\right], \tag{94}$$

in which

$$Cov\left(\hat{\alpha}_{t+1|t+1},\hat{\alpha}_{t|t+1}|\wp_t\right)=E\left[\hat{\alpha}_{t+1|t+1}\hat{\alpha}'_{t|t+1}|\wp_t\right]-E\left[\hat{\alpha}_{t+1|t+1}|\wp_t\right]E\left[\hat{\alpha}_{t|t+1}|\wp_t\right]'$$
$$=E\left[\hat{\alpha}_{t+1|t+1}\left(\hat{\alpha}_{t|t}+\hat{\Sigma}_t^{*}(\hat{\alpha}_{t+1|t+1}-\hat{\alpha}_{t+1|t})\right)'|\wp_t\right]-E\left[\hat{\alpha}_{t+1|t+1}|\wp_t\right]\hat{\alpha}'_{t|t}$$
$$=E\left[\hat{\alpha}_{t+1|t+1}(\hat{\alpha}_{t+1|t+1}-\hat{\alpha}_{t+1|t})'|\wp_t\right]\hat{\Sigma}_t^{*\prime}$$
$$=E\left[\hat{\alpha}_{t+1|t+1}\hat{\alpha}'_{t+1|t+1}|\wp_t\right]\hat{\Sigma}_t^{*\prime}-E\left[\hat{\alpha}_{t+1|t+1}|\wp_t\right](T_t\hat{\alpha}_{t|t}+G_t\beta_t)'\hat{\Sigma}_t^{*\prime}$$
$$=\hat{\Sigma}_{t+1|t+1}\hat{\Sigma}_t^{*\prime}+(T_t\hat{\alpha}_{t|t}+G_t\beta_t)(T_t\hat{\alpha}_{t|t}+G_t\beta_t)'\hat{\Sigma}_t^{*\prime}$$
$$-(T_t\hat{\alpha}_{t|t}+G_t\beta_t)(T_t\hat{\alpha}_{t|t}+G_t\beta_t)'\hat{\Sigma}_t^{*\prime}$$
$$=\hat{\Sigma}_{t+1|t+1}\hat{\Sigma}_t^{*\prime}. \tag{95}$$

Therefore,

$$\mathop{E}_{z_{t+1}}\left[\hat{\alpha}'_{t+1|t+1}A_{t+1}\hat{\alpha}_{t|t+1}|\wp_t\right] = (T_t\hat{\alpha}_{t|t} + G_t\beta_t)'A_{t+1}\hat{\alpha}_{t|t} + tr\left[A_{t+1}\hat{\Sigma}_{t+1|t+1}\hat{\Sigma}_t^{*\prime}\right]. \tag{96}$$

In similar way, the third and fourth expectations in 92 can be simplified as follows.

$$\mathop{E}_{z_{t+1}}\left[\hat{\alpha}'_{t|t+1}A_{t+1}\hat{\alpha}_{t+1|t+1}|\wp_t\right] = \hat{\alpha}'_{t|t}A_{t+1}(T_t\hat{\alpha}_{t|t} + G_t\beta_t) + tr\left[A_{t+1}\hat{\Sigma}_t^{*}\hat{\Sigma}_{t+1|t+1}\right], \tag{97}$$

$$\mathop{E}_{z_{t+1}}\left[\hat{\alpha}'_{t|t+1}A_{t+1}\hat{\alpha}_{t|t+1}|\wp_t\right] = \hat{\alpha}'_{t|t}A_{t+1}\hat{\alpha}_{t|t} + tr\left[A_{t+1}\hat{\Sigma}_{t|t+1}\right]. \tag{98}$$

Replacing Eq.'s 93, 96, 97 and 98 into 92 yields

$$\begin{aligned}
&\mathop{E}_{z_{t+1}}\left[\left(\hat{\alpha}_{t+1|t+1} - \hat{\alpha}_{t|t+1}\right)'A_{t+1}\left(\hat{\alpha}_{t+1|t+1} - \hat{\alpha}_{t|t+1}\right)|\wp_t\right] = (T_t\hat{\alpha}_{t|t} + G_t\beta_t)'A_{t+1}(T_t\hat{\alpha}_{t|t} + G_t\beta_t)\\
&\quad + tr\left[A_{t+1}\left(T_t\hat{\Sigma}_{t|t}T_t{}' + Q_t - \hat{\Sigma}_{t+1|t+1}\right)\right] - (T_t\hat{\alpha}_{t|t} + G_t\beta_t)'A_{t+1}\hat{\alpha}_{t|t} - tr\left[A_{t+1}\hat{\Sigma}_{t+1|t+1}\hat{\Sigma}_t^{*\prime}\right]\\
&\quad - \hat{\alpha}'_{t|t}A_{t+1}(T_t\hat{\alpha}_{t|t} + G_t\beta_t) - tr\left[A_{t+1}\hat{\Sigma}_t^{*}\hat{\Sigma}_{t+1|t+1}\right] + \hat{\alpha}'_{t|t}A_{t+1}\hat{\alpha}_{t|t} + tr\left[A_{t+1}\hat{\Sigma}_{t|t+1}\right]\\
&\quad = \left((T_t - I)\hat{\alpha}_{t|t} + G_t\beta_t\right)'A_{t+1}\left((T_t - I)\hat{\alpha}_{t|t} + G_t\beta_t\right)\\
&\quad + tr\left[A_{t+1}\left(T_t\hat{\Sigma}_{t|t}T_t{}' + Q_t - \hat{\Sigma}_{t+1|t+1} - \hat{\Sigma}_{t+1|t+1}\hat{\Sigma}_t^{*\prime} - \hat{\Sigma}_t^{*}\hat{\Sigma}_{t+1|t+1} + \hat{\Sigma}_{t|t+1}\right)\right].
\end{aligned} \tag{99}$$

□

Lemma 9.

$$tr\left[(A_{t+1} + P_{t+1})\left(T_t\hat{\Sigma}_{t|t}T_t{}'\right)\right] = tr\left[P_t\hat{\Sigma}_{t|t}\right] + tr\left[\left(\tilde{P}_{t+1} + A_{t+1}T_t + T_t{}'A_{t+1} - I\right)\hat{\Sigma}_{t|t}\right] \tag{100}$$

Proof of Lemma 9:

Proof. We know $tr\left[XY\right] = tr\left[YX\right]$, $tr\left[X\left(YZ\right)\right] = tr\left[\left(XY\right)Z\right]$ and $tr\left[\left(X + Y\right)Z\right] = tr\left[XZ\right] + tr\left[YZ\right]$. Therefore,

$$tr\left[(A_{t+1} + P_{t+1})\left(T_t\hat{\Sigma}_{t|t}T_t{}'\right)\right] = tr\left[\left(T_t{}'\left(A_{t+1} + P_{t+1}\right)T_t\right)\hat{\Sigma}_{t|t}\right] \tag{101}$$

Using Eq. 35 to replace $T_t{}'\left(A_{t+1} + P_{t+1}\right)T_t$ we have

$$\begin{aligned}
tr\left[\left(T_t{}'\left(A_{t+1} + P_{t+1}\right)T_t\right)\hat{\Sigma}_{t|t}\right] &= tr\left[\left(\tilde{P}_{t+1} + P_t + A_{t+1}T_t + T_t{}'A_{t+1} - I\right)\hat{\Sigma}_{t|t}\right]\\
&= tr\left[P_t\hat{\Sigma}_{t|t}\right] + tr\left[\left(\tilde{P}_{t+1} + A_{t+1}T_t + T_t{}'A_{t+1} - I\right)\hat{\Sigma}_{t|t}\right].
\end{aligned} \tag{102}$$

□

Appendix C Insight into Selecting an Aggressiveness Option

Many factors go into a doctor's decision of how aggressively to treat and monitor a patient's disease that cannot be captured adequately in a single mathematical model. Our model facilitates the translation of the clinician's desired aggressiveness level into optimal treatment controls and a monitoring plan to achieve those clinical goals with minimal disruption in terms of cost and inconvenience for the patient (i.e., lower the IOP the least amount necessary to achieve the clinical goals). While we think it is best to let the clinician use his/her expertise to choose an appropriate aggressiveness level based on individual patient needs, our model can provide some insight into when to switch aggressiveness level. At each time period that the doctor sees the patient, our decision support tool provides a personalized projection of the patient's progression trajectory over the next five years (similar to Figure 6). The doctor's requirement of how much progression is acceptable in T months (e.g., MD loss of $1dB$ in 6 months, and/or $4dB$ in 12 months, and/or $6dB$ in 24 months) can be directly compared to our system's predictions to determine the appropriate aggressiveness option.

Mathematically speaking, this can be accomplished as follows. Let $\Psi = \{\psi_1, \ldots, \psi_G\}$ be the ordered set of aggressiveness options sorted from the least severe to the most severe aggressiveness option (e.g., $\Psi = \{\text{super-low, low, medium, high, super-high}\}$). Let $\Xi = \{(t_1, \xi_1), \ldots, (t_K, \xi_K)\}$ be a set of clinically acceptable progression thresholds such that (t_k, ξ_k) means that no more than ξ_k loss of MD should be allowed in t_k number of time periods. Let the current time period be t. Our decision support tool can provide the optimal additional IOP controls for each aggressiveness option (i.e., $\beta^*(\psi_g) = \left\{\beta^*_t(\psi_g), \beta^*_{t+1}(\psi_g), \cdots\right\}$) as well as the optimal/filtered forecasts of disease progression trajectory under each aggressiveness option (i.e., $\hat{\alpha}_{.|t}(\psi_g) = \left\{\hat{\alpha}_{t|t}(\psi_g), \hat{\alpha}_{t+1|t}(\psi_g), \hat{\alpha}_{t+2|t}(\psi_g), \cdots\right\}$). Let $\widehat{MD}_{.|t}(\psi_g)$ represent the MD element of $\hat{\alpha}_{.|t}(\psi_g)$. Then, at time t, the recommended aggressiveness level is

$$\arg\min_{\psi_g \in \Psi} E\left[\widehat{MD}_{t|t}(\psi_g) - \widehat{MD}_{t+t_k|t}(\psi_g) \le \xi_k\right] \qquad \forall (t_k, \xi_k) \in \Xi. \tag{103}$$

Alternatively, we can use the following service-level type expression

$$\arg\min_{\psi_g \in \Psi} P\left(\left[\widehat{MD}_{t|t}(\psi_g) - \widehat{MD}_{t+t_k|t}(\psi_g) \le \xi_k\right] \ge s\right) \qquad \forall (t_k, \xi_k) \in \Xi, \tag{104}$$

where s is the probability that the loss of MD is limited to ξ_k. Similar expressions can be written for PSD and IOP as well.

Appendix D Results on Target IOP and MD Loss Averted

Since target IOP is an important metric that helps guide clinicians in selecting the appropriate treatment plan for the patient, the distribution of target IOPs is also of interest. Figure S1 shows the histogram of target IOPs for fast- and slow-progressing patients under the high and moderate aggressiveness policies. The range and mean of each category is clinically appropriate in the professional opinion of our glaucoma specialist collaborator.

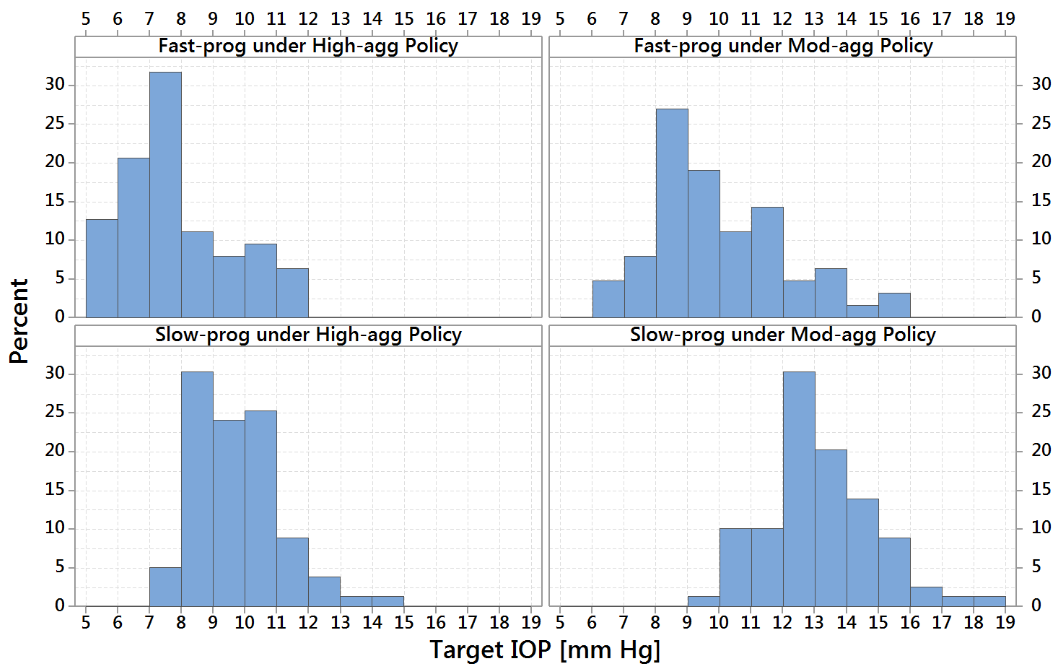

Figure S1: Histogram of target IOPs for CIGTS and AGIS patients under different aggressiveness policies.

Figure S2 graphs the MD loss averted in [dB] for fast- and slow-progressing patients under the high and moderate aggressiveness policies compared to the low aggressiveness policy over 10 years of following the IOP controls suggested by our model. As seen in the figure, fast-progressing patients will lose fewer MD points (i.e., experience better vision quality) resulting from further lowering their eye pressure in the short term, whether the doctor chooses moderate or high aggressiveness level. Slow-progressors, if treated under the high aggressiveness policy, could benefit from losing fewer MD points in the long term. However, this group of glaucoma patients does not gain evident benefit from employing the moderate aggressiveness policy even in the long term.

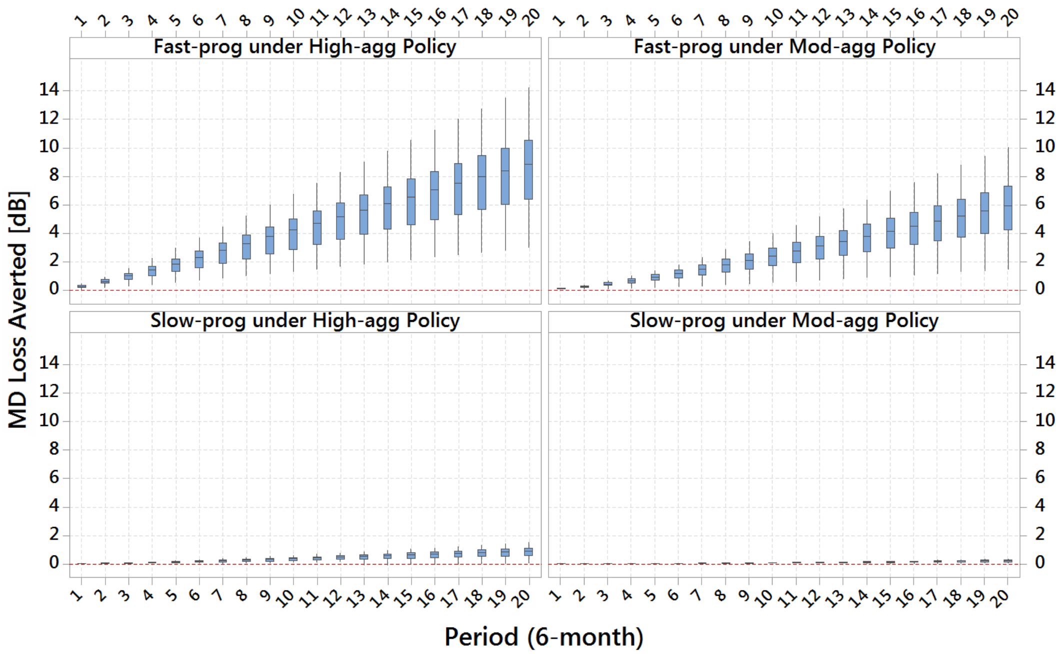

Figure S2: MD loss averted [dB] for fast- and slow-progressing patients under the high and moderate aggressiveness policies compared against the low aggressiveness policy (i.e., no additional IOP reduction beyond those employed in trials) over 10 years of following the IOP control suggested by our model. Period 1 is six months into the future; period 20 is 10 years into the future.

Table S1 summarizes the results of comparing super-high, high, moderate, and super-low aggressiveness policy options against the low aggressiveness policy (i.e., the IOP levels attained in the trials), averaged over all patients in the testing dataset. The formula used to obtain each metric for high aggressiveness policy is presented below. Similar formulas were used for the other policies.

- % less MD loss per year $= \frac{MD_{25}^{highagg} - MD_{25}^{lowagg}}{MD_{25}^{lowagg} - MD_5} * 100$
- % better MD value at 10 years $= \frac{MD_{25}^{highagg} - MD_{25}^{lowagg}}{MD_{25}^{lowagg}} * 100$
- % reduction in MD slope at 10 years $= \frac{\left(MD_{25}^{highagg} - MD_{24}^{highagg}\right) - \left(MD_{25}^{lowagg} - MD_{24}^{lowagg}\right)}{\left(MD_{25}^{lowagg} - MD_{24}^{lowagg}\right)} * 100$

As can be deduced from the table, achieving an IOP control suggested by our models not only results in patients having better vision quality (less loss of vision due to glaucoma) but also experiencing a significantly reduced glaucoma progression rate, which further benefits the patient in the long term. For instance, under the high aggressiveness policy, a fast-progressing patient can achieve, on average, 57.87% less peripheral vision loss per year or 31.71% better MD value after 10 years if the clinician is able to lower the IOP successfully to the target IOP specified by our model. Furthermore, by applying optimal IOP control, the doctor is able to slow the glaucoma progression rate. For instance, the slope/rate of MD worsening would be, on average, 74.54% reduced after 10 years for fast-progressing patients under the high aggressiveness policy compared to the low aggressiveness policy, which corresponds to the IOP achieved under no additional interventions beyond those employed in the CIGTS/AGIS trials. This results in more years of maintained sight over the ten-year period. As seen in the table, the fast-progressing patients (those who are at the highest risk for disease progression) are the ones who will benefit the most from achieving the more aggressive optimal IOP controls generated from our models.

		% less MD loss per year		% better MD value at 10 years		% reduction in MD slope (progression rate) at 10 years	
		median	IQR	median	IQR	median	IQR
Fast-progressors	Super-high-agg. Policy	73.31	18.09	37.87	11.34	82.53	21.72
	High-agg. Policy	57.87	13.59	31.71	12.93	74.54	14.69
	Moderate-agg. Policy	38.22	13.09	21.06	10.67	58.86	16.19
	Low-agg. Policy	baseline	baseline	baseline	baseline	baseline	baseline
	Super-low-agg. Policy	-27.49	6.83	-14.92	3.38	-30.30	8.77
Slow-progressors	Super-high-agg. Policy	55.30	15.24	21.35	18.59	51.67	7.08
	High-agg. Policy	22.56	10.72	7.89	6.70	31.08	12.73
	Moderate-agg. Policy	6.01	3.10	2.14	1.63	10.80	6.37
	Low-agg. Policy	baseline	baseline	baseline	baseline	baseline	baseline
	Super-low-agg. Policy	-23.16	6.80	-10.68	9.76	-23.05	3.16

Table S1: Comparison of the performance of different IOP control policies for patients in AGIS and CIGTS against the low aggressiveness policy that is no additional interventions beyond those employed in the trials.

Appendix E Monitoring Cost of the Optimal Policies

Our optimal policies for low, moderate, and high aggressiveness suggest, on average, more frequent IOP testing (a very cheap and fast test) and less frequent visual field (VF) testing compared to the current practice. Current practice involves testing IOP and VF every 1-2 years (see American Academy of Ophthalmology Clinical Practice Guidelines 2010). This concept is not widely used in practice and should lead to resource efficiencies while still providing good detection. If we know the prevalence of non- vs. slow- vs. fast-progressors in the U.S., we can calculate how many tests each optimal policy suggests on average and compare it against the 6, 12, 18, and 24-month fixed interval testing. Unfortunately, there is no gold standard for defining these progression categories. To overcome this issue, we use the proportions we found in CIGTS and AGIS. In those trials, 21%, 47%, and 32% of patients met our definition of fast-, slow-, and non-progressor, respectively.
We estimate that the cost of a visual field test is $75.94 (Blumberg et al. 2014). An IOP test is part of a routine eye exam, hence we could not find a separate number for the cost of an IOP test. We estimate it is $10. Based on these assumptions, the expected annual cost of fixed-interval testing is $172 (6-month), $86 (12-month), $57 (18-month), and $43 (24-month). The expected monitoring cost of following the recommendations of our model (Table 3) is $144 (high aggressiveness), $97 (moderate aggressiveness), and $59 (low aggressiveness).

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