Appendix

A. Conditional State Transition Probabilities

Table 7 shows $p_t(s'|s,a,o)$ values for $s,s' \in \mathbf{S}$, $a \in \mathbf{A}$, and $o = T-$. The state transitions follow the natural history of CRC after a $T-$ screening result. For example, if a patient is in the UCT state and lives through the year t (with probability $1-\delta^t_{9,T-}(a)$), the treatment may be completed within the year with probability γ^t_9. Then, the patient either stays lesion-free with probability $\rho^t_{6,6}$ or develops a new adenomatous polyp with probability $\rho^t_{6,7}$. If the treatment is not completed within year t (with probablity $(1-\gamma^t_9)(1-\delta^t_{9,T-}(a))$), then the patient stays in the UCT state.

	$LR0(0)$	$LR1(1)$	$LR2(2)$	$HR0(3)$	$HR1(4)$	$HR2(5)$
$LR0(0)$	$\rho^t_{0,0}[1-\delta^t_{0,T-}(a)]$	$\rho^t_{0,1}[1-\delta^t_{0,T-}(a)]$	0	0	0	0
$LR1(1)$	0	$\rho^t_{1,1}[1-\delta^t_{1,T-}(a)]$	$\rho^t_{1,2}[1-\delta^t_{1,T-}(a)]$	0	0	0
$LR2(2)$	0	0	$1-\delta^t_{2,T-}(a)$	0	0	0
$HR0(3)$	0	0	0	$\rho^t_{3,3}[1-\delta^t_{3,T-}(a)]$	$\rho^t_{3,4}[1-\delta^t_{3,T-}(a)]$	0
$HR1(4)$	0	0	0	0	$\rho^t_{4,4}[1-\delta^t_{4,T-}(a)]$	$\rho^t_{4,5}[1-\delta^t_{4,T-}(a)]$
$HR2(5)$	0	0	0	0	0	$1-\delta^t_{5,T-}(a)$
$PC0(6)$	0	0	0	0	0	0
$PC1(7)$	0	0	0	0	0	0
$PC2(8)$	0	0	0	0	0	0
$UCT(9)$	0	0	0	0	0	0
$D(10)$	0	0	0	0	0	0

	$PC0(6)$	$PC1(7)$	$PC2(8)$	$UCT(9)$	$D(10)$
$LR0(0)$	0	0	0	0	$\delta^t_{0,T-}(a)$
$LR1(1)$	0	0	0	0	$\delta^t_{1,T-}(a)$
$LR2(2)$	0	0	0	0	$\delta^t_{2,T-}(a)$
$HR0(3)$	0	0	0	0	$\delta^t_{3,T-}(a)$
$HR1(4)$	0	0	0	0	$\delta^t_{4,T-}(a)$
$HR2(5)$	0	0	0	0	$\delta^t_{5,T-}(a)$
$PC0(6)$	$\rho^t_{6,6}[1-\delta^t_{6,T-}(a)]$	$\rho^t_{6,7}[1-\delta^t_{6,T-}(a)]$	0	0	$\delta^t_{6,T-}(a)$
$PC1(7)$	0	$\rho^t_{7,7}[1-\delta^t_{7,T-}(a)]$	$\rho^t_{7,8}[1-\delta^t_{7,T-}(a)]$	0	$\delta^t_{7,T-}(a)$
$PC2(8)$	0	0	$1-\delta^t_{8,T-}(a)$	0	$\delta^t_{8,T-}(a)$
$UCT(9)$	$\rho^t_{6,6}\gamma^t_9[1-\delta^t_{9,T-}(a)]$	$\rho^t_{6,7}\gamma^t_9[1-\delta^t_{9,T-}(a)]$	0	$(1-\gamma^t_9)[1-\delta^t_{9,T-}(a)]$	$\delta^t_{9,T-}(a)$
$D(10)$	0	0	0	0	1

Table 7 $p_t(s'|s,a,o)$ **values for all** $a \in \mathbf{A}$**, when** $o = T-$

	$HR0(3)$	$HR1(4)$	$HR2(5)$	$PC0(6)$	$PC1(7)$	$PC2(8)$	$D(10)$
$LR1(1)$	$\rho^t_{3,3}[1-\delta^t_{1,P+}(Co)]$	$\rho^t_{3,4}[1-\delta^t_{1,P+}(Co)]$	0	0	0	0	$\delta^t_{1,P+}(Co)$
$HR1(4)$	$\rho^t_{3,3}[1-\delta^t_{4,P+}(Co)]$	$\rho^t_{3,4}[1-\delta^t_{4,P+}(Co)]$	0	0	0	0	$\delta^t_{4,P+}(Co)$
$PC1(7)$	0	0	0	$\rho^t_{6,6}[1-\delta^t_{7,P+}(Co)]$	$\rho^t_{6,7}[1-\delta^t_{7,P+}(Co)]$	0	$\delta^t_{7,P+}(Co)$

Table 8 $p_t(s'|s,a,o)$ **values for** $a = Co$ **and** $o = P+$

	$PC0(6)$	$PC1(7)$	$PC2(8)$	$UCT(9)$	$D(10)$
$LR2(2)$	$\rho^t_{2,6}\gamma^t_2[1-\delta^t_{2,o}(a)]$	$\rho^t_{2,7}\gamma^t_2[1-\delta^t_{2,o}(a)]$	$\rho^t_{2,8}\gamma^t_2[1-\delta^t_{2,o}(a)]$	$(1-\gamma^t_2)[1-\delta^t_{2,o}(a)]$	$\delta^t_{2,o}(a)$
$HR2(5)$	$\rho^t_{5,6}\gamma^t_5[1-\delta^t_{5,o}(a)]$	$\rho^t_{5,7}\gamma^t_5[1-\delta^t_{5,o}(a)]$	$\rho^t_{5,8}\gamma^t_5[1-\delta^t_{5,o}(a)]$	$(1-\gamma^t_5)[1-\delta^t_{5,o}(a)]$	$\delta^t_{5,o}(a)$
$PC2(8)$	$\rho^t_{8,6}\gamma^t_8[1-\delta^t_{8,o}(a)]$	$\rho^t_{8,7}\gamma^t_8[1-\delta^t_{8,o}(a)]$	$\rho^t_{8,8}\gamma^t_8[1-\delta^t_{8,o}(a)]$	$(1-\gamma^t_8)[1-\delta^t_{8,o}(a)]$	$\delta^t_{8,o}(a)$

Table 9 $p_t(s'|s,a,o)$ **values for all** $a \in \mathbf{A}$**, when** $o \in \{C+, SD\}$

Table 8 shows $p_t(s'|s,a,o)$ values for feasible s' when $s \in \{LR1,\ HR1,\ PC1\}$, $a = Co$, and $o = P+$. For example, the first row of Table 8 shows that if an adenomatous polyp is diagnosed and removed at the beginning of the year, the state transitions occur as if the patient is in the $HR0$ state as described in Table 7. The only difference arises in the annual death probability, $\delta^t_{i,P+}(a)$ for

$i \in \{1, 4, 7\}$, which accounts for the increased risk of colonoscopic complications after undergoing a polypectomy.

Table 9 shows $p_t(s'|s,a,o)$ values for feasible s' when $s \in \{LR2, HR2, PC2\}$, $a \in \mathbf{A}$, and $o \in \{C+, SD\}$, where γ_i^t for $i \in \{2,5,8\}$ refers to the probability that a cancer treatment which is initiated in year t will be completed within the same year. The transitions in Table 9 are very similar to those from the UCT state in Table 7. The main difference is the possibility of transition from $\{LR2, HR2, PC2\}$ to $PC2$, which represents local CRC recurrence around the curative surgery site within the first year after an imperfect treatment (Ohlsson and Pålsson 2003).

The annual death probabilities in Tables 7, 8, and 9 depend on action a because colonoscopy is associated with some fatal complications. For instance, we incorporate the risk of immediate death from such complications in $\delta_{i,T-}^t(Co)$ and $\delta_{i,P+}^t(Co)$ as follows:

$$\delta_{i,T-}^t(Co) = \mu_{i,T-}^t + (1-\mu_{i,T-}^t)\delta_{i,T-}^t(DN) \quad \forall i \in \{0,\ldots,8\} \tag{1}$$

$$\delta_{i,P+}^t(Co) = \mu_{i,P+}^t + (1-\mu_{i,P+}^t)\delta_{i,T-}^t(DN) \quad \forall i \in \{1, 4, 7\} \tag{2}$$

In Equation (1), $\mu_{i,T-}^t$ denotes the probability of mortality from complications such as perforation during a colonoscopy **without polypectomy** for $i \in \{0,\ldots,8\}$. Note that, lesions that are not associated with CRC (non-CRC related) can be detected and removed during a colonoscopy. We consider the risk of fatal complications after removal of non-CRC related lesions in $\delta_{i,T-}^t(Co)$ by defining $\mu_{i,T-}^t = \beta\overline{\mu}_{i,T-}^t + (1-\beta)\underline{\mu}_{i,T-}^t$ where β represents the probability of detecting a non-CRC related lesion and $\overline{\mu}_{i,T-}^t$ and $\underline{\mu}_{i,T-}^t$ represent the probabilities of mortality from complications with and without non-CRC related lesion removal for $i \in \{0,\ldots,8\}$. In Equation (2), $\mu_{i,P+}^t$ denotes the probability of mortality from complications during a colonoscopy **with polypectomy**. If the screening result is $P+$, a lesion will certainly be removed, therefore, $\mu_{i,P+}^t \geq \mu_{i,T-}^t$ and $\delta_{i,P+}^t(Co) \geq \delta_{i,T-}^t(Co)$, $\forall i \in \{1, 4, 7\}$.

Note that, in our model UCT refers to the clinical cancer stage while $LR2$, $HR2$, and $PC2$ refer to pre-clinical cancer stage where CRC has not been detected yet. The CRC treatment in the UCT state is different than those in the $LR2$, $HR2$, and $PC2$ states after CRC diagnosis, because patients move to the UCT state if their initial treatments in the $LR2$, $HR2$, and $PC2$ states fail and cancer is metastasized.

B. Table Form Representation of $q_t(s,a,o,s')$

Tables 10, 11, and 12 illustrate $q_t(s,a,o,s')$ values for different state, action and observation values. This table form representation of $q_t(s,a,o,s')$ is slightly different than the function-wise representation in Section 4.3. To keep the function in Section 4.3 short, we assign positive immediate reward values for some cases where $f_t(o|s',a)p_t(s'|s,a,o) = 0$. However, if

$f_t(o|s',a)p_t(s'|s,a,o)=0$, we set $q_t(s,a,o,s')=0$ in the Tables 10, 11, and 12 for simplification. For example, $q_t(LR0,DN,T-,HR1)=1-\underline{d}(a)$ according to the function in Section 4.3. However, because a patient cannot move from LRO to $HR1$ within one year, i.e., $p_t(HR2|LR0,DN,T-,)=0$, the corresponding immediate reward value in Table 10 is set to 0. Note that, these differences do not affect our numerical results because $q_t(s,a,o,s')f_t(o|s',a)p_t(s'|s,a,o)$ is equal to zero for such cases in the both forms of representation.

	$LR0(0)$	$LR1(1)$	$LR2(2)$	$HR0(3)$	$HR1(4)$	$HR2(5)$
$LR0(0)$	$1-\underline{d}(a)$	$1-\underline{d}(a)$	0	0	0	0
$LR1(1)$	0	$1-\underline{d}(a)$	$1-\underline{d}(a)$	0	0	0
$LR2(2)$	0	0	$1-d_C$	0	0	0
$HR0(3)$	0	0	0	$1-\underline{d}(a)$	$1-\underline{d}(a)$	0
$HR1(4)$	0	0	0	0	$1-\underline{d}(a)$	$1-\underline{d}(a)$
$HR2(5)$	0	0	0	0	0	$1-d_C$
$PC0(6)$	0	0	0	0	0	0
$PC1(7)$	0	0	0	0	0	0
$PC2(8)$	0	0	0	0	0	0
$UCT(9)$	0	0	0	0	0	0
$D(10)$	0	0	0	0	0	0

	$PC0(6)$	$PC1(7)$	$PC2(8)$	$UCT(9)$	$D(10)$
$LR0(0)$	0	0	0	0	$\left(0.5-\underline{d}(a)\right)\left(1-\kappa^t_{s,T-}(a)\right)$
$LR1(1)$	0	0	0	0	$\left(0.5-\underline{d}(a)\right)\left(1-\kappa^t_{s,T-}(a)\right)$
$LR2(2)$	0	0	0	0	$0.5\left(1-d_C\right)\left(1-\kappa^t_{s,T-}(a)\right)$
$HR0(3)$	0	0	0	0	$\left(0.5-\underline{d}(a)\right)\left(1-\kappa^t_{s,T-}(a)\right)$
$HR1(4)$	0	0	0	0	$\left(0.5-\underline{d}(a)\right)\left(1-\kappa^t_{s,T-}(a)\right)$
$HR2(5)$	0	0	0	0	$0.5\left(1-d_C\right)\left(1-\kappa^t_{s,T-}(a)\right)$
$PC0(6)$	$1-\underline{d}(a)$	$1-\underline{d}(a)$	0	0	$\left(0.5-\underline{d}(a)\right)\left(1-\kappa^t_{s,T-}(a)\right)$
$PC1(7)$	0	$1-\underline{d}(a)$	$1-\underline{d}(a)$	0	$\left(0.5-\underline{d}(a)\right)\left(1-\kappa^t_{s,T-}(a)\right)$
$PC2(8)$	0	0	$1-d_C$	0	$0.5\left(1-d_C\right)\left(1-\kappa^t_{s,T-}(a)\right)$
$UCT(9)$	$1-d_{UCT}$	$1-d_{UCT}$	0	$1-d_{UCT}$	$0.5\left(1-d_{UCT}\right)\left(1-\kappa^t_{UCT}\right)$
$D(10)$	0	0	0	0	1

Table 10 $q_t(s,a,o,s')$ **values for all** $a\in\mathbf{A}$**, when** $o=T-$

	$HR0(3)$	$HR1(4)$	$HR2(5)$	$PC0(6)$	$PC1(7)$	$PC2(8)$	$D(10)$
$LR1(1)$	$1-\overline{d}(Co)$	$1-\overline{d}(Co)$	0	0	0	0	$\left(0.5-\overline{d}(Co)\right)\left(1-\kappa^t_{s,P+}(Co)\right)$
$HR1(4)$	$1-\overline{d}(Co)$	$1-\overline{d}(Co)$	0	0	0	0	$\left(0.5-\overline{d}(Co)\right)\left(1-\kappa^t_{s,P+}(Co)\right)$
$PC1(7)$	0	0	0	$1-\overline{d}(Co)$	$1-\overline{d}(Co)$	0	$\left(0.5-\overline{d}(Co)\right)\left(1-\kappa^t_{s,P+}(Co)\right)$

Table 11 $q_t(s,a,o,s')$ **values for** $a=Co$ **and** $o=P+$

	$PC0(6)$	$PC1(7)$	$PC2(8)$	$UCT(9)$	$D(10)$
$LR2(2)$	$1-d_{CT}$	$1-d_{CT}$	$1-d_{CT}$	$1-d_{CT}$	$0.5\left(1-d_{UCT}\right)\left(1-\kappa^t_{UCT}\right)$
$HR2(5)$	$1-d_{CT}$	$1-d_{CT}$	$1-d_{CT}$	$1-d_{CT}$	$0.5\left(1-d_{UCT}\right)\left(1-\kappa^t_{UCT}\right)$
$PC2(8)$	$1-d_{CT}$	$1-d_{CT}$	$1-d_{CT}$	$1-d_{CT}$	$0.5\left(1-d_{UCT}\right)\left(1-\kappa^t_{UCT}\right)$

Table 12 $q_t(s,a,o,s')$ **values for all** $a\in\mathbf{A}$**, when** $o\in\{C+,SD\}$

C. Derivation of the Belief Update Formula

We can express $\tilde{b}^a_{b_t,o}(s)$ and $P(s_t=s'|b_t,a,o)$ for all $b_t\in\mathbf{B}$, $s\in\mathbf{S}$, $a\in\mathbf{A}$ and $o\in\mathbf{O}$ as follows:

$$\tilde{b}^a_{b_t,o}(s)=P_t(s_{t+1}=s|b_t,a,o)=\sum_{s'\in\mathbf{S}'}P_t(s_{t+1}=s|s_t=s',b_t,a,o)P(s_t=s'|b_t,a,o)$$

$$= \sum_{s' \in \mathbf{S}'} p_t(s|s',a,o) P(s_t = s'|b_t,a,o) \tag{3}$$

$$P(s_t = s'|b_t,a,o) = \frac{P(o|b_t,a,s_t=s')P(s_t=s'|b_t,a)}{\sum_{s'' \in \mathbf{S}'} P(o|s_t=s'',b_t,a)P(s_t=s''|b_t,a)} = \frac{f_t(o|s',a)b_t(s')}{\sum_{s'' \in \mathbf{S}'} f_t(o|s'',a)b_t(s'')} \tag{4}$$

We replace $P(s_t = s'|b_t,a,o)$ in Equation (3) with the right hand side of Equation (4). Then,

$$\tilde{b}^a_{b_t,o}(s) = \sum_{s' \in \mathbf{S}'} p_t(s|s',a,o) \frac{f_t(o|s',a)b_t(s')}{\sum_{s'' \in \mathbf{S}'} f_t(o|s'',a)b_t(s'')}$$

D. Proof of Theorem 1

We prove this theorem by induction where the base-case is $t = N$.

Step 0: By definition, $V^*_N(b_N) = W^*_N(b_N) = Y^*_N(b_N) = \sum_{s \in \mathbf{S}'} b_N(s) q_N(s)$.

Step *N*-*n*: We will prove that $W^*_n(b_n)$ is $PL\&C$ in b_n and omit the proofs for $V^*_n(b_n)$ and $Y^*_n(b_n)$ because they are very similar. Note that following equations hold according to the definitions of V^*_t and W^*_t.

$$V^*_t(b_t) = \max_{a \in \mathbf{A}}(V_t(b_t,a)) \; and \; W^*_t(b_t) = \max_{a \in \mathbf{A}}(W_t(b_t,a)) \tag{5}$$

where $V_t(b_t,a)$ and $W_t(b_t,a)$ refer to the maximum expected TQALYs for a $50+t$-year-old post-CRC and high-risk patient with belief state b_t when action a is selected. For example;

$$\begin{aligned} W_t(b_t,a) = &\sum_{s \in \mathbf{S}'} b_t(s) q_t(s,a) + \lambda_t \sum_{s \in \mathbf{S}'} \Big[\sum_{o \in \{T-,P+\}} b_t(s) f_t(o|s,a) l_t(b_t,a,o) W^*_{t+1}(b^a_{b_t,o}) \\ &+ \sum_{o \in \{C+,SD\}} b_t(s) f_t(o|s,a) \Big(l_t(b_t,a,o) V^*_{t+1}(b^a_{b_t,o}) + \tilde{b}^a_{b_t,o}(UCT) V^*_{t+1}(UCT) \Big) \Big], \quad t < N \end{aligned} \tag{6}$$

Assume that $V^*_{n+1}(b)$, $W^*_{n+1}(b)$, and $Y^*_{n+1}(b)$ are $PL\&C$ for all $b \in \mathbf{B}$. Then, $\exists \; \alpha_{n+1} = \{\alpha^1_{n+1}, \alpha^2_{n+1}, \ldots\}$, $\dot{\alpha}_{n+1} = \{\dot{\alpha}^1_{n+1}, \dot{\alpha}^2_{n+1}, \ldots\}$, and $\ddot{\alpha}_{n+1} = \{\ddot{\alpha}^1_{n+1}, \ddot{\alpha}^2_{n+1}, \ldots\}$ where

$$V^*_{n+1}(b) = \max_{0 \le k \le |\alpha_n|} \sum_{s \in \mathbf{S}'} b(s) \alpha^k_{n+1}(s); \;\; W^*_{n+1}(b) = \max_{0 \le k \le |\dot{\alpha}_n|} \sum_{s \in \mathbf{S}'} b(s) \dot{\alpha}^k_{n+1}(s); \;\; Y^*_{n+1}(b) = \max_{0 \le k \le |\ddot{\alpha}_n|} \sum_{s \in \mathbf{S}'} b(s) \ddot{\alpha}^k_{n+1}(s)$$

We define $\alpha^{a,o}_{b_n,n+1}$ and $\dot{\alpha}^{a,o}_{b_n,n+1}$ as follows:

$$\alpha^{a,o}_{b_n,n+1}(s) = \alpha^{k^*}_{n+1}(s) \;\; for \;\; s \in \mathbf{S}', \;\; where \;\; k^* \in \arg\max_k \sum_{s \in \mathbf{S}'} b^a_{b_n,o}(s) \alpha^k_{n+1}(s)$$

$$\dot{\alpha}^{a,o}_{b_n,n+1}(s) = \dot{\alpha}^{\dot{k}^*}_{n+1}(s) \;\; for \;\; s \in \mathbf{S}', \;\; where \;\; \dot{k}^* \in \arg\max_k \sum_{s \in \mathbf{S}'} b^a_{b_n,o}(s) \dot{\alpha}^k_{n+1}(s)$$

Next, we replace $V^*_{n+1}(b^a_{b_n,o})$ with $\sum_{s \in \mathbf{S}'} b^a_{b_n,o}(s) \alpha^{a,o}_{b_n,n+1}$, $W^*_{n+1}(b^a_{b_n,o})$ with $\sum_{s \in \mathbf{S}'} b^a_{b_n,o}(s) \dot{\alpha}^{a,o}_{b_n,n+1}$, and $b^a_{b_n,o}$ and $\tilde{b}^a_{b_n,o}(UCT)$ with the belief update formulas in Equation (6). Then,

$$\begin{aligned} W_n(a,b_n) = &\sum_{s \in \mathbf{S}'} b_n(s) q_n(s,a) \\ &+ \lambda_n \sum_{o \in O} \Big(\sum_{s \in \mathbf{S}'} b_n(s) f_n(o|s,a) \frac{\sum_{s' \in \mathbf{S}} \sum_{s'' \in \mathbf{S}'} p_n(s'|s'',a,o) f_n(o|s'',a) b_n(s'') \alpha^{a,o}_{b_n,n+1}(s')}{\sum_{s \in \mathbf{S}'} b_n(s) f_n(o|s,a)} \Big) \\ &+ \lambda_n \sum_{o \in \mathbf{O} \setminus O} \Big(\sum_{s \in \mathbf{S}'} b_n(s) f_n(o|s,a) \frac{\sum_{s' \in \mathbf{S}} \sum_{s'' \in \mathbf{S}'} p_n(s'|s'',a,o) f_n(o|s'',a) b_n(s'') \dot{\alpha}^{a,o}_{b_n,n+1}(s')}{\sum_{s \in \mathbf{S}'} b_n(s) f_n(o|s,a)} \Big) \\ &+ \lambda_n \sum_{o \in O} \Big(\sum_{s \in \mathbf{S}'} b_n(s) f_n(o|s,a) \frac{\sum_{s' \in \mathbf{S}} p_n(UCT|s',a,o) f_n(o|s',a) b_n(s') V^*_{n+1}(UCT)}{\sum_{s \in \mathbf{S}'} b_n(s) f_n(o|s,a)} \Big) \end{aligned} \tag{7}$$

$$= \sum_{s\in\mathbf{S}'} b_n(s)q_n(s,a) + \sum_{s\in\mathbf{S}'} b_n(s)\Big(\lambda_n \sum_{o\in O} f_n(o|s,a)\big(\sum_{s'\in\mathbf{S}} p_n(s'|s,a,o)\alpha^{a,o}_{b_n,n+1}(s')\big)\Big)$$
$$+ \sum_{s\in\mathbf{S}'} b_n(s)\Big(\lambda_n \sum_{o\in\mathbf{O}\setminus O} f_n(o|s,a)\big(\sum_{s'\in\mathbf{S}} p_n(s'|s,a,o)\dot{\alpha}^{a,o}_{b_n,n+1}(s')\big)\Big)$$
$$+ \sum_{s\in\mathbf{S}'} b_n(s)\Big(\lambda_n \sum_{o\in O} f_n(o|s,a)p_n(UCT|s,a,o)V^*_{n+1}(UCT)\Big) \quad (8)$$
$$= \sum_{s\in\mathbf{S}'} b_n(s)\Big(q_n(s,a) + \lambda_n \sum_{o\in O} f_n(o|s,a)\big(\sum_{s'\in\mathbf{S}} p_n(s'|s,a,o)\alpha^{a,o}_{b_n,n+1}(s') + p_n(UCT|s,a,o)V^*_{n+1}(UCT)\big)$$
$$+ \lambda_n \sum_{o\in\mathbf{O}\setminus O} f_n(o|s,a)\big(\sum_{s'\in\mathbf{S}} p_n(s'|s,a,o)\dot{\alpha}^{a,o}_{b_n,n+1}(s')\big)\Big) \quad (9)$$

Equations (9) and (5) imply that $W^*_n(b_n)$, $b_n \in \mathbf{B}$ can be written as follows, which means that $W^*_n(b_n)$ is $PL\&C$.

$$W^*_n(b_n) = \max_{a\in\mathbf{A}} \sum_{s\in\mathbf{S}'} \dot{\alpha}^a_{b_n,n}(s)b_n(s), \quad where$$

$$\dot{\alpha}^a_{b_n,n}(s) = \begin{cases} q_n(s,a) + \lambda_n \sum_{o\in O} f_n(o|s,a)\big(\sum_{s'\in\mathbf{S}'}[p_n(s'|s,a,o)\alpha^{a,o}_{b_n,n+1}(s')] \\ \quad + p_n(UCT/s,a,o)V^*_{n+1}(UCT)\big) \\ \quad + \lambda_n \sum_{o\in\mathbf{O}\setminus O} f_n(o|s,a)\big(\sum_{s'\in\mathbf{S}'} p_n(s'|s,a,o)\dot{\alpha}^{a,o}_{b_n,n+1}(s')\big) & for\ s\in\{3,4,5\} \\ 0 & \text{otherwise.} \end{cases}$$

E. Characterization of α-vectors

Our POMDP model can be solved by finding such α-vector sets α_t, $\dot{\alpha}_t$, and $\ddot{\alpha}_t$ $\forall t \in \mathbf{T}$. We define $\alpha^{a,o}_{b_t,t+1}$, $\dot{\alpha}^{a,o}_{b_t,t+1}$, and $\ddot{\alpha}^{a,o}_{b_t,t+1}$ as the maximizing α-vectors for year $t+1$ given belief state b_t, action a, and observation o in year t. Then, we can rewrite optimality equations by replacing $V^*_{t+1}(b^a_{b_t,o})$, $W^*_{t+1}(b^a_{b_t,o})$, and $Y^*_{t+1}(b^a_{b_t,o})$ with $\sum_{s\in\mathbf{S}'} b^a_{b_t,o}(s)\alpha^{a,o}_{b_t,t+1}(s)$, $\sum_{s\in\mathbf{S}'} b^a_{b_t,o}(s)\dot{\alpha}^{a,o}_{b_t,t+1}(s)$, and $\sum_{s\in\mathbf{S}'} b^a_{b_t,o}(s)\ddot{\alpha}^{a,o}_{b_t,t+1}(s)$, respectively (See Appendix D) where $O \equiv \{C+, SD\}$. That is,

$$V^*_t(b_t) = \max_{a\in\mathbf{A}}(V_t(b_t,a)) = \max_{a\in\mathbf{A}} \sum_{s\in\mathbf{S}'} \alpha^a_{b_t,t}(s)b_t(s), \quad W^*_t(b_t) = \max_{a\in\mathbf{A}}(W_t(b_t,a)) = \max_{a\in\mathbf{A}} \sum_{s\in\mathbf{S}'} \dot{\alpha}^a_{b_t,t}(s)b_t(s), \ and$$
$$Y^*_t(b_t) = \max_{a\in\mathbf{A}}(Y_t(b_t,a)) = \max_{a\in\mathbf{A}} \sum_{s\in\mathbf{S}'} \ddot{\alpha}^a_{b_t,t}(s)b_t(s), \ where$$

$$\alpha^a_{b_t,t}(s) = \begin{cases} q_t(s,a) + \lambda_t \sum_{o\in\mathbf{O}} f_t(o|s,a)\big(\sum_{s'\in\mathbf{S}'}[p_t(s'|s,a,o)\alpha^{a,o}_{b_t,t+1}(s')] \\ \quad + p_t(UCT|s,a,o)V^*_{t+1}(UCT)\big) & for\ s\in\{6,7,8\} \\ 0 & \text{otherwise.} \end{cases}$$

$$\dot{\alpha}^a_{b_t,t}(s) = \begin{cases} q_t(s,a) + \lambda_t \sum_{o\in O} f_t(o|s,a)\big(\sum_{s'\in\mathbf{S}'}[p_t(s'|s,a,o)\alpha^{a,o}_{b_t,t+1}(s')] \\ \quad + p_t(UCT/s,a,o)V^*_{t+1}(UCT)\big) \\ \quad + \lambda_t \sum_{o\in\mathbf{O}\setminus O} f_t(o|s,a)\big(\sum_{s'\in\mathbf{S}'} p_t(s'|s,a,o)\dot{\alpha}^{a,o}_{b_t,t+1}(s')\big) & for\ s\in\{3,4,5\} \\ 0 & \text{otherwise.} \end{cases}$$

$$\ddot{\alpha}^a_{b_t,t}(s) = \begin{cases} q_t(s,a) + \lambda_t \sum_{o\in O} f_t(o|s,a)\big(\sum_{s'\in\mathbf{S}'}[p_t(s'|s,a,o)\alpha^{a,o}_{b_t,t+1}(s')] \\ \quad + p_t(UCT/s,a,o)V^*_{t+1}(UCT)\big) \\ \quad + \lambda_t f_t(P+|s,a)\big(\sum_{s'\in\mathbf{S}'} p_t(s'|s,a,P+)\dot{\alpha}^{a,P+}_{b_t,t+1}(s')\big) \\ \quad + \lambda_t f_t(T-|s,a)\big(\sum_{s'\in\mathbf{S}'} p_t(s'|s,a,T-)\ddot{\alpha}^{a,T-}_{b_t,t+1}(s')\big) & for\ s\in\{0,1,2\} \\ 0 & \text{otherwise.} \end{cases}$$

The α-vectors of our POMDP model, $\alpha^a_{b_t,t}$, $\dot{\alpha}^a_{b_t,t}$, and $\ddot{\alpha}^a_{b_t,t}$, have an intuitive interpretation. For example, $\alpha^a_{b_t,t}(s)$ represents the maximum expected TQALYs of a post-CRC patient if s/he is in state s and action a is selected in year t. Note that the unique sets of $\alpha^a_{b_t,t}$, $\dot{\alpha}^a_{b_t,t}$, and $\ddot{\alpha}^a_{b_t,t}$ vectors $\forall a \in \mathbf{A}$ and $\forall b_t \in \mathbf{B}$ are finite, and they cover the desired α-vector sets; α_t, $\dot{\alpha}_t$, and $\ddot{\alpha}_t$.

F. Parameter Estimation

F.1. Health State Transition Probabilities

We estimate the transition probabilities for post-CRC patients using either the MCRC-NH simulation model (Erenay et al. 2011) or SEER data based on age and gender. We obtain most of the age-specific colorectal lesion progression probabilities from the National Polyp Study (Loeve et al. 2004). Because no study reports age- and gender-specific probabilities of polyp-to-CRC progression and mortality from undetected CRC, we calibrate them as described in Appendix F.4.

We obtain the annual death probabilities for cancer-free, low-, and high-risk patients who do not undergo colonoscopy screening, $\delta^t_{0,T-}(DN)$, for $i \leq 4$, from US life tables (Arias 2007). We also approximate the probability of mortality in the UCT state, $\delta^t_{9,T-}(DN)$, using the probability of mortality from distant CRC (SEER 2012). In addition, we quantify the annual probability of mortality after undergoing colonoscopy screening with a $T-$ or $P+$ result using Equations (1) and (2) (See Appendix A). We estimate the one-year probability of mortality after CRC treatment using CRC survival rates in SEER database. Lesion progression probabilities in CRC states, $\rho^t_{i,6}$, $\rho^t_{i,7}$, $\rho^t_{i,8}$ for $i \in \{2,5,8,9\}$, and the probability that a CRC treatment will be completed within one year given that the patient does not die, γ^t_i for $i \in \{2,5,8,9\}$, depend on metastatic recurrence of CRC. We derive these probabilities by conducting a meta-analysis using data from the literature and the MCRC-NH simulation.

F.2. Immediate Rewards

Using data from clinical studies listed in Table 4, we estimate the disutility values as follows:

- d_C: We estimate the disutility of having undetected CRC as 0.134 years using CRC stage distribution and QALYs for having CRC from the literature (Syngal et al. 1998, SEER 2012).
- d_{CT} and d_{UCT}: We derive the disutilities of CRC treatment and being in the UCT state as 0.4 and 0.75 years using data from the literature (Ness et al. 2000, SEER 2012).
- $\underline{d}(Co)$ and $\overline{d}(Co)$: We estimate the disutility of colonoscopy with and without polypectomy as 2.4 and 0.8 weeks using clinical data from the literature by considering the effects of pain and anxiety associated with the procedure, hospitalization time, and colonoscopic complications (Lieberman et al. 2000, Thomson et al. 2000, Nelson et al. 2002, Gerson et al. 2004, Aujesky et al. 2005, Spiegel et al. 2005, Levin et al. 2006, Chhatwal et al. 2010).

Note that, measuring disutility in life years or QALYs is a common method used by other public health studies (Syngal et al. 1998, Chhatwal et al. 2010, Aujesky et al. 2005). We approximate the terminal rewards, $q_N(s)$ where $N = 100$, by calculating the expected difference between lifetime and disutility for ages 100-125 using a Markov process. That is,

$$q_N(s) = \sum_{100 \le t \le 125} \sum_{s' \in \mathbf{S}} P_t(S_t = s' | S_{100} = s) \lambda^{t-100} q_t(s', DN) \ \ for\ s \in \mathbf{S}$$

We calculate the input parameters for ages over 100 by extrapolating the transition probabilities for ages 95-99 using linear regression. The estimated $q_N(s)$ values are illustrated in Table 13. Arias (2007) estimates the mean remaining lifetime for males and females as 2.3 and 2.6 years at age 100. We estimate these values as 2.35 and 2.66 years by weighting the terminal rewards in Table 13 with the health state distribution at age 100 which is derived using the simulation model described in Appendix F.4. Therefore, we contend that our estimation of terminal rewards is valid.

	$LR0(0)$	$LR1(1)$	$LR2(2)$	$HR0(3)$	$HR1(4)$	$HR2(5)$	$PC0(6)$	$PC1(7)$	$PC2(8)$	$UCT(9)$
$q_N(s)$ Values For Males	2.38	2.36	0.7	2.38	2.36	0.7	1.12	1.05	0.7	0.2
$q_N(s)$ Values For Females	2.69	2.67	0.7	2.69	2.67	0.7	1.30	1.15	0.7	0.1

Table 13 Terminal reward values for 100-year-old males and females (QALYs)

F.3. Other Input Parameters

We obtain the sensitivity of colonoscopy for polyps and CRC as 85% and 90% from the literature, respectively (Frazier et al. 2000, Vijan et al. 2007). We approximate the probability of CRC self-diagnosis for $a = DN$, ω_{DN}, as 0.49 using stage-based self-diagnosis probabilities (Frazier et al. 2000) and CRC stage distributions (SEER 2012). On the other hand, we assume that $\omega_{Co} = 0$ because severe symptoms that cause self-diagnosis are unlikely when CRC is missed by a colonoscopy. For the base-case analysis, we set the discount factor λ to 1 (0% discount rate), because we prefer not to discriminate the health benefits that occur late in the life. This is reasonable as many medical decision makers prefer not discounting health benefits (Smith and Gravelle 2001). On the other hand, we conducted a sensitivity analysis on the discount factor in Appendix I.2.

We derive most of the cost inputs from the cost-effectiveness analysis of Lansdorp-Vogelaar et al. (2009) mainly because they conducted a detailed cost analysis using MEDICARE cost data and, to the best of our knowledge, theirs is the only study that estimated CRC treatment and continuing care costs separately. Deriving them separately is important as we consider progression of CRC among post-CRC patients in our model. The cost inputs that are not reported in Lansdorp-Vogelaar et al. (2009) are derived from Vijan et al. (2007). We consider the cost of colonoscopy screening, biopsy and pathology, treatment of complications, CRC treatment, terminal care, and continuing care. All of the derived costs are translated into 2009 dollars using the medical care component of the Consumer Price Index (BLS 2010).

F.4. Calibration

The annual probability of polyp-to-CRC progression ($\rho^t_{1,2}$, $\rho^t_{4,5}$) and mortality from undetected CRC ($\delta^t_{2,T-}(DN)$, $\delta^t_{5,T-}(DN)$) are two important inputs of our model which are not available in any clinical database because detected polyps and CRC cases are immediately removed and treated. Therefore, we estimate these probabilities by calibrating a simulation model that mimics the progression of CRC. Calibration is a common method to derive unobservable natural history parameters for cancer. Stout et al. (2009) describe calibration as the process of determining the unobservable parameters by restricting the model to replicate observed data.

In our case, we determine the unobservable parameter combination for which our CRC simulation model accurately estimates the risk of developing CRC and risk of CRC mortality reported by SEER database for ages 51-95 (SEER 2012). Basically, we develop a simulation model that mimics CRC progression as it is modeled in our POMDP model and run this simulation model for different combinations of unobservable parameters systemically. Then, we choose the combination that minimizes the total square error. We perform 50,000 replications for each parameter combination. Note that, raw SEER data are associated with censoring issues such as limited data exist for older patients whose screening are terminated after a certain age. However, these censoring issues do not significantly affect our calibration process because: 1) We use processed SEER data (such as lifetime CRC risk that is estimated using statistical methods) for the calibration process instead of raw SEER data such as CRC incidence. 2) We explicitly model the events that cause censoring issues such as screening termination in the simulation model, which is used for calibration. Other details related to the calibration procedure are available in Erenay (2010).

G. Validation

We validated our model through three steps: 1) Face validity; 2) Comparison with clinical data; and 3) Comparison with other studies. First, we validated our model based on expert opinion. We built our model by collaborating with Dr. Adnan Said, the Chief of the Gastroenterology and Hepatology department in VA Medical Center in Wisconsin-Madison. He went over our CRC progression modeling framework and assumptions such as all non-recurrent colorectal lesions follow polyp-to-cancer sequence. He guided us in adjusting the dynamics of the model and our assumptions until he was content that our model reasonably represents current clinical knowledge about CRC progression. He also verified that our numerical results are clinically reasonable.

Next, we compared some of the model's outputs with the statistics from SEER database, the largest cancer registry in the US, for low-risk and high-risk patients (SEER 2012). We estimated the

cumulative risk of developing CRC and risk of CRC mortality between ages 50-95 using our model. We observed that the results of our model are very close to those derived from SEER database. For example, Figure 3 shows that the cumulative risk of developing CRC and CRC mortality estimated by our model and those estimated from SEER database are close to each other for 50-year-old males. Therefore, we are content that our model complies with the existing clinical information about CRC progression in the US.

We also verified that our model represents the CRC progression among post-CRC patients well by comparing our results with those reported in the literature and provided by medical databases. For example, for the post-CRC patients, we used the input parameters provided by a simulation study which uses data from MAYO Clinic-Rochester (Erenay et al. 2011). Based on this data, we estimated the lifetime MCRC incidence as 14.8% (two times of 5-year MCRC incidence as half of the metachronous lesions are detected in the first 5-years after the initial treatment (Fajobi et al. 1998)) and the lifetime metahcronous adenomatous polyp incidence is reported as 51% in the literature (Nusko et al. 2001). Our model estimated these lifetime incidences as 14.83% and 50.3%, respectively. We also estimated the post-CRC life expectancies for 10-years after the initial CRC treatment for several age-groups using our model and compared them with the results from SEER database (SEER 2012). We observed that our estimations comply with the results provided by SEER database. The close match between our model results and those presented in other sources convinced us that our model represents the progression of post-CRC patients well.

Finally, we compared the results of our model with that of an existing clinically-validated simulation model known as MISCAN CRC Simulation. Lansdorp-Vogelaar et al. (2009) used MISCAN simulation model to estimate the life-year savings for 50-year-old asymptomatic patients through different screening policies (e.g. screening every 5, 10, 15, and 20 years) compared to no screening option. In their analysis, they assumed that the lifetime savings are discounted with a rate of %3 and patients are screened between the ages of 50 and 80. Under the same assumptions, we estimated the lifetime savings for the same screening policies and observed that our estimations are very close to that of Lansdorp-Vogelaar et al. (2009). The detailed results are provided in Table 5. These results illustrate that our model represents CRC screening in the US population well.

H. The Optimal Colonoscopy Screening Decisions

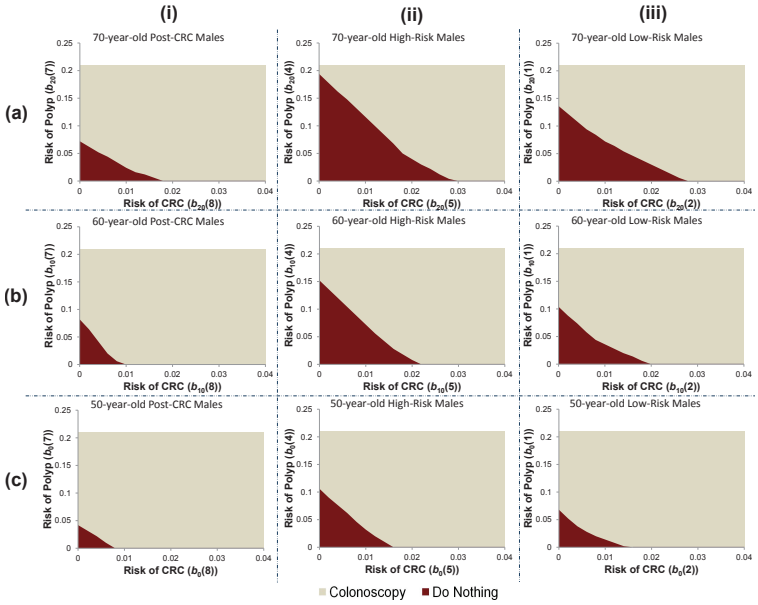

Figure 10 **The optimal colonoscopy screening decisions for males at various ages**

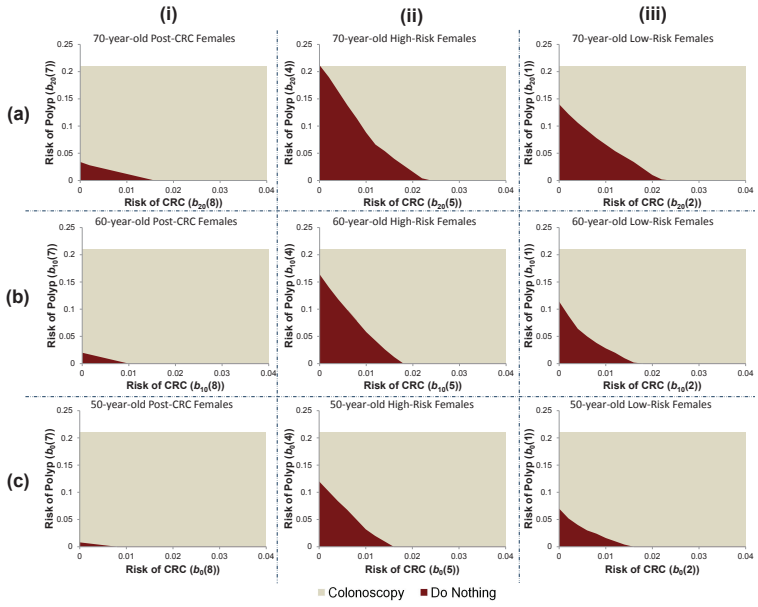

Figure 11 **The optimal colonoscopy screening decisions for females at various ages**

I. Sensitivity Analysis

We conducted two types of sensitivity analyses: 1) Robustness analyses which measure the performance of the base-case optimal policy with different parameter settings and 2) Sensitivity analyses that measure the effect of these parameters on the performance of the corresponding optimal policies. Note that we only measure the performance of the base-case optimal policy in the prior type of analyses; whereas, we derive an optimal policy for each parameter setting and measure its performance in the latter type.

For the sensitivity analyses on disutility levels, we multiply the base-case disutility levels given in Table 4 with a constant, $w \in \{0.5, 1, 1.5, 2\}$, to generate different disutility scenarios. We do not consider the cases where $w > 2$ for colonoscopy disutility and $w \geq= 2$ for other disutilities as such cases are not realistic. Frazier et al. (2000) and Vijan et al. (2007) report the sensitivity of colonoscopy for adenomatous polyps and CRC to vary between 80-90% and 85-95%, respectively. Therefore, we consider the following five scenarios for the sensitivity analysis on colonoscopy sensitivity: a) Low sensitivity, 80% for polyps and 85% for CRC lesions, b) Base-case, 85% v.s. 90%, c) High sensitivity, 90% v.s. 95%, d) Low sensitivity with high range, 80% v.s. 90% for CRC, e) High sensitivity with high range, 85% v.s. 95%. Based on the literature (Frazier et al. 2000, Vijan et al. 2007, Zauber et al. 2008), we consider the following compliance level scenarios: i) 100% for preventative screening, 100% for follow-up; ii) 80% v.s. 95%; iii) 70% v.s. 85%; iv) 50% v.s. 75%; v) 25% v.s. 50%. Finally, because most analyses use 3-5% discounting for costs and it is recommended to discount the QALYs 1-3.5% less than the costs (Severens and Milne 2004), we consider discount rates of 0%, 1%, 2%, and 3% for the sensitivity analyses.

I.1. Robustness of the Base-case Optimal Policies:

For the comparison of proposed policies and guidelines given in Section 6.3, the optimal policies are derived from the POMDP model using the base-case input parameters in Table 4. Note that the base-case parameters may not represent all possible clinical situations, or perspectives and preferences of patients. Therefore, we need to investigate the possible outcomes in case of applying the base-case optimal policies to different input parameter settings to measure their robustness.

Table 14 shows how the performance of the base-case optimal policies is affected by the changes in all-cause, colonoscopy, and CRC treatment disutilities. These results illustrate that colonoscopy and CRC treatment disutilities affect the performance of the base-case optimal policies differently. As colonoscopy screening disutilities increase, TQALY improvements decrease because increasing colonoscopy disutilities discourage aggressive screening policies. On the other hand, the increase in CRC treatment disutilities slightly increases the % improvements in TQALYs, which is reasonable because increasing the CRC treatment disutilities increase the significance of CRC prevention. Note that, changes in CRC treatment disutilities are significantly less effective on the performance of the base-case policies than those in colonoscopy disutilities. This observation is also supported by the fact that TQALY improvements in all-cause disutility analysis are very close to those in colonoscopy disutility analysis rather than those in CRC treatment disutility analysis. This is mainly because CRC treatment is applied to only at most 5-6% of patients, whereas, colonoscopy is applied to all of patients many times throughout their lives.

These results show that, the performance of the base-case optimal policies is sensitive to colonoscopy disutility and robust to the changes in CRC treatment disutility. This analysis also shows that aggressive screening such as the base-case optimal policies perform better than the guidelines even if the actual disutility preferences of patients differ from the base-case, unless disutilities are assessed extremely high.

		Low-Risk Patients					High-Risk Patients					Post-CRC Patients				
	Sensitivity Level	**80% & 85%**	**85% & 90%**	**90% & 95%**	**80% & 90%**	**85% & 95%**	**80% & 85%**	**85% & 90%**	**90% & 95%**	**80% & 90%**	**85% & 95%**	**80% & 85%**	**85% & 90%**	**90% & 95%**	**80% & 90%**	**85% & 95%**
	TQALYs	0.17%	0.16%	0.14%	0.17%	0.16%	0.23%	0.19%	0.16%	0.23%	0.19%	0.93%	0.90%	0.87%	0.93%	0.90%
Colonocopy Sensitivity	**# of Colonoscopies**	88.78%	87.10%	85.66%	88.76%	87.08%	65.15%	64.43%	63.83%	65.13%	64.42%	173.81%	174.73%	175.48%	173.71%	174.63%
	CRC Risk	40.00%	41.00%	41.91%	40.00%	41.00%	33.98%	34.06%	34.05%	33.98%	34.06%	66.85%	69.64%	72.13%	66.85%	69.64%
	CRC Mortality	44.85%	46.11%	47.25%	45.31%	46.63%	35.37%	35.38%	35.29%	35.71%	35.66%	73.89%	77.01%	79.85%	74.70%	77.80%
	Total Cost	5.14%	5.28%	5.41%	5.14%	5.28%	6.00%	6.39%	6.73%	5.98%	6.36%	1.57%	1.56%	1.55%	1.56%	1.55%
	Compliance Level	**100% & 100%**	**80% & 95%**	**70% & 85%**	**50% & 75%**	**25% & 50%**	**100% & 100%**	**80% & 95%**	**70% & 85%**	**50% & 75%**	**25% & 50%**	**100% & 100%**	**80% & 95%**	**70% & 85%**	**50% & 75%**	**25% & 50%**
	TQALYs	0.16%	0.14%	0.12%	0.10%	0.07%	0.19%	0.19%	0.18%	0.17%	0.15%	*	*	*	*	*
Compliance Rates	**# of Colonoscopies**	87.10%	88.41%	89.35%	92.34%	102.84%	64.43%	64.80%	65.66%	66.77%	71.43%	*	*	*	*	*
	CRC Risk	41.00%	26.52%	21.15%	12.78%	5.39%	34.06%	28.70%	20.70%	15.30%	7.27%	*	*	*	*	*
	CRC Mortality	46.11%	31.52%	26.43%	18.75%	12.40%	35.38%	30.56%	23.79%	19.73%	14.28%	*	*	*	*	*
	Total Cost	5.28%	4.12%	3.57%	2.48%	1.12%	6.39%	5.98%	5.21%	4.47%	2.72%	*	*	*	*	*

Table 15 **Performance of the base-case optimal policies for different colonoscopy sensitivity and compliance scenarios among 50-year-old males: Note that, sensitivity level of 85% & 90% and perfect compliance represent the base-case. Post-CRC patients are assumed to perfectly comply with surveillance screening, therefore, they are omitted from compliance rate analysis.**

	Disutility Level	**w = 0.5**	**w = 1**	**w = 1.5**	**w = 2**
All-Cause Disutilities	**Low-Risk Patients**	0.24%	0.16%	0.07%	*
	High-Risk Patients	0.30%	0.19%	0.08%	*
	Post-CRC Patients	1.11%	0.90%	0.69%	*
Colonoscopy Disutilities	**Low-Risk Patients**	0.25%	0.16%	0.06%	-0.04%
	High-Risk Patients	0.31%	0.19%	0.07%	-0.05%
	Post-CRC Patients	1.19%	0.90%	0.61%	0.32%
CRC Treatment Disutilities	**Low-Risk Patients**	0.15%	0.16%	0.16%	*
	High-Risk Patients	0.18%	0.19%	0.20%	*
	Post-CRC Patients	0.84%	0.90%	0.97%	*

Table 14 **Performance of the base-case optimal policies for different disutility scenarios among 50-year-old males: Note that w=1 represents the base-case. Because applying different disutility levels using the same screening policy only changes the TQALYs, the other performance measures are the same as those in Table 6, and thus, are omitted from this table.**

Table 15 shows how the performance of the base-case optimal policies are affected by the changes in colonoscopy sensitivity and compliance levels. Table 15 illustrates that small changes in colonoscopy sensitivity do not significantly affect the performance of the base-case optimal policies. For example, for all sensitivity scenarios, the base-case optimal policies are associated with around 0.15% TQALY improvement, 40% CRC risk, and 45% CRC mortality reductions, respectively. The base-case policies require patients to undergo colonoscopy several times. These results suggest that the cumulative accuracy of so many repetitive colonoscopy screenings is minimally affected by the small changes in the colonoscopy sensitivity. The changes on the compliance level have a greater effect on the performance of the base-case optimal policies because compliance determines the proportion of the population who will benefit from screening. Therefore, as the compliance level decreases % improvements associated with the base-case optimal

policies reduce. However, the base-case optimal policies perform better than the guidelines for all of the scenarios.

The optimal policies derived using our POMDP model appear to be robust to the changes in several parameters including colonoscopy sensitivity and CRC treatment disutility and somehow sensitive to the others. Colonoscopy disutility appears to be the most sensitive input parameter. However, this robustness analysis demonstrates that the base-case optimal policy, which is more aggressive than the guidelines, outperforms the guidelines regardless of the actual underlying parameter scenario except the extreme cases.

I.2. Sensitivity of the Optimal Policies to Parameter Changes:

It is also important to investigate how modifications in input parameters affect the optimal policies. For this purpose, we solved our POMDP model for several parameter scenarios. The performances of these scenario-specific optimal policies for 50-year-old males are given in Table 16. Like those in Appendix I.1, these results show that while colonoscopy disutilities significantly affect the performance of the optimal policies, the effect of CRC treatment disutilities on their performance is limited. For example, regardless of treatment disutility, the optimal policies for low-risk males improve TQALYs by around 0.16% and recommend around 85% more colonoscopies than the guidelines. On the other hand, as colonoscopy disutilities increase, the corresponding optimal policies recommend less frequent screening. Furthermore, improvements in TQALYs, CRC risk, and CRC mortality decrease because higher colonoscopy disutilities diminish the benefits of additional colonoscopy screenings. However, even in case of extremely high colonoscopy disutilities, the optimal policies recommend more frequent screening than the guidelines. These results provide justification for the clinicians who advocate more aggressive CRC screening. In addition, the performance of the optimal policies in all-cause disutility analysis is again closer to that in colonoscopy disutility analysis.

A comparison of the improvements in Tables 14 and 16 reveals that deriving the optimal policy according to the individual's actual disutility preferences is associated with significant performance improvements, especially in case of a high colonoscopy disutility. Therefore, it is best to measure an individual patient's disutility preferences and then apply our POMDP framework to determine the optimal policy for her/him. This observation identifies a particular way of using our POMDP framework for personalized CRC screening.

Table 16 illustrates that sensitivity of colonoscopy also has limited effect on the optimal policies. That is, colonoscopy sensitivity scenarios result in approximately 0.16% TQALY, 43% CRC risk, and 48% CRC mortality improvements by recommending around 80-105% more frequent screening

for low-risk males. As colonoscopy sensitivity increases, the optimal policy suggests relatively less frequent screening and the TQALY improvements slightly decrease. This is because colonoscopy is already an accurate technique. Therefore, small changes in its sensitivity have limited effect on its cumulative accuracy for detecting colorectal lesions in time; thus, as the sensitivity increases, the benefit of additional colonoscopies diminishes.

	Low-Risk Patients					High-Risk Patients					Post-CRC Patients				
All-Cause Disutility Level	**w = 0.5**	**w = 1**	**w = 1.5**	*	*	**w = 0.5**	**w = 1**	**w = 1.5**	*	*	**w = 0.5**	**w = 1**	**w = 1.5**	*	*
TQALYs	0.28%	0.16%	0.09%	*	*	0.34%	0.19%	0.13%	*	*	1.14%	0.90%	0.73%	*	*
# of Colonoscopies	170.19%	87.10%	52.19%	*	*	107.36%	64.43%	28.67%	*	*	250.30%	174.73%	120.39%	*	*
CRC Risk	60.03%	41.00%	29.29%	*	*	49.89%	34.06%	16.58%	*	*	78.50%	69.64%	59.31%	*	*
CRC Mortality	67.79%	46.11%	33.02%	*	*	57.16%	35.38%	11.71%	*	*	84.23%	77.01%	67.65%	*	*
Total Cost	12.87%	5.28%	2.56%	*	*	12.21%	6.39%	2.13%	*	*	3.23%	1.56%	0.55%	*	*
Colonoscopy Disutility Level	**w = 0.5**	**w = 1**	**w = 1.5**	**w = 2**	*	**w = 0.5**	**w = 1**	**w = 1.5**	**w = 2**	*	**w = 0.5**	**w = 1**	**w = 1.5**	**w = 2**	*
TQALYs	0.30%	0.16%	0.08%	0.05%	*	0.36%	0.19%	0.12%	0.09%	*	1.24%	0.90%	0.67%	0.53%	*
# of Colonoscopies	171.23%	87.10%	37.88%	8.85%	*	110.07%	64.43%	26.92%	6.26%	*	260.34%	174.73%	113.87%	85.46%	*
CRC Risk	60.28%	41.00%	21.65%	7.32%	*	50.92%	34.06%	15.42%	0.76%	*	80.04%	69.64%	56.42%	49.99%	*
CRC Mortality	68.14%	46.11%	22.60%	6.19%	*	59.03%	35.38%	9.79%	-9.97%	*	85.58%	77.01%	64.13%	57.64%	*
Total Cost	12.96%	5.28%	1.66%	-0.05%	*	12.59%	6.39%	1.95%	0.08%	*	3.42%	1.56%	0.52%	0.05%	*
CRC Treatment Disutility Level	**w = 0.5**	**w = 1**	**w = 1.5**	*	*	**w = 0.5**	**w = 1**	**w = 1.5**	*	*	**w = 0.5**	**w = 1**	**w = 1.5**	*	*
TQALYs	0.15%	0.16%	0.16%	*	*	0.18%	0.19%	0.20%	*	*	0.84%	0.90%	0.97%	*	*
# of Colonoscopies	81.38%	87.10%	87.41%	*	*	52.91%	64.43%	65.02%	*	*	172.61%	174.73%	177.66%	*	*
CRC Risk	40.46%	41.00%	41.11%	*	*	30.09%	34.06%	34.32%	*	*	69.04%	69.64%	70.80%	*	*
CRC Mortality	46.39%	46.11%	46.37%	*	*	31.28%	35.38%	35.90%	*	*	76.29%	77.01%	78.59%	*	*
Total Cost	4.75%	5.28%	5.30%	*	*	4.90%	6.39%	6.45%	*	*	1.53%	1.56%	1.58%	*	*
Colonocopy Sensitivity Level	**80% & 85%**	**85% & 90%**	**90% & 95%**	**80% & 90%**	**85% & 95%**	**80% & 85%**	**85% & 90%**	**90% & 95%**	**80% & 90%**	**85% & 95%**	**80% & 85%**	**85% & 90%**	**90% & 95%**	**80% & 90%**	**85% & 95%**
TQALYs	0.17%	0.16%	0.15%	0.17%	0.16%	0.23%	0.19%	0.16%	0.23%	0.19%	0.93%	0.90%	0.88%	0.93%	0.89%
# of Colonoscopies	104.51%	87.10%	79.45%	104.97%	81.48%	72.19%	64.43%	50.36%	72.48%	61.84%	175.84%	174.73%	148.01%	174.89%	175.24%
CRC Risk	44.12%	41.00%	41.30%	44.14%	40.48%	36.13%	34.06%	30.22%	36.22%	33.27%	67.21%	69.64%	69.21%	67.10%	69.81%
CRC Mortality	49.01%	46.11%	47.72%	49.48%	47.09%	37.44%	35.38%	32.75%	37.77%	35.21%	74.15%	77.01%	78.56%	74.87%	77.88%
Total Cost	6.43%	5.28%	4.82%	6.48%	4.76%	6.92%	6.39%	4.89%	6.93%	6.03%	1.61%	1.56%	0.93%	1.58%	1.56%
Discount Rate	**0%**	**1%**	**2%**	**3%**	*	**0%**	**1%**	**2%**	**3%**	*	**0%**	**1%**	**2%**	**3%**	*
TQALYs	0.16%	0.11%	0.08%	0.05%	*	0.19%	0.14%	0.10%	0.07%	*	0.90%	0.74%	0.60%	0.48%	*
# of Colonoscopies	87.10%	73.81%	58.10%	37.43%	*	64.43%	41.71%	36.11%	23.78%	*	174.73%	155.41%	143.52%	141.93%	*
CRC Risk	41.00%	38.30%	32.88%	23.06%	*	34.06%	24.79%	23.74%	16.71%	*	69.64%	67.25%	65.16%	64.89%	*
CRC Mortality	46.11%	44.54%	38.40%	25.82%	*	35.38%	24.68%	25.24%	15.76%	*	77.01%	75.52%	73.55%	73.29%	*
Total Cost	5.28%	4.94%	4.25%	2.91%	*	6.39%	4.36%	4.19%	2.98%	*	1.56%	1.40%	1.40%	1.61%	*

Table 16 Performance of the optimal policies for different parameter scenarios

Finally, Table 16 shows that the optimal policies recommend less frequent screening and health outcome improvements decrease as the discount rate increases. This is reasonable because CRC is a slow-developing disease, i.e., a significant part of the CRC cases are expected to occur at later ages. As the discount rate increases, life-year improvements in older ages contribute less and QALY reductions due to disutility of colonoscopies in earlier ages weigh more in the calculation of TQALYs. Therefore, increasing the discount rate decreases the contribution of additional screenings. However, the optimal policies still recommend more frequent screening than the guidelines for all discount rate scenarios.

We also conduct a sensitivity analysis on the probability of colonoscopy complication and death resulting from such a complication. For this purpose, we multiplied the base case values of these probabilities with factors 0.5, 1, 2, and 3 and run our POMDP model for for 50-year-old males.

Table 17 summarize the performance improvements of the optimal policies compared to the guidelines for these scenarios. We find that as the probability of complications and the probability of death resulting from complications increase, the optimal screening policies recommend less frequent colonoscopy screenings and percentage improvements decrease. However, in all cases, the optimal policies require more aggressive screening than the guidelines.

		TQALYs	# of Screening	CRC Risk	CRC Mortality	Total Cost	Lifetime	Screening Interval
LR Patients	Multiplier = 0.5	0.160%	89.01%	41.03%	45.44%	5.47%	0.33%	52.22%
	Multiplier = 1	0.156%	87.10%	41.00%	46.11%	5.28%	0.33%	51.20%
	Multiplier = 2	0.151%	81.37%	40.44%	46.44%	4.75%	0.32%	48.97%
	Multiplier = 3	0.143%	82.06%	39.24%	44.07%	4.89%	0.32%	50.44%
HR Patients	Multiplier = 0.5	0.198%	64.73%	34.24%	35.83%	6.42%	0.41%	43.62%
	Multiplier = 1	0.193%	64.43%	34.06%	35.38%	6.39%	0.40%	43.55%
	Multiplier = 2	0.184%	52.84%	30.06%	31.37%	4.89%	0.36%	39.09%
	Multiplier = 3	0.177%	50.01%	29.47%	31.45%	4.51%	0.35%	37.62%
Post-CRC Patients	Multiplier = 0.5	0.913%	175.66%	69.87%	77.16%	1.57%	1.30%	57.65%
	Multiplier = 1	0.902%	174.73%	69.64%	77.01%	1.56%	1.30%	57.50%
	Multiplier = 2	0.880%	174.40%	69.53%	76.92%	1.56%	1.30%	57.46%
	Multiplier = 3	0.860%	154.39%	66.89%	74.99%	1.13%	1.24%	53.78%

Table 17 Performance of the policies for different probabilities of colonoscopy complications and death resulting from colonoscopy complications

This sensitivity analysis demonstrates that the optimal policies recommend more frequent CRC screening regardless of the disutility levels, colonoscopy sensitivities, probability of complication, and the choice of discount rate. However, the actual colonoscopy disutility level and discount factor significantly affect the screening frequency of optimal policies as well as their performances. Therefore, these factors are important to specify for a particular patient for the best health outcome improvements.

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