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Optimal Policies for Reducing Unnecessary Follow-up Mammography Exams in Breast Cancer Diagnosis

Oguzhan Alagoz[†], Jagpreet Chhatwal[‡], and Elizabeth S. Burnside[§]

[†]Department of Industrial and Systems Engineering, University of Wisconsin-Madison, 1513 University Avenue, Madison, WI, 53705, alagoz@engr.wisc.edu

[‡]Department of Health Policy and Management and Industrial Engineering, University of Pittsburgh, 130 De Soto Street Pittsburgh, PA, 15261, chhatwal@pitt.edu

[§]Department of Radiology, University of Wisconsin-Madison, 600 Highland Ave, Madison, WI, 53792, eburnside@uwhealth.org

Abstract

Mammography is the most effective screening tool for early diagnosis of breast cancer. Based on the mammography findings, radiologists need to choose from one of the following three alternatives: 1) take immediate diagnostic actions including prompt biopsy to confirm breast cancer; 2) recommend a follow-up mammogram; 3) recommend routine annual mammography. There are no validated structured guidelines based on a decision-analytical framework to aid radiologists in making such patient management decisions. Surprisingly, only 15–45% of the breast biopsies and less than 1% of short-interval follow-up recommendations are found to be malignant, resulting in unnecessary tests and patient-anxiety. We develop a finite-horizon discrete-time Markov decision process (MDP) model that may help radiologists make patient-management decisions to maximize a patient's total expected quality-adjusted life years. We use clinical data to find the policies recommended by the MDP model and also compare them to decisions made by radiologists at a large mammography practice. We also derive the structural properties of the MDP model, including sufficiency conditions that ensure the existence of a double control-limit type policy.

Keywords

Markov decision processes; double control-limit policy; medical decision making; breast cancer diagnosis; mammography interpretation; practice

1 Introduction

Approximately 230,000 American women were diagnosed with, and 40,000 died of breast cancer in 2011, making breast cancer the most common non-skin cancer affecting women in the U.S (ACS 2011). The life-time probability for a woman to develop breast cancer is 1 in 8 in the U.S. Although breast cancer incidence has been the highest among all cancers for the

past four decades, death rates started decreasing in the late 1980s after steadily rising since 1952. This reversal was primarily due to the increased use of screening mammography that resulted in earlier diagnosis as well as advancements in breast cancer treatment (Berry et al. 2005).

While there exist several breast cancer screening (or diagnostic) methods such as self and clinical breast exams, x-ray mammography, magnetic resonance imaging (MRI) and ultrasound, mammography is the most common modality used in clinical practice. There has been significant controversy on when to start and end screening and how often to screen as reflected in the discussions surrounding the recent change of screening recommendations by the United States Preventative Service Task Forces (USPSTF 2009; Kolata 2009). Despite the controversy, many of the influential medical organizations such as the American Cancer Society, American Medical Association, American College of Radiology (ACR), and National Cancer Institute recommend annual mammography screening for all women over 40 years of age (Qaseem et al. 2007; USPSTF 2009). Around 70% of women over the age of 40 had reported having a mammogram in the last two years (National Center for Health Statistics (2007)).

Once radiologists identify abnormalities on a mammogram, they attempt to accurately determine the patient's risk of cancer and decide on appropriate management of the patients. Based on the mammography findings and their interpretation, radiologists need to make appropriate patient management decisions that include: (i) immediate diagnostic actions including prompt biopsy (examination of the breast tissue typically via image-guided, percutaneous core needle sampling) to confirm whether an abnormality is in fact a breast cancer; (ii) short-interval (six-month) follow-up mammography after categorizing the finding as "probably benign"; or (iii) routine (annual) mammography. In making this decision, radiologists must consider the tradeoff between detecting cancer early and sparing healthy women unnecessary procedures.

The primary reason for recommending short-interval follow-up is to avoid biopsies in lesions with low probability of malignancy without sacrificing the accurate detection of asymptomatic cancers at an early stage when the prognosis is still favorable (Cyrlak 1988; Hall et al. 1988). However, excessive follow-up recommendations have their own limitations. Early recall for follow-up testing on screening mammography causes anxiety, psychological morbidity, and increased health care utilization in the year after a false-positive mammogram is reported (Barton et al. 2004; Brodersen and Siersma 2013). Women experience less anxiety if mammography results are definitive, i.e. they prompt a recommendation for routine annual mammography. In addition, if not properly used, short-interval follow-up mammograms may entail additional mammographic examinations and, probably, more biopsies of benign lesions, thus resulting in economic and psychological consequences (Yasmeen et al. 2003).

There are several issues with the current clinical practice of recommending follow-up exams. Several published studies demonstrate that only 0.4% of mammograms requiring follow-up investigations result in breast cancer diagnosis (Sickles 1991; Varas et al. 1992; Varas et al. 2002; Vizcaíno et al. 2001). One study found only two breast cancers at a six-

month follow-up among 3184 mammograms (Ong et al. 1997). An analysis of Breast Cancer Surveillance Consortium (BCSC) data shows that the cancer detection rate is 8.4 per 1000 (684 out of 81,285) among short-interval follow-up recommendations (Sickles et al. 2005). In addition, there is significant variability in the percentage of follow-up recommendations among radiologists. While Geller et al. (2002) report that 40% of diagnostic mammography cases were associated with the recommendation for short-interval follow-up, Monticciolo and Caplan (2004) find that the percentage of short-interval follow-up recommendations varied by site from 1.1% to 12.2% in a study investigating the use of follow-up recommendations in multiple sites. As a result, Monticciolo and Caplan (2004) note that “the persistent wide variability in short-interval follow-up recommendations indicates further education and attention to the use of this recommendation is warranted.”

The purpose of this research is to develop structured guidelines based on a decision-analytical approach that are designed to help radiologists decide when to recommend biopsy or short-interval follow-up based on a patient-specific breast cancer risk. We develop a finite-horizon Markov decision process (MDP) model that optimizes the post-mammography diagnostic decisions for an individual woman that maximizes her total expected quality-adjusted life-years (QALYs). We solve our model using clinical data and compare the optimal policies to the actual decisions made by the radiologists.

Previous research by Chhatwal et al. (2010) and Burnside et al. (2012) consider only the optimal biopsy decision problem, i.e. when should a woman be sent for biopsy based on her mammographic features and demographic factors. In this paper, we consider a related but another important clinical decision: which patients need a short-interval follow-up exam? The consideration of short-interval follow-up makes our MDP model substantially Different from the MDP model of Chhatwal et al. (2010). Unlike the earlier MDP models, the transition probabilities of the two actions -short-interval follow-up mammography and annual mammography- are not independent of each other thus adding complexity to the structure of the model. In fact, the MDP model of Chhatwal et al. (2010) represents a special case of our model. Finally, since the focus of Chhatwal et al. (2010) and Burnside et al. (2012) is on breast biopsy decision making, they do not investigate the optimal rate of short-interval follow-up recommendations.

The remainder of this paper is organized as follows. We describe the issues related to the clinical practice on mammography interpretation and role of computer-aided diagnostic models to improve mammography diagnosis in Section 2. In Section 3, we present the problem formulation. We then derive the structural properties of the MDP model in Section 4. In Section 5, we provide the optimal policies obtained by solving our MDP model and compare the performance of the model with the clinical data. Finally, we conclude in Section 6 with the discussion of our results.

2 Background on Mammography Interpretation

2.1 Issues with Current Clinical Practice

There exists significant variability in mammography interpretation depending on a radiologist's skills and training, which decreases the accuracy and effectiveness of

mammography screening programs (Barlow et al. 2004; Beam et al. 1996; Kopans 1992). To reduce this variability, the ACR has developed a lexicon, the Breast Imaging Reporting and Data System (BI-RADS) (BI-RADS 1998), which standardizes the terminology used to describe mammogram features. BI-RADS lexicon includes more than 100 descriptors that radiologists use while reading and interpreting abnormalities on mammograms. Furthermore, BI-RADS (edition 3) classifies each mammographic finding into one of the six final assessment categories, i.e. BI-RADS final assessment codes, depending on the probability of cancer (Table 1).

As presented in the table, BI-RADS Category 3 includes cases with less than a 2% probability of cancer, BI-RADS Category 4 includes cases with a wide range of probabilities of malignancy (2 – 95%), whereas BI-RADS 5 includes mammography findings with a probability of cancer of 95% and higher. The recommendation for both BI-RADS categories 4 and 5 is biopsy.

While the use of the BI-RADS lexicon is an important step forward in standardizing reporting, there still exists variability in mammography interpretation (Berg et al. 2000; Kerlikowske et al. 1998). Furthermore, although the BI-RADS lexicon recommends short-interval (six-month) follow-up for “probably benign” (BI-RADS 3) lesions, the use of this guideline remains questionable (Orel et al. 1999; Sickles 1991) and needs re-examination (Yasmeen et al. 2003). Geller et al. (2002) report that among all BI-RADS final assessment codes, BI-RADS Category 3 “had the most variability in associated management recommendations.” Indeed, even the BI-RADS manual states that these recommendations will undergo modifications as more data become available. Kerlikowske et al. (2003) report that the use of short-interval follow-up to monitor BI-RADS 3 category lesions should be limited to as small a number of women as possible because the cancer yield is low for these lesions.

As discussed before, appropriate utilization of the BI-RADS 3 category is designed to decrease biopsy rates for abnormalities with a low likelihood of malignancy and thereby increase the positive predictive value (i.e. the proportion of patients who have cancer among those who underwent biopsy and the biopsy result was positive for cancer) of breast biopsy. However, an excessive and/or inappropriate recommendation rate of short-interval follow-up over *regular mammography* screening has been observed in clinical practice that causes unnecessary patient anxiety and increases the overall health care costs. On the other hand, excessive short-interval follow-up recommendations over *biopsies* can result in delay in breast cancer diagnosis. In this paper, we develop a decision-analytical model that balances these trade-offs quantitatively, as a step towards improving breast cancer diagnosis.

2.2 Computer Aided Diagnosis

In this study, we utilize the information from computer-aided diagnostic (CADx) models for determining the optimal policies for mammography management. The use of CADx models to predict the risk of breast cancer may help radiologists improve mammography decision making because the estimation of cancer risk becomes very complex for the radiologists due to a large number of mammography variables, i.e. 36 variables with multiple levels. Jiang et al. (2001) note that using CADx models help radiologists manage the large amount of

information available, make better decisions, detect more cancers at early stages, and reduce inter-observer variability. The output of CADx models is usually the probability of malignancy, which is more informative than BI-RADS final assessment codes. As a result, more accurate decisions may be made using probability of cancer as an outcome measure.

Researchers use various statistical and artificial intelligence techniques to build CADx models. Burnside et al. (2006,2009) developed a Bayesian network to predict risk of malignancy using mammography findings and demographic factors. Baker et al. (1995) and Ayer et al. (2010) used artificial neural networks, Jesneck et al. (2006) used decision fusion, and Chhatwal et al. (2009) developed a logistic regression model for breast cancer risk prediction using mammography findings. These studies suggest that more accurate decisions may be made using the probability of cancer as an outcome measure. However, CADx models only partly address the problem since they do not provide an optimal probability threshold for the decision to perform a biopsy or short-interval follow-up.

An important component of our MDP model is the patient state estimation, i.e. the current risk of cancer for which we use the Bayesian network (BN) model of Chhatwal et al. (2010) that computes the probability of cancer based on demographic risk factors and mammography findings. In general, a BN is an artificial intelligence technique that enables a domain expert to model uncertain relationships between a variable such as cancer and observable variables such as findings on a mammogram. Our BN includes 36 input variables based on BI-RADS descriptors such as masses, calcifications, etc. We present the list of these input variables in Table 2. We train and cross-validate our BN using mammography data from an academic mammography practice. Our data consist of 62,219 findings, whose outcomes were matched to a cancer registry for final diagnosis of cancer. Therefore, unlike most studies in the literature, we could identify cancers that were missed on mammograms but were later reported to the cancer registry.

We evaluate the performance of our BN using sensitivity (true positive rate), specificity (true negative rate), and area under the receiver operating characteristic curve (AUC) and conclude that our BN model performs better than that of the radiologists in aggregate (AUC= 0.961 vs. 0.939, $P < 0.05$). We used BI-RADS categories to generate radiologists' receiver operating characteristic (ROC) curve, as done in several studies in radiology (Barlow et al. 2004; Burnside et al. 2006; Burnside et al. 2009). However, caution is needed to interpret the results of ROC curves while using six BI-RADS categories (Jiang and Metz 2010). To reduce the bias, we ordered BI-RADS as 1, 2, 3, 0, 4, 5 as mentioned in Barlow et al. (2004). In addition to area under the ROC curve, we also compared the performance of radiologists and the BN using *sensitivity* at 90% specificity, and *specificity* at 85% sensitivity. We used these levels of sensitivity and specificity because they represent the minimal performance thresholds for screening mammography (Bassett et al. 1994). At 90% specificity, the sensitivity of BN was 89.0%, which was significantly better ($P < .001$) than that of the radiologists at 82.2%. At a fixed sensitivity of 85%, the specificity of BN at 94.9% was also significantly better ($P < .001$) than the radiologists at 88.2%. Note that we used linear interpolation for radiologists' performance since these points do not necessarily exist on the ROC curve.

More details about this BN model can be found elsewhere (Chhatwal et al. 2010). Below, we present two real-life cases to illustrate how the BN can be used to estimate the probability of cancer based on mammography findings.

Case 1: A 76-year old woman presents with a circumscribed, oval, equal density mass on her baseline mammogram. This finding was assigned BI-RADS 4 (suspicious) assessment by the radiologist (i.e. recommended action is to perform biopsy). The BN uses these findings and estimates her probability of cancer equal to 1.7%. Biopsy was performed on this woman that resulted in a benign outcome.

Case 2: A 52-year old woman with a personal history of breast cancer had a mammogram which demonstrated an ill-defined, oval-shaped equal density mass that was increasing in size. The radiologist assigned BI-RADS 3 (probably benign) assessment to this abnormality and the patient was not recommended a biopsy. The BN estimates a 3.8% probability of cancer. Six months later, biopsy of this abnormality revealed a malignant tumor.

According to the BN, *Case 2* had a higher likelihood of cancer in comparison to *Case 1*. However, radiologists took less aggressive action in *Case 2* in comparison to *Case 1*, showing inconsistency in radiologists' decision making. To find the optimal threshold for a biopsy or short-interval follow-up exam, we integrate the findings of our BN with an MDP model as described in the next section.

3 Problem Formulation

We develop a finite-horizon MDP model to address the optimal diagnostic decision problem faced by the radiologists. We assume that the decision maker is a radiologist and/or the patient whose objective is to maximize the patient's total expected QALYs. In computing the QALYs, we only consider expected life years and the disutilities of screening and biopsy and ignore age-related and treatment-related disutilities to explicitly evaluate the influence of diagnostic actions on the decision-making process. We consider the patient's perspective by excluding any costs (e.g. cost of treatment, or disease) from our study. We assume that women adhere to the decisions made by radiologists. We also assume that both the patient and radiologist are risk neutral. We assume that the decision ends with a biopsy, i.e. the patient leaves the system once a biopsy is performed because the decision process for a patient who had already undergone biopsy may be Different than that of a patient who has never undergone a biopsy. Patients who have a history of biopsy will have a higher risk profile (Gail et al. 1989) and may experience scarring due to a biopsy making future interpretation of mammograms more difficult. Such differences require the specific estimation of cancer risk, transition probabilities, and expected post-biopsy life years. Since we do not have any available data for this subset of women, we decided to focus on women who did not have an earlier biopsy.

Table 3 lists the notation used in this paper. The details of the definitions of these parameters are given in the appendix.

The decision process for this problem is as follows. At a decision epoch, when the patient undergoes mammography, the radiologist calculates the risk score of the patient representing

the woman's current risk of breast cancer based on demographic risk factors and mammography findings. To estimate the risk score (denoted by s_t), one can use the BN model (or any other CADx model) as described in Section 2.2 or a radiologist's assessment. We round the probability of breast cancer (outcome of the BN model) to an integer number between 0 and 100 to compute the risk score. For example, assuming that $S = 100$, if the BN calculates the probability of breast cancer as 0.018 (or 1.8%), then the corresponding risk score is 2.

Based on the risk score of a patient, the radiologist chooses one of the three actions: biopsy(Bx), short-interval follow-up (Fu), or wait until next annual mammography exam (Am). Each action in our MDP model has an associated disutility. We define the disutility of Bx , Fu , and Am as a reduction in the quality of life due to stress and trauma associated with each action. Without loss of generality, we assume that both dFu and dAm are constant for all ages.

If the action is Bx , the patient is assigned a lump-sum reward representing the post-biopsy reward for a given risk score, and the decision process ends. Examples of reward include expected life in years, or expected QALYs that incorporate risk-neutral utilities of health states into the expected life years to measure both the quality and the quantity of life years (Pliskin et al. 1980; Drummond 2005). If the action is Fu , the patient may either die during the next six months, stay at the current risk score, or move to another risk score. The patient accrues an intermediate reward representing the total expected QALYs over the next six months. If the patient is alive at the end of the six-month period, she undergoes another mammography exam and makes another decision. The transitions and the rewards for Am action are similar to those for Fu action, with the difference that the patient undergoes her next mammography exam two decision epochs later (i.e. one year later). Thus the next decision epoch depends upon the action taken in the current decision epoch.

The optimal solution for this MDP can be obtained by solving the following set of Bellman equations (Puterman 1994):

$$\vartheta_t(s_t) = \max \left\{ r_t(s_t, Bx), r_t(s_t, Fu) + \gamma \sum_{s' \in S} p_t(s'|s_t) \vartheta_{t+1}(s'), r_t(s_t, Am) + \gamma^2 \sum_{s' \in S} \tilde{p}_t(s'|s_t) \vartheta_{t+2}(s') \right\}, s_t \in \mathcal{S}, t = 1, 2, \dots, T-2.$$

For $t = T-1$, the optimality equations take the following form:

$$\vartheta_{T-1}(s_{T-1}) = \max \left\{ r_{T-1}(s_{T-1}, Bx), r_{T-1}(s_{T-1}, Fu) + \gamma \sum_{s' \in S} p_{T-1}(s'|s_{T-1}) \vartheta_T(s') \right\}, s_{T-1} \in \mathcal{S}.$$

Also for $t = T$, we add a boundary condition as follows:

$$\vartheta_T(s_T) = r_T(s_T, Bx) = r_T(s_T, Fu) = r_T(s_T, Am), \text{ for all } s_T \in \mathcal{S}.$$

4 Structural Properties

In this section, we investigate various model-specific structural properties of the MDP model described in Section 3 that are unique to our problem and provide insights on how optimal decisions are made in clinical practice. Furthermore, we provide a set of clinically intuitive sufficiency conditions that ensure the existence of optimal policies that are more appealing to the decision makers. Note that all proofs in this section are included in the appendix. We first make the following assumptions that are used throughout this section.

Assumption 1 (*As1*) *The functions $r_t(s_b, Fu)$, $r_t(s_b, Am)$, and $r_t(s_b, Bx)$ are non-increasing in s_t for all t and in t .*

We first show the monotonicity of $\vartheta_t(s_t)$ in s and t , which is essential to prove our main result. Proposition 1 (a) provides a sufficiency condition under which $\vartheta_t(s_t)$ is non-increasing in s_t , i.e. the patient's total expected QALYs never increase with her risk score (probability of cancer). Similarly, Proposition 1 (b) shows that $\vartheta_t(s_t)$ is non-increasing in t , i.e. the patient's total expected QALYs never increase with her age. The condition for this part of the proposition implies that as the patient ages, the probability of moving to a worse health state (i.e. higher probability of cancer states or death) increases (or remains constant) when she is not biopsied. This condition is intuitively reasonable since as the patient gets older, her probability of death from other causes also increases. We first introduce the definition of increasing failure rate on transition probability matrices, that is commonly assumed for the MDP models used in treatment optimization problems (Alagoz et al. 2004; Alagoz et al. 2007; Sandikçi et al. 2008; Shechter et al. 2008).

Definition 1 (Barlow and Proschan 1965) *If the rows of a Markov chain with S states are in increasing stochastic order, i.e. $q(i) = \sum_{j=m}^S P(j|i)$ is non-decreasing in i for all $m = 1, 2, \dots, S$, then this Markov chain is IFR (increasing failure rate).*

Proposition 1 (a) *If $\mathcal{P}_t$ and $\tilde{\mathcal{P}}_t$ are IFR for all $t = 1, 2, \dots, T$, then $\vartheta_t(s_t)$ is non-increasing in s_t for $s_t = 1, \dots, S$ and $t = 0, 1, 2, \dots, T$. (b) *If $\mathcal{P}_t$ and $\tilde{\mathcal{P}}_t$ satisfy the following:**

$$\sum_{s'=j}^{S+1} p_t(s'|i) \leq \sum_{s'=j}^{S+1} p_{t+1}(s'|i) \sum_{s'=j}^{S+1} \tilde{p}_t(s'|i) \leq \sum_{s'=j}^{S+1} \tilde{p}_{t+1}(s'|i) \quad (1)$$

for $i, j \in \mathcal{S} \setminus \{S+2\}$. Then, the optimal value function, $\vartheta_t(s_t)$, is non-increasing in t for all $s_t \in \mathcal{S}$.

We next introduce a new type of structured policy in our problem's context which is similar to the double-threshold policies previously used in the equipment maintenance literature using MDPs (Iravani and Duenyas 2002). Compared to a conventional optimal policy that includes the optimal action for each possible system state, such a structured policy is more appealing to the radiologists and is easier to implement in clinical practice.

Definition 2 *A policy $\pi = [a_t^*(s_t)]_{t=0, \dots, T-1}$ is a double-control-limit (DCL) policy if there exist $s_t^*, s_t^{**} \in \mathcal{S} \setminus \{S+2\}$ for $t = 0, 1, \dots, T-1$ such that*

$$a_t^*(s_t) = \begin{cases} Am & \text{if } s_t \leq s_t^* \\ Fu & \text{if } s_t^* < s_t < s_t^{**} \\ Bx & \text{if } s_t \geq s_t^{**} \end{cases}$$

An example of a DCL policy is shown in Figure 1. Unlike single control-limit type policies, a DCL type policy specifies two control limits that divide the state space into three sets of states (regions) where only one action is optimal in each region. For example, in Figure 1, for age 70, $s^* = 1$ and $s^{**} = 3$; that is, if the risk score of the patient is 1 or less, the optimal action is *Am*, if it is between 1 and 3, the optimal action is *Fu*, and if it is 3 or higher, then the optimal action is *Bx*.

Next, we provide Lemmas 1, 2, 3, and 4 that are used to prove Theorem 1, our main result that presents a set of sufficiency conditions for the existence of an optimal DCL policy. Note that although several studies applying MDPs to equipment maintenance problems prove the existence of optimal DCL-type policies under various sufficiency conditions, their conditions do not apply to our model due to the existence of absorbing states in our MDP model.

Lemma 1 (Chhatwal et al. (2010)) *Let $\mathbb{P} = [p_t(j|i)]$ for $i, j = 1, 2, \dots, N$ be an IFR transition probability matrix such that $\sum_{k=i+1}^{k^*} p_t(k|i+1) \geq \sum_{k=i+1}^{k^*} p_t(k|i)$ for $i < k^* - N$ and $t = 1, 2, \dots, T - 1$. If $f(i)$ is a non-increasing function in i , then the following holds:*

a.

$$\sum_{k=1}^i \{p_t(k|i) - p_t(k|i+1)\} f(k) \geq \sum_{k=1}^i \{p_t(k|i) - p_t(k|i+1)\} f(i)$$

b.

$$\sum_{k=i+1}^{k^*} \{p_t(k|i) - p_t(k|i+1)\} f(k) \geq \sum_{k=i+1}^{k^*} \{p_t(k|i) - p_t(k|i+1)\} f(i+1)$$

Lemma 2 provides an upper bound on the difference in the total QALYs if *Am* is recommended over *Fu*, which is equal to the difference between the disutility of two consecutive follow-up actions and the disutility of an annual mammogram. In Lemma 2, $\vartheta_t(s_t, Am)$ and $\vartheta_t(s_t, Fu)$ represent the total expected QALYs obtained when the patient is in risk score s_t and actions *Am* and *Fu* are selected, respectively.

Lemma 2 $\vartheta_t(s_t, Am) - \vartheta_t(s_t, Fu) \leq 2dFu - dAm$ for all $s_t \in \mathcal{S} \setminus \{S + 2\}$, and t .

Lemma 3 provides an upper-bound, $r_t^*(0)$, on $\vartheta_t(0, Fu)$, where $r_t^*(0)$ represents the total expected life of a patient if her risk of cancer remains zero for the rest of her life and she never undergoes biopsy.

Lemma 3 Let $r_t^*(0) = r_t(0, Fu) + \sum_{i=t}^{T-1} \gamma^{i+1-t} \left\{ \prod_{j=t}^i \{1 - p_j(S+1|0)\} \right\} r_{i+1}(0, Fu)$ and $r_t^*(0) \geq r_t(0, Bx)$ then $v_t(0) \leq r_t^*(0)$ for all $t = 1, 2, \dots, T-1$.

Lemma 4 provides an upper bound on the reward attained by a patient if “short-interval follow-up” is recommended. It states that the maximum total reward that a patient can attain at a given state if the radiologist recommends “short-interval follow-up” is equal to the total reward obtained by waiting for six months and then either: (i) the reward from biopsying her if the risk of cancer increases to the biopsy-threshold, or (ii) the maximum reward she can attain if her risk of cancer is zero for the rest of her life and she never undergoes a biopsy.

Lemma 4 Define $r_t^{max}(s_t, Fu)$ as follows:

$$r_t^{max}(s_t, Fu) = r_t(s_t, Fu) + \gamma \sum_{s' < s_t^{**}} p_t(s'|s_t) r_{t+1}^*(0) + \gamma \sum_{s' \geq s_t^{**}} p_t(s'|s_t) r_{t+1}(s', Bx) \quad (2)$$

for all $s_t \in \mathcal{S} \setminus \{S+2\}$ and t , where $r_{t+1}^*(0)$ is as defined in Lemma 3 and s_t^{**} is the risk threshold to biopsy i.e. the optimal action at time t is always Bx if $s_t \geq s_t^{**}$ and Am/Fu , otherwise; then $v_t(s_t, Fu) \leq r_t^{max}(s_t, Fu)$.

In Theorem 1, we provide a set of sufficiency conditions under which there exists an optimal DCL policy.

Theorem 1 If $\mathcal{P}_t$ and $\tilde{\mathcal{P}}_t$ are IFR and the following hold for all $s_t \in \mathcal{S} \setminus \{S+2\}$ and $t = 1, 2, \dots, T-1$:

$$\frac{r_t(s_t, Bx) - r_t(s_t+1, Bx)}{\gamma^2 r_{t+2}(s_t+1, Bx)} \leq p_t(S+1|s_t+1) - p_t(S+1|s_t) \quad (3)$$

$$\sum_{s'=s_t+1}^S \tilde{p}_t(s'|s_t+1) \geq \sum_{s'=s_t+1}^S \tilde{p}_t(s'|s_t) \quad (4)$$

$$p_t(i|s_t) \geq p_t(i|s_t+1) \text{ if } i \leq s_t \quad (5)$$

$$p_t(j|s_t) \leq p_t(j|s_t+1) \text{ if } j > s_t \quad (6)$$

$$\begin{aligned}
& \sum_{s'=s_t}^S \{p_t(s'|s_t) \\
& \quad - p_t(s'|s_t \\
& \quad - 1)\} \{r_{t+1}(s', Bx) \\
& \quad - r_{t+1}^{max}(s', Fu) + \{p_t(S \\
& \quad + 1|s_t) \\
& \quad - p_t(S \\
& \quad + 1|s_t \\
& \quad - 1)dFu \geq \sum_{s'=0}^{s_t-1} \{p_t(s'|s_t \\
& \quad - 1) - p_t(s'|s_t)\} \left| 2dFu - dAm \right|
\end{aligned} \tag{7}$$

then there exists an optimal DCL type policy.

In Theorem 1, (3) implies that as the risk score increases, the annual percentage reduction in the post-biopsy reward is less than the increase in the discounted risk of death associated with waiting until the next decision epoch. Inequality (4) implies that as the patient's risk of cancer increases, she is more likely to move to a higher risk score in the future. The clinical explanation of (5) is that the probability of moving to a lower risk score, i in the next decision-epoch decreases with the increase in the patient's current risk score; whereas, (6) implies that the probability of moving to a higher risk score, j in the next decision-epoch increases with the increase in the patient's current risk score. Though Condition (7) looks complex, it has an intuitive clinical interpretation. It implies that as the patient's risk increases, the relative benefit of Bx over Fu increases greater than the relative benefit of Fu over Am .

The proof of Theorem 1 is given in the appendix. We prove this result in three steps. We first show that there exists an s^{**} such that for all risk scores equal or higher than this threshold the optimal action is Bx . To show this, we use proof by contradiction, where we show that when the optimal action is Bx , it is impossible to have the Fu or Am actions being optimal. In the second step, again using proof by contradiction, we show that there exists an s^* such that for all risk scores equal to or lower than this threshold the optimal action is Am . Finally, we consider possible cases between risk scores s^* and s^{**} and show that the optimal action has to be Fu for each of these cases.

5 Computational Results

In this section, we first describe our data sources and the details of the estimation of the states, transition probabilities, and rewards from the clinical data. Secondly, we present the optimal policy given by our model using base parameters. Then, we test our model on the clinical data and compare our results to the decisions made by radiologists in practice. Finally, we perform sensitivity analyses on the various model parameters.

5.1 Estimating Model Parameters

Our clinical data come from the mammography database of an academic breast cancer screening practice that was collected between April 5, 1999 and February 9, 2004. The data consist of 65,892 consecutive mammography findings of 48,744 mammograms belonging to 18,269 patients. Unlike most of the existing mammography databases, our data includes information about false negative cases, malignant mammograms that were missed by the radiologists but later reported to the centralized state cancer registries. For this purpose, we compared the final assessment of the radiologists (malignant versus benign) to the cancer registry for all cases.

We estimate the *states* of the MDP model (i.e. probability of cancer) using the BN of Chhatwal et al. (2010) (unless noted otherwise) that is also briefly described in Section 2.2. We estimate $\mathcal{P}_t$ (and hence $\mathcal{P}_t^*$) by counting the transitions from each risk score (as estimated by the BN) in the consecutive mammographic examinations from the clinical database. For this purpose, we start with populating missing risk score values using a linear interpolation method, which is necessary since patients do not undergo mammography in regular time intervals. For example, suppose a woman undergoes mammography at time 0 and her risk score is 1 (probability of cancer is 1%). Suppose that her next mammography exam is observed after 2 years (i.e. time 4 in our model) and her risk score is 5. In this case, we have no observations for her risk scores during the intermediate times 1, 2, and 3. We populated these missing values using linear interpolation. That is, we assume that her risk score at time 1 is 2, at time 2 it is 3, and at time 3 it is 4. We then decompose the sequence of risk scores of each patient into pairs of two sequential risk scores. After that, we count the transitions from each risk score to other risk scores and compute a discrete probability distribution to compute the transition probabilities among risk scores. We calculate the probability of death using life tables from the National Center for Health Statistics (NCHS) of Center for Disease Control and Prevention (CDC) (Arias 2006) and normalize the probability distribution among risk scores by calculating the probability of being alive in the next time period.

We assume that the *expected intermediate reward* accrued in the current time period when the patient's state is s_t and the Fu action is selected ($r_t^\dagger(s_t, Fu)$) is equal to six-months if the patient is alive in that year, and three months, otherwise, to account for half-cycle correction as explained in Section 3. We then estimate $r_t^\dagger(s_t, Am)$. We estimate the age-dependent *post-biopsy rewards* ($r_t^\dagger(s_t, Bx)$) of breast cancer by using age-specific probabilities of death from breast cancer (Jemal et al. 2007), and no-cancer from the 2003 US life tables reported by the NCHS of CDC (Arias 2006). More details for estimating the expected life from the probability of death calculations are available in Arias (2006). To assign a higher probability of death to cancer patients when they are not treated to that when they are treated, we use the *treatment-effectiveness factor*, which is a measure of reduction in breast cancer mortality because of treatment and is defined as the ratio of the probability of death *without* treatment to that *with* treatment. There exists evidence that treatment effectiveness depends on age (Haybittle 1998) therefore, we define it as a function of age. We define the treatment-effectiveness factor at age 40, $TxFactor@40 = 2.0$ whereas we define the treatment-

effectiveness factor at age 100, $TxFactor@100 = 1.05$ (Haybittle 1998). That factor is defined similarly for other ages using the model of Haybittle (1998).

Note that our reward functions include the disutilities for only the short-interval follow-up, mammography, and biopsy actions, i.e. we assume that the age-related quality of life factor is equal to 1 for all other states and actions to focus our attention on the diagnostic decisions of mammography.

Another important component of our parameter estimation is related to the disutilities associated with various actions. We assume the following disutility values for our base-case analysis and perform an extensive sensitivity analysis on these parameters.

- Disutility associated with short-interval follow-up (dFu) is 0.25 days.
- Disutility associated with annual mammogram (dAm) is 0.25 days.
- Disutility associated with biopsy at age 40 ($dBx@40$) is 2 weeks (Velanovich 1995).
- Disutility associated with biopsy at age 100 ($dbxFac@100$) is 2 times of that at age 40, i.e., $dbxFac@100$ of 2 implies that the $dBx@100 = 2 * dBx@40$.

We define an age-based disutility of biopsy that increases with age because, as the patient ages, the co-morbidities in older women make breast biopsy more difficult and complex. For example, an older patient is more likely to be on anticoagulation medication and therefore experience bleeding if these medications are not stopped or untoward effects if they are stopped.

5.2 Optimal Policies for the Base Case

Figure 1 shows the optimal policy of our MDP model for the base-case, which can be interpreted as follows: the radiologist should recommend biopsy for women between the age 40 and 67 with a risk of cancer 2% and higher, short-interval follow-up if the risk is between 1% and 2%, and annual mammogram if the risk is below 1%. For women between the age 67 and 78, the radiologist should recommend biopsy if the risk is higher than 3%, short-interval follow-up if the risk is between 1% and 3%, and a routine annual mammogram if the risk is below 1%. Similarly, the optimal policy can be interpreted for older ages. Note that the optimal probability thresholds to biopsy and follow-up are non-decreasing with the patient's age. Compared to the optimal policy obtained by Chhatwal et al. (2010) where there is a single non-biopsy alternative, we observe that the biopsy thresholds are slightly higher for some ages. This implies that for some ages, short-term follow-up may save some unnecessary biopsies. That is, a “wait-and-see” approach may become more feasible for some women when there are two non-biopsy alternatives. Figure 1 also shows the optimal policy of radiologists using risk scores as a proxy for BI-RADS categories. We used a 1% probability of breast cancer as the threshold for recommending short-interval follow-up (Yasmeen et al. 2003; Vizcaíno et al. 2001) and a 2% threshold for recommending biopsy as defined in the BI-RADS lexicon.

5.3 Comparison of the Optimal Policies with a Real Mammography Practice

We compare the performance of our MDP model to that of radiologists using our clinical database of all mammographies performed. After removing unmatched findings, duplicates, findings with incomplete information, and mammograms belonging to patients younger than 40, our final dataset consisted of 42,315 mammograms (358 malignant and 41,957 benign). For a direct comparison, ideally we need the number of mammograms recommended for biopsy, follow-up, and annual mammogram by radiologists as compared to the MDP model. The recommendations of the radiologists are given by the BI-RADS assessment codes: BIRADS 1 and 2 are associated with annual mammogram, BI-RADS 3 is associated with short-interval follow-up, BI-RADS 4 and 5 are associated with biopsy, and BI-RADS 0 is associated with a recommendation for additional imaging (this is an intermediate assessment; a final recommendation is rendered when imaging exams such as magnetic resonance imaging, ultrasound, etc. are completed). We do not have access to the ultimate recommendation for these BI-RADS 0 mammograms in our database, making a direct comparison of the MDP model to that of radiologists impossible. However, we can estimate the ultimate disposition of these intermediate, BI-RADS 0, interpretations based on the literature. Geller et al. (2002) report that approximately 24% of BI-RADS 0 cases were recommended “either a consultation or biopsy,” therefore in our dataset, we assume that approximately 24% of BIRADS 0 cases were recommended biopsy whereas the remaining cases are recommended an annual mammogram. To provide advantage to radiologists, we further assigned all malignant BI-RADS 0 cases (a total of 56) to biopsy. Thus our results provide an upper-limit on the performance of the radiologists.

Table 4 compares the performance of the MDP model to that of the radiologists for the base case when the BN model of Chhatwal et al. (2010) is used to estimate the risk scores. The radiologists recommended 32,825 annual mammograms while the MDP model recommends 39,580 annual mammograms. The radiologists recommended 7,652 mammograms for short-interval follow-up, whereas, the MDP model recommends only 1,088 short-interval follow-ups. The radiologists recommended 1,838 biopsies and the MDP model recommends 1,647 biopsies.

We also estimate the total expected QALYs obtained by the MDP model and the radiologists. We found that average QALYs obtained by our MDP model is 25.379 QALYs whereas the average QALYs obtained by the radiologists is 25.378 QALYs. This translates into 1.986 potential QALY savings per 10,000 women. Note that although potential QALY savings obtained by using the MDP model appear to be low, small gains in QALYs in screening programs can be substantial at population level. (Wright and Weinstein 1998) We further analyzed our results by age and risk score to identify the subgroups that will have higher savings (Table 9 in the Appendix). We found that the maximum savings are obtained in women in risk scores 1–2 and the age group 40–50, followed by age group 50–60 in the same risk scores. The QALY gains are 0 in 38,027 women who have risk score < 1 . This is due to the fact that there is no discrepancy between the MDP model and radiologists when the risk of cancer is close to 0 (both recommend annual mammogram as the optimal action).

The performance of diagnostic tests are commonly measured by true positive rate (TPR) and true negative rate (TNR). The TPR in our case indicates the probability of labeling a

mammogram positive given that the patient has cancer, and TNR indicates the probability of labeling a mammogram negative given that the patient is cancer free. For this purpose, we define the recommendation of an annual mammogram or a short-interval follow-up as negative and of a biopsy as positive. We find that the TPR of radiologists and the MDP model were 0.916 and 0.911, respectively; and the TNR of radiologists and the MDP model were 0.964 and 0.969, respectively. These results show that compared to the radiologists, our MDP model recommends an annual mammogram for a higher number of benign cases, while missing only two extra malignant cases (32 versus 30). In addition, our MDP model suggests that a substantial number of “short-term follow-up” recommendations by radiologists were unnecessary in this clinical practice.

We also test the robustness of our MDP model’s performance to the choice of the CADx model. For this purpose, we use the logistic regression (LR) model of Chhatwal et al. (2009) to estimate the risk scores of mammograms in our clinical dataset, and implement the optimal policy for the base case. As demonstrated in Table 5, the trends in Table 4 are generally preserved.

In Tables 4 and 5, we assume that all patients have the same disutilities as in our base case. Next, we test the robustness of our model’s findings to the changes in disutility functions. Table 6 summarizes the results of our model’s performance under various disutilities. We find that the number of follow-ups recommended by the MDP model is substantially lower than that recommended by radiologists for the majority of cases where the disutility of follow-up is positive. In addition, we observe that while the TPR of the model is comparable to that of the radiologists, the TNR of the model is always higher than radiologists, reflecting that the false-positive rate of the model is significantly lower than radiologists. The last column of Table 6 presents the difference between QALYs obtained by implementing the radiologists’ policy and those obtained by implementing the MDP model’s base-case policy as defined in Figure 1 for various disutility values. Note that this column represents the robustness of the MDP model’s savings over the radiologists under uncertain disutility values. The QALY gains obtained by implementing the MDP model’s policy over radiologists’ policy were between -0.201 and 2.279 per 10,000 women. We observe that the MDP model has positive QALY gains for most disutility values, indicating the robustness of the MDP model to the uncertainties in disutility values.

5.4 Sensitivity Analysis

We conduct extensive sensitivity analyses to check the robustness of our optimal policy and to determine the most critical input parameters. In particular, there is uncertainty about the disutility of various diagnostic actions, therefore, we focus on the disutility estimates in our sensitivity analysis. First, we vary the disutility associated with follow-up from 0.25 to 1.5 days fixing the disutility of annual mammogram to 0.5 days. Figures 2 and 3 show the change in the optimal policy. As expected, with the increase in the disutility, the follow-up becomes less preferable. The change in the disutility of follow-up has a little effect on the threshold to biopsy. As the disutility of the follow-up increases, the threshold for biopsy in younger patients decreases. The clinical explanation of this trend is that in the younger patients the cancer growth is more aggressive (Anders et al. 2008); hence they should be

biopsied more often if the follow-up is not preferred due to the higher disutility. Note that the follow-up is never optimal when the disutility of annual mammogram is 0.5 days and the disutility of follow-up increases to 2 days.

Figure 4 shows the optimal policy when the disutility of an annual mammogram is 0, and the disutility of follow-up increases from 0 to 1.25 days. When both disutilities are 0, the annual mammogram action is never optimal. Note that the optimal policy recommends follow-up even if the disutility of the annual mammogram is 0 and that of the follow-up is up to 1 day. This may appear counter-intuitive. However, note that the follow-up action can be optimal if a cancer is caught six months later instead of one year later. Figure 4(d) days shows that the follow-up action is never optimal if its disutility increases to 1.25 days when the disutility of an annual mammogram is 0.

We also perform sensitivity analyses on the disutility associated with biopsy. Figure 5(a)–(b) shows the optimal policy when the disutility of biopsy is constant for all ages (2 weeks and 4 weeks, respectively). The thresholds to biopsy and follow-up increase with age which show that the less aggressive management is preferred in older women. Figure 5(c) shows the optimal policy when the disutility of biopsy increases with age from 2 weeks at age 40 to 4 weeks at age 100. The biopsy becomes less preferable with the increase in the disutility. As a consequence of the higher biopsy thresholds, follow-up also becomes more preferable. Note that the policy for recommending the annual mammogram shows a little change. Figure 5(d) shows the optimal policy when the disutility of biopsy decreases from 2 weeks at age 40 to 1 week at age 100. Interestingly, the threshold to biopsy still increases with age, showing less potential benefit of a biopsy in older ages in terms of QALYs, even when the disutility of biopsy is lower for older ages.

We also perform sensitivity analyses on the performance measures (TPR and TNR) of the MDP model when tested on the clinical data. Table 7 shows the baseline and range of values of parameters for sensitivity analysis. Figures 6 and 7 show the changes in the TPR and TNR of the MDP model as a result of one-way sensitivity analysis on the model's parameters, respectively. As before, we define a Bx action as positive and Am and Fu actions as negative in calculating the TPR and TNR. While the disutility associated with a biopsy is the most important factor affecting the TPR and TNR of the model, the disutility associated with an annual mammogram has the least effect on the TPR and TNR of the model.

6 Conclusions

In this study, we develop a finite-horizon MDP model that can be used to determine the optimal decisions for patient management from a decision-analytical viewpoint after a mammography exam, which can provide insights to improve decision-making in clinical practice. Significant variability is observed in mammography practice. In particular, the excessive use of a short-interval follow-up exam remains questionable. Our model provides patient-specific recommendations for breast biopsy and short-interval follow-up, in contrast to population-based guidelines observed in the current clinical practice. The decisions in our model are based on the probability of cancer instead of the BI-RADS final assessment

codes. Our model is the first step to provide structured guidelines in a decision-analytical framework for the recommendation of biopsy and follow-up.

We find that the probability of cancer threshold for recommending a biopsy is around 2% for women in younger ages. This result is consistent with the BI-RADS stated probability threshold for a biopsy. However, our results show that the biopsy threshold increases with age; whereas, the current BI-RADS recommendations do not take age into consideration explicitly. We also find that the disutility of a biopsy affects this threshold substantially whereas there is no evidence that the current clinical practice explicitly considers disutility in biopsy decisions. The biopsy thresholds are higher for older women even if the disutilities remain constant with age (Figure 5(a)–(b)) because potential savings are less in older women due to limited life expectancy and co-morbidities, which affect the remaining life years of a woman at a given age. As a result, our model recommends less aggressive biopsies in older women.

We compare the performance of the MDP model's optimal policies to the decisions made by radiologists on real-life mammography data and find that our model recommends substantially fewer short-interval follow-ups than radiologists. While the radiologists recommended 7,652 short-interval follow-ups, our model recommended between 0 and 1,175 short-interval follow-ups for the majority of the cases where the disutility of follow-up is positive. Interestingly, when the disutility of follow-up is over 1.5 days, our model does not recommend any short-interval follow-ups.

The appropriateness and optimal rate of short-term interval follow-up recommendation has been discussed extensively in the radiology literature. Rubin (1999b) notes that encouraging short-interval follow-up for the majority of women is unnecessarily anxiety-provoking and costly with little demonstrable benefit to those who comply. Instead, she suggests some of these patients should be recommended annual mammography or percutaneous biopsy. On the other hand, Sickles (1999a) argues that the primary reason for recommending short-interval follow-up is to avoid biopsies in low risk lesions. Because short-interval follow-up mammography induces significantly less anxiety than does percutaneous biopsy, it is a useful intermediate assessment. He further notes that although short-interval follow-up enables detection of cancer earlier in only a few cases (eight of 7,484 [0.1%]), this represents an acceptable detection rate that is helpful especially for hyper-aggressive cancers (Sickles 1999b). More recently, Baum et al. (2011) report that in a large-scale mammography screening trial that may not represent the population-based screening practices, radiologists used short-term interval follow-up in 2.3% of the cases, which is very similar to our model's recommendation for the base case (2.6% or 1088 out of 42315 cases). In any case, researchers and experts alike generally agree that many radiologists use short-interval follow-up mammography inappropriately, as a (poor) substitute for either a full imaging work-up including biopsy or routine annual mammography (Rubin 1999a; Sickles 1999a). Therefore, our study is important in providing a decision-analytical framework for determining when radiologists should recommend short-interval follow-up exam.

This study has several limitations. First, although our MDP model includes age-based transition probabilities, the progression of risk scores is not age-dependent in our numerical

experiments due to limited data. Second, we assume that the radiologist and the patient are risk neutral, which allows us to use the objective function of maximizing QALYs of a patient in making the breast cancer diagnostic decisions. If we used a risk-averse function, we would observe that the biopsy thresholds would become lower, reflecting the patient's risk aversion towards cancer. Furthermore, under a risk-averse assumption, our main conclusion of unnecessary use of short-interval follow-up exams in practice will not change. Relaxing this assumption would first require the identification of an appropriate utility function of an individual patient's risk preference, which to the best of our knowledge is not available in the literature. The use of various utility functions and investigation of their effects on the optimal policies would be beyond the scope of this paper, therefore it is left for future research.

Third, we made several assumptions while estimating the model's parameters. We estimated the progression of breast disease (transition probabilities associated with Am and Fu) using 5-year data from a large mammography practice. Though our dataset is one of the largest of its kind, caution must be taken to generalize our results since it may not be representative of the US population. In addition, we made linear interpolations of risk scores for missing mammograms, which may add some bias to our transition probability estimates. We also had to make assumptions regarding disutility associated with biopsy and follow-up exams because they have not been widely studied. In addition, we ignored the effects of radiation exposure from extra mammography exams when a follow-up is aggressively recommended.

While our study's findings imply a superior performance of the MDP model compared to radiologists, our results should be interpreted with caution. In particular, as stated above, there are several uncertainties in model parameters where we had to make assumptions such as the disutility of the patients regarding diagnostic actions. Inherent uncertainties in these assumptions may have affected our major findings significantly as demonstrated by the sensitivity analysis. For example, it is possible that some of the monotonicity arguments may disappear if we were able to model cancer risk progression as a function of age. In addition, we assume risk neutrality whereas it is likely that patients may have Different risk attitudes. In fact, the recommendations made by the radiologists may have been influenced by the risk attitudes of the patients, which may also explain the disparities between radiologists' policies and the MDP model's policies.

While our study highlights a potential to reduce unnecessary exams, further research is needed to fully understand the causes of suboptimal policies by radiologists, and implement a decision support tool in practice. In particular, further research on estimating more granular risk scores and developing age-based disease progression models would be valuable. We evaluated the state of practice with technology available at the time. Increased penetration of digital mammography, which has occurred in the interim since our study, may affect some trends, however overall conclusions are unlikely to be radically changed by this natural evolution of technology. As further technical innovation is adopted and improves breast cancer detection and diagnosis, this analysis may need to be adjusted.

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APPENDIX

DETAILS OF PARAMETER DEFINITIONS

In this section, we define our model's parameters whose details were not presented in Section 3.

- $p_t(S+2|s_t) = 0$ for all $s_t \in \mathcal{S} \setminus \{S+2\}$.
- $p_t(S+1|S+1) = p_t(S+2|S+2) = 1$, i.e. both post-biopsy and death states are absorbing.
- We define $p_t(\tilde{s}_{t+2}|s_t)$ as:

$$\tilde{p}_t(s_{t+2}|s_t) = \sum_{s'=0}^{S+1} p_t(s'|s_t) p_{t+1}(s_{t+2}|s') \quad (8)$$

and $p_t(\tilde{S}+2|S+2) = 1$.

- We define $p_t(S+1|s_t) = w_t(s_t) * [p_t^{dntx}(S+1)] + [1 - w_t(s_t)] * [p_t^{ben}(S+1)]$ for $s_t \in \mathcal{S} \setminus \{S+1, S+2\}$, where $w_t(s_t)$ represents the probability of cancer at time t when the current state is s_t , $p_t^{ben}(S+1)$ represents the probability of death during the decision epoch t when the patient is cancer-free, and $p_t^{dntx}(S+1)$ represents the probability of death during the decision epoch t when the patient has breast cancer but has not started receiving treatment (i.e. the patient is unaware of the cancer).
- $p_t(\tilde{s}_{t+1}|s_t) = 0$ for all $s_t, s_{t+1} \in \mathcal{S}$, i.e. under annual mammogram action, no transition to time $t+1$ is possible.
- We define $\tilde{\mathcal{P}}_t = [p_t(\tilde{s}_{t+2}|s_t)]$ for all $s_t \in \mathcal{S}$ and $\mathcal{P}_t = [p_t(s_{t+1}|s_t)]$ for all $s_t \in \mathcal{S}$.
- Let $p_t^{Bx}(s_{t+1}|s_t)$ represent the probability that the patient will move to state s_{t+1} at time $t+1$, given that she is in state $s_t \in \mathcal{S}$ at time t , and action Bx is chosen. We define $p_t^{Bx}(S+1|s_t) = 1$ for all $s_t \in \{0, 1, \dots, S\}$. Moreover, $p_t^{Bx}(S+2|S+2) = 1; p_t^{Bx}(S+2|S+1) = 0; p_t^{Bx}(s_{t+1}|s_t) = 0$ for all $t, s_t \in \mathcal{S}, s_{t+1} \in \mathcal{S} \setminus \{S+2\}$.
- We set $r_t(s_b, Fu)$ as 6 months (0.5 years) if the patient is alive in the current decision epoch, and 3 months (0.25 years), otherwise, to account for half-cycle correction (i.e. a patient can die in the first or the second half of the decision epoch).

$$r_t^\dagger(s_t, Fu) = 0.5 * P(\text{alive in the current decision epoch}) + 0.25 * P(\text{death in the current decision epoch})$$

$$r_t^\dagger(s_t, Fu) = 0.5 * \{1 - p_t(S+1|s_t)\} + 0.25 * \{p_t(S+1|s_t)\}$$

$$r_t^\dagger(s_t, Am) = r_t^\dagger(s_t, Fu) + \gamma \sum_{s'=0}^{S+1} p_t(s'|s_t) r_{t+1}^\dagger(s', Fu) \quad (9)$$

$$r_t^\dagger(s_t, Bx) = q_t(-|s_t) * r_t(s_t, Bx, -) + q_t(+|s_t) * r_t(s_t, Bx, +), \quad (10)$$

where $r_t(s_t, Bx, -)$ and $r_t(s_t, Bx, +)$ represent the total expected discounted post-biopsy life years when the patient's state is s_t at time t and the biopsy's outcome is negative (benign) and positive (malignant), respectively. Furthermore, $q_t(-|s_t)$ and $q_t(+|s_t)$ represent the probability that the outcome of the biopsy is negative and positive, respectively when the patient was in state s_t at time t .

- We set $r_t(S+1, Fu) = r_t(S+2, Fu) = r_t(S+1, Am) = r_t(S+2, Am) = r_t(S+1, Bx) = r_t(S+2, Bx) = 0$.

PROOFS OF THE ANALYTICAL RESULTS

Proof of Proposition 1 (a) The proof of this part is given in Theorem 4.7.3 in Puterman (Puterman 1994), and hence is omitted.

(b) The proof of the proposition is similar to the proof of Proposition 3.6. in Chhatwal (2008) and Proposition 2 in Chhatwal et al. (2010) hence is omitted.

Proof of Lemma 1 This lemma is the same as Lemma 2 of Chhatwal et al. (2010). The proof of the lemma is similar to the proof of Lemma 1 in Alagoz et al. (2004), hence is omitted. Part (b) of this lemma may appear to be counterintuitive. Part (b) holds because all terms in part (b) are negative. As noted in the conditions of this theorem, since $f(i+1) \leq f(k)$ and $\sum_{k=i+1}^{k^*} p_t(k|i+1) \geq \sum_{k=i+1}^{k^*} p_t(k|i)$, all terms in (b) are negative. Therefore, the result holds.

Proof of Lemma 2

$$\begin{aligned}
& \vartheta_t(s_t, Am) \\
& \quad - \vartheta_t(s_t, Fu) \\
& = r_t(s_t, Am) \\
& \quad + \gamma^2 \sum_{s'=0}^{S+1} \tilde{p}_t(s'|s_t) \vartheta_{t+2}(s') \\
& \quad - r_t(s_t, Fu) \\
& \quad - \gamma \sum_{s'=0}^{S+1} p_t(s'|s_t) \vartheta_{t+1}(s') \leq r_t(s_t, Am) \quad (11) \\
& \quad + \gamma^2 \sum_{s'=0}^{S+1} \tilde{p}_t(s'|s_t) \vartheta_{t+2}(s') \\
& \quad - r_t(s_t, Fu) \\
& \quad - \gamma \sum_{s'=0}^{S+1} p_t(s'|s_t) \vartheta_{t+1}(s', Fu) \\
& = r_t(s_t, Am) \\
& \quad + \gamma^2 \sum_{s'=0}^{S+1} \tilde{p}_t(s'|s_t) \vartheta_{t+2}(s') \\
& \quad - r_t(s_t, Fu) \\
& \quad - \gamma \sum_{s'=0}^{S+1} p_t(s'|s_t) \left\{ r_{t+1}(s', Fu) + \gamma \sum_{s''=0}^{S+1} p_{t+1}(s''|s') \vartheta_{t+2}(s'') \right\} = r_t(s_t, Am) \\
& \quad + \gamma^2 \sum_{s'=0}^{S+1} \tilde{p}_t(s'|s_t) \vartheta_{t+2}(s') \quad (12) \\
& \quad - r_t(s_t, Fu) \\
& \quad - \gamma \sum_{s'=0}^{S+1} p_t(s'|s_t) r_{t+1}(s', Fu) \\
& \quad - \gamma^2 \sum_{s''=0}^{S+1} \tilde{p}_t(s''|s_t) \vartheta_{t+2}(s'')
\end{aligned}$$

$$\begin{aligned}
&= r_t^\dagger(s_t, Am) \\
&\quad - dAm \\
&\quad - \{r_t^\dagger(s_t, Fu) \\
&\quad \quad - dFu\} \\
&\quad - \gamma \sum_{s'=0}^{S+1} p_t(s'|s_t) \{r_{t+1}^\dagger(s', Fu) - dFu\} = r_t^\dagger(s_t, Am) \\
&\quad - dAm \\
&\quad + 2dFu \\
&\quad - \left\{ r_t^\dagger(s_t, Fu) \right. \\
&\quad \quad \left. + \gamma \sum_{s'=0}^{S+1} p_t(s'|s_t) r_{t+1}^\dagger(s', Fu) \right\}
\end{aligned} \tag{13}$$

$$= 2dFu - dAm \tag{14}$$

Inequality (11) follows from the fact that $\vartheta_{t+1}(s') \leq v_{t+1}(s', Fu)$; and (12) follows from (8), the definitions of $r_t(s_t, Fu)$ and $r_t(s_t, Am)$. Using (9), we get (14) from (13).

Proof of Lemma 3

The proof of the lemma is similar to the proof of Lemma 3.4 in Chhatwal (2008) and Lemma 4 in Chhatwal et al. (2010), hence is omitted.

Proof of Lemma 4

$$\begin{aligned}
&\vartheta_t(s_t, Fu) \\
&= r_t(s_t, Fu) \\
&\quad + \gamma \sum_{s'=0}^{S+1} p_t(s'|s_t) \vartheta_{t+1}(s') \\
&= r_t(s_t, Fu) \\
&\quad + \gamma \sum_{s' < s_{t+1}^{**}} p_t(s'|s_t) \vartheta_{t+1}(s') + \gamma \sum_{s' \geq s_{t+1}^{**}} p_t(s'|s_t) r_{t+1}(s', Bx) \leq r_t(s_t, Fu) \tag{15} \\
&\quad + \gamma \sum_{s' < s_{t+1}^{**}} p_t(s'|s_t) \vartheta_{t+1}(0) \\
&\quad + \gamma \sum_{s' \geq s_{t+1}^{**}} p_t(s'|s_t) r_{t+1}(s', Bx)
\end{aligned}$$

$$\leq r_t(s_t, Fu) + \gamma \sum_{s' < s_{t+1}^{**}} p_t(s'|s_t) r_{t+1}^*(0) + \gamma \sum_{s' \geq s_{t+1}^{**}} p_t(s'|s_t) r_{t+1}(s', Bx) = r_t^{max}(s_t, Fu) \tag{16}$$

Inequality (15) follows from Proposition 1 (a). Using Lemma 3, we can replace $\vartheta_{t+1}(0)$ by $r_{t+1}^*(0)$ in (16).

Proof of Theorem 1

We prove this result in three steps. We first show that there exists a $s^{**} \in \mathcal{S} \setminus \{S+2\}$ such that for any $s_t = s^{**}$, $a_t^*(s_t) = Bx$ and for any $s_t < s^{**}$, $a_t^*(s_t) = Am$ or $a_t^*(s_t) = Fu$. We then show that there exists a s^* such that for any $s_t < s^*$, $a_t^*(s_t) = Am$. Finally, we consider possible cases regarding s^* and s^{**} .

Step 1. In order to prove that there exists a $s^{**} \in \mathcal{S} \setminus \{S+2\}$ such that for any $s_t = s^{**}$, $a_t^*(s_t) = Bx$ and for any $s_t < s^{**}$, $a_t^*(s_t) = Am$ or $a_t^*(s_t) = Fu$, we consider two cases. In the first case, we show that if $a_t^*(s_t) = Bx$, then $a^*(s_t + 1) = Am$. In the second case, we show that if $a_t^*(s_t) = Bx$, then $a^*(s_t + 1) = Fu$. Then the proof of Step 1 will be complete.

Case 1. Suppose $a_t^*(s_t) = Bx$ and $a_t^*(s_t + 1) = Am$ uniquely for $t = 0, 1, \dots, T-1$. Then

$$\begin{aligned} r_t(s_t, Bx) &\geq r_t(s_t, Am) + \gamma^2 \sum_{s' \in \mathcal{S}} \tilde{p}_t(s'|s_t) \vartheta_{t+2}(s') \\ r_t(s_t + 1, Bx) &< r_t(s_t + 1, Am) + \gamma^2 \sum_{s' \in \mathcal{S}} \tilde{p}_t(s'|s_t + 1) \vartheta_{t+2}(s') \end{aligned} \quad (17)$$

$$r_t(s_t, Bx) - r_t(s_t + 1, Bx) > r_t(s_t, Am) - r_t(s_t + 1, Am) + \gamma^2 \sum_{s'=0}^{S+1} \{\tilde{p}_t(s'|s_t) - \tilde{p}_t(s'|s_t + 1)\} \vartheta_{t+2}(s') \geq \gamma^2 \sum_{s'=0}^S \{\tilde{p}_t(s'|s_t) - \tilde{p}_t(s'|s_t + 1)\} \vartheta_{t+2}(s') \quad (18)$$

$$\begin{aligned} &= \gamma^2 \sum_{s'=0}^{s_t} \{\tilde{p}_t(s'|s_t) - \tilde{p}_t(s'|s_t + 1)\} \vartheta_{t+2}(s') \\ &\quad + \gamma^2 \sum_{s''=s_t+1}^S \{\tilde{p}_t(s''|s_t) - \tilde{p}_t(s''|s_t + 1)\} \vartheta_{t+2}(s'') \geq \gamma^2 \sum_{s'=0}^{s_t} \{\tilde{p}_t(s'|s_t) - \tilde{p}_t(s'|s_t + 1)\} \vartheta_{t+2}(s_t + 1) \\ &\quad + \gamma^2 \sum_{s''=s_t+1}^S \{\tilde{p}_t(s''|s_t) - \tilde{p}_t(s''|s_t + 1)\} \vartheta_{t+2}(s_t + 1) \end{aligned} \quad (19)$$

$$\geq \gamma^2 \sum_{s'=0}^{s_t} \{\tilde{p}_t(s'|s_t) - \tilde{p}_t(s'|s_t + 1)\} \vartheta_{t+2}(s_t + 1) + \gamma^2 \sum_{s''=s_t+1}^S \{\tilde{p}_t(s''|s_t) - \tilde{p}_t(s''|s_t + 1)\} \vartheta_{t+2}(s_t + 1) \quad (19)$$

$$= \gamma^2 \sum_{s'=0}^S \{\tilde{p}_t(s'|s_t) - \tilde{p}_t(s'|s_t+1)\} \vartheta_{t+2}(s_t+1) \geq \gamma^2 \sum_{s'=0}^S \{\tilde{p}_t(s'|s_t) - \tilde{p}_t(s'|s_t+1)\} r_{t+2}(s_t+1, Bx) \quad (20)$$

$$= \gamma^2 \{\tilde{p}_t(S+1|s_t+1) - \tilde{p}_t(S+1|s_t)\} r_{t+2}(s_t+1, Bx) \quad (21)$$

where (17) follows from (AsI), and $p_t(\tilde{j}|s) = 0$ for $j \in \{S+2\}$. Inequality (18) follows

because of Proposition 1(a), condition (4), and Lemma 1. The IFRness of $\mathcal{P}_t^{Am}$ implies that

$$\sum_{s'=s_t+1}^{S+1} \tilde{p}_t(s'|s_t) \leq \sum_{s'=s_t+1}^{S+1} \tilde{p}_t(s'|s_t+1) \text{ and } \sum_{s'=0}^{s_t} \tilde{p}_t(s'|s_t) \geq \sum_{s'=s_t}^{s_t} \tilde{p}_t(s'|s_t+1).$$

Since $\vartheta_{t+2}(s_t) \leq \vartheta_{t+2}(s_t+1)$, by Proposition 1(a), we can replace $\vartheta_{t+2}(s_t)$ in (18) by $\vartheta_{t+2}(s_t+1)$ in (19). Inequality (20) follows from the fact that $\mathcal{P}_t^{Am}$ is IFR and $\vartheta_{t+2}(s_t+1) \leq r_{t+2}(s_t+1, Bx)$. We can replace (21) by:

$$\frac{r_t(s_t, Bx) - r_t(s_t+1, Bx)}{\gamma^2 r_{t+2}(s_t+1, Bx)} > \tilde{p}_t(S+1|s_t+1) - \tilde{p}_t(S+1|s_t) \quad (22)$$

$$\geq p_t(S+1|s_t+1) - p_t(S+1|s_t) \quad (23)$$

Equation (23) follows from the fact that $p_t(\tilde{S}+1|s_t+1) - p_t(\tilde{S}+1|s_t) \leq p_t(S+1|s_t+1) - p_t(S+1|s_t)$ for all $s_t \in \{0, 1, \dots, S\}$, which contradicts (3). Hence if $a_t^*(s_t) = Bx$, then $a_t^*(s_t+1) \neq Am$.

Case 2. Suppose $a_t^*(s_t) = Bx$ and $a_t^*(s_t+1) = Fu$ uniquely for $t = 0, 1, \dots, T-1$. Then

$$\begin{aligned} r_t(s_t, Bx) &\geq r_t(s_t, Fu) + \gamma \sum_{s' \in \mathcal{S}} p_t(s'|s_t) \vartheta_{t+1}(s') \\ r_t(s_t+1, Bx) &\leq r_t(s_t+1, Fu) + \gamma \sum_{s' \in \mathcal{S}} p_t(s'|s_t+1) \vartheta_{t+1}(s') \\ r_t(s_t, Bx) - r_t(s_t+1, Bx) &> r_t(s_t, Fu) - r_t(s_t+1, Fu) \\ &+ \gamma \sum_{s'=0}^{S+1} \{p_t(s'|s_t) - p_t(s'|s_t+1)\} \vartheta_{t+1}(s') \geq \gamma \sum_{s'=0}^S \{p_t(s'|s_t) - p_t(s'|s_t+1)\} \vartheta_{t+1}(s') \end{aligned}$$

Similarly, it follows that:

$$\frac{r_t(s_t, Bx) - r_t(s_t+1, Bx)}{\gamma r_{t+1}(s_t+1, Bx)} > p_t(S+1|s_t+1) - p_t(S+1|s_t) \frac{r_t(s_t, Bx) - r_t(s_t+1, Bx)}{\gamma^2 r_{t+2}(s_t+1, Bx)} > p_t(S+1|s_t+1) - p_t(S+1|s_t) \quad (24)$$

Equation (24) follows from (AsI), which contradicts (3). Hence if $a_t^*(s_t) = Bx$, then

$$a_t^*(s_t+1) \neq Fu.$$

Because if $a_t^*(s_t) = Bx$ then $a_t^*(s_t+1) \neq Am$ or $a_t^*(s_t+1) \neq Fu$, there exists a s^{**} such that $a_t^*(s_t) = Bx$ for all $s_t < s^{**}$ or equivalently $a_t^*(s_t) \in \{Am, Fu\}$ for all $s_t < s^{**}$.

Step 2. In this step, we show that there exists a s^* such that for any $s_t < s^*$, $a_t^*(s_t) = Am$.

Suppose $a_t^*(s_t) = Am$ and $a^*(s_t - 1) = Fu$ uniquely, then

$$\vartheta_t(s_t, Am) \geq \vartheta_t(s_t, Fu) \quad (25)$$

and

$$\vartheta_t(s_t - 1, Am) < \vartheta_t(s_t - 1, Fu) \quad (26)$$

Subtracting (25) from (26), we get:

$$\begin{aligned} \vartheta_t(s_t - 1, Am) - \vartheta_t(s_t, Am) &< \vartheta_t(s_t - 1, Fu) - \vartheta_t(s_t, Fu) \\ r_t(s_t - 1, Am) + \gamma^2 \sum_{s' \in \mathcal{S}} \tilde{p}_t(s' | s_t^* - 1) \vartheta_{t+2}(s') - r_t(s_t, Am) - \gamma^2 \sum_{s' \in \mathcal{S}} \tilde{p}_t(s' | s_t) \vartheta_{t+2}(s') &< r_t(s_t - 1, Fu) + \gamma \sum_{s' \in \mathcal{S}} p_t(s' | s_t - 1) \vartheta_{t+1}(s') - r_t(s_t, Fu) - \gamma \sum_{s' \in \mathcal{S}} p_t(s' | s_t) \vartheta_{t+1}(s') \end{aligned} \quad (27)$$

Rearranging (27), we get the following inequality:

$$\begin{aligned} &r_t(s_t - 1, Am) \\ &\quad - r_t(s_t, Am) < r_t(s_t - 1, Fu) \\ &\quad - r_t(s_t, Fu) \\ &\quad + \gamma \sum_{s' \in \mathcal{S}} p_t(s' | s_t - 1) \vartheta_{t+1}(s') - \gamma^2 \sum_{s' \in \mathcal{S}} \tilde{p}_t(s' | s_t - 1) \vartheta_{t+2}(s') \\ &\quad - \left\{ \gamma \sum_{s' \in \mathcal{S}} p_t(s' | s_t) \vartheta_{t+1}(s') - \gamma^2 \sum_{s' \in \mathcal{S}} \tilde{p}_t(s' | s_t) \vartheta_{t+2}(s') \right\} \end{aligned} \quad (28)$$

Define $R_t(s_t - 1) = r_t(s_t - 1, Am) - r_t(s_t, Am)$. Using (8), we can write (28) as follows:

$$\begin{aligned}
& \Delta R_t(s_t - 1, Am) < \{r_t(s_t - 1, Fu) - r_t(s_t, Fu)\} \\
& + \gamma \sum_{s' \in \mathcal{S}} p_t(s' | s_t - 1) \vartheta_{t+1}(s') \\
& - \gamma^2 \sum_{s' \in \mathcal{S}} p_t(s' | s_t - 1) \sum_{s'' \in \mathcal{S}} p_{t+1}(s'' | s') \vartheta_{t+2}(s'') \\
& - \left\{ \gamma \sum_{s' \in \mathcal{S}} p_t(s' | s_t) \vartheta_{t+1}(s') - \gamma^2 \sum_{s' \in \mathcal{S}} p_t(s' | s_t) \sum_{s'' \in \mathcal{S}} p_{t+1}(s'' | s') \vartheta_{t+2}(s'') \right\} \quad (29) \\
& = \{r_t(s_t - 1, Fu) - r_t(s_t, Fu)\} \\
& + \gamma \sum_{s' \in \mathcal{S}} p_t(s' | s_t - 1) \{ \vartheta_{t+1}(s') - \gamma \sum_{s'' \in \mathcal{S}} p_{t+1}(s'' | s') \vartheta_{t+2}(s'') \} \\
& - \gamma \sum_{s' \in \mathcal{S}} p_t(s' | s_t) \{ \vartheta_{t+1}(s') - \gamma \sum_{s'' \in \mathcal{S}} p_{t+1}(s'' | s') \vartheta_{t+2}(s'') \}
\end{aligned}$$

Define:

$$\bar{\vartheta}_{t+1}(s') = \vartheta_{t+1}(s') - \gamma \sum_{s'' \in \mathcal{S}} p_{t+1}(s'' | s') \vartheta_{t+2}(s'') \quad (30)$$

$$= \vartheta_{t+1}(s') - v_{t+1}(s', Fu) + r_{t+1}(s', Fu) \quad (31)$$

Using the above definition, (29) can be written as:

$$\begin{aligned}
& \Delta R_t(s_t - 1, Am) < \{r_t(s_t \\
& \quad - 1, Fu) \\
& \quad - r_t(s_t, Fu)\} \\
& + \gamma \sum_{s' \in \mathcal{S}} p_t(s'|s_t \\
& \quad - 1) \bar{v}_{t+1}(s') \\
& - \gamma \sum_{s' \in \mathcal{S}} p_t(s'|s_t) \bar{v}_{t+1}(s') \\
& = \{r_t(s_t - 1, Fu) - r_t(s_t, Fu)\} \\
& + \gamma \sum_{s' \in \mathcal{S}} \{p_t(s'|s_t \\
& \quad - 1) - p_t(s'|s_t)\} \bar{v}_{t+1}(s')
\end{aligned} \tag{32}$$

$$\begin{aligned}
&= \{r_t(s_t - 1, Fu) \\
&\quad - r_t(s_t, Fu)\} \\
&\quad + \gamma \sum_{s' \in \mathcal{S}} \{p_t(s'|s_t \\
&\quad \quad - 1) - p_t(s'|s_t)\} \\
&\quad \times \{\vartheta_{t+1}(s') \\
&\quad \quad - v_{t+1}(s', Fu) \\
&\quad \quad + r_{t+1}(s', Fu)\} \\
&= \{r_t(s_t \\
&\quad - 1, Fu) \\
&\quad - r_t(s_t, Fu)\} \\
&\quad + \gamma \sum_{s'=0}^S \{p_t(s'|s_t \\
&\quad \quad - 1) - p_t(s'|s_t)\} r_{t+1}(s', Fu) \\
&\quad + \gamma \sum_{s'=0}^S \{p_t(s'|s_t \\
&\quad \quad - 1) - p_t(s'|s_t)\} \{\vartheta_{t+1}(s') \\
&\quad \quad - v_{t+1}(s', Fu)\} \\
&= \{r'_t(s_t - 1, Fu) - r'_t(s_t, Fu)\} \\
&\quad + \gamma \sum_{s'=0}^S \{p_t(s'|s_t \\
&\quad \quad - 1) - p_t(s'|s_t)\} \{r'_{t+1}(s', Fu) \\
&\quad \quad - dFu\} \\
&\quad + \gamma \sum_{s'=0}^S \{p_t(s'|s_t \\
&\quad \quad - 1) - p_t(s'|s_t)\} \{\vartheta_{t+1}(s') \\
&\quad \quad - v_{t+1}(s', Fu)\} \\
&= r'_t(s_t \\
&\quad - 1, Am) \\
&\quad - r'_t(s_t, Am) \\
&\quad - \gamma \sum_{s'=0}^S \{p_t(s'|s_t \\
&\quad \quad - 1) - p_t(s'|s_t)\} dFu \\
&\quad + \gamma \sum_{s'=0}^S \{p_t(s'|s_t \\
&\quad \quad - 1) - p_t(s'|s_t)\} \{\vartheta_{t+1}(s') \\
&\quad \quad - v_{t+1}(s', Fu)\}
\end{aligned} \tag{33}$$

$$\begin{aligned}
&= \Delta R_t(s_t - 1, Am) \\
&\quad - \gamma \{p_t(S \\
&\quad + 1|s_t) \\
&\quad - p_t(S \\
&\quad + 1|s_t \\
&\quad - 1)\} dFu \\
&\quad + \gamma \sum_{s'=0}^{s-1} \{p_t(s'|s_t \\
&\quad - 1) - p_t(s'|s_t)\} \{\vartheta_{t+1}(s') - v_{t+1}(s', Fu)\} \\
&\quad - \gamma \sum_{s'=s_t}^S \{p_t(s'|s_t) \\
&\quad - p_t(s'|s_t \\
&\quad - 1)\} \{\vartheta_{t+1}(s') \\
&\quad - v_{t+1}(s', Fu)\}
\end{aligned} \tag{34}$$

$$\begin{aligned}
&\leq \Delta R_t(s_t - 1, Am) \\
&\quad - \gamma \{p_t(S \\
&\quad + 1|s_t) \\
&\quad - p_t(S \\
&\quad + 1|s_t \\
&\quad - 1)\} dFu \\
&\quad + \gamma \sum_{s'=0}^{s-1} \{p_t(s'|s_t \\
&\quad - 1) - p_t(s'|s_t)\} \{\vartheta_{t+1}(s') - v_{t+1}(s', Fu)\} \\
&\quad - \gamma \sum_{s'=s_t}^S \{p_t(s'|s_t) \\
&\quad - p_t(s'|s_t \\
&\quad - 1)\} \{r_{t+1}(s', Bx) \\
&\quad - v_{t+1}(s', Fu)\}
\end{aligned} \tag{35}$$

$$\begin{aligned}
&\leq \Delta R_t(s_t - 1, Am) \\
&\quad - \gamma \{p_t(S \\
&\quad + 1|s_t) \\
&\quad - p_t(S \\
&\quad + 1|s_t \\
&\quad - 1)\} dFu \\
&\quad + \gamma \sum_{s'=0}^{s_t-1} \{p_t(s'|s_t \\
&\quad - 1) - p_t(s'|s_t)\} \left| v_{t+1}(s', Am) - v_{t+1}(s', Fu) \right| - \gamma \sum_{s'=s_t}^S \{p_t(s'|s_t) \\
&\quad - p_t(s'|s_t \\
&\quad - 1)\} \{r_{t+1}(s', Bx) \\
&\quad - v_{t+1}(s', Fu)\}
\end{aligned} \tag{36}$$

$$\begin{aligned}
&\leq \Delta R_t(s_t - 1, Am) \\
&\quad - \gamma \{p_t(S \\
&\quad + 1|s_t) \\
&\quad - p_t(S \\
&\quad + 1|s_t \\
&\quad - 1)\} dFu \\
&\quad + \gamma \sum_{s'=0}^{s_t-1} \{p_t(s'|s_t \\
&\quad - 1) - p_t(s'|s_t)\} \left| 2dFu - dAm \right| - \gamma \sum_{s'=s_t}^S \{p_t(s'|s_t) \\
&\quad - p_t(s'|s_t \\
&\quad - 1)\} \{r_{t+1}(s', Bx) \\
&\quad - v_{t+1}(s', Fu)\}
\end{aligned} \tag{37}$$

$$\begin{aligned}
&\leq \Delta R_t(s_t - 1, Am) \\
&\quad - \gamma \{p_t(S \\
&\quad + 1|s_t) \\
&\quad - p_t(S \\
&\quad + 1|s_t \\
&\quad - 1)\} dFu \\
&\quad + \gamma \sum_{s'=0}^{s_t-1} \{p_t(s'|s_t \\
&\quad - 1) - p_t(s'|s_t)\} \left| 2dFu - dAm \right| - \gamma \sum_{s'=s_t}^S \{p_t(s'|s_t) \\
&\quad - p_t(s'|s_t \\
&\quad - 1)\} \{r_{t+1}(s', Bx) \\
&\quad - r_{t+1}^{max}(s', Fu)\}
\end{aligned} \tag{38}$$

Inequality (33) follows from the definition of $r'_t(s_t, Am)$ as defined in (9). Inequality (34) follows from Conditions (5) and (6). Dropping the last term from (34), we get (35). Since, $\vartheta_{t+1}(s') - v_{t+1}(s', Fu) = \max\{v_{t+1}(s', Am), v_{t+1}(s', Fu)\} - v_{t+1}(s', Fu) = |v_{t+1}(s', Am) - v_{t+1}(s', Fu)|$, (36) follows. Using Lemma (2), we get (37) from (36). Since, $v_t(s, Fu) \leq r_t^{max}(s, Fu)$, we can replace $v_t(s, Fu)$ in (37) by $r_t^{max}(s, Fu)$. Rearranging (38), we get the following inequality, which contradicts condition (7).

$$\begin{aligned}
&\sum_{s'=s_t}^S \{p_t(s'|s_t) \\
&\quad - p_t(s'|s_t \\
&\quad - 1)\} \{r_{t+1}(s', Bx) \\
&\quad - v_{t+1}(s', Fu) + \{p_t(S \\
&\quad + 1|s_t) \\
&\quad - p_t(S \\
&\quad + 1|s_t \\
&\quad - 1)dFu < \sum_{s'=0}^{s_t-1} \{p_t(s'|s_t \\
&\quad - 1) - p_t(s'|s_t)\} \left| 2dFu - dAm \right|
\end{aligned}$$

Therefore, there exists a s^* such that for any $s_t < s^*$, $a_t^*(s_t) = Am$.

There are three possible relationships for s^{**} and s^* : $s^{**} > s^*$, $s^{**} = s^*$, and $s^{**} = s^*$. The case for $s^{**} < s^*$ is not feasible since for $s^{**} = s_t < s^*$, Step 1 of the proof implies that $a_t^*(s_t) = Bx$ and Step 2 of the proof implies that $a_t^*(s_t) = Am$, which is a contradiction.

When $s^{**} > s^*$ holds, then $a_t^*(s_t) = Bx$ for $s_t = s^{**}$ from Step 1, $a_t^*(s_t) = Am$ for $s_t = s^*$ from Step 2, and $a_t^*(s_t) = Fu$ for $s^* < s_t < s^{**}$ from Step 1 and Step 2, therefore a DCL policy is optimal. Similarly, when $s^{**} = s^*$, then action Fu is never optimal as a result of Step 1 and Step 2 of the proof, for which case a DCL policy is still optimal.

VIOLATION OF CONDITIONS USED IN THE STRUCTURAL PROPERTIES

Table 8 shows the maximum and average violations of all assumptions and conditions used in our structural results on the available clinical data and other data sets. Formal definitions for these violations are available below. As presented in the table, all violations are very small. Violations $\varepsilon_1 - \varepsilon_6$ are in probabilities and violation ε_7 is in days. Note that despite the violations, the optimal policy is always of double control-limit type for all ages (Figure 1).

Maximum violation of Condition (1):

$$\varepsilon_1^{max} = \max_{i,j,t} \left\{ \max \left\{ 0, \sum_{s'=j}^{S+1} p_t(s'|i) - \sum_{s'=j}^{S+1} p_{t+1}(s'|i) \right\} \right\}, i, j \in \mathcal{S} \setminus \{S+2\}, t=1, 2, \dots, T-1.$$

Maximum violation of IFRness of $\mathcal{P}$:

$$\varepsilon_2^{max} = \max_{i,j,t} \left\{ \max \left\{ 0, \sum_{s'=j}^{S+1} p_t(s'|i) - \sum_{s'=j}^{S+1} p_t(s'|i+1) \right\} \right\}, i, j \in \mathcal{S} \setminus \{S+2\}, t=1, 2, \dots, T.$$

Maximum violation of Condition (3):

$$\varepsilon_3^{max} = \max_{s,t} \left\{ \max \left\{ 0, \frac{r_t(s, Bx) - r_t(s+1, Bx)}{\gamma^2 r_{t+2}(s+1, Bx)} - p_t(S+1|s+1) - p_t(S+1|s) \right\} \right\}$$

for $s = 0, 1, 2, \dots, S-1, t = 1, 2, \dots, T-1$.

Maximum violation of Condition (4):

$$\varepsilon_4^{max} = \max_{s,t} \left\{ \max \left\{ 0, \sum_{s'=s+1}^S \tilde{p}_t(s'|s) - \sum_{s'=s+1}^S \tilde{p}_t(s'|s+1) \right\} \right\}$$

for $s = 0, 1, 2, \dots, S, S+1, t = 1, 2, \dots, T-1$.

Maximum violation of Condition (5):

$$\varepsilon_5^{max} = \max_{i,j,t} \left\{ \max \{0, p_t(i|j+1) - p_t(i|j)\} \right\}$$

for all $i \neq j$, where $i, j \in \mathcal{S} \setminus \{S+2\}$, and $t = 1, 2, \dots, T$.

Maximum violation of Condition (6):

$$\varepsilon_6^{max} = \max_{i,j,t} \{ \max \{ 0, p_t(i|j) - p_t(i|j+1) \} \}$$

for all $i > j$, where $i, j \in \mathcal{S} \setminus \{S+2\}$, and $t = 1, 2, \dots, T$.

Maximum violation of Condition (7):

$$\begin{aligned} \varepsilon_7^{max} = \max_{s,t} \left\{ \max \left\{ 0, \sum_{s'=0}^{s-1} \{ p_t(s'|s) \right. \right. \\ \left. \left. - 1) - p_t(s'|s) \right\} \left| 2dFu \right. \right. \\ \left. \left. - dAm \right| \right. \\ \left. - \sum_{s'=s}^S \{ p_t(s'|s) \right. \\ \left. - p_t(s'|s) \right. \\ \left. - 1) \} \{ r_{t+1}(s', Bx) \right. \\ \left. - r_{t+1}^{max}(s', Fu) \} \right. \\ \left. - \{ p_t(S \right. \\ \left. + 1|s) \right. \\ \left. - p_t(S \right. \\ \left. + 1|s - 1) \} dFu \} \right\} \end{aligned}$$

for $s < s_t^{**}$, where $s_t^{**} = 0, 1, 2, \dots, S-1$, and $t = 1, 2, \dots, T-1$.

The average violation of the first part of (AsI) is defined below. Similarly, we define

$\varepsilon_2^{avg}, \dots, \varepsilon_7^{avg}$.

$$\varepsilon_1^{avg} = \frac{1}{|S+2||S+2||T-1|} \sum_{t=1}^{T-1} \sum_{j \in \mathcal{S}} \sum_{i \in \mathcal{S}} \left\{ \max \left\{ 0, \sum_{s'=j}^{S+1} p_t(s'|i) - \sum_{s'=j}^{S+1} p_{t+1}(s'|i) \right\} \right\}$$

PERFORMANCE COMPARISON OF MDP MODEL AND RADIOLOGISTS

Table 9 compares the performance of the optimal policy of MDP model to that with radiologists' policy by risk score and age group.

Figure 1.
Optimal Policy of the MDP Model for the Base Case

(a) $dAm = 0.25$ days and $dFu = 0.25$ days (b) $dAm = 0.25$ days and $dFu = 0.50$ days (c) $dAm = 0.25$ days and $dFu = 1$ day (d) $dAm = 0.25$ days and $dFu = 1.5$ days

Figure 2.
Optimal Policy for Different dFu Values when $dAm=0.25$ days

(a) $dAm = 0.5$ days and $dFu = 0.25$ days (b) $dAm = 0.5$ days and $dFu = 0.50$ days (c) $dAm = 0.5$ days and $dFu = 1$ day (d) $dAm = 0.5$ days and $dFu = 2$ days **Figure 3.**Optimal Policy for Different dFu Values when $dAm = 0.5$ days

Figure 4.
Optimal Policy for Different dFu Values when $dAm=0$

Figure 5.
Optimal Policy for various $dBx@40$ and $dbxFac@100$ Values

Figure 6.

Tornado Diagram of the TPR of the MDP Model (★ represents the TPR of radiologists)

Figure 7.

Tornado Diagram of the TNR of the MDP Model (★ represents the TNR of radiologists)

Table 1

BI-RADS final assessment codes with the recommended actions (BI-RADS 1998)

Category	Definition	Recommended Action
0	Need additional imaging evaluation	Additional imaging
1	Negative finding	None (Annual mammography)
2	Benign finding	None (Annual mammography)
3	Probably benign finding (less than a 2% probability of cancer)	short-interval follow-up (6 months)
4	Suspicious abnormality (probability of cancer is between 2% and 95%)	Biopsy
5	Highly suggestive of malignancy (95% probability of cancer)	Biopsy

Table 2

List of Mammography Features (BI-RADS Descriptors) Used in the BN Model as Input Variables

Category	Variables	Instances
Patient Demographics	Age	Age < 45, 45–50, 51–54, 55–60, 61–64, 65
	Hormone Therapy	None, Less than 5 years, More than 5 years
	Personal History of BC	No, Yes
	Family History of BC	None, Minor, Major
	Prior history of surgery	No, Yes
	Post-operative Change	No, Yes
Findings: Mass	Mass Shape	Circumscribed, Ill-defined, Microlobulated, Spiculated, Not present
	Mass Stability	Decreasing, Stable, Increasing, Not present
	Mass Margins	Oval, Round, Lobular, Irregular, Not present
	Mass Density	Fat, Low, Equal, High, Not present
	Mass Size	None, Small (< 3 cm), Large (≥ 3 cm)
Findings: Calcifications	Popcorn	Present, Not Present
	Milk	Present, Not Present
	RodLike	Present, Not Present
	Eggshell	Present, Not Present
	Dystrophic	Present, Not Present
	Lucent	Present, Not Present
	Dermal	Present, Not Present
	Round	Scattered, Regional, Clustered, Segmental, Linearductal
	Punctate	Scattered, Regional, Clustered, Segmental, Linearductal
	Amorphous	Scattered, Regional, Clustered, Segmental, Linearductal
	Pleomorphic	Scattered, Regional, Clustered, Segmental, Linearductal
	FineLinear	Scattered, Regional, Clustered, Segmental, Linearductal
Findings: Other	Breast Density	Predominantly Fatty, Scattered Fibroglandular, Heterogeneously Dense, Extremely Dense
	Lymph Node	Present, Not Present
	Asymmetric Density	Present, Not Present
	Skin Thickening	Present, Not Present
	Tubular Density	Present, Not Present
	Skin Retraction	Present, Not Present
	Nipple Retraction	Present, Not Present
	Skin Thickening	Present, Not Present
	Trabecular Thickening	Present, Not Present
	Skin Lesion	Present, Not Present
	Axillary Adenopathy	Present, Not Present
	Architectural distortion	Present, Not Present
BI-RADS Assessments	BI-RADS category	0, 1, 2, 3, 4, 5

Table 3

Notation used in the MDP Model

Symbol	Description
t	Decision epochs; $t \in 0, 1, 2, \dots, T, T < \infty$, i.e., number of six-month periods since age 40
s_t	System state at time t ; $s_t \in \mathcal{S}$
$\mathcal{S}$	State space; $\mathcal{S} = \{0, 1, 2, \dots, S, S + 1, S + 2\}$
$S + 1$	Death
$S + 2$	Post-biopsy state
$a_t(s_t)$	Action at time t ; $a_t(s_t) \in \{Am, Fu, Bx\}$
Am	Annual Mammography
Fu	Short-interval Follow-up
Bx	Biopsy
$p_t(s_{t+1} s_t)$	Probability that the patient will move to state $s_{t+1} \in \mathcal{S}$ at time $t + 1$, given that she is in state $s_t \in \mathcal{S}$ at time t
$p_t(s_{t+2} s_t)$	Probability that the patient will be in state $s_{t+2} \in \mathcal{S}$ at time $t + 2$, given that she is in state $s_t \in \mathcal{S}$ at time t
$\mathcal{P}_t$	Transition probability matrix at time t when action Fu is selected
$\tilde{\mathcal{P}}_t$	Transition probability matrix at time t when action Am is selected
$dBx(t)$	Disutility of biopsy at time t .
dFu	Disutility associated with follow-up
dAm	Disutility associated with annual mammogram
γ	Discount factor over 6 months; ($0 < \gamma < 1$)
$r_t^\dagger(s_t, Fu)$	Intermediate expected reward (in years) accrued at time t when the patient's state is s_t and Fu is selected
$r_t(s_t, Fu)$	Intermediate QALYs accrued at time t when the patient's state is s_t and Fu is chosen, i.e. $r_t(s_t, Fu) = r_t^\dagger(s_t, Fu) - dFu$
$r_t^\dagger(s_t, Am)$	Intermediate expected life years accrued at time t , when the patient's state is s_t and Am is selected
$r_t(s_t, Am)$	Intermediate QALYs accrued at time t when the patient's state is s_t and Am is selected, i.e. $r_t(s_t, Am) = r_t^\dagger(s_t, Am) - dAm$
$r_t^\dagger(s_t, Bx)$	Total expected discounted post-biopsy life years when the patient's state is s_t at time t
$r_t(s_t, Bx)$	Total expected discounted post-biopsy QALYs when the patient's state is s_t at time t , i.e. $r_t(s_t, Bx) = r_t^\dagger(s_t, Bx) - dBx(t)$
$\vartheta_t(s_t)$	Maximum total expected discounted QALYs that the patient can attain when her current state is s_t at time t

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Table 4
MDP Model versus Radiologists: Base-case using BN. The numbers in parentheses represent malignant cases.

MDP Model			
	<i>Am</i>	<i>Fu</i>	<i>Bx</i>
<i>Am</i>	31,714 (8)	498 (2)	613 (1) 32,825 (11)
<i>Fu</i>	6,973 (8)	469 (5)	210 (6) 7,652 (19)
<i>Bx</i>	893 (5)	121 (4)	824 (319) 1,838 (328)
	39,580 (21)	1,088 (11)	1,647 (326)

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Table 5
MDP Model versus Radiologists: Base-case using LR. The numbers in parentheses represent malignant cases.

MDP Model			
	<i>Am</i>	<i>Fu</i>	<i>Bx</i>
<i>Am</i>	31,670 (9)	608 (0)	547 (2)
<i>Fu</i>	6,898 (8)	572 (10)	182 (1)
<i>Bx</i>	852 (4)	157 (4)	829 (320)
	39,420 (21)	1,337 (14)	1,558 (323)

Table 6
Performance of the MDP Model on the Real Mammography Data for Various Disutilities

dAm (days)	dFu (days)	$dBx@40$ (weeks)	$dbxFac$ @100	$\#Am$	$\#Fu$	$\#Bx$	$Fu-Ben$	$FP-Bx$	FN	TPR	TNR	$QALY$ gains
0	0	2.0	2.0	0	40678	1637	40644	1313	34	0.905	0.969	2.279
0	0.25	2.0	2.0	39,886	747	1682	739	1356	32	0.911	0.968	1.780
0	1.5	2.0	2.0	40,578	0	1737	0	1411	32	0.911	0.966	0.364
0.25	0.25	2.0	2.0	39,580	1088	1647	1077	1321	32	0.911	0.969	1.986
0.25	0.5	2.0	2.0	40,189	444	1682	438	1356	32	0.911	0.968	0.565
0.25	1.0	2.0	2.0	40,520	69	1726	67	1400	32	0.911	0.967	0.532
0.25	1.5	2.0	2.0	40,578	0	1737	0	1411	32	0.911	0.966	0.523
0.5	0.25	2.0	2.0	0	40678	1637	40644	1313	34	0.905	0.969	0.640
0.5	0.5	2.0	2.0	39,886	761	1668	753	1342	32	0.911	0.968	0.590
0.5	1.0	2.0	2.0	40,520	77	1718	75	1392	32	0.911	0.967	0.548
0.5	2.0	2.0	2.0	40,578	0	1737	0	1411	32	0.911	0.966	0.530
1.0	2.0	2.0	2.0	40,589	0	1726	0	1400	32	0.911	0.967	0.551
0.25	0.25	1.0	1.0	39,556	278	2481	276	2146	23	0.936	0.949	-0.201
0.25	0.25	1.0	2.0	39,559	555	2201	549	1870	27	0.925	0.955	-0.030
0.25	0.25	1.0	4.0	39,580	847	1888	837	1561	31	0.913	0.963	0.427
0.25	0.25	2.0	0.5	39,556	985	1774	976	1446	30	0.916	0.966	-0.103
0.25	0.25	2.0	1.0	39,578	997	1740	987	1413	31	0.913	0.966	0.084
0.25	0.25	2.0	4.0	39,591	1160	1564	1146	1241	35	0.902	0.970	1.897
0.25	0.25	3.0	2.0	39,585	1175	1555	1160	1233	36	0.899	0.971	1.430
Radiologists												
				32,825	7,652	1,838	7,633	1,553	30	0.916	0.875	

Note. The total number of cases is 42,315. $\#Am$ = number of annual mammography recommendations, $\#Fu$ = number of follow-ups, $\#Bx$ = number of biopsies, $Fu-Ben$ = number of follow-ups with a benign outcome, $FP-Bx$ = number of biopsies with a benign outcome, FN = number of false negative cases, i.e. number of annual mammograms and follow-ups with malignant outcome (i.e. missed cancers), TPR = true positive rate, and TNR = true negative rate. QALY gains compared to radiologists are reported per 10,000 women (the details of this computation are given in the text).

Table 7

Range of MDP Model's Parameters for Sensitivity Analysis

<i>Parameters</i>	<i>Range</i>		
	Baseline	Low	High
dAm (days)	0.25	0	0.5
dFu (days)	0.5	0.25	1.5
<i>TxFactor@40</i>	2	1.5	3
Invasive %	75	65	85
dBx@40 (weeks)	2	1	3
<i>dbxFac@100</i>	2	0.5	4

Table 8

Violation of Conditions used in the Structural Properties

Violation (units)	Definition	Maximum	Average
ε_1 (probability)	Violation of Condition (1)	0.0000	0.0000
ε_2 (probability)	Violation of IFRness of $\mathcal{P}$	0.0022	< 0.0001
ε_3 (probability)	Violation of Condition (3)	0.0033	0.0018
ε_4 (probability)	Violation of Condition (4)	0.0000	0.0000
ε_5 (probability)	Violation of Condition (5)	0.0048	< 0.0001
ε_6 (probability)	Violation of Condition (6)	0.0000	0.0000
ε_7 (days)	Violation of Condition (7)	0.0726	0.0024

Table 9

QALY gains (per 10,000 women) by MDP policy in comparison to radiologists' policy by risk score and age. The top value of each combination of risk-score and age represents the QALY gains per 10,000 women and the bottom value represents the number of women.

Risk Group	Age Group						Total
	40–50	50–60	60–70	70–80	80–90	90–100	
0	0	0	0	0	0	0	0
	11,687	11,320	7,698	5,573	1,649	100	38,027
1	19,696	12,244	5,112	1,445	0,000	0,000	10,392
	673	622	494	371	133	10	2,303
2	182,081	97,267	24,398	0,000	0,000	0,000	84,169
	177	215	154	82	46	2	676
3	0,000	0,000	0,000	0,000	75,462	376,334	9,635
	23	68	60	52	13	3	219
4	0,000	0,000	0,000	0,000	34,048	225,000	4,796
	24	42	57	51	21	1	196
5	0,000	0,000	0,000	0,000	0,000	0,000	0,000
	33	47	28	21	4	0	133
6	0,000	0,000	0,000	0,000	0,000	0,000	0,000
	15	12	10	9	0	0	46
7	0,000	0,000	0,000	0,000	0,000	0,000	0,000
	10	15	8	3	1	2	39
8	0,000	0,000	0,000	0,000	0,000	0,000	0,000
	3	11	15	10	4	0	43
9	0,000	0,000	0,000	0,000	0,000	6,666	0,328
	7	17	18	11	5	3	61
10	0,000	0,000	0,000	0,000	0,000	0,000	0,000
	14	15	21	22	14	0	86
10–15	0,000	0,000	0,000	0,000	0,000	0,000	0,000
	21	28	31	32	3	1	116
15–20	0,000	0,000	0,000	0,000	0,000	0,000	0,000
	7	11	17	20	6	1	62

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Risk Group	Age Group					Total
20–25	0.000	0.000	0.000	0.000	0.000	0.000
	6	16	3	5	3	0
25–50	0.000	0.000	0.000	0.000	0.000	412.998
	29	34	28	34	7	1
50–75	0.000	0.000	0.000	0.000	0.000	0.000
	32	51	33	16	10	0
75–100	0.000	0.000	0.000	0.000	0.000	0.000
	22	30	34	33	7	2
Total	3.558	2.272	0.721	0.085	0.881	14.183
	12,783	12,554	8,709	6,345	1,926	126
						42,443