Treatment Policy Learning in Multiobjective Settings with Fully Observed Outcomes

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Abstract

In several medical decision-making problems, such as antibiotic prescription, laboratory testing can provide precise indications for how a patient will respond to different treatment options. This enables us to “fully observe” all potential treatment outcomes, but while present in historical data, these results are infeasible to produce in real-time at the point of the initial treatment decision. Moreover, treatment policies in these settings often need to trade off between multiple competing objectives, such as effectiveness of treatment and harmful side effects.

We present, compare, and evaluate three approaches for learning individualized treatment policies in this setting: First, we consider two indirect approaches, which use predictive models of treatment response to construct policies optimal for different trade-offs between objectives. Second, we consider a direct approach that constructs such a set of policies without any intermediate models of outcomes. Using a medical dataset of Urinary Tract Infection (UTI) patients, we show that all approaches are able to find policies that achieve strictly better performance on all outcomes than clinicians, while also trading off between different objectives as desired. We demonstrate additional benefits of the direct approach, including flexibly incorporating other goals such as deferral to physicians on simple cases.

1 Introduction

Many medical treatment settings involve time-intensive or expensive laboratory testing that provide information about patient responses to all treatments of interest, but which are unavailable to doctors when they must first make a treatment decision. For instance, in antibiotic prescription, patients are tested for resistance to several antibiotics, not just those used for treatment, providing us with information about their response to all relevant
treatments. However, these results take days to obtain, and doctors have to make an immediate treatment decision in the meantime.

A similar setting arises in cancer treatment. In patient-derived xenografts (PDX) models, a patient’s tumor tissue is implanted in a mouse, where its response to various cancer treatments can be recorded. Moreover, these models take 2-8 months to develop, so physicians typically need to start patients on treatment without knowing the optimal choice (Wang and Shi 2019).

Treatment decisions in many medical settings also require doctors to make trade-offs between competing objectives. For instance, a doctor might aim to maximize treatment effectiveness while constraining the risk of adverse side-effects to the patient or overall treatment cost. In the case of antibiotic prescription, doctors have to make a trade-off between the objectives of treatment effectiveness and minimizing usage of 2nd line, or broad spectrum, antibiotics. Broad spectrum antibiotics have a higher likelihood of being effective, but overuse leads to increased population-level resistance rates in the long run. In this setting, the objective is to maximize antibiotic effectiveness while limiting usage of 2nd line antibiotics.

In this work, we present methods for learning treatment policies in such multi-objective settings with fully observed outcomes for the treatments of interest. We present both indirect and direct policy learning approaches for learning a set of treatment policies that exhibit various trade-offs between the objectives. We then apply these methods to learn policies for making antibiotic prescription decisions in patients with urinary tract infections (UTIs). Our primary contributions in this work are as follows:

• We present three treatment policy learning methods for settings with fully observed outcomes and multiple objectives, and highlight the trade-offs across the various approaches.

• Using a clinical dataset of Urinary Tract Infection (UTI) patients, we show that all methods are able to significantly exceed clinician performance with respect to multiple important treatment objectives.

• We show that our methods are able to learn a set of policies that can effectively trade off between treatment objectives, enabling practitioners can select a policy with the desired trade-off at decision time.

• We use a synthetic environment to demonstrate that direct policy learning learns superior treatment policies relative to indirect approaches in settings with complex outcome models, but simple optimal treatment rules.

• We show that the direct learning framework naturally accommodates other considerations, such as deferral to clinician decisions in situations where physicians typically perform well. We demonstrate this use case in the antibiotic prescription setting as well.
2 Related Work

There are several related areas of research that deal with learning policies from retrospective data of contexts, actions, and outcomes, and we outline some connections here. Several lines of research focus on the setting where the only observed outcome corresponds to the action that was taken. In the contextual bandits literature, this is referred to as bandit feedback, and the retrospective setting is referred to as the “batch” setting (Swaminathan and Joachims, 2015). In biostatistics, epidemiology, and causal inference more broadly, the outcomes are referred to as “potential” or “counterfactual” outcomes (Imbens and Rubin, 2015; Hernan and Robbins, 2020) and the fact that we only observe a single outcome per individual is referred to as the fundamental problem of causal inference.

Within epidemiology and biostatistics, a policy is sometimes referred to as an individualized treatment rule (ITRs), and two broad approaches exist to learning them, an indirect and a direct approach. In the indirect approach, the conditional distribution of the outcome (given patient characteristics) for each action is modeled directly, and a decision rule is obtained by choosing the action that maximizes the outcome of interest. This includes approaches such as Q-learning, A-learning, and regret regression (Nahum-Shani et al., 2012; Schulte et al., 2014; Henderson et al., 2010). However, the model class of the resulting ITR is dependent on the model class used for the conditional outcomes: If a linear ITR is desired, then it necessitates the use of a linear model class for the conditional outcome models. In cases where a simple outcome model does not accurately capture the true conditional outcome function, the learned ITR may be sub-optimal (Min and Murphy, 2011). By contrast, the direct approach develops an estimator of the expected conditional outcome as a function of a decision rule, and directly optimize the value of this estimator by searching over the space of treatment decision rules. This removes the dependence between the complexity of the learned ITR and the outcome models to avoid misspecification. For problems with binary treatments, this direct optimization problem is equivalent to weighted binary classification, and is referred to as outcome weighted learning (Zhao et al., 2012). Recent work has also focused on developing and analyzing convex surrogates for this problem to allow for efficient optimization of the objective (Zhao et al., 2019) and extend this to the multi-action setting (Huang et al., 2019).

In our setting, we have access to counterfactual outcomes of all possible treatments. Thus, a close setting to ours is that of cost-sensitive multi-class classification (Elkan, 2001), where the true loss function is the multi-class equivalent of a weighted 0-1 loss in binary classification. In this setting, smooth convex surrogates for this objective are used for learning (Zou et al., 2008), with the desideratum that they are consistent for the Bayes optimal classifier (Zhang, 2004; Tewari and Bartlett, 2007), and Huang et al. (2019) use the same multinomial deviance risk that we use as our direct policy learning approach. All of these cases, as well as our own, are concerned with deterministic policies, because these are generally optimal for cases where exploration is not required (and stochastic policies introduce further optimization difficulties, as studied in the bandits literature (Chen et al., 2019)).

Multi-objective decision-making has been long-studied in the context of single decisions (Zeleny and Cochrane, 1982; Vira and Haines, 1983) and recently in the context of sequential decision-making, typically formulated as a Markov Decision Process with a vector-valued
objective (Roijers et al., 2013) and a scalarization function (to convert the vector-valued objective into a scalar reward) that is unknown at train-time, but often assumed to be a linear combination (Natarajan and Tadepalli, 2005). Many of these methods seek to maintain a set of policies that are optimal for different linear scalarization functions (Natarajan and Tadepalli, 2005; Barrett and Narayanan, 2008; Lizotte et al., 2012), and can be seen as indirect methods in their use of Q-functions to do so. The set of objective values achieved by the set of optimal policies (each optimal for a different possible scalarization function) is known as the Pareto frontier (Yang et al., 2019). Our indirect approach of expected reward maximization can be seen as roughly the one-step (and therefore much simpler) equivalent of some of these methods. Our direct approach borrows (albeit more conceptually) from these methods as well, in that we learn a set of policies corresponding to a set of fixed linear preferences.

In our specific application area of antibiotic prescription in urinary tract infections, recent work (Yelin et al., 2019) learned treatment policies in a setting with fully observed outcomes, but with the single objective of maximizing treatment effectiveness. They used an indirect approach, training models to predict resistance and selecting the antibiotic with the minimum predicted resistance probability. Their work did not address the multi-objective nature of the antibiotic prescription problem. Another recent paper (Oonsivilai et al., 2018) develops models for predicting resistance to a single antibiotic using a utility-based objective that accounts for factors beyond treatment effectiveness, such as drug cost. However, they do not address how these resistance predictions or their proposed utility-based framework could be used to construct a treatment policy that selects among several antibiotics.

3 Policy Learning Methods

3.1 Overview

In the general formulation of the multi-objective policy learning problem, we let \( A = [K] \) denote the action space, where \( K \) is the number of discrete actions, we denote features as \( X \in \mathbb{R}^m \), and we will seek to choose a policy \( \pi : \mathbb{R}^m \to A \) which maps from features (i.e., patient characteristics) to recommended actions. Note that we use bold-faced symbols like \( X \) to denote vectors, and \( X(i) \) to denote the \( i \)-th entry of a vector.

In our particular setting, we will focus on optimizing over two objectives, and will adapt our notation accordingly. Our dataset is of the form \( \{(X_i, Y_i, C_i)\}_{i=1}^n \), where \( X_i \in \mathbb{R}^m \) are patient features, and \( Y_i, C_i \) represent our competing objectives, a benefit and a cost respectively. In the antibiotic prescription setting, \( Y_i \in \{0, 1\}^K \), where \( Y(a) \) is an indicator for whether antibiotic \( a \) is effective in treating an infection, and \( C_i \in \{0, 1\} \), where \( C(a) \) is an indicator for whether the chosen antibiotic is broad-spectrum, whose use we wish to minimize in the interests of avoiding population-level antibiotic resistance. We make two remarks: First, broad-spectrum antibiotics tend to be more effective in expectation, leading to a trade-off between these two objectives. Second, we observe outcomes for all treatments / actions, not just the one received by a patient, as our dataset contains laboratory results that indicate the susceptibility of the infection to different drugs.

We present three approaches in this section. Each approach will seek to return a set of policies \( \Pi \), where each element \( \pi \in \Pi \) represents an optimal policy for some trade-off
between $Y$ and $C$. The first two methods can be viewed as \textit{indirect} approaches, in that they require learning a separate model for the conditional mean of $Y$ under each treatment $\mathbf{1}$ denoted $f_a(x) \approx \mathbb{E}(Y(a) \mid X = x)$. The third approach is a \textit{direct} approach, in that it does not require predictive models for the individual outcomes, but optimizes directly for a treatment policy. To summarize these approaches:

1. **Thresholding**: Use a set of carefully-chosen thresholds to convert $f_a(x)$ into a binary prediction of effectiveness $Y(a)$ for each treatment, and then choose the lowest-cost treatment which is predicted to be effective.

2. **Expected Reward Maximization**: Combine $Y$ and $C$ into a single objective $r_\omega$ (the “reward”) by taking linear combinations with varying weights, and choose the treatment which maximizes this reward according to the models $f_a(x)$.

3. **Direct Policy Optimization**: Using the same definition of reward $r_\omega$, learn a single model that directly predicts which treatment is optimal by optimizing a surrogate loss.

### 3.2 Thresholding

In this section, we introduce a simple method whose decision logic is intuitive: Predict which treatments will be effective, and then choose the effective treatment with the lowest cost. Given our learned models $f_a(x)$ of predicted effectiveness, which output numbers between 0 and 1, we use carefully-chosen thresholds to make a binary prediction for each $Y(a)$. We combine these predictions with the fixed cost associated with broad-spectrum antibiotics to choose the lowest-cost treatment that is still predicted to be effective.

More formally, we denote the set of thresholds used to binarize each prediction as $\{t_a\}_{a=1}^K$. We let $e_a(x)$ be an indicator\textsuperscript{2} that represents whether treatment $a$ is predicted to be effective for patient with features $x$, given by

$$e_a(x) = \mathbf{1}[f_a(x) \geq t_a]$$

The treatment policy is then defined as the action that minimizes cost, among the treatments that are predicted to be effective

$$\pi(x) = \arg\min_a \{c(a) \mid e_a(x) = 1\}$$

In the event where $e_a(x) = 0$ for all $a \in \mathcal{A}$, the treatment policy falls back to an option $a$ that minimizes the cost $c(a)$. In our setting, this corresponds to defaulting to a first-line antibiotic.

**Choosing thresholds**: A single set of thresholds implicitly defines a policy with a fixed trade-off between effectiveness and other costs. To construct a set of policies $\Pi$ that

\footnote{1}{In our case, costs are determined by the choice of treatment itself, so we only need to model the conditional mean of treatment effectiveness, but it is straightforward to extend both methods to the case where all objectives must be modelled.}

\footnote{2}{Throughout, we use $\mathbf{1}[P]$ as an indicator function that is equal to 1 if the expression $P$ is true, and 0 if $P$ is false.}
express varying preferences between treatment effectiveness and other costs, we perform an exhaustive search over different choices of threshold combinations \( \{t_a\}_{a=1}^K \in \mathcal{T} \), where \( \mathcal{T} \) is a large (but finite) search space.

Each policy \( \pi \) implied by our models \( f_a \) and thresholds \( t_a \) is then evaluated on a held-out validation set to get an empirical estimate of their expected benefit \( \mathbb{E}[Y(\pi(x))] \) and expected cost \( \mathbb{E}[C(\pi(x))] \). We then enumerate over a set of cost constraints \( \{b_j\}_{j=1}^J \), and return the \( J \) policies which satisfy

\[
\pi^* = \arg \max_\pi \{ \mathbb{E}[Y(\pi(x))] : \mathbb{E}[C(\pi(x))] \leq b_j \}
\]

In other words, we choose the policy for each \( b_j \) which achieves the highest mean value of \( Y \) in our validation set, subject to the constraint that the mean cost is less than \( b_j \).

This approach, while straightforward and interpretable, does have drawbacks. It requires enumeration over a large set of thresholds \( \mathcal{T} \), and thresholding predicted probabilities throws away information: For instance, two treatments with equal cost could both have predicted probabilities of effectiveness greater than their respective thresholds, but where the model is far more confident in one over the other. In the next section, we present a method that circumvents these issues, while making the trade-off that the resulting decision logic (maximizing an expected reward) may be less interpretable to a lay audience.

### 3.3 Expected Reward Maximization

In a single objective setting, a simple approach for converting predictions of treatment effectiveness into a policy for a patient with features \( x \) would be to select the treatment \( a^* = \arg \max_a f_a(x) \), i.e., choose the treatment that is most likely to work, based on our model predictions.

In our setting we have multiple objectives, but if we combine our objectives into a single number indicating a notion of value or reward, then we can construct a similar policy that optimizes this quantity.

More formally, recall that our goal is to learn a deterministic treatment policy \( \pi : \mathbb{R}^m \rightarrow \mathcal{A} \), which maps patient features to a deterministic decision. To combine our objectives, we will use a linear preference parameter \( \omega \in [0,1] \) such that the reward is linear combination of our competing objectives. In our particular case, we parameterize this as follows, to account for the fact the our cost is a binary variable

\[
r_\omega(a) = \omega \cdot Y + (1 - \omega) \cdot (1 - C),
\]

where \( r_\omega(a) \) represents the reward under treatment \( a \). We will omit the subscript where it is clear from context.

In the setting of linear preferences, commonly used in the multi-objective optimization literature ([Stewart 1992](#), [Natarajan and Tadepalli 2005](#)), we do not lose anything by restricting ourselves to deterministic policies, because there exists an optimal policy that is deterministic ([Roijers et al. 2013](#)). Under this preference \( \omega \), we define the Bayes optimal policy \( \pi_{\omega}^* \) as the one that maximizes the expected reward for a given \( x \), and is defined with respect to the true (unknown) conditional expectations

\[
\pi_{\omega}^*(x) = \arg \max_{a \in \mathcal{A}} \mathbb{E}[r_\omega(a) \mid x]
\]

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In the setting we consider, we adopt a strategy of learning a set of policies $\Pi$ that are each optimal according to some preference $\omega$, allowing users to select a policy from this set which corresponds to their desired trade-off. This is referred to as the “decision support” setting (Rojers et al., 2013) in that we do not solicit an explicit preference $\omega$ from decision makers, but instead provide a set of alternatives that are each optimal for some $\omega$.

Using this formalism and the definition of reward in Equation (1), we can use our models $f_a(x)$, which approximate $\mathbb{E}[Y(a)|X = x]$, to construct a prediction of this reward under each action $a$, and then define our treatment policy $\pi_\omega(x)$ as the one that chooses the action with the highest predicted reward

$$\pi_\omega(x) = \arg \max_a \omega f_a(x) + (1 - \omega) \cdot (1 - C(a))$$

Constructing such a decision rule for each $\omega$ produces our desired set of policies $\Pi$. This approach has the benefit of not requiring enumeration over a large set of thresholds, and it takes the predicted probabilities into account directly.

However, this approach requires us to build predictive models of treatment effectiveness, and can introduce a trade-off between policy performance and interpretability. For instance, representing the outcome models $f_a$ with linear functions allows us to interpret the learned policy and gain insight into features driving decisions by examining differences in coefficients.

In many settings, linear models may be too simple to accurately model outcomes, which can lead to poor performing models (and therefore policies). On the other hand, more complex models sacrifice the interpretability of the resulting policy. In the next section, we present a method which instead seeks to find a policy of the desired model class (e.g., linear) directly.

### 3.4 Direct Policy Optimization

In this approach, we seek to directly learn a policy which has an interpretable form, without learning any specific models of treatment effectiveness. We will use the same notion of reward defined in Section 3.3 and will optimize the (estimated) value of a treatment policy $\pi, \hat{V}_\omega(\pi)$. As before, we learn a range of policies corresponding to different values of $\omega$.

In this case, our objective is to find a function $\pi: \mathbb{R}^m \rightarrow A$ which maximizes the following objective, and we note that any such policy can be written as $\pi(x) = \arg \max_{a \in A} d(x,a)$ for some function $d : \mathbb{R}^m \times A \rightarrow \mathbb{R}$, leading to the formulation

$$\pi^*_\omega = \arg \max_\pi V_\omega(\pi) := \mathbb{E}_{x,r} \left[ \sum_{a \in A} r_\omega(a) 1[a = \pi(x)] \right]$$

$$= \mathbb{E}_{x,r} \left[ \sum_{a \in A} r_\omega(a) 1\left[a = \arg \max_{a \in A} d(x,a)\right] \right]$$

We will omit $\omega$ in the remainder of this section, as we will choose a finite set of values for $\omega$ to generate a set of optimal policies $\pi_\omega$ for each.

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3If there are two actions, then this is a direct consequence of the formulation, and for more than two actions the policy can be interpreted as a set of linear classifiers by comparing the difference in coefficients for models of pairs of treatments.
To find an optimal policy, we wish to optimize over the space of decision functions \( d \) using the empirical estimate of \( V(\pi) \), but the argmax operation causes this objective to be non-convex. Instead, we will use a differentiable convex surrogate objective (Tewari and Bartlett, 2007; Zou et al., 2008), in our case the multinomial deviance loss (Zou et al., 2008; Huang et al., 2019), which has the appealing property that it is not only convex and differentiable, but that when solved to optimality it yields a consistent estimator of the Bayes-optimal policy. Concretely, we optimize over functions \( f_a : \mathbb{R}^m \rightarrow \mathbb{R} \), where our resulting policy will be given by \( \pi(x) = \arg \max_a f_a(x) \), and seek to minimize the following quantity in our empirical sample

\[
\mathbb{E}_{x,r} \tilde{L}(f, x, r) := -\mathbb{E} \left[ \sum_{a \in A} r(a) \log \frac{\exp f_a(x)}{\sum_{a'} \exp f_{a'}(x)} \right] \tag{3}
\]

In this work, we parameterize the functions \( f_a \) with a linear model, such that \( f_a(x) = \theta_a^T x \). As noted, this objective has the appealing property that, when solved to optimality, it will yield a policy that is consistent for the Bayes-optimal policy in the following sense (proof provided in the appendix)

**Proposition 1.** For nonnegative rewards \( r \), and for an \( f^* \) that satisfies \( f^* = \inf_f \mathbb{E}_{x,r} \tilde{L}(f, x, r) \), the corresponding policy \( \pi^*(x) = \arg \max_a f^*_a(x) \) is equivalent to the the Bayes-optimal policy \( \pi^*(x) = \arg \max_a \mathbb{E}[r(a) | X] \)

Directly optimizing for a treatment policy in this way decouples the complexity of the outcome models in a given setting from the complexity of an effective treatment policy. This enables the learning of interpretable decision-making policies even in a setting where modeling outcomes requires extremely sophisticated models.

### 4 Experiments

We evaluate each of the three policy learning approaches in the setting of antibiotic prescription for urinary tract infections (UTIs). We begin with some clinical background and motivation for the problem of antibiotic prescription and some details regarding our clinical dataset. Our main findings are as follows

1. **Improvement in both objectives:** All three methods are able to recover policies that strictly outperform clinicians in both treatment effectiveness and 2nd line usage rates to a clinically meaningful degree.

2. **Variety of policies along the frontier:** All three methods recover a variety of policies that encode different trade-offs between objectives. For instance, all methods are able to reduce IAT by over 20% relative to clinicians with minor reductions to 2nd-line usage. For other points on the frontier, all methods are able to achieve nearly zero 2nd-line usage, while still reducing IAT by nearly 10% relative to clinicians.

3. **Interpretation of policies:** We examine one of the policies learnt by the direct method, and confirm the factors driving particular treatment decisions are consistent with clinical intuition.
We then highlight, through synthetic and real-data experiments, two advantages of the direct policy learning approach over the other two approaches.

1. **Incorporating Deferral**: First, we demonstrate how this framework can elegantly incorporate other desiderata though simple changes to the reward function. For this, we use the example of deferral to clinician decisions: Through a change in the reward specification, we encourage the model to defer to clinicians in cases where physicians tend to perform well. We empirically demonstrate that this works as desired, where the cases prioritized by the model align with those where physicians perform poorly.

2. **Sample Efficiency**: We demonstrate through synthetic experiments that when (a) the Bayes-optimal policy is simple (e.g., linear), but (b) the true conditional outcomes are complex (e.g., nonlinear), then the direct policy optimization approach can take advantage of this structure and learn good policies with fewer samples than the indirect approach of expected reward maximization.

### 4.1 Background: Antibiotic Resistance

When a patient presents at the hospital with an infection, clinicians typically need to make an immediate decision on which antibiotic to administer. While laboratory tests can assess the susceptibility of an infection to each antibiotic, they take time: The bacteria must be grown in culture to sufficient quantities where the effectiveness of antibiotics can be tested directly, and this process takes several days to return results.

This is known as the ‘empiric treatment setting’, where doctors must make the initial prescription decision without the benefit of tests, using the patient’s medical history and their own clinical experience. They must weigh two competing concerns: Avoiding an inappropriate antibiotic therapy (IAT) where the pathogen is resistant to the antibiotic, while also avoiding overuse of broad-spectrum therapies that lead to higher resistance rates at an individual and population level.

This problem is particularly prevalent in UTIs, a common class of infection with more than 150 million annual cases worldwide [Stamm and Norrby, 2001]. Resistance rates to commonly prescribed agents in UTIs can exceed 20%, highlighting the difficulty of prescribing an effective antibiotic [Farrell et al., 2003]. Doctors frequently use 2nd-line antibiotics [Kabbani et al., 2018] because they are more effective at the individual level, but this contributes to higher prevalence of antibiotic-resistant pathogens in the future at the population level. Conversely, 1st-line (narrow spectrum) antibiotics are more likely to be resisted at an individual level, but pose less risk of increasing population-level resistance.

In practice, this trade-off is difficult to balance. Antibiotic resistance is influenced by a wide range of risk factors, from individual history of infection to population-level resistance rates and antibiotic usage trends, which are difficult to incorporate in real time decision-making. This motivates the need for learning data-driven antibiotic treatment policies that can make this trade-off in an optimal fashion.

### 4.2 Data

Our dataset is derived from the electronic health record (EHR) of Massachusetts General Hospital and the Brigham & Women’s Hospital in Boston, MA, containing the full medical
record for every patient who has undergone an antibiotic resistance test. This study was approved by the Institutional Review Board of Massachusetts General Hospital with a waived requirement for informed consent.

4.2.1 Cohort

Our cohort for this work consisted of 15,806 microbiological specimens collected from 13,682 women with UTIs between 2007 and 2016. We filtered specifically for patients with uncomplicated UTI, which refers to an infection in an otherwise healthy female. This excludes males, pregnant women, or women who had surgical procedures performed in the last 90 days. Patients with uncomplicated UTI typically receive prescriptions from a well-defined set of antibiotics, allowing us to clearly specify our action space for policy learning and evaluate performance of learned policies against clinician decisions.

4.2.2 Features

The dataset contains demographics (e.g., age, race), medications (including antibiotic prescriptions), basic lab test results, medical procedures, and comorbidities for each patient. It also contains information about the date and location that a specimen was collected, ground-truth antibiotic resistance profiles, and any previous resistance test results or infections in a patient’s history.

4.2.3 Treatments

Our treatment space consists of common antibiotics used in treating UTIs: nitrofurantoin (NIT), trimethoprim-sulfamethoxazole (SXT), ciprofloxacin (CIP), and levofloxacin (LVX). NIT and SXT are 1st-line (narrow spectrum) antibiotics, and CIP and LVX are 2nd-line (broad spectrum) antibiotics. We filter for uncomplicated UTI specimens that were treated with exactly one of the four agents in the empiric treatment setting, defined as the period spanning 2 days before to 1 day after the date of specimen collection. Empiric prescription information is not used during policy learning, as our goal is not to imitate clinician actions, but to improve on them. They are solely used to compare the decisions made by our learned policy to clinician actions. We also filter out specimens missing resistance test results for any of these four antibiotics, since this information is necessary for a full evaluation of policy decisions.

4.2.4 Feature Construction

We directly used age, race, and location of specimen collection as features in the model. We constructed binary features for antibiotic exposure, prior antibiotic resistance, prior infections, and comorbidities over the 7, 14, 30, 90, and 180-day periods from the specimen collection date. The values for a feature over each period were included separately in the model. We also construct a population-level feature called colonization pressure, defined as the proportion of resistant specimens to a given antibiotic within a specified location and time window. Finally, we compute the cumulative antibiotic usage rates across all hospitals in the 90-day window preceding specimen collection, normalized by total patient volume.
Table 1: Cohort Statistics

|                        | Train (2007-13) | Test (2014-16) |
|------------------------|-----------------|----------------|
| \textbf{\textit{n}}    | 11,865          | 3,941          |
| Age                    | 34.1 (10.8)     | 33.6 (11.1)    |
| % White                | 64.6%           | 63.0%          |
| \% Resistant NIT       | 12.3%           | 11.2%          |
| \% Resistant SXT       | 19.6%           | 19.6%          |
| \% Resistant CIP       | 5.3%            | 6.4%           |
| \% Resistant LVX       | 5.1%            | 6.5%           |
| \% Prescribed NIT      | 15.9%           | 34.5%          |
| \% Prescribed SXT      | 41.5%           | 32.0%          |
| \% Prescribed CIP      | 39.2%           | 32.5%          |
| \% Prescribed LVX      | 3.3%            | 1.0%           |

These last two features are the same for all patients who have specimens collected at the same location on the same date.

4.2.5 Train / Test Split

Out of the total 15,806 specimens, our training set consisted of 11,865 specimens collected from 2007-13, and we evaluated the learned policies on a held-out test set consisting of 3,941 specimens from 2014-16. This is after removing any specimens from the test set that came from patients who were also present in the training set to avoid any data leakage between train and test sets. Table 1 contains basic statistics about the cohort, including resistance rates and the distribution of empiric prescriptions in both train and test sets.

4.3 Experiment Setup and Evaluation

Treatment policies were learned using the training set, containing specimens from 2007-13, and evaluated on the test set, containing specimens from 2014-16. We used data containing specimens from 2012-13 as a validation set for hyperparameter selection across all approaches.

4.3.1 Thresholding and Expected Reward Maximization

We trained logistic regression models to predict treatment effectiveness for each of the four antibiotic treatment options: NIT, SXT, CIP, and LVX. Regularization type and strength were tuned using the validation set. For the thresholding-based approach, the search space of thresholds \( T \) for each model was chosen for a diversity of false-positive rates (for prediction of susceptibility), using ROC curves on the training set, and \( T \) is defined as all possible combinations of these threshold values.
Table 2: Policy Comparison: Constant 2nd line usage

|                | IAT  | 2nd line usage |
|----------------|------|----------------|
| Doctor         | 11.9%| 33.6%          |
| Thresholding   | 9.2% | 30.6%          |
| Expected reward maximization | 9.4% | 28.7%          |
| Direct learning| 9.4% | 30.4%          |

4.3.2 Direct Policy Optimization

The surrogate loss function (3) was optimized with the Adam optimizer and L2 regularization. The number of training epochs was chosen with an early stopping criteria based on the mean reward on the validation set. All models were implemented using PyTorch (Paszke et al., 2019).

4.3.3 Evaluation

We evaluated the learned policies with respect to two primary outcomes: IAT rate and 2nd line usage. IAT rate is the proportion of antibiotics to which a specimen is resistant, and 2nd line usage is the proportion of antibiotics which are CIP or LVX. We compute clinician performance and the performance of our policy using the results of the antibiotic resistance lab test, enabling a head-to-head comparison with our learned treatment policy.

4.4 Reward Function

We now recall the definition of the composite reward function given in Section 3.3 used for the indirect expected reward maximization and direct policy learning approaches. The treatment effectiveness vectors $Y$ correspond to a patient’s susceptibility to each antibiotic $Y_i(a) = 1$ [patient $i$ is susceptible to antibiotic $a$], the cost vector $C$ for the treatments are a function of the class of the chosen antibiotic $C_i(a) = 1$ [$a$ is a 2nd line antibiotic], and the composite treatment reward is defined as a linear combination of the effectiveness and costs for each antibiotic using the preference $\omega \in [0, 1]$, given by $r_i = \omega \cdot Y_i + (1 - \omega) \cdot (1 - C_i)$. As $\omega$ is reduced, more weight is placed on avoiding 2nd line antibiotic usage, even at the cost of additional cases of IAT. By varying $\omega$, we can learn a set of treatment policies that achieve different trade-offs between treatment effectiveness and broad spectrum usage.

4.5 Results

We present the results of learning policies using both the indirect and direct policy learning approaches outlined in Section 3 for several settings of the cost constraints $b_j$ (for the thresholding approach) and reward weights $\omega$ (for the reward maximization and direct learning approaches). Figure 1 shows the performance of the resulting set of policies for each approach on the 2014-16 patient cohort with respect to the IAT and 2nd line usage rates.
We observe that the sets of policies learned by all three approaches achieve similar performance for a broad range of IAT and 2nd line usage rates. In the reward maximization and direct learning approaches, the reward weight $\omega$ is able to successfully control the trade-off learned by the policy. As $\omega$ is reduced (i.e., treatment effectiveness is less important), the policy performance moves down and to the right along the performance frontier shown in Figure 1.

We compare the performance of our learned policies to that of doctors on the same patient cohort in Tables 2 and 3. In Table 2, we choose a policy from the policy set constructed by each method that does no worse than clinicians on 2nd line usage rate, and compare the corresponding IAT rates. All three approaches reduce the IAT rate by over 20% relative to clinicians, while also producing a minor reduction in the 2nd line usage rate. In Table 3, we choose a policy from the policy set constructed by each method that improves both IAT and 2nd line usage rates relative to clinicians. All three approaches are able to virtually eliminate 2nd line usage while also reducing the IAT rate by nearly 10% relative to clinicians.

Overall, we find that the frontier of policy performance for all three approaches lies...
Table 4: Top features driving recommendation of NIT over SXT, both 1st-line agents. Numbers in parentheses correspond to the time window, in days, over which feature was computed. For instance, “Prior resistance: SXT (180)” is an indicator for resistance in the past 180 days.

| Recommendation of NIT over SXT |
|--------------------------------|
| Prior resistance: SXT (180)    |
| Prior resistance: SXT (90)     |
| Location A                     |
| Prior treatment: folate-inhibitor (7) |
| Prior treatment: SXT (7)       |
| Location B                     |
| Prior treatment: folate-inhibitor (14) |
| Prior resistance: SXT (30)     |
| Prior treatment: SXT (90)      |
| Prior resistance: GEN (180)    |

significantly below and to the left of the point representing clinician performance, and we can achieve significant improvements relative to clinical practice by selecting appropriate points along the frontier.

4.6 Policy Interpretation

The direct policy learning approach enables interpretation of the learned treatment policy to understand features important for decision-making. The linear model learns a $d \times K$ weight matrix $\theta$, where each column contains the coefficients used to calculate the output for a particular antibiotic.

We examine the features important in our policy’s decisions for recommending antibiotic $a$ over antibiotic $a'$ by looking at pairwise differences in coefficient values in the corresponding columns of $\theta$. We extract the features $i$ for which $\theta_a(i) - \theta_{a'}(i)$ is large. We can perform this comparison for all pairwise combinations of antibiotics in our action space to extract the features of interest.

In our analysis here, we specifically focus on the factors driving recommendation of NIT over SXT (both 1st line antibiotics). The populations of patients that are resistant to NIT and SXT are largely disjoint (i.e., there are many patient resistant to exactly one of these agents), so accurately deciding when to use one agent over another is crucial for good policy performance. For a policy trained using a reward function with $\omega = 0.88$, these features are listed in Table 4.

We find that many of these features align with knowledge that prior resistance or exposure to an antibiotic promotes resistance to that antibiotic in the future. For instance, prior resistance to SXT is an important factor in driving recommendation of NIT, along with prior treatment with SXT in the recent past. We note that almost all the features shown above are features specific to an individual’s personal history of antibiotic exposure and resistance, with the exception of two features for specific hospital locations. Population-level
Figure 2: Comparison of doctor and algorithm IAT / 2nd line usage on the ‘decision cohort’ - the subset of examples where the model makes a decision - at different deferral rates. As the deferral rate increases, the model’s IAT rate remains relatively constant, while the doctor’s IAT rate increases more sharply. The model learns to take action on the cases where the clinician exhibits the poorest performance.

4.7 Deferring to Doctors

When integrating decision algorithms into medical settings, it is useful to give the algorithm the option to defer to the clinician’s decision. For instance, one might only want the algorithm to provide input on cases where the clinician’s decision is particularly likely to result in ineffective treatment. Designing a system in this way may help doctors avoid ‘alarm fatigue’ from excessive computerized alerts and increases the likelihood that they will incorporate algorithm input into their decision-making process.

The ability to incorporate deferral in a straightforward manner is a significant advantage of the direct learning approach. Adding this option in an indirect learning framework would require us to develop models of clinician behavior to calculate the expected reward of the doctor making the prescription decision for a given patient, which may be difficult to do. In this direct approach, incorporating a deferral option is no more difficult than incorporating an additional antibiotic treatment option. We simply expand our action space to include a ‘defer’ action, and define the reward for this action as:

\[ r_i(\text{defer}) = r_i(a) + \lambda_{\text{defer}} \]

where \( a \) is the action taken by the doctor and \( \lambda_{\text{defer}} \) is a positive parameter that controls the extent to which we incentivize deferral. Adding this ‘deferral reward’ encourages the
learned policy to defer on cases where the doctor takes a reward-maximizing action, and to make a decision when doctors are likely to make an error.

We examine the learned policy’s performance for a fixed $\omega$ and several values of $\lambda_{\text{defer}}$. In Figure 3, we compare the IAT and 2nd line usage performance of doctors and the learned policy on the ‘decision cohort’, the subset of patients where the algorithm makes a decision. The results are shown for policies learned using a reward function with $\omega = 0.92$ and values of $\lambda_{\text{defer}}$ in the range [0, 0.05].

On the left plot in Figure 3 we can observe that the gap in IAT rate between doctor and algorithm performance widens as the policy’s deferral rate is increased (i.e, the decision cohort shrinks). As the deferral rate increases from 5% to 70%, the gap in IAT rate between algorithm and doctor on the decision cohort grows from 2.6% to 3.8%, a relative increase of over 45%. This trend indicates that the learned policy is successfully able to identify the subset of patients where it can provide the most improvement when constrained to only take action on a limited number of cases. On the right plot, we also show the 2nd line usage on the decision cohort for each of these policies. We note that while there is higher variance in the fluctuations of the 2nd line usage rate as the deferral rate is changed, the range of observed 2nd line usage is still relatively limited and does not affect the interpretation of the observed trend in the IAT gap.

4.8 Synthetic Evaluation: Direct vs. Indirect

Even though direct and indirect methods achieved similar performance on our real-world antibiotic dataset, we demonstrate in this section a scenario where direct policy learning
can significantly outperform an indirect approach. In particular, this can occur when the true treatment outcome models are complex, but the optimal treatment rule is simple. For clarity, we illustrate the benefit of direct learning in a single-objective setting in these synthetic experiments, but an extension to multi-objective settings in the framework discussed previously is straightforward.

Our environment consists of $m$-dimensional feature vectors $\mathbf{X} \in \mathbb{R}^m$ and an action space $\mathcal{A}$ with 3 actions. All feature values are drawn i.i.d. from a standard Gaussian distribution. We use the binary random variable $Y(a)$ to denote the outcome of action $a$. The values of each $Y(a)$ for a given $X$ are generated according to the following models:

$$Y(a) \mid X \sim \text{Bernoulli} \left( \sigma \left( X_a + \sum_{i=4}^{m} \alpha_i X_i^2 + \sum_{(i,j) \in S} \beta_i X_i X_j \right) \right)$$  \hspace{1cm} (5)

for $a = 1, 2, 3$, where $\alpha_i, \beta_i$ are coefficients that are fixed across all 3 outcome models and $S$ is a subset of all distinct pairs of features. These are all nonlinear functions of the features $X$, but the Bayes-optimal treatment rule for maximizing under these outcome models is given by an argmax over linear functions

$$\pi^*(X) = \arg \max_{a \in \{1,2,3\}} X_a.$$  \hspace{1cm} (6)

We compare the performance of an indirect approach (expected reward maximization) and the direct policy optimization approaches for policy learning in this environment. In the indirect approach, we independently train logistic regression models $h_a$ to predict the outcomes $Y(a)$ for each $a$. The treatment rule is then defined as $\arg \max_a h_a(x)$. In the direct approach, we optimize the following loss function, where $f$ is parameterized by a linear model:

$$\tilde{L}(f, x) = -\sum_{i=1}^{n} \sum_{a \in \mathcal{A}} \left[ Y(a) = 1 \right] \log \frac{\exp f_a(x)}{\sum_{a'} \exp f_{a'}(x)}$$  \hspace{1cm} (7)

The results are shown in Figure 3. We plot the mean outcome of both approaches on a held-out test set for various training set sizes. We only compute the mean performance on the subset of examples in the test set for which outcomes were not uniform across all 3 actions (i.e., not all 0 or 1), as performance on the remaining samples does not depend on the policy. We also plot the mean performance of the Bayes-optimal policy given in Equation (6).

We observe that direct policy learning significantly outperforms the indirect approach across a wide range of training set sizes and rapidly approaches the Bayes-optimal performance with far fewer samples. This synthetic experiment demonstrates that the direct learning approach, in contrast to the indirect approach, is able to take advantage of scenarios where the optimal treatment policy is simple, even when the true conditional outcome models are complex.

5 Conclusion

In this work, we presented three approaches for learning treatment policies in clinical settings with multiple treatment objectives and access to retrospective data that provides
strong indicators for counterfactual treatment outcomes. We applied these approaches for learning antibiotic treatment policies for UTIs, and found that all our approaches achieved comparable performance and exceeded clinician performance across multiple treatment objectives. We also evaluated trade-offs among these approaches, and highlighted some significant advantages of direct learning in both real-world and synthetic experiments. We note that if one were in a setting without access to all counterfactual outcomes, one could still use the methods presented in this work in conjunction with appropriate estimators for the unobserved treatment outcomes.

Our empirical evaluation provides a real-world example for how to use machine learning to guide treatment selection. The fully observed setting has important impactful applications in settings such as antibiotic prescribing and precision medicine using patient-derived xenograft (PDX) models. At the same time, it is clearly a special case and is much simpler than the partially observed setting, where one has to simultaneously grapple with counterfactual estimation from biased data. As such, it is an ideal test bed for studying more subtle aspects of policy learning for guiding treatment selection. In this work, we addressed two important aspects of making treatment decisions in the real world: handling trade-offs between multiple objectives and deferring to clinician decisions when appropriate; future work using this type of data could examine the impact of nonstationarity on policy learning methods or techniques for developing more interpretable policies.

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References

Leon Barrett and Srini Narayanan. 2008. Learning all optimal policies with multiple criteria. Proceedings of the 25th International Conference on Machine Learning (2008), 41–47. https://doi.org/10.1145/1390156.1390162

Minmin Chen, Ramki Gummadi, Chris Harris, and Dale Schuurmans. 2019. Surrogate Objectives for Batch Policy Optimization in One-step Decision Making. Neural Information Processing Systems (NeurIPS) (2019).

Charles Elkan. 2001. The foundations of cost-sensitive learning. IJCAI International Joint Conference on Artificial Intelligence (2001), 973–978.

D J Farrell, I Morrissey, D De Rubeis, M Robbins, and D Felmingham. 2003. A UK multicentre study of the antimicrobial susceptibility of bacterial pathogens causing urinary tract infection. The Journal of infection 46, 2 (Feb 2003), 94–100.
Robin Henderson, Phil Ansell, and Deyadeen Alshibani. 2010. Regret-regression for optimal dynamic treatment regimes. *Biometrics* 66, 4 (Dec 2010), 1192–201. [https://doi.org/10.1111/j.1541-0420.2009.01368.x](https://doi.org/10.1111/j.1541-0420.2009.01368.x)

Miguel Hernan and Jamie Robbins. 2020. *Causal Inference*. Chapman & Hall/CRC, Boca Raton.

Xinyang Huang, Yair Goldberg, and Jin Xu. 2019. Multicategory individualized treatment regime using outcome weighted learning. *Biometrics* August 2018 (2019), 1216–1227. [https://doi.org/10.1111/biom.13084](https://doi.org/10.1111/biom.13084)

Guido W Imbens and Donald B Rubin. 2015. *Causal Inference for Statistics, Social, and Biomedical Sciences*. Cambridge University Press.

Sarah Kabbani, Adam Hersh, Daniel Shapiro, Katherine Fleming-Dutra, Andrew Pavia, and Lauri Hicks. 2018. Opportunities to Improve Fluoroquinolone Prescribing in the United States for Adult Ambulatory Care Visits. *Clinical Infectious Diseases* 67, 1 (2018), 134–136.

Daniel J. Lizotte, Michael Bowling, and Susan A. Murphy. 2012. Linear fitted-Q iteration with multiple reward functions. *Journal of Machine Learning Research* 13, 1 (2012), 3253–3295.

Qian Min and S.A. Murphy. 2011. Performance Guarantees for Individualized Treatment Rules. *The Annals of Statistics* 39 (2011), 1180–1210.

Inbal Nahum-Shani, Min Qian, Daniel Almirall, William E Pelham, Beth Gnagy, Gregory A Fabiano, James G Waxmonskey, Jihnhee Yu, and Susan A Murphy. 2012. Q-learning: a data analysis method for constructing adaptive interventions. *Psychological methods* 17, 4 (Dec 2012), 478–94. [https://doi.org/10.1037/a0029373](https://doi.org/10.1037/a0029373)

Sriraam Natarajan and Prasad Tadepalli. 2005. Dynamic preferences in multi-criteria reinforcement learning. *Proceedings of the 22nd International Conference on Machine Learning* (2005), 601–608. [https://doi.org/10.1145/1102351.1102427](https://doi.org/10.1145/1102351.1102427)

Mathupanee Oonsivilai, Yin Mo, Nantasit Luangasanatip, Yoel Lubell, Thyl Miliya, Pisey Tan, Lorn Loeuk, Paul Turner, and Ben Cooper. 2018. Using machine learning to guide targeted and locally-tailored empiric antibiotic prescribing in a children’s hospital in Cambodia. *Wellcome Open Research* 3 (2018).

Adam Paszke, Sam Gross, Francisco Massa, Adam Lerer, James Bradbury, Gregory Chanan, Trevor Killeen, Zeming Lin, Natalia Gimelshein, Luca Antiga, Alban Desmaison, Andreas Kopf, Edward Yang, Zachary DeVito, Martin Raison, Alykhan Tejani, Sasank Chilamkurthy, Benoit Steiner, Lu Fang, Junjie Bai, and Soumith Chintala. 2019. PyTorch: An Imperative Style, High-Performance Deep Learning Library. In *Advances in Neural Information Processing Systems 32*. Curran Associates, Inc., 8024–8035.

Diederik M. Roijers, Peter Vamplew, Shimon Whiteson, and Richard Dazeley. 2013. A survey of multi-objective sequential decision-making. *Journal of Artificial Intelligence Research* 48 (2013), 67–113. [https://doi.org/10.1613/jair.3987](https://doi.org/10.1613/jair.3987) arXiv:1402.0590
Philip Schulte, Anastasios Tsiatis, Eric Laber, and Marie Davidian. 2014. Q- and A-learning Methods for Estimating Optimal Treatment Regimes. *Statist. Sci.* 29, 4 (2014), 640–661.

Walter E Stamm and S Ragnar Norrby. 2001. Urinary tract infections: disease panorama and challenges. *Journal of infectious diseases* 183, Supplement 1 (2001), S1–S4.

TJ Stewart. 1992. A critical survey on the status of multiple criteria decision making theory and practice. *Omega* 20, 5-6 (1992), 569–586. https://doi.org/10.1016/0305-0483(92)90003-P

Adith Swaminathan and Thorsten Joachims. 2015. Batch Learning from Logged Bandit Feedback through Counterfactual Risk Minimization. *Journal of Machine Learning Research* 16, 52 (2015), 1731–1755.

Ambuj Tewari and Peter L. Bartlett. 2007. On the consistency of multiclass classification methods. *Journal of Machine Learning Research* 8 (2007), 1007–1025. https://doi.org/10.1007/11503415_10

C. Vira and Y. Y. Haimes. 1983. *Multiobjective Decision Making: Theory and Methodology*. North-Holland.

C. F. Wang and X. J. Shi. 2019. Generation and application of patient-derived xenograft models in pancreatic cancer research. *Chin. Med. J.* 132, 22 (Nov 2019), 2729–2736.

Runzhe Yang, Xingyuan Sun, and Karthik Narasimhan. 2019. A Generalized Algorithm for Multi-Objective Reinforcement Learning and Policy Adaptation. In *Advances in Neural Information Processing Systems 32*, H Wallach, H Larochelle, A Beygelzimer, F dAlché Buc, E Fox, and R Garnett (Eds.). Curran Associates, Inc., 14610–14621.

Idan Yelin, Olga Snitser, Gal Novich, Rachel Katz, Ofir Tal, Miriam Parizade, Gabriel Chodick, Gideon Koren, Varda Shalev, and Roy Kishony. 2019. Personal clinical history predicts antibiotic resistance of urinary tract infections. *Nature Medicine* 25, July (2019). https://doi.org/10.1038/s41591-019-0503-6

M. Zeleny and J. L. Cochrane. 1982. *Multiple Criteria Decision Making*. McGraw-Hill, New York, NY, USA.

Tong Zhang. 2004. Statistical analysis of some multi-category large margin classification methods. *Journal of Machine Learning Research* 5 (2004), 1225–1251.

Yingqi Zhao, Donglin Zeng, A. John Rush, and Michael R. Kosorok. 2012. Estimating Individualized Treatment Rules Using Outcome Weighted Learning. *J. Amer. Statist. Assoc.* 107 (2012), 1106–1118. Issue 499.

Ying-qi Zhao, Eric B Laber, and Bruce E Sands. 2019. Efficient augmentation and relaxation learning for individualized treatment rules using observational data. *Journal of Machine Learning Research* 20 (2019), 1–23.

Hui Zou, Ji Zhu, and Trevor Hastie. 2008. New multiclassification boosting algorithms based on multiclassification fisher-consistent losses. *Annals of Applied Statistics* 2, 4 (2008), 1290–1306. https://doi.org/10.1214/08-AOAS198
A Theoretical Results for Direct Policy Learning

In this section we provide a self-contained proof of the consistency of our chosen loss function, which is known as the multinomial deviance loss \cite{Huang2019} in the literature on multi-category cost-sensitive classification with convex surrogates. First, we note the following fact.

**Proposition 2.** The function $E_{r|x}\tilde{L}(f, x, r)$ is convex in $f$ for non-negative rewards $r$

**Proof.** The expectation $E_{r|x}$ preserves convexity, so we just need to confirm that $\tilde{L}(f, x, r)$ is convex in $f$, which we can do so by rewriting as

$$\tilde{L}(f, x, r) = \sum_{a \in A} r(a) \left( \log \sum_{a'} \exp f_{a'}(x) \right) - f_a(x) \quad (8)$$

The inner term is a convex function of $f$ because it is a non-negative sum of convex functions of $f$, namely log-sum-exp and $-f$. The outer sum is a non-negative sum, since the rewards are specified to be non-negative, which preserves convexity.

**Proposition 3.** For non-negative rewards $r$, and for an $f^*$ that satisfies $f^* = \inf_f E_{x,r}\tilde{L}(f, x, r)$, the corresponding policy $\pi^*(x) = \arg \max_a f_a^*(x)$ is equivalent to the Bayes-optimal policy $\pi^*(x) = \arg \max_a E[r(a)|X]$

**Proof.** First, we can write this as

$$\inf_f E_{x,r}\tilde{L}(f, x, r) = E_x \inf_f E_{r|x}\tilde{L}(f, x, r)$$

Because $E_{r|x}\tilde{L}(f, x, r)$ is convex in $f$ (see Proposition 2), we just need to find a critical point where $\frac{\partial}{\partial f_a^*} E_{r|x}\tilde{L}(f, x, r) = 0$, $\forall a^* \in A$. We can see that

$$\frac{\partial}{\partial f_a^*} E_{r|x}\tilde{L}(f, x, r)$$

$$= -\frac{\partial}{\partial f_a^*} \sum_{a \in A} E[r(a)|X] \log \sum_{a'} \exp f_{a'}(x)$$

$$= -\frac{\partial}{\partial f_a^*} E[r(a^*)|X] \log \sum_{a'} \exp f_{a'}(x)$$

$$- \frac{\partial}{\partial f_a^*} \sum_{a \neq a^*} E[r(a)|X] \log \sum_{a'} \exp f_{a'}(x)$$

$$= -E[r(a^*)|X] \left[ 1 - \frac{\exp f_{a^*}}{\sum \exp f_{a'}} \right] + \sum_{a \neq a^*} E[r(a)|X] \sum_{a'} \exp f_{a'}$$

$$= -E[r(a^*)|X] + \frac{\exp f_{a^*}(x)}{\sum_{a'} \exp f_{a'}(x)} \sum_a E[r(a)|X] = 0$$

$$\implies \frac{E[r(a^*)|X]}{\sum_a E[r(a)|X]} = \frac{\exp f_{a^*}(x)}{\sum_{a'} \exp f_{a'}(x)}$$

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From this, we can see that

$$\arg \max_{a \in \mathcal{A}} \mathbb{E}[r(a)|X] = \arg \max_{a \in \mathcal{A}} \frac{\mathbb{E}[r(a)|X]}{\sum_{a'} \exp f_{a'} \sum_{a'} \exp f_{a'}}$$

$$= \arg \max_{a \in \mathcal{A}} \log \left( \frac{\exp f_a}{\sum_{a'} \exp f_{a'}} \right)$$

$$= \pi^*(x)$$

Completing the proof that at optimality, the optimal

$$f^* = \arg \inf_{f(x)} \mathbb{E}_{r|x} \tilde{L}(f, x, r)$$

yields a calibrated decision rule $\pi^*(x)$ ∎

We make two minor remarks: First, as a practical matter, we drop the usual constraint (used to ensure uniqueness) that $\sum_a f_a(x) = 0$, as we impose $\ell_2$ regularization on the weights of our $f_a(x) = \theta_a^T x$ functions in our experiments. Second, this formulation requires that the reward vector $r$ is non-negative, but this can be relaxed in a straightforward way by replacing $r(a)$ with $\max_{a'} r(a') - r(a)$ in the below. We tried this latter formulation in our experiments and it did not have a significant impact on results.

## B Dataset

### B.1 Feature Details

In this section, we provide additional details about the construction of a few features used in the models.

**Lab Values.** For a given lab test and backward window, the corresponding feature value is the mean result of all results for that lab value within the specified time window. The dataset contains lab results for white blood counts (WBC), absolute neutrophil counts (ANC), absolute lymphocyte counts (ALC), and CD4/CD8 counts.

**Colonization pressure.** Colonization pressure is defined as the proportion of resistant specimens to a given antibiotic across a specified location and time window. We calculate the colonization pressure for 25 different antibiotics in the window from 7 days prior to 90 days prior to the specimen collection date among all patients with UTIs. We calculate colonization pressure values at 3 different location hierarchies: (1) the ward/clinic of specimen collection, (2) the hospital of collection, and (3) across the entire dataset.

## C Experiments

This section contains details about the experiments conducted in this paper. Code will be made available in the future, and more specific information (e.g., exact hyperparameter settings used for tuning) can be found there.
C.1 Thresholding

We use sklearn’s logistic regression implementation to train models for predicting resistance to each of the four antibiotic treatments. Hyperparameters are tuned using validation on the cohort of patients from 2012-13.

Our threshold search space is defined implicitly by a fixed set of 9 false negative rates as follows: for each FNR value and antibiotic, the corresponding probability threshold is the one that achieves that FNR rate among the training set resistance predictions for that drug. Since there is a strong correlation between resistance to CIP and LVX, we constrain $T$ to combinations where thresholds for CIP and LVX are the same. Our threshold space $T$ consists of $9^3 = 729$ possible combinations.

When a threshold combination results in predictions of resistance for all antibiotic treatments, the policy falls back on a default 1st-line antibiotic. We chose to always default to recommending NIT, as it has a significantly lower overall resistance rate than SXT in the training set.

In Figure 1, we show the results of optimal policies $\pi_j$ for budget constraint values $b_j$ in $[0.01, 0.05]$ (in increments of 0.01) and $(0.05, 1.0]$ (in increments of 0.05).

C.2 Expected Reward Maximization

We follow the same procedure for training logistic regression models as described for the thresholding approach. The indirect learning policy frontier in Figure 1 contains the performance of models learned using values of $\omega$ in the range $[0.85, 1]$ (in increments of 0.005).

C.3 Direct Learning

Models are trained using an Adam optimizer with a learning rate of $10^{-4}$ and L2 regularization with penalty $10^{-3}$, and are trained for 15 epochs. Models were implemented in PyTorch. The policy frontier in Figure 1 contains the performance of models learned using values of $\omega$ in the range $[0.85, 1]$ at increments of 0.005. We plot the mean IAT and 2nd line usage outcomes for each setting of $\omega$ from policy learning across 30 trials.

The direct learning model with the deferral action was trained using the same learning rate and regularization hyperparameters. The values for $\lambda_{\text{defer}}$ were selected from the range $[0, 0.05]$ (in increments of 0.0025). Mean deferral rates and IAT / 2nd line usage rates shown in Figure 2 were calculated over 30 trials for each setting of $\lambda_{\text{defer}}$.

C.4 Synthetic Experiments

Our synthetic environment consists of a 10-dimensional feature space and an action space $A$ with 3 actions. Each feature value is drawn i.i.d. from a standard normal distribution. The feature coefficient values (i.e, $\alpha_i, \beta_i$) are selected manually to ensure that the mean outcomes for each action in the dataset are roughly 0.5. All these coefficients have magnitude larger than 1, to ensure that learning approximations to these values is necessary for learning a good predictive model.

In the indirect approach, we train logistic regression models to predict treatment outcomes for each action. We use the saga solver in sklearn’s logistic regression implementation to train models. Hyperparameters - L1 vs. L2 regularization and regularization...
strength - are tuned using 10-fold cross validation on the training set. Models are trained for a maximum of 100 iterations.

In the direct approach, the convex surrogate loss is optimized using SGD with a learning rate of 0.1 and L2 regularization with $\lambda = 0.001$. Models are trained for 50 epochs. This model was implemented using PyTorch.

Figure 3 shows the outcomes of indirect and direct policy learning using training sets of various sizes on a fixed test set of $10^6$ samples drawn from the specified generative model. We only evaluate outcomes on samples where there was at least one ineffective and one effective treatment (i.e., not all 0 or 1 outcomes), as these are the only examples where the policy’s decision can affect the outcome. We train both indirect and direct approaches on the same 10 randomly drawn training sets for each sample size, and plot the mean outcome and standard deviations for each setting across these samples in Figure 3.