A Prescriptive Analytics Method for Cost Reduction in Clinical Decision Making

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ABSTRACT

Containing skyrocketing health care costs is imperative. Toward that end, prescriptive analytics that analyzes health care data to recommend optimal decisions is both relevant and crucial. We develop a novel prescriptive analytics method to improve the cost effectiveness in clinical decision making (CDM), a critical health care dimension that can greatly benefit from analytics. Effective prescriptive analytics for CDM has to address its probabilistic, cost-sensitive, and investment-related characteristics simultaneously. Unlike existing methods that often overlook the investment-related characteristic, the proposed method accounts for all of these characteristics. Specifically, our method considers two sets of costs associated with clinical decisions—before and after an investment—in combination with the probabilities of cost changes due to the investment. In contrast, prevalent methods only emphasize one set of costs, before an investment. Furthermore, the proposed method involves both clinical and investment decisions, whereas existing methods ignore investment decisions. Empirical evaluations with two real-world clinical data sets indicate that the proposed method consistently and significantly outperforms several salient methods from previous research, thereby demonstrating the value of addressing the investment-related characteristic in efforts to improve CDM.

Keywords: machine learning, cost-sensitive learning, prescriptive analytics, health care, clinical decision making

INTRODUCTION

Health care costs are skyrocketing. According to the Centers on Medicare & Medicaid Services, health care spending accounted for 17.92% of the U.S. gross domestic product (GDP) in 2017, with total costs reaching $3.5 trillion in 2017.[1] Substantial, pronounced efforts have been undertaken to reduce health care costs and improve service quality and patient outcomes (e.g., Agarwal et al. 2010; Aron et al. 2011; Menon and Kohli 2013; Menon et al. 2000). However, without proper cost containment measures, the growth of U.S. health care expenditures is projected to outpace that of the nation's GDP during 2018–2027 (Centers for Medicare & Medicaid Services). As Berwick and Hackbarth (2012, p. 1513) caution, "The need is urgent to bring US health care costs into a sustainable range for both public and private payers." It is therefore imperative to develop viable solutions to curb rapidly rising costs in health care (Mango and Riefberg 2009).

Data-driven analytics is promising for increasing the cost effectiveness of health care, which is an inherently data-intensive sector (Dhar 2014; Fang et al. 2013). For example, the U.S. health care system has accumulated enormous amounts of data that pertain to clinical services and patient care (e.g., electronic health records [EHR]), medical claims, medications and their adverse effects, and pharmaceutical research and development. These data, rich in both breadth and depth, enable the development of analytics methods for optimal decision making (Davenport 2013). Indeed, data-driven analytics is central to health information technology (HIT), which represents a crucial and consequential research opportunity for information systems (IS) (Agarwal and Dhar 2014; Agarwal et al. 2010; Fichman et al. 2011).

[1] https://www.cms.gov/research-statistics-data-and-systems/statistics-trends-and-reports/nationalhealthexpenddata/nhe-fact-sheet.html; accessed on February 13, 2019.

Effective analytics can generate clinical intelligence about patients' risks for future adverse health events (Lin et al. 2017), such that an "emerging avenue for knowledge discovery arises from using digital technology to enable new kinds of mathematical healthcare modeling and simulations.… [The] implementation and use of healthcare analytics tools and how they should be integrated with electronic health records warrants future research attention" (Fichman et al. 2011, p. 425). Echoing this call, Kohli and Tan (2016, p. 564) advocate that "IS researchers with technical and analytical interests can contribute to the design of algorithms and modeling … to further enrich EHR use in analytics." The significance of data-driven analytics in health care also resonates with design science research that emphasizes the development and utilization of effective information technology artifacts, such as mathematical models and computational methods and systems, to address practical needs, as has been a focus of IS research since its inception (Hevner et al. 2004).

Toward that end, prescriptive analytics is particularly important and relevant, in that it seeks the best solution and outcome, given various choices and known parameters (Phillips-Wren et al. 2015; Wang and Hajli 2017; Watson 2014). For clinical decision making (CDM)—a process of using clinical data to make decisions about patient care and management[2]—prescriptive analytics can identify at-risk patients and recommend optimal clinical solutions (Kohli and Tan 2016), which could better support physicians' CDM with patient-level analyses. A growing emphasis on patient-level analytics has emerged as researchers and clinicians recognize that the ultimate impacts of HIT need to be measured at the patient level (Bardhan et al. 2014). In considering the values and uses of prescriptive analytics, we respond to calls for more attention to patient-level data analyses to generate useful, actionable insights (Angst et al. 2010; Gao et al. 2010).

[2] Our definition of CDM follows the Merck Manuals (http://www.merckmanuals.com/), a widely referenced, comprehensive medical resource for health care researchers, clinical professionals, and the general public.

Accordingly, we seek to develop a novel prescriptive analytics method to contain costs in the CDM realm. To achieve this goal, we need to address several eminent characteristics of CDM. First, CDM is intrinsically probabilistic because it builds on probabilistic diagnoses. Take mechanical ventilation, an invasive intervention to assist a patient's respiration, as an example. An important clinical decision facing the physician is whether a patient should be removed from ventilation and rely on his or her own respiration system for breathing. Physicians usually make this decision on the basis of an estimated likelihood that the patient has gained sufficient recovery to breathe independently, which is a probabilistic diagnosis. Second, CDM is cost sensitive, because different decisions lead to differential costs. Continuing with the ventilation example, a physician's decision to remove a patient from mechanical ventilation, when the patient actually should stay on ventilation, can result in complications that differ from those commonly associated with not removing a patient from ventilation when the patient in effect does not need it. These resulting complications require varying costs to treat. Third, the costs associated with clinical decisions could be altered by an investment. For example, an investment in putting patients on advanced ventilation (at an approximate cost of $1,636 in the United States) could avoid a particular complication that normally would occur in the absence of this investment, thereby obviating the cost of treating that complication (Antonelli et al. 1998; Dasta et al. 2005), which in turn would alter the costs associated with distinct clinical decisions.

Existing prescriptive analytics methods usually consider the probabilistic and cost-sensitive characteristics of CDM but ignore its investment-related characteristic (Ling et al. 2006; Qiu et al. 2015; Turney 1995). For example, Qiu et al. (2015) develop a method to support physicians' bed reservation decisions for patients by considering the probabilistic diagnosis that a patient needs a bed in the hospital. This method is cost sensitive in that it accounts for various costs

associated with different decisions. However, effective support for CDM requires prescriptive analytics methods to address investment-related characteristic too. Our proposed method differs from extant methods by considering all three characteristics simultaneously. For the investment-related characteristic, we consider two sets of costs associated with clinical decisions—before and after an investment—in conjunction with the probabilities of cost changes due to the investment, while existing methods focus on the costs before an investment only. Furthermore, a physician's decision to make a particular investment may have considerable cost implications, such that the investment could alter the costs associated with his or her decision. Thus our method targets both clinical and investment decisions, while existing methods overlook the latter.

In the next section, we review related works and highlight several essential differences that separate our study from previous research. We then formally define the focal problem and propose a novel prescriptive analytics method to solve it. Next, we use two real-world clinical data sets to evaluate the proposed method, with several prevalent methods as benchmarks. We conclude by discussing some important contributions, implications, and limitations of this study.

LITERATURE REVIEW

Typically, a clinical decision classifies a patient into one of several predefined classes, such as being a candidate for removal from mechanical ventilation or not. Existing prescriptive analytics methods treat clinical decisions as classification decisions and often take a cost-sensitive learning approach to support CDM (e.g., Ling et al. 2006; Qiu et al. 2015; Turney 1995). The stream of cost-sensitive learning research closely relates to our study. Common inputs for a cost-sensitive learning method include a training data set that comprises previously classified instances and a cost matrix in which each element indicates the cost of classifying an instance as class i if it

actually belongs to class *j*. A method learns from training data to construct a classifier that then can be used to assign an unclassified instance to one of the predefined classes, which minimizes the expected cost of classifying the instance. Existing cost-sensitive learning methods can be broadly categorized as threshold moving, distribution altering, or test cost-sensitive learning. In the following, we review representative methods of each category and then discuss how our method differs from these prevalent methods.

Threshold Moving

A classification method assigns unlabeled instances to maximize classification accuracy. For example, a binary classification method predicts the probability that an instance belongs to a particular class, then assigns the instance to be of that class if the predicted probability exceeds an accuracy-maximization threshold (e.g., 0.5) or of the other class otherwise (Elkan 2001). In general, threshold moving employs a classification method to predict the probability that an instance belongs to a particular class and classifies the instance on the basis of a cost-sensitive threshold calculated from the given classification costs (Elkan 2001; Fang 2013; Margineantu 2002; Pazzani et al. 1994). For example, Zhou and Liu (2006) propose a threshold moving method to train cost-sensitive neural networks; Sheng and Ling (2006) develop a method to search for a cost-sensitive threshold that minimizes the total cost of classifying training instances, then use the threshold to classify unlabeled instances. Unlike most threshold moving methods that use class-dependent classification costs, Zadrozny and Elkan (2001) develop a method that relies on instance-dependent classification costs. Recent threshold moving research features both novel methods (Fang 2013) and innovative applications (Qiu et al. 2015). For example, Fang (2013) proposes a cost-sensitive naïve Bayes method that infers the order relation between an instance's probability of belonging to a particular class and the cost-sensitive

threshold (e.g., greater than, equal to, less than). This method iteratively learns and infers the order relations from training data, then uses the inferred order relations to classify unlabeled instances. Qiu et al. (2015) apply threshold moving to develop a method to support physicians' bed reservation decisions for patients in the emergency department, with the objective of minimizing the expected bed reservation cost.

Distribution Altering

Distribution altering instead changes the class distribution in training data, according to the specified classification costs (Breiman et al. 1984; Domingos 1999; Jiang et al. 2014). The class distribution in training data can be altered with undersampling or oversampling. Undersampling removes instances from training data; oversampling instead adds instances to training data. Such sampling can be further categorized as random or intelligent. Random undersampling randomly selects training data instances to eliminate, whereas intelligent undersampling chooses appropriate instances to remove. One-sided selection (Kubat and Matwin 1997) represents an intelligent undersampling method; it identifies borderline, noisy, and redundant instances for removal. Similarly, random oversampling randomly duplicates instances in training data, whereas intelligent oversampling (e.g., synthetic minority oversampling, or SMOTE; Chawla et al. 2002) generates appropriate, synthetic instances and incorporates them into training data. Li et al. (2017) follow Chawla et al. (2002) and propose methods for setting two key parameters in SMOTE: oversampling rate and size of neighborhood. Weiss (2004) provides a comprehensive review; Gao et al. (2017) offer a more recent survey of undersampling and oversampling methods originally developed for learning from imbalanced data sets.

Class distribution altering can be accomplished with instance weighting (Zhao 2008) as well. For example, the class distribution in training data could be implicitly altered with instances in

the training data, weighted in proportion to their classification costs (Lee and Zhu 2011; Ting 2002). In an iterative naïve Bayes method, the updates to the class-attribute distributions learned by the naïve Bayes approach follow predefined increments, so it weights training instances differently (Gama 2000). Ting (2002) also proposes an instance weighting method to induce a cost-sensitive decision tree from training data. By assigning greater weights to instances with higher classification costs, this method steers decision tree induction to focus more on instances with higher classification costs, thereby reducing the likelihood of misclassifying them and ultimately lowering total classification costs. With a similar approach, Jiang et al. (2014) develop an instance weighting method to make the Bayesian networks cost sensitive. MetaCost, a prevalent distribution altering method (Domingos 1999), alters the class distribution in training data by relabeling instances instead of sampling or weighting them. The rationale is that if instances in training data are relabeled as their optimal classes, according to classification costs, a conventional method can be applied to the modified training data to induce an optimal cost-sensitive classifier. MetaCost follows this logic by computing the optimal class for each instance in the training data and relabeling the instance if the current class differs from its optimal class.

Test Cost-Sensitive Learning

Both threshold moving and distribution altering aim to minimize classification costs; test cost-sensitive learning also considers attribute costs, or the costs of acquiring attribute values of a particular instance (Turney 1995). For example, physicians can order medical tests for patients (e.g., blood tests) before making clinical decisions; the costs of the prescribed tests are attribute costs. Test cost-sensitive learning classifies unclassified instances to minimize the sum of attribute and classification costs (Ling et al. 2006; Turney 1995; Weiss et al. 2013). Turney (1995) proposes a hybrid method, built on genetic algorithms and decision trees, for test cost-

sensitive learning. Ling et al. (2004, 2006) also build test cost-sensitive learning methods on a decision tree by extending the tree induction to develop a method that comprises two phases: training and testing. In the training phase, a test cost-sensitive decision tree is learned from training data, with the objective of minimizing the sum of the attribute and classification costs. In the testing phase, an unclassified instance is classified by the learned decision tree, with an attribute cost incurred if any attribute value of the instance is not available. Unlike these methods, a test cost-sensitive learning method for naïve Bayes learns a naïve Bayes model from training data and then, in the testing phase, deliberately selects unknown attributes to acquire their values, which minimizes the sum of attribute and classification costs (Chai et al. 2004). Another proposed test cost-sensitive learning method learns from training data to discover a subset of attributes whose values need to be obtained (Weiss et al. 2013).

This review of extant literature reveals several important differences that separate the proposed method from existing ones. First, our method employs two classification cost matrixes and recognizes that an investment could alter classification costs probabilistically. That is, in our method, classification costs are probabilistic, whereas existing methods only use one classification cost matrix to classify instances and view classification costs as deterministic. Second, both threshold moving and distribution altering make classification decisions only: to which class an unclassified instance should be assigned. Instead, our method makes both investment and classification decisions. An investment decision differs from a test decision in test cost-sensitive learning, such that it entails whether to make an investment, whereas the latter targets which attribute values to obtain. Third, our method is distinct in its objective. Both threshold moving and distribution altering attempt to minimize classification costs; test cost-sensitive learning seeks to minimize the sum of attribute and classification costs. Our method

instead aims to minimize the sum of investment and classification costs. An investment cost, incurred with an investment to alter the classification costs, differs from an attribute cost incurred to obtain the value of a particular attribute. In Table 1, we highlight these distinctions.

	Proposed Method	**Threshold Moving**	**Distribution Altering**	**Test Cost-Sensitive**
Number of Cost Matrixes Considered	Two	One	One	One
Classification Cost	Probabilistic	Deterministic	Deterministic	Deterministic
Decision	Investment and classification	Classification	Classification	Test and classification
Objective	Minimize the sum of investment and classification costs	Minimize classification costs	Minimize classification costs	Minimize the sum of attribute and classification costs
Representative Studies		Elkan (2001); Qiu et al. (2015)	Domingos (1999); Ting (2002); Zhao (2008); Jiang et al. (2014)	Turney (1995); Ling et al. (2006); Weiss et al. (2013)

Table 1: Key Differences between Proposed Method and Existing Cost-Sensitive Learning Methods

THEORETICAL FOUNDATION

Although our method is analytical, its conceptualization stems from a foundation in prospect theory (Kahneman and Tversky 1979), which explains how people decide among alternatives (choices) in scenarios that involve risk and uncertainty. This theory posits that people evaluate probabilities nonlinearly, unlike expected utility theory suggesting that people evaluate them linearly (Gonzalez and Wu 1999; Prelec 2000; Tversky and Wakker 1995). As Kahneman and Tversky (1979, p. 279) indicate, “the aggravation that one experiences in losing a sum of money appears to be greater than the pleasure associated with gaining the same amount.” Decision making thus might reflect separate evaluations of gains and losses, such that people tend to be risk averse in choices involving gains but risk seeking in choices involving losses (Shafir and LeBoeuf 2002; Tversky and Kahneman 1992).

From a psychological perspective, a strong feeling of fear arises due to uncertainty or variability with regard to gains, because a genuine fear of losing a sure gain is more painful than the pleasure associated with a potential gain, even if the latter promises potentially greater payoffs. As Clark and Lisowski (2017, p. 7433) explain, people's greater concerns about "losing what they have than about what they might gain" guide their behaviors. In the gain domain, "certainty increases the aversiveness of losses as well as the desirability of gains" (Kahneman and Tversky 1979, p. 269), but in the loss domain, fearing an outcome, uncertainty increases the attractiveness of risk and hope.

Such considerations also could apply to clinical decision making, in that dealing with patient complications involves financial costs, similar to losses. Physicians might perceive their decision tasks according to a loss domain (i.e., cost of treating the resulting complications) and thus prefer an option that might reduce misclassification probability and costs, which also lowers the total cost of treating the patient. In such a setting, physicians could seek risk and choose to make an investment, such as prescribing advanced ventilation for patients currently on mechanical ventilation, in an attempt to mitigate the total costs of patient care, assuming the investment amount is reasonable. In line with Tversky and Kahneman (1992), people tend to be risk seeking in a scenario filled with information about losses, such that they are more willing to make an investment to alter misclassification probabilities and costs.

This reasoning also implies a reflection, such that "risk aversion in the positive domain is accompanied by risk seeking in the negative domain" (Kahneman and Tversky 1979, p. 268). A preference reversal, from risk averse to risk seeking, thus might occur if the choice options switch from gains to losses (Kahneman and Tversky 1979). For example, in a loss domain with negative values (e.g., costs), people might prefer probabilistic, larger losses over known, smaller

losses. As Kahneman and Tversky (1979, p. 269) note, this reflection effect "eliminates aversion for uncertainty or variability as an explanation of the certainty effect."

Our theoretical foundation also integrate regret theory (Zeelenberg et al. 1996), which asserts "first, that many people experience the sensations we call regret and rejoicing; and second, that in making decisions under uncertainty, they try to anticipate and take account of those sensations" (Loomes and Sugden 1982, p. 820). By and large, people have a tendency of avoiding negative feelings (regret) and embracing positive feeling (rejoice) (Larrick et al. 1995); thus they compare the outcomes of different choices, and their emotions are inherent to the decision (Zeelenberg et al. 1996). For example, people experience regret if an option not chosen ultimately would have been better (Loomes and Sugden 1982). Comparing the respective outcomes of different choices can be viewed as a process in people's minds; that is, people compare the outcome of the option they chose with the outcome that "might have been," had they chosen differently, which implies people take potential regret into account when choosing among alternatives (Bell 1983). The amount of regret a person feels depends on the difference between outcomes, in line with prospect theory, so he or she might be risk averse if choices involve gains and risk seeking if choices involve losses (Bell 1983; Loomes and Sugden 1982). In our context, physicians might tend to estimate the plausible outcomes of different alternatives and choose the one that minimizes their estimated feeling of regret. For example, they might choose to make an investment to mitigate (total) costs, if the "no investment" choice seems to be associated with a higher level of regret.

INVESTMENT-ADJUSTED COST-SENSITIVE LEARNING: PROBLEM AND METHOD

To consider the probabilistic, cost-sensitive, and investment-related characteristics of CDM simultaneously, we formulate a new cost-sensitive learning problem (i.e., the investment-adjusted cost-sensitive learning problem) and propose a novel method to solve it.

Problem Formulation

Let $\boldsymbol{T}$ be training data, in which each record corresponds to an already classified instance. A record consists of a vector of *n* attributes that jointly describe an instance, $X = < x_1, x_2, \ldots, x_n >$, and a class label y of the instance, $y \in \{0,1\}$. Let $\boldsymbol{C}$ be the classification cost matrix. As we show in Table 2, an element c_{ij} of $\boldsymbol{C}$ represents the cost of classifying an instance as class i when it actually belongs to class j, $i, j \in \{0,1\}$.

	Actually Belonging to Class 0	**Actually Belonging to Class 1**
Classifying as Class 0	c_{00}	c_{01}
Classifying as Class 1	c_{10}	c_{11}

Table 2: Classification Cost Matrix *C*

With an investment, there is a probability of p_{ij} that the classification cost c_{ij} changes to $\bar{c}_{ij}$ and a probability of $1 - p_{ij}$ that the investment fails and c_{ij} remains the same, $i, j \in \{0,1\}$. Table 3 reveals the (new) classification cost matrix $\overline{\boldsymbol{C}}$, and Table 4 summarizes the probability p_{ij} that a classification cost changes due to the investment, $i, j \in \{0,1\}$.

	Actually Belonging to Class 0	**Actually Belonging to Class 1**
Classifying as Class 0	$\bar{c}_{00}$	$\bar{c}_{01}$
Classifying as Class 1	$\bar{c}_{10}$	$\bar{c}_{11}$

Table 3: New Classification Cost Matrix $\overline{\boldsymbol{C}}$

Probability of Changing from c_{00} to $\bar{c}_{00}$	**Probability of Changing from c_{01} to $\bar{c}_{01}$**	**Probability of Changing from c_{10} to $\bar{c}_{10}$**	**Probability of Changing from c_{11} to $\bar{c}_{11}$**
p_{00}	p_{01}	p_{10}	p_{11}

Table 4: Probability p_{ij} of Cost Change Due to an Investment

We define the investment-adjusted cost-sensitive learning problem as follows: Given training data $\boldsymbol{T}$, cost matrixes $\boldsymbol{C}$ and $\overline{\boldsymbol{C}}$, the amount V of an investment, and the probability p_{ij} of classification cost change due to the investment, $i, j \in \{0,1\}$, we need to learn from $\boldsymbol{T}$ to make two decisions for an unclassified instance: (1) whether to make the investment and (2) to which class we should classify an instance to minimize the expected total cost (i.e., sum of the investment cost and expected classification cost).

Investment-Adjusted Cost-Sensitive Learning Method

To solve the problem, we make two assumptions. First, the cost of incorrectly classifying an instance logically is higher than that of classifying the instance correctly (Elkan 2001). We therefore assume $c_{10} > c_{00}$, $\bar{c}_{10} > \bar{c}_{00}$, $c_{01} > c_{11}$, and $\bar{c}_{01} > \bar{c}_{11}$. Second, we assume that making an investment could reduce classification costs (Antonelli et al. 1998; Dasta et al. 2005), so $c_{00} > \bar{c}_{00}$, $c_{01} > \bar{c}_{01}$, $c_{10} > \bar{c}_{10}$, and $c_{11} > \bar{c}_{11}$.[3] These assumptions are both appropriate and consistent with previous research (Elkan 2001).

Next, we propose a way to make investment and classification decisions for an unclassified instance. Let p be the probability that the unclassified instance belongs to class 1. We can compute the expected total cost for that instance, for each possible combination of investment and classification decisions:

(i) If the investment decision is "no investment" and the instance is classified as class 1, the expected total cost C_1 is given by

$$C_1 = pc_{11} + (1-p)c_{10}. \tag{1}$$

[3] If costs in $\overline{\boldsymbol{C}}$ are higher than their counterparts in $\boldsymbol{C}$, the optimal investment decision is always "no investment." In this case, the decision problem can be solved with existing cost-sensitive methods. Such scenarios, in which costs in $\overline{\boldsymbol{C}}$ are greater than their counterparts in $\boldsymbol{C}$, are not the focus of this study.

The expected total cost is the sum of the investment cost and the expected classification cost. In this case, the investment cost is 0, because no investment occurs. For the same reason, we calculate the expected classification cost using the cost matrix $\boldsymbol{C}$ in Table 2, and the expected classification cost is $pc_{11} + (1-p)c_{10}$.

(ii) If the investment decision is "no investment" and the instance is classified as class 0, the expected total cost C_2 is

$$C_2 = pc_{01} + (1-p)c_{00}. \tag{2}$$

Likewise, the investment cost is 0, because no investment is made. Using the cost matrix $\boldsymbol{C}$ in Table 2, we compute the expected classification cost as $pc_{01} + (1-p)c_{00}$.

(iii) If the investment decision is "investment" and the instance is classified as class 1, the expected total cost C_3 is

$$C_3 = V + pc_{11}(1-p_{11}) + p\bar{c}_{11}p_{11} + (1-p)c_{10}(1-p_{10}) + (1-p)\bar{c}_{10}p_{10}, \tag{3}$$

and the investment cost is V, because an investment has been made. The instance has a probability p of actually belonging to class 1 and is classified as class 1, so the expected classification cost becomes

$$\begin{cases} pc_{11} + (1-p)c_{10} & \text{if using cost matrix } \boldsymbol{C} \text{ in Table 2,} \\ p\bar{c}_{11} + (1-p)\bar{c}_{10} & \text{if using cost matrix } \overline{\boldsymbol{C}} \text{ in Table 3.} \end{cases}$$

As we show in Table 4, with an investment, there is a probability of p_{11} that c_{11} changes to $\bar{c}_{11}$ and a probability of $(1-p_{11})$ that c_{11} remains intact. Also, there is a probability of p_{10} that c_{10} changes to $\bar{c}_{10}$ and a probability of $(1-p_{10})$ that c_{10} remains the same. Thus, the expected classification cost becomes

$$pc_{11}(1-p_{11}) + p\bar{c}_{11}p_{11} + (1-p)c_{10}(1-p_{10}) + (1-p)\bar{c}_{10}p_{10}.$$

(iv) If the investment decision is "investment" and the instance is classified as class 0, the expected total cost C_4 is calculated as

$$C_4 = V + pc_{01}(1 - p_{01}) + p\bar{c}_{01}p_{01} + (1 - p)c_{00}(1 - p_{00}) + (1 - p)\bar{c}_{00}p_{00}. \quad (4)$$

The investment is made, and the investment cost V is included in Equation (4). Because the instance has probability p of actually belonging to class 1 but is classified as class 0, the expected classification cost becomes

$$\begin{cases} pc_{01} + (1 - p)c_{00} & \text{if using cost matrix } \boldsymbol{C} \text{ in Table 2,} \\ p\bar{c}_{01} + (1 - p)\bar{c}_{00} & \text{if using cost matrix } \overline{\boldsymbol{C}} \text{ in Table 3.} \end{cases}$$

With the investment, as indicated in Table 4, there is a probability of p_{01} that c_{01} changes to $\bar{c}_{01}$ and a probability of $(1 - p_{01})$ that c_{01} remains the same. Also, there is a probability of p_{00} that c_{00} changes to $\bar{c}_{00}$ and a probability of $(1 - p_{00})$ that c_{00} remains unchanged. Therefore, the expected classification cost becomes

$$pc_{01}(1 - p_{01}) + p\bar{c}_{01}p_{01} + (1 - p)c_{00}(1 - p_{00}) + (1 - p)\bar{c}_{00}p_{00}.$$

The optimal combination of investment and classification decisions incurs the least cost among C_1, C_2, C_3, and C_4. Therefore, in Lemmas 1–4, we derive conditions for the optimal combination by comparing C_1, C_2, C_3, and C_4. In the following lemmas, we set $T_0 = c_{10} - c_{00}$, $\overline{T}_0 = \bar{c}_{10} - \bar{c}_{00}$, $T_1 = c_{01} - c_{11}$, $\overline{T}_1 = \bar{c}_{01} - \bar{c}_{11}$, $D_{00} = p_{00}(c_{00} - \bar{c}_{00})$, $D_{01} = p_{01}(c_{01} - \bar{c}_{01})$, $D_{10} = p_{10}(c_{10} - \bar{c}_{10})$, and $D_{11} = p_{11}(c_{11} - \bar{c}_{11})$.

Lemma 1. For an unclassified instance with probability p of belonging to class 1, it is optimal to invest and classify the instance as class 1 if Conditions (5) and (6) are satisfied:

$$\begin{cases} p \geq \max\left(\frac{V - D_{10}}{D_{11} - D_{10}}, \frac{V + T_0 - D_{10}}{D_{11} - D_{10} + T_0 + T_1}\right) & \text{if } D_{11} > D_{10}, \\ \frac{V + T_0 - D_{10}}{D_{11} - D_{10} + T_0 + T_1} \leq p \leq \frac{D_{10} - V}{D_{10} - D_{11}} & \text{if } D_{10} - T_0 - T_1 < D_{11} < D_{10}, \\ p \leq \min\left(\frac{D_{10} - V}{D_{10} - D_{11}}, \frac{D_{10} - V - T_0}{D_{10} - D_{11} - T_0 - T_1}\right) & \text{if } D_{11} < D_{10} - T_0 - T_1. \end{cases} \quad (5)^4$$

[4] If $D_{11} = D_{10}$, the condition for the optimal combination of investment and classification decisions is independent of p, and the investment-adjusted cost-sensitive learning problem becomes trivial. Therefore, the equality situation $D_{11} = D_{10}$ is not included in Condition (5). In line with this reasoning, equality situations do not appear in Conditions (6)–(12). Please see Appendix A for detailed discussions.

$$\begin{cases} p \geq \frac{D_{00}+T_0-D_{10}}{D_{11}-D_{10}-D_{01}+D_{00}+T_0+T_1} & \text{if } D_{00}+D_{11}+T_0+T_1 > D_{10}+D_{01}, \\ p \leq \frac{D_{10}-D_{00}-T_0}{D_{10}+D_{01}-D_{11}-D_{00}-T_0-T_1} & \text{if } D_{00}+D_{11}+T_0+T_1 < D_{10}+D_{01}. \end{cases} \tag{6}$$

Proof: See Appendix A1.

Lemma 2. For an unclassified instance with probability p of belonging to class 1, it is optimal to invest and classify the instance as class 0 if Conditions (7) and (8) are satisfied:

$$\begin{cases} p \geq \max\left(\frac{V-D_{00}-T_0}{D_{01}-D_{00}-T_0-T_1}, \frac{V-D_{00}}{D_{01}-D_{00}}\right) & \text{if } D_{01} > D_{00}+T_0+T_1, \\ \frac{V-D_{00}}{D_{01}-D_{00}} \leq p \leq \frac{D_{00}+T_0-V}{D_{00}+T_0+T_1-D_{01}} & \text{if } D_{00} < D_{01} < D_{00}+T_0+T_1, \\ p \leq \min\left(\frac{D_{00}+T_0-V}{D_{00}+T_0+T_1-D_{01}}, \frac{D_{00}-V}{D_{00}-D_{01}}\right) & \text{if } D_{01} < D_{00}. \end{cases} \tag{7}$$

$$\begin{cases} p \geq \frac{D_{10}-T_0-D_{00}}{D_{01}-D_{00}-D_{11}+D_{10}-T_1-T_0} & \text{if } D_{01}+D_{10} > D_{00}+D_{11}+T_1+T_0, \\ p \leq \frac{D_{00}-D_{10}+T_0}{T_1+T_0-D_{01}+D_{00}+D_{11}-D_{10}} & \text{if } D_{01}+D_{10} < D_{00}+D_{11}+T_1+T_0. \end{cases} \tag{8}$$

Proof: See Appendix A2.

Lemma 3. For an unclassified instance with probability p of belonging to class 1, it is optimal not to invest and classify the instance as class 1 if Conditions (9) and (10) are satisfied:

$$\begin{cases} p \geq \frac{D_{10}-V}{D_{10}-D_{11}} & \text{if } D_{11} < D_{10}, \\ p \leq \frac{V-D_{10}}{D_{11}-D_{10}} & \text{if } D_{11} > D_{10}. \end{cases} \tag{9}$$

$$\begin{cases} p \geq \max\left(\frac{T_0+D_{00}-V}{T_1+T_0+D_{00}-D_{01}}, \frac{T_0}{T_1+T_0}\right) & \text{if } T_1+T_0+D_{00} > D_{01}, \\ \frac{T_0}{T_1+T_0} \leq p \leq \frac{V-T_0-D_{00}}{D_{01}-T_1-D_{00}-T_0} & \text{if } T_1+T_0+D_{00} < D_{01}. \end{cases} \tag{10}$$

Proof: See Appendix A3.

Lemma 4. For an unclassified instance with probability p of belonging to class 1, it is optimal not to invest and classify the instance as class 0 if Conditions (11) and (12) are satisfied:

$$\begin{cases} p \leq \min\left(\frac{T_0+V-D_{10}}{T_0+T_1+D_{11}-D_{10}}, \frac{T_0}{T_1+T_0}\right) & \text{if } T_0+T_1+D_{11} > D_{10}, \\ \frac{D_{10}-T_0-V}{D_{10}-T_0-T_1-D_{11}} \leq p \leq \frac{T_0}{T_1+T_0} & \text{if } T_0+T_1+D_{11} < D_{10}. \end{cases} \tag{11}$$

$$\begin{cases} p \geq \frac{D_{00}-V}{D_{00}-D_{01}} & \text{if } D_{01} < D_{00}, \\ p \leq \frac{V-D_{00}}{D_{01}-D_{00}} & \text{if } D_{01} > D_{00}. \end{cases} \tag{12}$$

Proof: See Appendix A4.

Building on Lemmas 1–4, we propose the investment-adjusted cost-sensitive learning (ICSL) method. As we illustrate in Figure 1, this method first employs a classification method, such as decision tree or naïve Bayes, to learn a classification model from training data $\boldsymbol{T}$, then uses the learned model to estimate the probability p that an unclassified instance belongs to class 1. Next, the proposed method makes the investment and classification decisions for the unclassified instance according to Lemmas 1–4.

ICSL ($\boldsymbol{T}$, $\boldsymbol{C}$, $\overline{\boldsymbol{C}}$, V, p_{ij})
$\boldsymbol{T}$: training data
$\boldsymbol{C}$, $\overline{\boldsymbol{C}}$: cost matrixes shown in Tables 2 and 3
V: investment amount
p_{ij}: probability of classification cost change due to an investment, $i, j \in \{0,1\}$

Learn a classification model by applying a classification method to $\boldsymbol{T}$.
For each unclassified instance
    Use the learned classification model to estimate its probability p of belonging to class 1.
    Make the investment and classification decisions for the instance according to Lemmas 1– 4.
End for

Figure 1: ICSL Method

Having introduced the ICSL method, we characterize it in relation to existing cost-sensitive learning methods. The ICSL method yields the minimum cost among C_1, C_2, C_3, and C_4, or $\min(C_1, C_2, C_3, C_4)$; existing cost-sensitive learning methods instead return the minimum cost between C_1 and C_2, or $\min(C_1, C_2)$, because they consider the cost matrix $\boldsymbol{C}$ only, without involving any investment decision (Elkan 2001; Jiang et al. 2014; Qiu et al. 2015). Thus, the proposed method should outperform existing cost-sensitive learning methods; that is, $\min(C_1, C_2, C_3, C_4) < \min(C_1, C_2)$ when $\min(C_3, C_4) < \min(C_1, C_2)$. At a minimum, our method

should be as good as existing methods, or $\min(C_1, C_2, C_3, C_4) = \min(C_1, C_2)$ when $\min(C_3, C_4) \geq \min(C_1, C_2)$.[5] We characterize the advantage of our proposed method over existing cost-sensitive learning methods as follows:

Proposition 1. When $\min(C_3, C_4) < \min(C_1, C_2)$, the cost reduction by the proposed ICSL method, compared with existing cost-sensitive learning methods, $\min(C_1, C_2) - \min(C_1, C_2, C_3, C_4)$, is greater if

(i) the investment amount V is smaller;

(ii) the classification cost reduction by the investment, $c_{ij} - \bar{c}_{ij}$, is larger, $i, j \in \{0,1\}$; or

(iii) the probability p_{ij} of classification cost reduction by the investment is higher, $i, j \in \{0,1\}$.

Proof: See Appendix B.

According to Proposition 1, the proposed method is particularly advantageous and useful when the cost of an investment is reasonably small but the investment can significantly reduce the classification costs from c_{ij} to $\bar{c}_{ij}$ with high probabilities, $i, j \in \{0,1\}$.

EMPIRICAL EVALUATION

We empirically evaluated the proposed method with two real-world clinical data sets: one consisting of 1,122 mechanical ventilation cases and another comprising 102,294 breast cancer cases. We report the evaluation results from the mechanical ventilation data in this section, then summarize the results from the breast cancer data, which are qualitatively similar, in Appendix D. Here we describe our data and parameter calibrations, detail the benchmark methods and experimental procedure, and report the evaluation results for the mechanical ventilation data.

[5] For example, when every cost saving due to investment is less than the cost of investment (i.e., $c_{ij} - \bar{c}_{ij} < V$ for all $i, j \in \{0,1\}$, we have $\min(C_3, C_4) \geq \min(C_1, C_2)$.

Data and Parameter Calibrations

Mechanical ventilation is an invasive intervention commonly used in the intensive care unit (ICU) to assist patients' respiration. According to Carson et al. (2006) and Wunsch et al. (2010), expenditures on mechanical ventilation in the United States, mainly for treating ventilation-related complications, have increased substantially, amounting to approximately $31.39 billion in 2014. A common but critical clinical decision is whether a patient should be removed from mechanical ventilation and depend on his or her own respiration for breathing. By making this decision correctly, health care providers can greatly mitigate ventilation-related complications and reduce patient care costs (Boles et al. 2007). In our empirical evaluation, we used 1,122 mechanical ventilation cases, collected from a major tertiary medical center located in southern Taiwan, to illustrate the prescriptive performance of the proposed method, compared with several prevalent methods.[6] As we summarize in Table 5, each case is described by 17 attributes that could affect the physician's ventilation removal decision and a class label attribute that indicates whether a patient actually should be removed from ventilation.[7]

Attribute	Attribute Type	Description
Gender	Nominal	Patient's gender: male or female
Age	Numeric	Patient's age
BH	Numeric	Patient's height
BW	Numeric	Patient's weight
BMI	Numeric	Patient's body mass index
Diagnosis	Nominal	Patient's diagnosis, such as lung disease or heart disease
ICU days	Numeric	Length of stay in ICU (in days)
Ventilation hours	Numeric	Length of using mechanical ventilation (in hours)

[6] This medical center offers comprehensive general and tertiary care, spanning a wide array of specialty and subspecialty areas; operates in three locations approximately 35 miles apart that together have 2,000+ beds; and employs more than 400 medical doctors and 2,500 nurses on a full-time basis.

[7] A panel of three experienced physicians individually reviewed these attributes and indicated their relevance to the mechanical ventilation removal decision.

APACHE II	Numeric	Patient's score in Acute Physiology and Chronic Health Evaluation II system
GCS	Numeric	Patient's score in Glasgow Coma Scale Assessment
Cough function	Nominal	Whether a patient has cough: Yes or No
Sedation	Nominal	Whether a patient uses sedatives: Yes or No
PEEP	Numeric	Patient's positive end-expiratory pressure in lung
Mode	Nominal	Patient's ventilation mode: PSP (pressure support pressure) or PSV (pressure support ventilation)
Mg	Numeric	Content of Mg in patient's blood
Restless	Nominal	Whether patient is restless: Yes or No
Cold sweats	Nominal	Whether patient has cold sweats: Yes or No
Liberation	Nominal	Whether patient should be removed from mechanical ventilation: Yes or No

Table 5: List of Attributes Considered for Mechanical Ventilation Removal Decision

We calibrated parameters that were essential for our empirical evaluation. Table 6 lists the classification costs for mechanical ventilation removal. With a $1,636 investment in using advanced ventilation, the classification costs in Table 6 change to the new classification costs in Table 7, with the probabilities listed in Table 8. We summarize the parameter calibration details in Appendix C.

	Actually Not Removing	**Actually Removing**
Classifying as Not Removing	c_{00}= $9,760	c_{01}= $16,549
Classifying as Removing	c_{10}= $12,476	c_{11}= $0

Table 6: Classification Cost Matrix *C* for Mechanical Ventilation Removal

	Actually Not Removing	**Actually Removing**
Classifying as Not Removing	$\bar{c}_{00}$= $3,030	$\bar{c}_{01}$= $9,819
Classifying as Removing	$\bar{c}_{10}$= $5,746	$\bar{c}_{11}$= $0

Table 7: New Classification Cost Matrix $\bar{C}$ for Mechanical Ventilation Removal

Probability of Changing from c_{00} to $\bar{c}_{00}$	**Probability of Changing from c_{01} to $\bar{c}_{01}$**	**Probability of Changing from c_{10} to $\bar{c}_{10}$**	**Probability of Changing from c_{11} to $\bar{c}_{11}$**
p_{00} = 0.875	p_{01}= 0.875	p_{10} = 0.875	p_{11}= 0

Table 8: Probability p_{ij} of Cost Change Due to an Investment (Mechanical Ventilation Removal)

Benchmark Methods and Experimental Procedure

As described, existing prescriptive analytics methods for CDM primarily rely on cost-sensitive learning that can be categorized as threshold moving, distribution altering, or test cost-sensitive learning. Test cost-sensitive learning targets attribute costs, or the cost of obtaining attribute values (Ling et al. 2006; Turney 1995; Weiss et al. 2013); it is not relevant to the investment-adjusted cost-sensitive learning problem, which involves no attribute costs. Therefore, we only consider threshold moving and distribution altering methods as benchmarks. The classical threshold moving method by Elkan (2001) is effective for cost-sensitive learning (Zhou and Liu 2006); applied to our focal problem, we can calculate a cost-sensitive threshold $thr = \frac{c_{10}-c_{00}}{c_{10}+c_{01}-c_{00}-c_{11}}$, where c_{ij} is a classification cost in the cost matrix $\boldsymbol{C}$ in Table 6, $i, j \in \{0,1\}$. A patient is then classified as "not removing" if $p < thr$ or as "removing" if $p \geq thr$, where p denotes the probability that the patient should be removed from ventilation. In general, distribution altering can be achieved with sampling (Chawla et al. 2002), instance weighting (Zhao 2008), or MetaCost (Domingos 1999). We compare the proposed method with synthetic minority oversampling (SMOTE; Chawla et al. 2002), a prevalent sampling method that is frequently included as a benchmark in previous cost-sensitive learning studies (e.g., Zhou and Liu 2006). We include a salient instance weighting method, implemented with a previously suggested weighting scheme (Jiang et al. 2014; Ting 2002; Zhao 2008). MetaCost is another benchmark; we follow Domingos (1999) to implement it. Because existing cost-sensitive learning methods do not involve investment decisions, benchmark methods note no investment costs and rely on the cost matrix $\boldsymbol{C}$ to make classification decisions. Table 9 summarizes these comparative methods.

Method	Abbreviation	Role in our Evaluation	Cost Considered for Decision Making
Investment-adjusted cost-sensitive learning	ICSL	Proposed Method	Investment Cost and Classification Cost
Threshold moving	THR	Benchmark	Classification Cost
Synthetic minority over-sampling	SMOTE	Benchmark	Classification Cost
Instance weighting	IW	Benchmark	Classification Cost
MetaCost	MC	Benchmark	Classification Cost

Table 9: Summary of Comparison Methods

Using the mechanical ventilation data set, the classification costs and probabilities of cost changes from Tables 6–8, and the investment amount (V = \$1,636), we comparatively examine the proposed method and benchmark methods. First, we randomly select two-thirds of the cases in the data set as training data and use the remainder as test data. Second, the proposed method learns from the training data to make the investment and classification decisions for each test case (i.e., cases in the test data); each benchmark method learns from the training data to make the classification decision for each test case.[8] Third, we calculate the cost incurred by each method. For a benchmark method, the cost is the sum of the cost of classifying each test case, according to the cost matrix $\boldsymbol{C}$ in Table 6. For example, the cost of classifying a test case as "not removing" when it actually is "removing" is \$16,549. The cost incurred by our method is the sum of the investment and classification costs of each test case. For example, if our method decides not to invest and makes a classification decision for the case, the investment cost is \$0, and the classification cost is determined according to the classification cost matrix $\boldsymbol{C}$ in Table 6. If our method instead decides to invest and makes a classification decision for the case, the

[8] As described, none of the benchmark methods involves investment decisions.

investment cost becomes $1,636, and the classification cost is obtained from the new classification cost matrix $\overline{\boldsymbol{C}}$ (Table 7) with probability p_{ij} (Table 8) or the classification cost matrix $\boldsymbol{C}$ (Table 6) with probability $1 - p_{ij}$.[9]

Experimental Results and Analyses

With this procedure, we conducted experiments to evaluate the effectiveness of our method, in comparison with that of each benchmark method. In addition, we examined the robustness of the performance improvements achieved.

Effectiveness Analysis

We performed 100 experiments to assess the effectiveness of our method. To ensure an equal basis for comparison, in all investigated methods, we used the same classification algorithm to estimate the probability p that a patient should be removed from ventilation. Specifically, we estimated p using C4.5, a prevalent decision tree learning algorithm (Quinlan 1993; Zhao and Ram 2004), coupled with m-estimation (Cussens 1993).[10] Figure 2 plots the costs incurred by the proposed and each benchmark method, across 100 experiments; as shown, these costs are consistently lower for our method than for any benchmark. We also applied a Wilcoxon signed-rank test (Snedecor and Cochran 1989) to the cost data in Figure 2, which revealed that the proposed method significantly outperformed each benchmark method, at $p < 0.001$. As we summarize in Table 10, the cost of our method, averaged across 100 experiments, is $255,987, whereas that of IW, the best-performing benchmark, is $429,790. On average, the cost of our

[9] In our implementation, we generate a random number. If the number is lower than or equal to p_{ij}, the new classification cost matrix $\overline{\boldsymbol{C}}$ is used; otherwise, the cost matrix $\boldsymbol{C}$ is employed.

[10] We first used C4.5 to learn a decision tree from the training data. Then, for a test case, we sought a leaf node of the learned decision tree, according to the values of the test case attributes. According to m-estimation (Cussens 1993), the estimated probability for the test case is $p = \frac{n_1 + mP(1)}{n_L + m}$, where n_L is the number of training cases in the reached leaf node, n_1 denotes the number of training cases in the node that should be removed from ventilation, $= \sqrt{n_L}$, and $P(1)$ is the ratio of training cases that should be removed from ventilation in the entire training data set. Across 100 experiments, the area under the curve value for employing decision tree learning (coupled with m-estimation) to estimate p is 0.88.

method is 40.44% lower than that of IW and 42.04% lower than that of THR (worst-performing benchmark).[11]

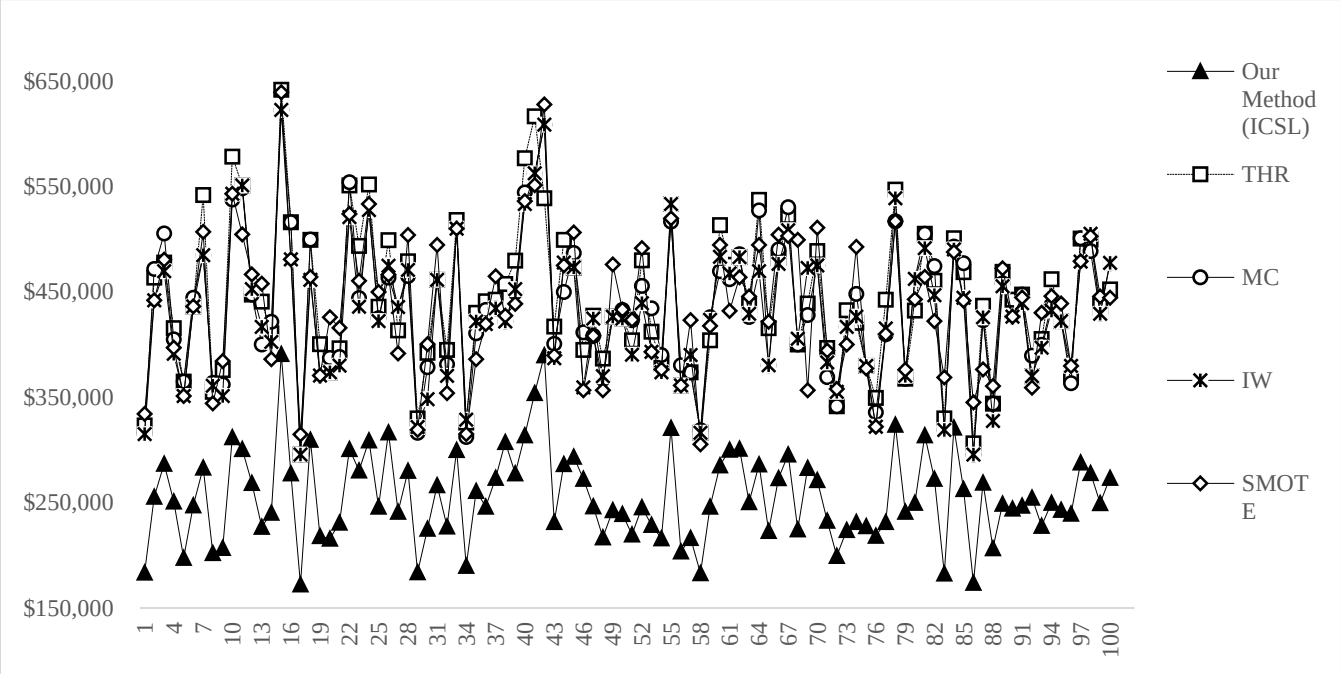

Figure 2: Cost Incurred by Each Investigated Method, across 100 Experiments

Method	Cost: Average (± SD)	Average Cost Reduction by ICSL
ICSL (Our Method)	$255,987 (±$42,989)	
THR	$441,903 (±$69,227)	42.04%
SMOTE	$435,899 (±$65,844)	41.14%
IW	$429,790 (±$66,068)	40.44%
MC	$434,924 (±$66,734)	41.13%

Table 10: Average Cost Incurred: Our Method versus Benchmark Methods

Robustness Analysis

We examined the robustness of our method's performance in several different scenarios. First, though we set the classification costs, probabilities of cost change, and investment amount by

[11] Because the benchmark methods have no judicious conditions for investment versus no investment, they (i) choose investment for all test cases, (ii) randomly choose no investment or investment for each test case, or (iii) choose no investment for all test cases. In case (iii), the substantial performance improvement of the proposed method over the benchmarks is obvious in Table 10. We also conducted experiments for cases (i) and (ii). The proposed method consistently and substantially outperformed the benchmarks, with cost reductions of 67.74% to 67.95% for case (i) and 58.08% to 58.44% in case (ii).

reviewing relevant literature and consulting with experienced physicians, it is important to confirm the robustness of our findings, using different classification costs, probabilities of cost change, or investment amount. Second, the proposed and benchmark methods used a decision tree algorithm to estimate the probability p that a patient should be removed from ventilation, so we reexamined their performance according to other classification algorithms (such as support vector machine) that also can estimate p.

Robustness Analysis in Scenario I: We considered the cost estimates over the range -40% to +40% by altering the classification costs in Table 6 from $c_{ij} \times 60\%$ to $c_{ij} \times 140\%$ for all $i, j \epsilon \{0,1\}$, in increments of 10%.[12] We then conducted 100 experiments to compare the performance of our method and those of the benchmarks for each cost alteration. Table 11 summarizes the average costs; again, our proposed method substantially outperformed each benchmark method, and the average cost reduction increased with the classification costs c_{ij}, in line with Proposition 1. For example, the average cost reduction by our method, compared with IW (best-performing benchmark), improved from 10.83% to 51.63% as the classification costs increased from $c_{ij} \times 60\%$ to $c_{ij} \times 140\%$. The Wilcoxon signed-rank test results reveal that the proposed method consistently and significantly outperformed every benchmark method ($p <$ 0.001) across all cost alterations under analysis.

	ICSL (Our Method)	**THR**		**SMOTE**		**IW**		**MC**	
	Cost: Average (± SD)	**Cost: Average (± SD)**	**Average Cost Reduction by ICSL**	**Cost: Average (± SD)**	**Average Cost Reduction by ICSL**	**Cost: Average (± SD)**	**Average Cost Reduction by ICSL**	**Cost: Average (± SD)**	**Average Cost Reduction by ICSL**
$c_{ij} \times 60\%$	\$ 227,259.97 (±\$30,244.24)	\$ 263,452 (±\$35,122)	13.71%	\$ 254,937 (±\$29,584)	10.86%	\$ 254,786 (±\$30,345)	10.83%	\$ 261,299 (±\$33,439)	12.93%

[12] The lower bound is constrained by the assumption that making an investment could reduce classification costs. If we further decrease this boundary condition by 10% (from -40% to -50%), classification costs c_{ij} becomes \$4,880, \$8,274.5, \$6,238, and \$0 respectively and consequently alter c_{01} to \$8,274.5, lower than $\bar{c}_{01}$ (\$9,819), which violates the assumption that c_{01} must be greater than $\bar{c}_{01}$. To maintain symmetry in the investigated range, we use +40% as the upper bound. We also further expand the upper bound (not constrained by any assumptions or limits) to +100% and observe consistent results: when the cost differences resulted from the investment increase, the average cost reduction by our proposed method becomes larger, in line with Proposition 1.

$c_{ij} \times 70\%$	$ 225,329.56 (±$27,484.19)	$ 299,247 (±$34,951)	24.65%	$ 293,943 (±$33,019)	23.19%	$ 290,378 (±$34,244)	22.36%	$ 294,782 (±$34,441)	23.48%
$c_{ij} \times 80\%$	$ 240,324.70 (±$40,981.73)	$ 354,870 (±$54,159)	32.38%	$ 353,844 (±$48,605)	32.13%	$ 346,030 (±$51,519)	30.65%	$ 350,411 (±$53,302)	31.43%
$c_{ij} \times 90\%$	$ 238,043.40 (±$37,426.11)	$ 384,861 (±$60,324)	38.08%	$ 381,927 (±$57,559)	37.45%	$ 370,826 (±$51,645)	35.90%	$ 377,511 (±$55,864)	36.91%
c_{ij}	$255,987.12 (±$42,989.37)	$441,903 (±$69,227)	42.04%	$435,899 (±$65,844)	41.14%	$429,790 (±$66,068)	40.44%	$434,924 (±$66,734)	41.13%
$c_{ij} \times 110\%$	$ 265,925.40 (±$44,734.20)	$ 487,853 (±$69,325)	45.57%	$ 476,194 (±$67,678)	44.13%	$ 469,276 (±$64,633)	43.41%	$ 476,033 (±$65,171)	44.21%
$c_{ij} \times 120\%$	$ 271,100.84 (±$45,341.69)	$ 524,685 (±$65,615)	48.47%	$ 508,468 (±$61,219)	46.72%	$ 506,599 (±$63,404)	46.58%	$ 515,388 (±$68,248)	47.44%
$c_{ij} \times 130\%$	$ 276,093.94 (±$35,623.07)	$ 575,280 (±$64,281)	51.97%	$ 562,644 (±$61,330)	50.78%	$ 553,949 (±$60,909)	50.15%	$ 558,904.42 (±$63,394)	50.55%
$c_{ij} \times 140\%$	$ 279,792.10 (±$38,431.92)	$ 596,035 (±$75,270)	53.03%	$ 586,878 (±$70,891)	52.25%	$ 578,268 (±$68,475)	51.63%	$ 582,677 (±$70,580)	51.91%

Table 11: Average Cost of Respective Methods across Different Classification Costs

	ICSL (Our Method)	**THR**		**SMOTE**		**IW**		**MC**	
	Cost: Average (± SD)	**Cost: Average (± SD)**	**Average Cost Reduction by ICSL**	**Cost: Average (± SD)**	**Average Cost Reduction by ICSL**	**Cost: Average (± SD)**	**Average Cost Reduction by ICSL**	**Cost: Average (± SD)**	**Average Cost Reduction by ICSL**
$p_{ij} \times 60\%$	$ 350,056 (±$41,273)	$ 436,389 (±$50,024)	19.77%	$ 422,173 (±$40,365)	17.12%	$ 422,350 (±$46,961)	17.12%	$ 428,108 (±$48,200)	18.19%
$p_{ij} \times 70\%$	$ 328,698 (±$37,324)	$ 441,858 (±$46,980)	25.62%	$ 438,316 (±$51,853)	24.76%	$424,693 (±$41,134)	22.55%	$433,981 (±$49,192)	24.13%
$p_{ij} \times 80\%$	$ 304,994 (±$42,447)	$ 439,232 (±$57,833)	30.57%	$ 433,087 (±$59,098)	29.41%	$ 423,810 (±$54,379)	27.99%	$ 432,966 (±$58,331)	29.41%
$p_{ij} \times 90\%$	$ 282,745 (±$46,419)	$ 441,031 (±$62,858)	36.00%	$ 430,870 (±$57,717)	34.42%	$ 428,632 (±$57,519)	34.20%	$ 434,690 (±$61,516)	35.00%
p_{ij}	$255,987 (±$42,989)	$441,903 (±$69,227)	42.04%	$435,899 (±$65,844)	41.14%	$429,790 (±$66,068)	40.44%	$434,924 (±$66,734)	41.13%
$p_{ij} \times 110\%$	$ 221,389 (±$32,520)	$ 433,349 (±$59,801)	48.88%	$ 426,498 (±$62,039)	47.84%	$ 420,411 (±$58,055)	47.34%	$ 424,100 (±$59,814)	47.75%

Table 12: Average Cost of Respective Methods across Different Probabilities

	ICSL (Our Method)	**THR**		**SMOTE**		**IW**		**MC**	
	Cost: Average (± SD)	**Cost: Average (± SD)**	**Average Cost Reduction by ICSL**	**Cost: Average (± SD)**	**Average Cost Reduction by ICSL**	**Cost: Average (± SD)**	**Average Cost Reduction by ICSL**	**Cost: Average (± SD)**	**Average Cost Reduction by ICSL**
$V \times 60\%$	$ 231,007 (±$37,805)	$ 432,269 (±$51,061)	46.64%	$ 427,389 (±$52,495)	45.88%	$ 421,243 (±$47,955)	45.28%	$ 431,436 (±$52,921)	46.41%
$V \times 70\%$	$ 241,515 (±$43,964)	$ 442,041 (±$64,397)	45.51%	$ 431,653 (±$53,487)	44.23%	$ 432,709 (±$59,453)	44.34%	$ 437,172 (±$60,449)	44.90%
$V \times 80\%$	$ 237,165 (±$38,264)	$ 428,272 (±$61,164)	44.68%	$ 429,169 (±$58,247)	44.75%	$ 419,833 (±$57,501)	43.60%	$ 424,035 (±$59,866)	44.01%
$V \times 90\%$	$ 242,504 (±$41,191)	$ 432,748 (±$61,203)	44.09%	$ 427,187 (±$52,050)	43.41%	$ 421,639 (±$56,718)	42.58%	$ 425,525 (±$58,479)	43.15%
V	$255,987 (±$42,989)	$441,903 (±$69,227)	42.04%	$435,899 (±$65,844)	41.14%	$429,790 (±$66,068)	40.44%	$434,924 (±$66,734)	41.13%
$V \times 110\%$	$ 262,391 (±$33,331)	$ 439,853 (±$52,105)	40.33%	$ 438,371 (±$46,253)	39.95%	$ 428,214 (±$44,681)	38.78%	$ 436,585 (±$51,505)	39.86%
$V \times 120\%$	$ 275,580 (±$45,026)	$ 450,043 (±$66,066)	38.82%	$ 437,675 (±$63,049)	36.96%	$ 431,465 (±$54,804)	36.29%	$ 439,792 (±$60,886)	37.38%

$V \times 130\%$	\$ 269,883 (±\$43,126)	\$ 432,751 (±\$61,459)	37.69%	\$ 426,434 (±\$69,739)	36.25%	\$ 422,759 (±\$63,565)	36.07%	\$ 422,717 (±\$60,077)	36.05%
$V \times 140\%$	\$ 275,135 (±\$36,254)	\$ 433,999 (±\$57,183)	36.51%	\$ 421,774 (±\$50,832)	34.62%	\$ 421,136 (±\$52,962)	34.56%	\$ 422,720 (±\$51,052)	34.83%

Table 13: Average Cost of Respective Methods across Different Investment Amount

Similarly, we altered the probabilities of the classification cost change in Table 8 from $p_{ij} \times 60\%$ to $p_{ij} \times 110\%$, in increments of 10%, for all $i, j \in \{0,1\}$, and varied the investment amount from $V \times 60\%$ to $V \times 140\%$, in increments of 10%.[13] We conducted 100 experiments to compare our method against the benchmarks for each probability alteration or investment amount variation and report the results in Tables 12 and 13. Again, the proposed method consistently and substantially outperformed all the benchmark methods, across all the investigated probability alterations or investment amounts. For example, the cost reduction attained with our method, relative to IW, improved from 17.12% to 47.34% as the probabilities of the cost change increased from $p_{ij} \times 60\%$ to $p_{ij} \times 110\%$, and from 34.56% to 45.28% as the investment amount decreased from $V \times 140\%$ to $V \times 60\%$. Overall, the cost reduction by the proposed method, relative to the benchmark methods, increases with the probabilities of cost changes and decreases with the investment amount, in line with Proposition 1. Furthermore, according to the Wilcoxon signed-rank test results, our method significantly outperformed all the benchmark methods ($p < 0.001$), across all investigated probabilities or investment amounts.

Robustness Analysis in Scenario II: We also assessed the robustness of the comparative evaluation results by using other classification algorithms. That is, the proposed and benchmark methods could estimate the probability p that a patient should be removed from ventilation using classification algorithms such as logistic regression, support vector machine, and naïve Bayes. For each classification algorithm, we conducted 100 experiments to compare the performance of

[13] Because $p_{ij} \times 120\%$, $p_{ij} \times 130\%$, and $p_{ij} \times 140\%$ exceed 1, they are not included in these experiments.

our method with those of the benchmarks. As we summarize in Tables 14–16, with each investigated classification algorithm, the cost of our method, averaged across 100 experiments, was substantially lower than that of any benchmark method. The Wilcoxon signed-rank test results show that our method consistently and significantly outperformed each benchmark method ($p < 0.001$) for each classification algorithm under evaluation.

Method	Cost: Average (± SD)	Average Cost Reduction by ICSL
ICSL (Our Method)	$440,532 (±$61,510)	
THR	$520,693 (±$66,868)	15.37%
SMOTE	$634,172 (±$85,979)	29.95%
IW	$565,667 (±$72,469)	22.11%
MC	$539,182 (±$70,793)	18.25%

Table 14: Average Cost of Each Investigated Method (*p* Estimated with Logistic Regression)

Method	Cost: Average (± SD)	Average Cost Reduction by ICSL
ICSL (Our Method)	$415,647 (±$54,668)	
THR	$503,859 (±$70,167)	17.34%
SMOTE	$704,839 (±$87,981)	40.61%
IW	$555,416 (±$71,709)	24.94%
MC	$529,880 (±$70,401)	21.33%

Table 15: Average Cost of Each Investigated Method (*p* Estimated with Support Vector Machine)

Method	Cost: Average (± SD)	Average Cost Reduction by ICSL
ICSL (Our Method)	$501,912 (±$61,495)	
THR	$550,629 (±$88,048)	8.12%
SMOTE	$1,240,117 (±$119,745)	59.36%
IW	$816,913 (±$90,742)	38.21%
MC	$786,859 (±$97,728)	35.79%

Table 16: Average Cost of Each Investigated Method (*p* Estimated with Naïve Bayes)

Overall, the evaluation results reveal that the proposed method consistently and significantly outperforms all the benchmark methods, across various scenarios. The observed cost reductions by our method can be partially explained by its simultaneous consideration of the probabilistic, cost-sensitive, and investment-related characteristics of CDM, whereas existing methods

overlook the investment-related characteristic. As a result, our proposed method is more effective for cost reduction in CDM and incurs lower costs than any benchmark methods.

DISCUSSION

Containing fast-growing costs is critical to the sustainability of health care services (Mango and Riefberg 2009), and prescriptive analytics for CDM can offer significant relevance and benefits (Manyika et al. 2011). From a research standpoint, prescriptive analytics in general and their support for CDM specifically represent high-impact areas in IS research (Chen et al. 2012; Goes 2015; Kohli and Tan 2016). As an illustrating example of such impacts, we develop a novel method to reduce health care costs. In light of the knowledge contribution framework of design science research (Gregor and Hevner 2013), our study contributes to extant literature in both problem formulation and solution development. We formulate a new cost-sensitive learning problem, distinctive in its consideration of the investment-related characteristic of CDM. We also develop a novel solution, the investment-adjusted cost-sensitive learning method, which takes the investment characteristic of CDM into account and considers classification costs as probabilistic, unlike prevalent cost-sensitive learning methods that regard them as deterministic. Furthermore, the proposed ICSL method integrates clinical (classification) and investment decisions to minimize the sum of classification and investment costs, unlike existing cost-sensitive learning methods that overlook the investment decision.

This study offers research implications for prescriptive analytics in general and their support for CDM in particular. First, our study indicates that continued research should approach prescriptive analytics problems by extending the cost-sensitive perspective that seeks to minimize expected costs. Second, we highlight the inherently probabilistic nature of prescriptive analytics problems that often involve different events and outcomes in the future. That is, future

outcomes are probabilistic and the solutions to prescriptive analytics problems require accurate predictions of future outcomes. Third, we show that costs in prescriptive analytics problems can be altered probabilistically through an investment, reinforcing our claim that such problems should be regarded as probabilistic rather than deterministic. Then prescriptive analytics methods can encourage optimal decisions about a potential investment, in addition to offering classifications. Fourth, our problem formulation and method development should inform future research, by highlighting the value and feasibility of addressing probabilistic, cost-sensitive, investment-related characteristics of CDM simultaneously to improve cost effectiveness in health care. As a point of departure, this study encourages researchers to approach classification costs probabilistically, rather than deterministically, to better support CDM in health care and plausibly decisions in other contexts.

For health care practice, because we consider all three eminent characteristics of CDM, the proposed method better supports clinical decisions and could help contain health care costs more effectively than existing methods. As we demonstrate with the mechanical ventilation data set, our method reduces the costs associated with mechanical ventilation removal decisions substantially, compared with the best-performing benchmarks. The U.S. expenditures on mechanical ventilation are substantial, for example reaching $31.39 billion in 2014 (Carson et al. 2006; Wunsch et al. 2010), so the use of our proposed method could result in considerable cost reductions. As we detail in Appendix D, the use of our proposed method to support breast cancer diagnoses and decisions also can result in substantial cost reductions, compared with prevalent benchmark methods.

The proposed method arguably could be applied to other clinical decisions too. For example, diabetes is a common chronic disease, affecting approximately 366 million people worldwide,

with projections that this number will increase to 552 million by 2030 (Whiting et al. 2011). Type 2 diabetes represents the most common form, accounting for 95% of all adult diabetes cases. Yet about 183 million patients are unaware of their disease, which causes serious diagnosis delays after its onset (Harris et al. 1992; Roche and Wang 2014) and significantly increases their risk of hyperglycemia, insulin resistance, low-grade inflammation, and accelerated atherogenesis (Schlienger 2013). These complications in turn can lead to cardio-cerebrovascular disease, renal disease, or diabetic foot (Schlienger 2013). According to the UK Prospective Diabetes Study Group (1998), intensive blood glucose control with sulphonylureas or insulin represents a promising investment for reducing the risk of renal disease, so to reduce clinical decision-making costs, physicians might apply our proposed method to predict (classify) whether a patient has Type 2 diabetes and determine whether to treat that patient with intensive blood glucose controls.

Overall, to apply the proposed method, physicians and health care organizations also need to estimate the probabilities of different outcomes (Bhugra 2008). Before reaching a diagnosis decision, physicians should consider the consequences of all plausible decisions, by answering several questions before applying our proposed method:

(1) What are plausible diagnosis decisions, according to the patient's symptoms and laboratory results? For example, a patient's symptoms might suggest two possible outcomes: benign versus malignant tumor.

(2) What is the probability of each decision outcome (e.g., 60% probability of benign, 40% probability of malignant)? Such probabilities could be assessed with machine learning algorithms such as decision trees, naïve Bayes, logistic regression, or support vector machines.

(3) What potential treatments are associated with each decision: surgery, chemotherapy, or other therapeutic interventions if the patient's tumor is malignant?

(4) What are the consequences and complications likely result from a diagnosis decision?

(5) What are the estimated costs of these consequences and resulting complications? Physicians might obtain reasonable cost estimates from different sources, such as clinical literature and their health care organization's proprietary systems.

(6) Are there measures or means available to mitigate the estimated costs? Equipped with clinical knowledge and personal experiences, physicians can evaluate potential measures to prevent specific complications or consequences. These measures and means are equivalent to an investment in our proposed method.

(7) What is the probability that the investment will be effective? It might fail to prevent foreseen consequences or complications effectively. Physicians and health care organizations can learn this probability from clinical literature reviews and their experiences and observations.

(8) What are the new estimations of the resulting costs associated with the complications and consequences after the investment? If the investment is successful, a patient can avoid some adverse consequences or complications.

Together, these questions can guide physicians and health care organizations in identifying decision outcomes; categorizing them into classes; deriving the probability p that a unclassified instance belongs to class 1; calculating the classification costs c_{00}, c_{01}, c_{10}, and c_{11}, as well as the amount V of an investment; estimating the probability p_{ij} of a classification cost change due to the investment; and finally analyzing the new classification costs $\bar{c}_{10}, \bar{c}_{00}, \bar{c}_{01}, and\ \bar{c}_{11}$. Our method is applicable to clinical decision-making tasks that fit our stated problem definition and

scope. Taking the illustrating evaluation as an example, the proposed method cannot be utilized if patients are initially on advanced ventilation, because of the unavailability of the investment option.

We also expect that the proposed method might be applicable to important decisions in other domains, especially those with probabilistic, cost-sensitive, and investment-related characteristics. For example, our method could facilitate new product development (NPD) decisions, which tend to be risky and plagued by high failure rates (Ogawa and Piller 2006). To determine whether to proceed after the initial product design stage, the firm faces a probabilistic decision built on the estimated likelihood that the product will succeed in the market. Furthermore, NPD decisions are cost sensitive. If a firm erroneously classifies a subpar new product as a likely success, it will face substantial overstock costs; if it classifies a great new product as a failure, it suffers significant revenue losses. Finally, NPD decisions involve investments, such that a firm might invest in attractive incentives to get customers to co-design and preorder, which would reduce potential overstock costs (Ogawa and Piller 2006). Many real-world business decisions—loan approval decisions by financial institutions, offshore drilling decisions by petroleum companies, player drafting decisions by professional sports organizations—similarly have probabilistic, cost-sensitive, and investment-related characteristics and might benefit from our proposed method. For example, a financial institution could invest in additional in-depths background checks before approving a loan application, or a petroleum company could invest in advanced ocean bed explorations before deciding whether to proceed with offshore drilling operations.

CONCLUSION

Effective prescriptive analytics for supporting CDM must address its probabilistic, cost-sensitive, and investment-related characteristics simultaneously. We formulate a new cost-sensitive learning problem that considers all these characteristics and propose a novel prescriptive analytics method to improve the cost effectiveness of CDM. Our method development relies on both prospect theory (Kahneman and Tversky 1979) and regret theory (Zeelenberg et al. 1996). The inputs include two sets of costs associated with clinical decisions, before and after an investment, and the probabilities of cost changes due to investments. Thus the proposed method can analyze the costs of different combinations of clinical and investment decisions and recommend optimal decisions to reduce total costs. Empirical evaluations with two real-world clinical data sets show that our method consistently and significantly outperforms several salient methods from previous research.

Our study also has several limitations that suggest the need for further research. First, we develop this method to support clinical decisions with two distinctive outcomes (e.g., removing or not removing a patient from mechanical ventilation). Many clinical decisions similarly involve dichotomous decision outcomes, but others have more than two decision outcomes. It is important to extend our method to accommodate such clinical decisions. Second, our study objective is to reduce costs for CDM, so our method development focuses only on cost factors, not other factors (e.g., patient risk) that also are essential to physicians' clinical decision making. Our method could be extended to incorporate other considerations, such as pursuing minimal costs, subject to a constraint of maintaining patient risk below a particular threshold. Third, it would be interesting to adapt our method to support critical decisions in other domains, such as NPD. Continued studies could solve different, challenging, decision-making problems and produce new empirical evidence of the effectiveness of our method. Fourth, the ICLS problem

might be solved by extending instance weighting methods (Ting 2002; Zhao 2008). However, traditional methods only consider one cost matrix and make classification decisions, whereas our focal problem involves two cost matrices and both classification and investment decisions. Direct applications of traditional instance weighting methods thus are not viable, but further research arguably might design novel instance weighting methods to handle two cost matrices and support both classification and investment decisions.

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APPENDICES

Appendix A: Proofs of Lemmas

A1: Proof of Lemma 1

If $C_1 \geq C_3, C_2 \geq C_3$, and $C_4 \geq C_3$, it is optimal to invest and classify the instance as class 1. By substituting C_1 and C_3 with Equations (1) and (3) respectively and rearranging terms, $C_1 \geq C_3$ becomes

$$p(D_{11} - D_{10}) \geq V - D_{10}. \tag{A1}$$

To satisfy $C_1 \geq C_3$, the following condition must hold:

$$\begin{cases} p \geq \frac{V - D_{10}}{D_{11} - D_{10}} & \text{if } D_{11} > D_{10}, \\ p \leq \frac{D_{10} - V}{D_{10} - D_{11}} & \text{if } D_{11} < D_{10}. \end{cases} \tag{A2}$$

If $D_{11} = D_{10}$, inequality (A1) is independent of p, and the investment-adjusted cost-sensitive learning problem becomes trivial. Then the equality situation $D_{11} = D_{10}$ is not considered by Condition (A2). In line with this reasoning, equality situations are not considered throughout Appendix A.

Similarly, $C_2 \geq C_3$ implies

$$p(D_{11} - D_{10} + T_0 + T_1) \geq V + T_0 - D_{10}.$$

To satisfy $C_2 \geq C_3$, the following condition must hold:

$$\begin{cases} p \geq \frac{V + T_0 - D_{10}}{D_{11} - D_{10} + T_0 + T_1} & \text{if } D_{11} + T_0 + T_1 > D_{10}, \\ p \leq \frac{D_{10} - V - T_0}{D_{10} - D_{11} - T_0 - T_1} & \text{if } D_{11} + T_0 + T_1 < D_{10}. \end{cases} \tag{A3}$$

Combining Conditions (A2) and (A3) yields Condition (5).

For $C_4 \geq C_3$, we have

$$p(\, D_{11} - D_{10} - D_{01} + D_{00} + T_0 + T_1) \geq D_{00} + T_0 - D_{10}.$$

By solving this inequality, we obtain Condition (6). ■

Lemmas 2–4 can be proved in similar ways.

A2: Proof of Lemma 2

If $C_1 \geq C_4, C_2 \geq C_4$, and $C_3 \geq C_4$, it is optimal to invest and classify the instance as class 0. By replacing C_1 and C_4 with Equations (1) and (4), respectively, and rearranging terms, $C_1 \geq C_4$ becomes

$$p(D_{01} - D_{00} - T_0 - T_1) \geq V - D_{00} - T_0.$$

Solving this inequality leads to the following condition:

$$\begin{cases} p \geq \frac{V - D_{00} - T_0}{D_{01} - D_{00} - T_0 - T_1} & \text{if } D_{01} > D_{00} + T_0 + T_1, \\ p \leq \frac{D_{00} + T_0 - V}{D_{00} + T_0 + T_1 - D_{01}} & \text{if } D_{01} < D_{00} + T_0 + T_1. \end{cases} \tag{A4}$$

Similarly, $C_2 \geq C_4$ becomes

$$p(D_{01} - D_{00}) \geq V - D_{00}.$$

To satisfy $C_2 \geq C_4$, the following condition must hold:

$$\begin{cases} p \geq \frac{V - D_{00}}{D_{01} - D_{00}} & \text{if } D_{01} > D_{00}, \\ p \leq \frac{D_{00} - V}{D_{00} - D_{01}} & \text{if } D_{01} < D_{00}. \end{cases} \tag{A5}$$

By integrating Conditions (A4) and (A5), we derive Condition (7). Specifically, if $D_{01} > D_{00} + T_0 + T_1$, by (A4), the condition $p \geq \frac{V - D_{00} - T_0}{D_{01} - D_{00} - T_0 - T_1}$ must be satisfied. Because $D_{01} > D_{00} + T_0 + T_1$ implies $D_{01} > D_{00}$, according to (A5), the condition $p \geq \frac{V - D_{00}}{D_{01} - D_{00}}$ must also be satisfied. Thus, if $D_{01} > D_{00} + T_0 + T_1$, the condition $p \geq \max(\frac{V - D_{00} - T_0}{D_{01} - D_{00} - T_0 - T_1}, \frac{V - D_{00}}{D_{01} - D_{00}})$ must be satisfied. Similarly, if $D_{01} < D_{00}$, by (A4) and (A5), the condition $p \leq \min\left(\frac{D_{00} + T_0 - V}{D_{00} + T_0 + T_1 - D_{01}}, \frac{D_{00} - V}{D_{00} - D_{01}}\right)$ must be satisfied. If $D_{00} < D_{01} < D_{00} + T_0 + T_1$, by combining the condition for $D_{01} < D_{00} + T_0 + T_1$

in (A4) and the condition for $D_{00} < D_{01}$ in (A5), we derive the condition $\frac{V-D_{00}}{D_{01}-D_{00}} \leq p \leq \frac{D_{00}+T_0-V}{D_{00}+T_0+T_1-D_{01}}$.

For $C_3 \geq C_4$, we have

$$p(D_{01} - D_{00} - D_{11} + D_{10} - T_1 - T_0) \geq D_{10} - T_0 - D_{00}.$$

Solving this inequality yields Condition (8). ■

A3: Proof of Lemma 3

If $C_2 \geq C_1, C_3 \geq C_1$, and $C_4 \geq C_1$, it is optimal not to invest and classify the instance as class 1. By substituting C_3 and C_1 with Equations (3) and (1), respectively, and rearranging terms, $C_3 \geq C_1$ becomes

$$p(D_{11} - D_{10}) \leq V - D_{10}.$$

Solving the inequality leads to Condition (9). Similarly, by substituting C_2 and C_1 with Equations (2) and (1), respectively, and rearranging terms, $C_2 \geq C_1$ becomes

$$p(T_1 + T_0) \geq T_0.$$

Thus, to satisfy $C_2 \geq C_1$, the following condition must hold:

$$p \geq \frac{T_0}{T_1+T_0}. \tag{A6}$$

For $C_4 \geq C_1$, we have

$$p(T_0 + T_1 + D_{00} - D_{01}) \geq T_0 + D_{00} - V.$$

To satisfy $C_4 \geq C_1$, the following condition must hold:

$$\begin{cases} p \geq \frac{T_0+D_{00}-V}{T_1+T_0+D_{00}-D_{01}} & \text{if } T_1 + T_0 + D_{00} > D_{01}, \\ p \leq \frac{V-T_0-D_{00}}{D_{01}-T_1-D_{00}-T_0} & \text{if } T_1 + T_0 + D_{00} < D_{01}. \end{cases} \tag{A7}$$

By combining Conditions (A6) and (A7), we obtain Condition (10). ■

A4: Proof of Lemma 4

If $C_1 \geq C_2, C_3 \geq C_2$, and $C_4 \geq C_2$, it is optimal not to invest and classify the instance as class 0. By substituting C_1 and C_2 with Equations (1) and (2), respectively, and rearranging terms, $C_1 \geq C_2$ becomes

$$p(T_0 + T_1) \leq T_0.$$

Solving the inequality leads to the following condition:

$$p \leq \frac{T_0}{T_0+T_1}. \tag{A8}$$

Similarly, for $C_3 \geq C_2$, we have

$$p(T_0 + T_1 + D_{11} - D_{10}) \leq T_0 + V - D_{10}.$$

To satisfy $C_3 \geq C_2$, the following condition must hold:

$$\begin{cases} p \leq \frac{T_0+V-D_{10}}{T_0+T_1+D_{11}-D_{10}} & \text{if } T_0 + T_1 + D_{11} > D_{10}, \\ p \geq \frac{D_{10}-T_0-V}{D_{10}-T_0-T_1-D_{11}} & \text{if } T_0 + T_1 + D_{11} < D_{10}. \end{cases} \tag{A9}$$

Combining Conditions (A8) and (A9) yields Condition (11). For $C_4 \geq C_2$, we have

$$p(D_{01} - D_{00}) \leq V - D_{00}.$$

Solving the inequality leads to Condition (12). ■

Appendix B: Proof of Proposition 1

Because $\min(C_3, C_4) < \min(C_1, C_2)$, the cost reduction by our method compared with existing cost-sensitive learning methods, $\min(C_1, C_2) - \min(C_1, C_2, C_3, C_4)$, becomes

$$\min(C_1, C_2) - \min(C_1, C_2, C_3, C_4) = \min(C_1, C_2) - \min(C_3, C_4).$$

We analyze the cost reduction in several scenarios.

(i) If $C_1 \leq C_2$ and $C_3 \leq C_4$,

$$\min(C_1, C_2) - \min(C_3, C_4)$$
$$= C_1 - C_3$$
$$= (1-p)p_{10}(c_{10} - \bar{c}_{10}) + pp_{11}(c_{11} - \bar{c}_{11}) - V\ .$$

Accordingly, the cost reduction is greater if the investment amount V is smaller, or if $c_{10} - \bar{c}_{10}$ or $c_{11} - \bar{c}_{11}$ (i.e., the classification cost reduction due to the investment) is larger, or if p_{10} or p_{11} (i.e., the probability of classification cost reduction due to the investment) is greater. Thus, Proposition 1 holds when $C_1 \leq C_2$ and $C_3 \leq C_4$.

(ii) If $C_1 \leq C_2$ and $C_4 \leq C_3$,

$$\min(C_1, C_2) - \min(C_3, C_4)$$
$$= C_1 - C_4$$
$$= pp_{01}(c_{01} - \bar{c}_{01}) + (1-p)p_{00}(c_{00} - \bar{c}_{00}) - V + (1-p)c_{10} + p\,c_{11} - (1-p)c_{00} - pc_{01}.$$

That is, the cost reduction is greater if the investment amount V is smaller, or if $c_{01} - \bar{c}_{01}$ or $c_{00} - \bar{c}_{00}$ (i.e., the classification cost reduction due to the investment) is larger, or if p_{01} or p_{00} (i.e., the probability of classification cost reduction due to the investment) is greater. Proposition 1 holds when $C_1 \leq C_2$ and $C_4 \leq C_3$.

(iii) If $C_2 \leq C_1$ and $C_3 \leq C_4$,

$$\min(C_1, C_2) - \min(C_3, C_4)$$
$$= C_2 - C_3$$
$$= pp_{11}(c_{11} - \bar{c}_{11}) + (1-p)p_{10}(c_{10} - \bar{c}_{10}) - V + pc_{01} + (1-p)c_{00} - pc_{11} - (1-p)c_{10}.$$

Accordingly, the cost reduction is greater if the investment amount V is smaller, or if $c_{11} - \bar{c}_{11}$ or $c_{10} - \bar{c}_{10}$ (i.e., the classification cost reduction due to the investment) is larger, or if p_{11} or p_{10} (i.e., the probability of classification cost reduction due to the investment) is higher. Proposition 1 holds when $C_2 \leq C_1$ and $C_3 \leq C_4$.

(iv) If $C_2 \leq C_1$ and $C_4 \leq C_3$,

$$\min(C_1, C_2) - \min(C_3, C_4)$$
$$= C_2 - C_4$$
$$= pp_{01}(c_{01} - \bar{c}_{01}) + (1-p)p_{00}(c_{00} - \bar{c}_{00}) - V\ .$$

That is, the cost reduction is greater if the investment amount V is smaller, or if $c_{01} - \bar{c}_{01}$ or $c_{00} - \bar{c}_{00}$ (i.e., the classification cost reduction due to the investment) is larger, or if p_{01} or p_{00} (i.e., the probability of classification cost reduction due to the investment) is higher. Proposition 1 holds when $C_2 \leq C_1$ and $C_4 \leq C_3$.

In summary, we show that Proposition 1 holds in all possible scenarios. ■

Appendix C: Parameter Calibrations

To calibrate the classification costs in the cost matrix $\boldsymbol{C}$, we identified common complications associated with different ventilation removal decisions by reviewing relevant literature and consulting experienced physicians knowledgeable about the clinical use of mechanical ventilation and related complications. We summarize the complications in Table C1. As an example, the top-right cell of Table C1 indicates five common complications if the decision is not to remove mechanical ventilation but a patient should have it removed. We then calculated the expected cost of treating each identified complication, as summarized in Table C2. Taking the estimated cost for treating ventilator-associated pneumonia as an example, for which Kellie et al. (2014, p. 166) estimated costs ranging from $10,019 to $39,828. We used the average of the cost range ($24,924) in our evaluation. The estimated probability of ventilator-associated pneumonia (VAP) is 9%–27% for all mechanically ventilated patients (Kalanuria et al. 2014, p. 1), similar to a VAP occurrence rate of 27% reported in other studies (Koenig and Truwit 2006).

We therefore included a 0.27 probability of developing VAP. The expected cost of treating this complication is \$6,730 (= \$24,924 × 0.27). We list the treatment cost and probability of developing each common complication in Table C2, with the sources in Tables C3 and C4[14].

	Not Removing	**Removing**
Classified as Not Removing	(a) Ventilation-associated pneumonia (Carroll and Zucker 2006) (b) Pneumothorax (Hofmann et al. 2002)	(a) Ventilation-associated pneumonia (Carroll and Zucker 2006) (b) Pneumothorax (Kao et al. 2013) (c) Gastrointestinal bleeding (Eskandar and Apostolakos 2007) (d) Heart failure (Hayashi et al. 2013) (e) Rhabdomyolysis (Carroll and Zucker 2006)
Classified as Removing	(a) Post-extubation distress (Heunks and van der Hoeven 2010) (b) Dyspnea (Vassilakopoulos et al. 1998) (c) Post-traumatic stress (Girard et al. 2007) (d) Ventilation-associated pneumonia (Carroll and Zucker 2006) (e) Pneumothorax (Kao et al. 2013)	No complications

Table C1: Common Complications Associated with Different Ventilation Removal Decisions

Complication	**Probability of Developing Complication**	**Treatment Cost**	**Expected Treatment Cost**
Ventilator-associated pneumonia (VAP)	0.27 (Kalanuria et al. 2014)	\$24,924 (Kellie et al. 2014)	\$6,730
Pneumothorax	0.30 (Hsu and Sun 2014; Terzi et al. 2014)	\$10,101 (Lopez et al. 2014; Roeggla et al. 1996; Torresini et al. 2001)	\$3,030

[14] We acknowledge that our parameter calibrations are imperfect and consider the cost estimations used in the evaluation adequate for the intended demonstration purpose.

Gastrointestinal bleeding	0.47 (Chu et al. 2010)	$10,712 (Raphaeli et al. 2012; Saltzman et al. 2015)	$5,035
Heart failure	0.07 (Hayashi et al. 2013)	$15,767 (Sharma et al. 2014)	$1,104
Rhabdomyolysis	0.13 (Grigorakos et al. 2010)	$5,000 (Newman et al. 2008)	$650
Post-extubation distress	0.11 (Kashefi et al. 2015)	$8,052 (Azoulay et al. 2014; Tolwani 2012)	$886
Dyspnea	0.31 (Severgnini et al. 2013)	$ 3,664 (Peitz et al. 2014)	$1,136
Post-traumatic stress	0.22 (Le Guennec et al. 2014)	$3,151 (Hedman et al. 2014)	$694

Notes: According to Carroll and Zucker (2006), VAP is a common complication of a prolonged use of mechanical ventilation; its probability is mostly the same across different decision scenarios. Similarly, the probability of developing pneumothorax is similar in various decision scenarios (Carroll and Zucker 2006).

Table C2: Cost of Treating Each Common Complication Associated with Ventilation Removal Decisions

Complication	Treatment Cost	Explanation and Justification
Ventilator-associated pneumonia	$24,924	The estimated treatment cost ranges from $10,019 to $39,828 (Kellie et al. 2014, p. 166). We used the average ($24,924) in the evaluation.
Pneumothorax	$10,101	Surgery is a preferred treatment, and the cost ranges from $3,380 to $19,702 (Lopez et al. 2014, p. 573). The 95% confidence interval of the cost of using conventional intercostal chest tube drainage to treat pneumothorax is between $3,100 and $14,270, and that of using thoracic vents ranges from $500 to $2,480 (Roeggla et al. 1996). Two treatment costs—$2,750 and $1,925 per patient—are associated with pleural drainage and video-assisted thoracic surgery treatment, respectively (Torresini et al. 2001). Thus the lowest treatment cost is $500 and the highest is $19,702. We used $10,101 (the midpoint) as the treatment cost in the evaluation.
Gastrointestinal bleeding	$10,712	Gastrointestinal (GI) bleeding includes upper and lower forms.[15] The cost of treating upper GI bleeding ranges between $5647 and $15,776 (Saltzman et al. 2015). The cost of treating lower GI bleeding ranges from $9,700 to $11,800 (Raphaeli et al. 2012). We combined these cost ranges, derived a range of treating GI bleeding from $5,647 to $15,776, and used $10,712 (the midpoint) in the evaluation.

[15] https://www.uspharmacist.com/article/differentiating-upper-and-lower-gi-bleeds; accessed on March 5, 2019.

Heart failure	$15,767	A low cost (i.e., average at the 20th percentile and below) is $2,946, and a high cost (i.e., average at the 80th percentile and above) is $28,588 (Sharma et al. 2014). We used $15,767 (the midpoint) in the evaluation.
Rhabdomyolysis	$5,000	The treatment cost is $5,000 (Newman et al. 2008, p.38). We used this estimated cost in the evaluation.
Post-extubation distress	$8,052	Renal replacement therapy is a treatment (Azoulay et al. 2014), and its average cost is $8,052 (Tolwani 2012, p. 2511). We used this value in the evaluation.
Dyspnea	$3,664	The mean cost is $3,663 (Peitz et al. 2014, p.294), which we used in the evaluation.
Post-traumatic stress	$3,151	Post-traumatic stress is an anxiety disorder, and two treatment methods for anxiety disorder are Internet-based cognitive behavior therapy (ICBT) and cognitive behavioral group therapy (CBGT), with costs of $464 and $2,687, respectively (Hedman et al. 2014, p. 22). Because ICBT is a lower cost alternative to CBGT (Williams et al. 2014), the minimum treatment cost is $464. The maximum is $3,151 (i.e., $464 + $2,687), if ICBT are used first and followed by CBGT. We used $3,151 in the evaluation.

Notes: For probabilities or treatment costs that span ranges of values, we used a typical value of the range, such as its median.

Table C3: Treatment Costs for Complications Associated with Ventilation Removal Decisions

Complication	Probability	Explanation and Justification
Ventilator-associated pneumonia	0.27	VAP occurs in 9%–27% of all mechanically ventilated patients (Kalanuria et al. 2014, p. 1), and the rate of 27% is supported by other studies (Koenig and Truwit 2006). We used 0.27 in the evaluation.
Pneumothorax	0.30	The probability of developing pneumothorax ranges from 14% to 87% (Hsu and Sun 2014, p. 9). We used 0.30 in the evaluation, because it is within the range and supported by other studies (Terzi et al. 2014).
Gastrointestinal bleeding	0.47	The probability of developing GI bleeding is 46.7% (Chu et al. 2010, p. 32). We used 0.47 (rounded from 46.7%) in the evaluation.
Heart failure	0.07	The occurrence rate of heart failure is 7.2% (Hayashi et al. 2013, p. 474); so we used 0.07 (rounded from 7.2%) in the evaluation.

Rhabdomyolysis	0.13	Of 16 patients with mechanical ventilation, 2 develop rhabdomyolysis (Grigorakos et al. 2010). Thus we used 0.13 (i.e., 2/16) in the evaluation.
Post-extubation distress	0.11	Kashefi et al. (2015) mention that 11.1% of patients in each of their studied groups develop post-extubation distress. We thus used 0.11 (rounded from 11.1%).
Dyspnea	0.31	The probability that patients with standard ventilation develop dyspnea is 30.8% (Severgnini et al. 2013, p.1318). We used 0.31 (rounded from 30.8%) in the evaluation.
Post-traumatic stress	0.22	The probability of developing post-traumatic stress is 22% (Le Guennec et al. 2014, p. 220); so we used 0.22.

Table C4: Probabilities for Complications Associated with Ventilation Removal Decisions

Different ventilation removal decisions can lead to various complications. In Table 6, we estimated the classification cost incurred by a ventilation removal decision as the total cost of treating the complications associated with the decision. For example, as we show in Table C1, patients are likely to suffer from five complications if the decision is not to remove mechanical ventilation when it should be removed. By summing the expected treatment costs of the five complications in Table C2, we can derive the classification cost (i.e., c_{01} in Table 6) for the decision not to remove mechanical ventilation from a patient who should have it removed.

With an investment in advanced, non-invasive, positive pressure ventilation, we expect a probability of 87.5% that patients will not develop ventilation-associated pneumonia (Antonelli et al. 1998). By obviating the need to treat ventilation-associated pneumonia, we obtain a new classification cost matrix (Table 7). For example, according to Table C2, the expected cost of treating ventilation-associated pneumonia is $6,730; if this cost is avoided, the classification cost c_{01} in Table 6 (i.e., $13,632) changes to $\bar{c}_{01}$ in Table 7 (i.e., $13,632 – $6,730). We summarize in Table 8 the probabilities of changes in classification costs due to an investment. The investment amount V is the expense of using advanced non-invasive positive pressure ventilation, which is $1,636 (Dasta et al. 2005; Elliott et al. 2002).

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Appendix D: Empirical Evaluation with Breast Cancer Data

The American Cancer Society estimated that, in 2015 alone, there were approximately 292,130 new breast cancer patients in the United States.[16] A crucial clinical decision is whether a patient should be diagnosed as having malignant tumors in her breast(s). We use 102,294 breast cancer cases, obtained from KDD Cup 2008, to demonstrate the performance of our method in support of CDM, compared with the benchmark methods in Table 9.[17] Each case consists of 117 breast image features of a patient and a class label attribute that indicates whether the patient actually has malignant tumors. To calibrate the classification costs in the cost matrix $\boldsymbol{C}$, we first identified the common complications associated with different diagnosis decisions by reviewing extant literature and consulting experienced medical experts. In Table D1, the top-right cell lists common complications if a patient is diagnosed as normal but has malignant tumors. The bottom-left and bottom-right cells indicate the frequent complications associated with common cancer treatments, such as chemo-therapy and radiation therapy. Typically, patients receive such

[16] Source: http://www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-key-statistics, accessed on October 12, 2015.

[17] KDD Cup is a global data mining and knowledge discovery competition organized by the ACM Special Interest Group on Knowledge Discovery and Data Mining. We downloaded the breast cancer data set from http://kdd.org/kdd-cup/view/kdd-cup-2008/Data, accessed on August 26, 2015.

common treatments if they are diagnosed to have malignant tumors. We obtained the cost of treating each of the frequently associated complications summarized in Table D2. The average cost of treating breast cancer increases by stage (Mittmann et al. 2014, p. 281): $29,938 for stage 1, $46,893 for stage 2, $65,369 for stage 3, and $66,627 for stage 4. Patients in our breast cancer data set were already at stage 3. The development and spread of malignant tumor cells could cause them to migrate and develop stage 4 breast cancer, which costs $66,627 to treat. Thus, we used $66,627 as the estimated treatment cost for the development and spread of malignant tumor cells to stage 4. Caplan (2014, p.2) reports a 0.12 probability that patients in stage 3 will develop to stage 4 breast cancer, so the expected cost for treating this complication is $7,995 (= $66,627 × 0.12). In Table D3, we estimate the classification cost associated with each diagnosis decision as the total expected cost of treating the complications associated with that decision. We further detail how we derived the estimated treatment costs and probabilities in Tables D3 and D4.

	Actual Benign (i.e., Normal)	**Actual Malignant**
Classifying as Benign (i.e., Normal)	No complications	(a) Development and spread of malignant tumor cells (Caplan 2014) (b) Ovarian failure (Shapiro and Recht 2001) (c) Oxidative stress (Shapiro and Recht 2001) (d) Cardiotoxicity (Shapiro and Recht 2001) (e) Chemotherapy-associated leukemia (Shapiro and Recht 2001) (f) Radiation pneumonitis (Shapiro and Recht 2001; Yi et al. 2009) (g) Overlying bone fractures (Yi et al. 2009)
Classifying as Malignant	(a) Ovarian failure (Shapiro and Recht 2001) (b) Oxidative stress (Shapiro and Recht 2001) (c) Cardiotoxicity (Shapiro and Recht 2001)	(a) Ovarian failure (Shapiro and Recht 2001) (b) Oxidative stress (Shapiro and Recht 2001) (c) Cardiotoxicity (Shapiro and Recht 2001)

	(d) Chemotherapy-associated leukemia (Shapiro and Recht 2001) (e) Radiation pneumonitis (Shapiro and Recht 2001; Yi et al. 2009) (f) Overlying bone fractures (Yi et al. 2009)	(d) Chemotherapy-associated leukemia (Shapiro and Recht 2001) (e) Radiation pneumonitis (Shapiro and Recht 2001; Yi et al. 2009) (f) Overlying bone fractures (Yi et al. 2009)

Table D1: Complications Commonly Associated with Different Breast Cancer Diagnosis Decisions

Complication	Probability of Developing Complication	Treatment Cost	Expected Treatment Cost
Development and spread of malignant tumor cells	0.12 (Caplan 2014)	$66,627 (Mittmann et al. 2014)	$7,995
Ovarian failure	0.30[18]	$59,700 (Archer et al. 2015) [19]	$17,910
Peripheral neuropathy	0.35 (Areti et al. 2014)	$12,492 (Sadosky et al. 2014)	$4,372
Cardiotoxicity	0.27 (Tian et al. 2014)	$15,656 (Mann 2012)	$4,227
Chemotherapy-associated leukemia	0.0005 (Wolff et al. 2015)	$178,800 (Larson et al. 2014)	$89
Radiation pneumonitis	0.146 (Plastaras et al. 2014)	$10,134 (Sher et al. 2011)	$1,480
Overlying bone fractures	0.067 (Denham et al. 2014)	$4,452 (Misra 2014)	$298

Table D2: Cost of Treating Each Complication Associated with Breast Cancer Diagnosis Decisions

Complication	Treatment Cost	Explanation and Justification
Development and spread of malignant tumor cells	$66,627	The average cost of breast cancer treatment increases by stage (Mittmann et al. 2014, p. 281): $29,938 for stage 1, $46,893 for stage 2, $65,369 for stage 3, and $66,627 for stage 4. Patients were already at stage 3. The development and spread of malignant tumor cells could cause them to develop stage 4 breast cancer, and the treatment cost would be $66,627.

[18] Source: http://www.uptodate.com/contents/overview-of-infertility-and-pregnancy-outcome-in-cancer-survivors, accessed on October 12, 2015.
[19] Infertility resource: http://www.ihr.com/infertility/egg-donation/egg-donation-egg-donor-costs.html

Ovarian failure	$59,700	The treatment of ovarian failure consists of estrogen/progestin therapy and egg donation.[20] Archer et al. (2015) estimate $530 million to $1.1 billion for hormone therapy (estrogen therapy), and the prescriptions are estimated for 500,000 to 1 million women. The maximum possible cost for estrogen therapy is $1.1 billion/500,000 = $2,200. The minimum possible cost for estrogen therapy is $530 million/1 million = $530. The cost of egg donation consists of donation expenses across categories ($26,550 to $47,450) and donor expenses ($4,000 to $10,000).[21] The minimum cost of egg donation is $30,550 ($26,550 + $4,000), and the maximum cost is $57,450 ($47,450 + $10,000). Therefore, the maximum treatment cost for ovarian failure is $59,700 ($57,450 + $2,200 = $59,650, rounded up to $59,700); the minimum treatment cost is $31,100 ($30,550 + $530 = $31,080, rounded to $31,100). We used $59,700 in the evaluation.
Peripheral neuropathy	$12,492	According to Sadosky et al. (2015, p.216), the cost of treating diabetic peripheral neuropathy, the most common peripheral neuropathy, ranges between $12,492 and $30,755.[22] We used $12,492 in the evaluation.
Cardiotoxicity	$15,656	Multi-gated acquisition scanning is the "gold-standard" and most accepted treatment method for cardiotoxicity, with an average treatment cost of $15,656 (Mann 2012, p. 338).
Chemotherapy-associated leukemia	$178,800	The strategy for treating leukemia includes using imatinib ($76,800) and dasatinib or nilotinib ($102,000) (Larson et al. 2014). We used $178,800, or $76,800 + $102,000.
Radiation pneumonitis	$10,134	According to Sher et al. (2011), the monthly treatment cost for Grade 2 pneumonitis is $90.25, and the treatment lasts for three months. Thus, the treatment cost for Grade 2 pneumonitis is $271, or $90.25 × 3 = $270.75 (rounded up to $271). According to Sher et al. (2011, p.3), the monthly treatment cost for Grade 3 pneumonitis is 1,643.76 ($1,371.32 + $272.44), and the treatment lasts for six months. Thus, the treatment cost for Grade 3 pneumonitis is $9,863, or $1,643.76 × 6 = $9,862.56 (rounded up to $9,863). The

[20] Advanced fertility center of Chicago: http://www.advancedfertility.com/premature-ovarian-failure.htm
[21] Infertility resource: http://www.ihr.com/infertility/egg-donation/egg-donation-egg-donor-costs.html
[22] National Institute of Neurological Disorders and Stroke https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Peripheral-Neuropathy-Fact-Sheet

		minimum cost is the cost to treat Grade 2 pneumonitis, $271. The maximum cost occurs when the treatment for grade 2 pneumonitis fails and the patient develops grade 3 pneumonitis. The maximum cost thus is $271 + $9,863 = $10,134. We used $10,134 in the evaluation.
Overlying bone fractures	$4,452	Treatment costs for eight bone injuries (fractures) range from $2,294 to $7,666 (Misra 2014, p. 5). The average of the eight treatment costs is $4,452, so we used this value.

Table D3: Treatment Costs for Complications Associated with Breast Cancer Diagnosis Decisions

Complication	Probability	Explanation and Justification
Development and spread of malignant tumor cells	0.12	Patients in our breast cancer data set were already in stage 3. According to Caplan (2014, p. 2), the probability of developing stage 4 breast cancer from stage 3 ranges from 0.05 to 0.12. We used 0.12 in the evaluation.
Ovarian failure	0.30	According to the Cardonick's (2015) "Overview of infertility and pregnancy outcome in cancer survivors" (subsection "Risk of infertility among cancer survivors"), the cumulative incidence of premature menopause (ovarian failure) approached 30%. We thus used 0.30 in the evaluation. Please see Footnote 17 for details
Peripheral neuropathy	0.35	Around 30%–40% of patients undergoing chemotherapy develop peripheral neuropathy (Areti et al. 2014, p. 289). We used 0.35 (the average) in the evaluation.
Cardiotoxicity	0.27	Anthracyclines (AC), used alone or in combination with other chemotherapy agents, are common treatment agents (Tian et al. 2014, p.1). When chemotherapy is provided together with ACs, the probability of cardiotoxicity can be as high as 27%. We used 0.27 in the evaluation.
Chemotherapy-associated leukemia	0.0005	According to the National Cancer Institute (U.S.), leukemia usually begins in the bone marrow.[23] Wolff et al. (2015) analyzed 109,560 person-years of patient follow-up and reported that the overall rate of marrow neoplasms (leukemia) after the treatment of breast cancer was 0.46 per 1,000 person-years. We rounded up to 0.05%.

[23] National Cancer Institute: https://www.cancer.gov/types/leukemia.

Radiation pneumonitis	0.146	Of 89 patients treated with chemotherapy and photon or proton radiation therapy, 13 were diagnosed with radiation pneumonitis, or 14.6% (Plastaras et al. 2014), We used 0.146 in the evaluation.
Overlying bone fractures	0.067	The frequency of bone fractures after radiation is 72 of 1071 patients, or 6.7% (Denham et al. (2014, p. 347). We used 0.067 in the evaluation.

Table D4: Probabilities for Complications Associated with Breast Cancer Diagnosis Decisions

	Actually Benign	**Actually Malignant**
Classifying as Benign	c_{00}= \$0	c_{01}= \$36,371
Classifying as Malignant	c_{10}= \$28,376	c_{11}= \$28,376

Table D5: Classification Cost Matrix *C* for Breast Cancer Diagnosis

Investing in the medication Goserelin to protect a patient's ovaries increases the estimated probability that a patient will not develop ovarian failure to 66.70% (Moore et al. 2015). We obtain the new classification cost matrix in Table D6. For example, according to Table D2, the expected cost of treating ovarian failure is \$17,910; if this cost is obviated, classification cost c_{10} (\$28,376) in Table D5 changes to $\bar{c}_{10}$ (\$28,376− \$17,910) in Table D6. We also summarize in Table D7 the probabilities of classification cost changes due to this investment. The investment amount *V* is the expense of applying Goserelin, which costs \$1,153 (Cheng et al. 2012; Dinkelspiel et al. 2015). After calibrating the parameters, we performed experiments to examine the effectiveness and robustness of our method, using the procedure described in the Empirical Evaluation section in the main text.

	Actually Benign	**Actually Malignant**
Classifying as Benign	$\bar{c}_{00}$= \$0	$\bar{c}_{01}$= \$18,461
Classifying as Malignant	$\bar{c}_{10}$= \$10,466	$\bar{c}_{11}$= \$10,466

Table D6: New Classification Cost Matrix $\bar{C}$ for Breast Cancer Diagnosis

Probability of Changing from c_{00} to $\bar{c}_{00}$	**Probability of Changing from c_{01} to $\bar{c}_{01}$**	**Probability of Changing from c_{10} to $\bar{c}_{10}$**	**Probability of Changing from c_{11} to $\bar{c}_{11}$**
p_{00} = 0	p_{01}= 0.667	p_{10} = 0.667	p_{11}= 0.667

Table D7: Probability p_{ij} of Cost Change Due to an Investment (Breast Cancer Diagnosis)

Effectiveness Analysis

We conducted 100 experiments to examine the effectiveness of our method. For both the proposed and benchmark methods, we used C4.5, coupled with m-estimation, to estimate the probability p that a patient has malignant tumors. Overall, our method consistently recorded the lowest cost among all the investigated methods, across all the experiments. We applied a Wilcoxon signed-rank test to the experimental results, and our method significantly outperformed each benchmark method ($p < 0.001$). Furthermore, we observed substantial cost reductions over the benchmark methods, as summarized in Table D8. For example, the average cost of our method is $7,079,357 across all 100 experiments, whereas that of MC (best-performing benchmark) is $8,604,710. On average, the cost of our method, 20.43% lower than that of THR, 17.73% lower than that of MC, and 34.09% lower than that of SMOTE (worst-performing benchmark).

Method	**Cost: Average (± Standard Deviation)**	**Average Cost Reduction by ICSL**
Our Method (ICSL)	$7,079,357 (±$355,771)	
THR	$8,638,207 (±$334,353)	20.43%
SMOTE	$10,769,447 (±$708,135)	34.09%
IW	$9,803,830 (±$371,288)	27.77%
MC	$8,604,710 (±$227,070)	17.73%

Table D8: Average Cost of Each Investigated Method, across 100 Experiments[24]

Robustness Analysis in Scenario I: We created different evaluation situations by changing the investment amount from $V \times 60\%$ to $V \times 140\%$, setting the classification costs in Table D5 from $c_{ij} \times 60\%$ to $c_{ij} \times 140\%$ for all $i, j \in \{0,1\}$, or altering the probabilities of cost change in

[24] The performance improvement attained with the breast cancer data is lower than that attained with the ventilation data. The differentials might reflect the relatively high imbalance in the breast cancer data: 101,671 records belong to class 0 (i.e., benign), and 623 records belong to class 1 (i.e., malignant).

Table D7 from $p_{ij} \times 60\%$ to $p_{ij} \times 140\%$ for all $i, j \in \{0,1\}$, in increments of 10%.[25] Then we conducted 100 experiments to compare the performance outcomes. Again, our method significantly and substantially outperformed each benchmark method, at $p < 0.001$. Moreover, the cost reduction by our method increased with the classification costs and probabilities of cost change, and it decreased with the investment amount, in line with Proposition 1. For example, the cost reduction by our method relative to MC, the best-performing benchmark method, increased from 15.50% to 20.73% as the investment amount dropped from $V \times 140\%$ to $V \times 60\%$.

Robustness Analysis in Scenario II: For all investigated methods, we used other classification algorithms to estimate the probability p that a patient has malignant tumors, including logistic regression, support vector machines, and naïve Bayes. We conducted 100 experiments for each method. As Tables D9–D11 reveal, the average cost of our method, across 100 experiments, was substantially lower than that of any benchmark method, for all the alternative classification algorithms. Furthermore, according to the Wilcoxon signed-rank test results, our method consistently and significantly outperformed each benchmark method ($p < 0.001$), for all the classification algorithms.

Method	**Cost: Average (± Standard Deviation)**	**Average Cost Reduction by ICSL**
Our Method (ICSL)	\$6,499,451 (±\$321,509)	
THR	\$7,527,023 (±\$364,708)	13.65%
SMOTE	\$8,214,865 (±\$300,924)	20.91%
IW	\$7,873,894 (±\$347,888)	17.46%

[25] We perform similar robustness checks for the breast cancer evaluation results and continue using -40% as the lower bound. If we further decrease the lower bound (e.g., from -40% to -50%), the original cost c_{01} then becomes \$18,186, lower than the adjusted $\bar{c}_{01} = \$18{,}461$, which violates the assumption that classification costs would be reduced after the investment. To maintain symmetry in the investigated range, we use +40% as the upper bound. We also further expand the upper bound (not constrained by any assumptions or limits) to +100% and observe consistent results: when the cost differences resulted from the investment increase, the average cost reduction by our proposed method becomes larger as well, in line with Proposition 1.

MC	$7,857,071 (±$372,739)	17.28%

Table D9: Average Cost of Each Investigated Method (*p* Estimated with Logistic Regression)

Method	Cost: Average (± Standard Deviation)	Average Cost Reduction by ICSL
Our Method (ICSL)	$6,663,296 (±$337,369)	
THR	$7,548,001 (±$361,195)	11.73%
SMOTE	$8,211,726 (±$303,896)	18.89%
IW	$7,821,624 (±$339,069)	14.83%
MC	$7,727,714 (±$320,242)	13.80%

Table D10: Average Cost of Each Investigated Method (*p* Estimated with Support Vector Machine)

Method	Cost: Average (± Standard Deviation)	Average Cost Reduction by ICSL
Our Method (ICSL)	$103,467,473 (±$15,188,529)	
THR	$159,124,779 (±$23,734,101)	34.95%
SMOTE	$186,939,406 (±$24,457,512)	44.74%
IW	$173,324,005 (±$25,425,072)	40.30%
MC	$258,753,201 (±$53,077,896)	59.46%

Table D11: Average Cost of Each Investigated Method (*p* Estimated with Naïve Bayes)

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