Teaching deep learning causal effects improves predictive performance

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Abstract
Causal inference is a powerful statistical methodology for explanatory analysis and individualized treatment effect (ITE) estimation, a prominent causal inference task that has become a fundamental research problem. ITE estimation, when performed naively, tends to produce biased estimates. To obtain unbiased estimates, counterfactual information is needed, which is not directly observable from data. Based on mature domain knowledge, reliable traditional methods to estimate ITE exist. In recent years, neural networks have been widely used in clinical studies. Specifically, recurrent neural networks (RNN) have been applied to temporal Electronic Health Records (EHR) data analysis. However, RNNs are not guaranteed to automatically discover causal knowledge, correctly estimate counterfactual information, and thus correctly estimate the ITE. This lack of correct ITE estimates can hinder the performance of the model. In this work we study whether RNNs can be guided to correctly incorporate ITE-related knowledge and whether this improves predictive performance. Specifically, we first describe a Causal-Temporal Structure for temporal EHR data; then based on this structure, we estimate sequential ITE along the timeline, using sequential Propensity Score Matching (PSM); and finally, we propose a knowledge-guided neural network methodology to incorporate estimated ITE. We demonstrate on real-world and synthetic data (where the actual ITEs are known) that the proposed methodology can significantly improve the prediction performance of RNN.

1 Introduction
In recent years, deep learning methods have been widely used in clinical studies to solve complex health care research problems [19, 20]. Their power lies in their ability to extract underlying complex non-linear relationships from a large number of variables in observation data. As a class of ANN, the recurrent neural network (RNN), enables the modeling of temporal dynamic behavior from longitudinal Electronic Health Records (EHR) data [5, 7]. Due to this feature, RNN has also been utilized to discover causality from time-series data [4, 28].

The task of estimating the effect size of a casual relationship is referred to as causal inference [11], which has gained an essential role for explainable decision making and other important applications in clinical studies [9, 29]. Confounders, factors that have a causal relationship with both an intervention and an outcome, tend to make the estimation of treatment effects more difficult, introducing biases into the estimates. Classical statistical methods and modern neural network based methods [24, 26, 27] have been proposed to overcome this challenge.

The need to develop deconfounding solutions to NNs indicates that they lack the ability to automatically extract causal knowledge, especially for individualized treatment effects (ITE). The absence of correct ITE estimates for many interventions can adversely affect the model’s ability to estimate outcomes. In this paper, we first describe a Causal-Temporal Structure, which is a common pattern in time-series EHR data. Then, based on this structure, we introduce the sequential estimation of ITE along the timeline, utilizing the powerful statistical tool Propensity Score Matching (PSM); Finally, we propose an RNN-based knowledge-guided methodology, to help RNN better utilize the estimated ITE to improve the performance of diagnosis prediction.

All experiments are evaluated on real-world EHR data as a clinical application, and also on synthetic EHR data to simulate ideal performance. The real EHR dataset contains information on patients with type-II diabetes mellitus (T2DM) and its complications. Diabetes is a complex chronic disease with clinically significant micro- and macrovascular complications affecting 80 million Americans [16]. Prevention and management of T2DM requires multi-factorial risk reduction strategies [17] hence identifying patients at high risk of T2DM and its complications is of high importance. From a technical perspective, T2DM is heterogeneous, its manifestation, including the effect of intervention strategies, can differ from patient to patient [18]; risk factors are causally or associatively intertwined; and the disease progresses gradually over a long period of time [13].

Our contributions can be summarized as follows:

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1. We described a **Causal-Temporal Structure** for the EHR data, and proposed a method to simulate synthetic EHR data with this structure.

2. We proposed the **Knowledge-Guided RNN** methodology which leverages the domain knowledge of treatment effect to improve predictive performance.

3. Our work has confirmed the hypothesis is valid that regular RNN architecture cannot fully discover the casual effect information by its nature.

## 2 Related Work

The gold standard approach to estimate treatment effect sizes is to run a Randomized Controlled Trial (RCT) [12], where the treatment is randomly assigned to subjects and does not depend on the covariates. This provides an unbiased estimate of the treatment effect because it isolates the effect of the treatment from the effect of the covariates. RCTs are costly, can be unethical (treatments that are known to work cannot be withheld from patients) or even infeasible (there can be combinatorially many treatment options). Estimating treatment effect from observational data provides an alternative but it can lead to confounding bias between treatment and covariates. To reduce this bias, the data is transformed, de-confounded, so that the treatment becomes independent of the covariates. Classical de-confounding methods include matching methods [8], propensity score based methods [14], and confounder balancing techniques [15].

While the above classical methods aim to provide a cohort-level estimate of the treatment effect size, more recent work focuses on individual-level treatment effects [1]. The estimation of individualized treatment effects (ITE) from observational data has been a fundamental research problem in various applications including precision medicine [10], understanding the heterogeneous effects of drugs [2], and verifying causes of certain diseases [3].

The key challenge of ITE estimation is that it requires an individual’s potential outcomes, which have to be learned from the biased data and without access to the counterfactuals. A wide variety of statistical methodologies have been utilized to solve this problem, for instance, propensity score matching based methods [23], k-nearest neighbor methods [2, 9], and tree-based modeling methods [25].

ITE estimation methods based on neural networks has also been proposed. Alaa et al. (2017) applied both the multi-task model and neural network method [26, 27] to account for the counterfactual outcomes. Yoon et al. (2018) utilized Generative Adversarial Nets (GAN) to estimate ITE [24].

RNNs has also been applied to estimate ITE and their applications can be divided into two categories. First, RNN architecture is directly used to perform disease prediction, especially for chronic diseases [5, 7]. Second, RNN is utilized to capture desired features or extract data representations [6]. It remains unclear whether RNNs actually learn ITEs correctly and whether the correct ITEs can improve predictive performance. In this work, differently from the previous works, we aim to verify providing the correct ITE can improve RNN, and also study how the correct ITE can be incorporated into the RNNs to maximize the predictive performance gain.

## 3 Methodology

In this section, we propose a knowledge-guided RNN for modeling temporal EHR data with underling causality. The implementation of this method has two steps: 1) obtain the sequential individualized treatment effects (ITE) under the guidance of domain knowledge, and 2) improve the RNN performance by leveraging the domain knowledge of ITE.

We will start this section with the basic problem setting description (subsection 3.1), where the concept of Causal-Temporal Structure will be established; secondly introduce the definition of sequential ITE estimator $\Delta$ (subsection 3.2); then present the propensity score matching (PSM) technique (subsection 3.3); finally describe the proposed Knowledge-guided RNN methodology (subsection 3.4).

### 3.1 Problem Setting.

In this paper, we define the medical treatment combination $M^t$ as a vector of binary random variables, $M^t = (M^t_1, M^t_2, \ldots, M^t_m)$, $M^t_i \in \{0, 1\}, i \in [1, m], t \in \tau$, where each binary variable $M^t_i$ indicates a specific treatment. 1 means the patient was treated and 0 means not treated in time window $t$. The set $\tau$ consists of all observable time windows, $\tau = \{[t_0, t_1], [t_1, t_2], \ldots\}$, and $m$ indicates the number of treatment. $X^t = (X^t_1, X^t_2, \ldots, X^t_d)$ is the vector of predictors (e.g. lab results) observed in time window $t$, where $d$ is the dimension of $X^t$. Any outcome $Y$ (e.g. a specific diagnosis code) must happen in one of the subsequent time windows after $t$.

Figure 1 describes the casual structure along the timeline. In temporal data, predictors in a subsequent window $X^{t+1}$ depend on the predictors in the previous time window $X^t$ and the assignment of treatment $M^t$, which, in turn, also depends on $X^t$, leading to confounding bias when estimating the effect of the treatment on $X^{t+1}$ and ultimately on the outcome $Y$. To obtain an unbiased estimate of $Y$, it can be
beneficial to know the unbiased effect of $M^i$ on $X^{t+1}$ for all patients and all time windows $t$. This is the individualized treatment effect that we discuss in the next section.

3.2 Individualized Treatment Effect. Given a combination of medications $M = (M_1, M_2, \ldots, M_i = 0, \ldots, M_m)$ in time window $t$, the individualized treatment efficacy (ITE) is defined as the effect of adding $M_i$ on the outcome $Y$. The $M_i$ is added in $t$, while ITE is estimated in time window $t'(t' > t)$. $Y$ could be a specific diagnosis, any $X_j \in X$ (e.g., a future lab result value), or even another medicine use in future. In this paper we define ITE as a vector, quantifying the ITE of the medication on each element of the $X$ predictor vector.

ITE is difficult to estimate because of the complex confounding relationships along the timeline. Suppose we want the effect of $M_i$ on $X_j$ in $t + 1$, there exist four possible effects: the causal effect 1) of $X_j^i$ on $M_i'$, 2) of $X_j^i$ on $X_j^{t+1}$, 3) of $M_i'$ on $X_j^{t+1}$, 4) influence (may not causal) from another variable $X_k^i$ to $X_j^{t+1}$. ITE is the third effect but we cannot simply isolate it.

To isolate the ITE, we adapt the traditional propensity matching (PSM) methodology to create a de-confounded pseudo-population. This population consists of pairs of patients, one treated with the new medication and one not treated; and apart from treatment, the patients within each pair are comparable. The matched untreated patients provide estimates of the counterfactual lab results relevant to the outcomes in the next time window. In each subsequent time window $t'$, the effect of treatment on the relevant lab results is computed, which is specific to the individual treated patient and each lab result, and varies over time.

Definition 1. The patient group defined by $M$ consists of patients having treatment $M$ in any specific time window individually. If $M_1$ and $M_2$ define a pair of Comparable Patient Groups, treated and untreated group respectively, then there exists a specific digit subset $M_{add} = \{M_1', \ldots, M_m'\}$ that $M_i' = 1$ in $M_1$ and $M_i' = 0$ in $M_2$ for each $M_i' \in M_{add}$. $M_{add}$ indicates the newly-added treatment combination, $M_{add} \subseteq \{M_1, \ldots, M_m\}$, and $n \leq m$.

Definition 2. Let patient $P_1$ have treatment $M_1$ in time window $t_1$, with predictor vector value $X_{P_1}^{t_1}$, then $P_2$ is $P_1$’s Best Matched Patient on $t_1$, if and only if $P_2$ has treatment $M_2$ (comparable to $M_1$) in time window $t_2$, and $P(P_2 \in M_1|X_{P_2}^{t_2})$ has the smallest difference to $P(P_1 \in M_1|X_{P_1}^{t_1})$ among all patients from group $M_2$.

Definition 3. By definition 2, in time window $t_1 + 1$, $P_1$ has Individualized Treatment Effect (ITE) defined as $\Delta_{P_1}^{t_1+1} = L_{P_1}^{t_1+1} - L_{P_2}^{t_1+1}$, where $L \subseteq X$, denotes the subset of variables relevant to the outcomes.

Let $M_1$ and $M_2$ be a pair of comparable patient groups, treated and untreated respectively. Propensity matching is to create a pseudo-population, in which pairs of treated ($P_1 \in M_1$) and untreated ($P_2 \in M_2$) patients have the same $X'$ so that observed differences on $X^{t+1}$ between $P_1$ and $P_2$ are due to the newly-added medicine(s) $M_{add}$ and nothing else.

For convenience, we introduce a new variable: the binary indicator $Z$ for being treated ($Z = 1$) or untreated ($Z = 0$) by $M_{add}$. Our goal is to create a pseudo-population in which $X \perp \perp Z$.

Specifically, we train a logistic regression model for $P(Z|X)$ from the union population defined by $M_1 \cup M_2$. Then for $P_1 \in M_1$, we select the best matched patient $P_2 \in M_2$, such that the difference between $P(Z|X_{P_1})$ and $P(Z|X_{P_2})$ is within a small caliber $\epsilon$, and $X_{P_2}$ has the smallest difference over all candidates from the untreated group $M_2$. Then the counterfactual $X^{t+1}$ for $P_1$ is $X_{P_2}^{t+1}$.

All available pairs of $P_1$ and $P_2$ compose the desired pseudo-population, which is ready to perform unbiased modeling on it.

Theoretically, $(M_1, M_2)$ pairs could be numerous. However, in reality, the possibly newly-added treatment combination $M_{add}$ is limited, instead of in a exponentially large number.

3.3 Knowledge-guided Recurrent Neural Networks. Given that $\Delta$ encodes the general effect of each newly-added treatment combination, for each patient, and on each corresponding lab result (or vital sign), such extracted knowledge can be used to improve the prediction of outcomes for any patients. In the following, we will discuss two ways of incorporating $\Delta$ into a predictive RNN architecture (Figure 2).

Data Augmentation Method: We simply make the ITE information available by adding the $\Delta$ vectors as new predictors. Specifically,
Causal-Temporal
Raw Data
Processing based 
on Domain 
Knowledge
Sequential ITE 
Estimator ∆ 
RNN ... window. However, since the cohorts
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for each patient $P$ in each time window $t$ with new medicine(s) added, we couple $X$ with the corresponding $\Delta$ vector, i.e., the augmented data $X_p^t = [X_p^t, \Delta_p^t]$. In $t$ without new medicine added, $\Delta_p^t = 0$. Then we use such augmented data as input to RNN model.

Unsupervised Pre-training Method:

An alternative approach is to use estimated ITE information to guide the learning process of the RNN model. The idea is that we can use $\Delta \sim X$ to inform the initialization of the RNN model such that RNN can learn the medical knowledge directing from $X$ to $\Delta$.

In particular, we pre-train the RNN such that the model predicts $\Delta_p^t$ from $X_p^t$ at every time window $t$ for each patient $P$. One advantage of this approach is that the computation of $\Delta_p^t$ does not require any true disease labels. Hence, we can conduct pre-training using unlabeled data as well. Figure 3 shows the RNN structure of the unsupervised pre-training method, using LSTM cells, and marks the training error flows of the pre-training and fine-tuning processes.

Figure 2: Knowledge-guided RNN methods that leverage the additional ITE information $\Delta$ through (a) data augmentation and (b) unsupervised pre-training.

Figure 3: The pretraining LSTM structure. $c^t$ is the cell state and $h$ is the cell output.

4 Data Sets

We prepared two datasets for our experiments: 1) a real-world EHR dataset of type-II diabetes patients; and 2) a synthetic EHR dataset that contains underlying temporal-causal structure. Because in real data the true effect of medicines is unknown, the synthetic dataset is necessary to illustrate the performance of our method.

In this section, we will describe the real data, then introduce the generation method of the synthetic data.

4.1 Real Diabetes Dataset. Mayo Clinic (MC) provides primary care to residents of Olmsted County, Minnesota, and it has an integrated electronic health record system including diagnoses, medications, laboratory results and clinical notes.

We used a retrospective cohort of de-identified data from 73,045 primary care patients at Mayo Clinic, Rochester, MN with research consent. The cohort consists of patients aged $\geq 18$ and $\leq 89$ at baseline on Jan. 1st, 2005, having at least one visit before and after baseline. These patients were followed until 2017 (median follow-up time is 10 years). We extracted patient demographics, and diagnoses (ICD-9), laboratory results, vital signs, and medications longitudinally for six non-overlapping time windows: before-2004, 2005-2006, 2007-2008, 2009-2010, 2011-2012, 2013-after. For the outcomes happened in time window t, we make predictions based on observations from previous time windows t-1, t-2, ..., In each time window, the latest observed values are taken for the predictors. A more detailed description is provided in the Supplements.

4.1.1 Learning Tasks. We design two leaning tasks for the real diabetes data:

1. Disease diagnosis prediction tasks.

We aim to predict whether a patient develops diabetes (T2DM) and three complications (CAD, CKD, Stroke) in the subsequent time window using predictors from the immediately preceding time window (2011-2012): the preceding two time windows (2009-2010 and 2011-2012); ...; or the previous four time windows (2003-2004,...,2011-2012).

2. Future lab results forecast tasks.

We aim to forecast the values of several critical lab results in the immediately subsequent time window using one, two, ..., four previous time windows consistently with the 1st task. Due to the space constraint, the results for this task are presented only in the Supplements.

4.1.2 Predictors. Predictor variables include patient demographics (age, gender, race), vital signs (BMI, SBP and DBP), and lab results (LDL, HDL, triglycerides, creatinine, GFR, and fasting plasma glucose, i.e. FPG).

These data yield dataset with six different time windows, and each contains the latest measurements in the corresponding time window. However, since the cohorts
may be randomly unobserved in the real EHR data from MC, we define the time window without any observed available measurement, medicine record, or diagnosis code as an unobserved time window for a patient, and simply conduct cohort mean value imputation on the missing vital signs and laboratory results.

4.1.3 Outcomes. The outcomes of the disease prediction tasks includes T2DM, coronary artery disease (CAD), kidney disease (CKD), and stroke, defined jointly by ICD-9 diagnoses codes and clinical criterion. For example, T2DM is defined by the first appearance of the ICD-9 diagnosis code or a fasting glucose measurement in excess of 125 mg/dl.

The outcomes of the value forecasting tasks includes the values of low-density lipoprotein (LDL), triglycerides (TG), and systolic blood pressure (SBP).

4.1.4 Medication Combination. We adopted three medication classes: T2DM drugs, Hyperlipidemia (HL) drugs, and Hypertension (HTN) drugs. In each class, medications are rolled up to National Drug File Reference Terminology NDF-RT pharmaceutical subclasses and are encoded for analysis as indicator variables with five increasing treatment intensity levels. Higher levels suggest higher severity of the disease. Details of the five treatment levels are included in the Supplements. For each class, the indicator vector \( M \) is defined as binary vector with length equal to the number of treatment levels, and 1 digit per level.

4.2 Synthetic EHR Dataset. To synthesize data that follows a known underlying causal-temporal structure, we first generate a causal structure, and then simulate a large number of patients temporally through following the causal structure.

Figure 4 depicts an example of a causal structure with two diseases. The structure involves 5 types of variables: 1) Latent disease severity, depicted in rectangles, variables encapsulate all information about the severity of each disease as it relates to other diseases. Over time, disease severity progresses on its own and is also influenced by the severity other diseases (their causal parents). They are not explicitly observable from the data set. 2) Lab results are influenced by latent severity. 3) Medicine prescription, triggered by lab results, may include multiple lines (corresponding to the treatment levels). Each level leads to a different and time-varying degree of severity reduction in subsequent time windows. 4) Diagnosis codes (Dx), determined by the observed values of lab results. 5) Designated outcomes are labelled by \( Y \). They do not have labs and medications, so we simply model the diagnosis of \( Y \) directly. They are jointly caused by multiple diseases (their causal parents).

![Figure 4: Example of causal structure generation.](image)

| Notation | Description |
|----------|-------------|
| \( F(s) \) | a pre-defined natural progression of \( s \) over time. Depends on \( s \) in the preceding time window |
| \( P(s,t) \) | is the severities of the parents of the disease \( s \) at time \( t \) |
| \( M \) | medication binary indicator vector in time window \( t \) |
| \( S \) | vector of latent disease severity in time window \( t \) |
| \( L \) | set of all lab results |
| \( D \) | vector of disease diagnosis at \( t \) |
| \( C(L) \) | pre-defined disease diagnostic criterion function based on \( L \) |

The medication effect \( E \) is designed as the product of two variables: \( E = E^p \times E^f \), where \( E^p \) denotes a population level effect (which is common across all patients) and \( E^f \) denotes an individual level multiplicative effect.

Figure 5 displays a virtual patient’s simulated values of one lab results. The x-axis represents the timeline, and y-axis represents the lab value. The blue line corresponds to lab value trajectory in the absence of either diseases or medications, the red line to the lab value in the absence of medications, and the green line corresponds to the lab values after treatment. Note that
in the resulting dataset, only the "treated values", i.e. the green colored trajectory, is observable.

In Figure 5, the patient has ever taken two medicine treatments. After the first line medication gradually failed, his lab result exceeded the disease criterion by more than 10% and triggered the second line treatment.

Our synthetic data spans 30 years, with two time windows per year, which implies that the patients has an encounter every half a year, resulting in at most 60 measurements along the timeline. Based on the real EHR data, we set the observation rate to 50%, which implies that only half of the lab results observed (depicted as filled markers in Figure 5) and the rest are missing data.

5 Experiment

5.1 Experimental Design. For the real diabetes data, we conduct two types of learning tasks: 1) disease diagnosis prediction on four outcomes (T2DM, CAD, CKD, and stroke), and 2) the next-time-window lab results forecast on three labs or vitals (LDL, Trig, and SBP). For the synthetic data experiments, we focus on the disease diagnosis prediction task, by randomly choosing four diagnosis codes as the predicted outcomes.

In disease prediction tasks, the patients who have been confirmed the target diagnosis in any previous time window have become meaningless to the modeling, since \( P(Y = 1) = 1 \) for them, thus removed from the cohort.

In each learning task, we implement four models, including Generalized linear model (GLM for binary label prediction, LM for regression), Generalized linear mixed effect model (GLMER for binary label prediction, LMER for regression), de-identified patient index used as the random-effect vector), RNN with Long Short Term Memory (LSTM), RNN with Gated Recurrent Unit (GRU).

Both LSTM and GRU are widely-used networks, with different structure inside the RNN unit. However, both of them are designed to capture the effect of long-term dependencies and have comparable performance [21] [22].

We implement each of the four models in up to three ways for comparison:

1. The baseline method, without any ITE information input, denoted as "No ∆".
2. The data augmentation method, where ∆ is concatenated with existing predictors and input into the model learning, denoted as "∆ Augment".
3. The unsupervised pre-training RNN method, denoted as "∆ PreTrain". In this method, we firstly use ∆ to pre-train the RNN, to let the RNN pre-learn the causal effect information, and then fine-tune the pre-trained model with the original predictors and outcomes.

Since the unsupervised pre-training method is only applicable on neural networks, the GLM and GLMER models do not have the corresponding implementation.

In synthetic data experiments, for brevity, we skip the "∆ Augment" method for LSTM and GRU models, and only compare "No ∆" and "∆ PreTrain".

5.2 Parameter Setting. The observable time span for predictors is an important parameter and strongly impact the results. Ideally, if we assume the desired model is capable of handling as many variables as possible, then the longer observable time span would achieve better performance, since more information is included.

In our experiments, we refer the predictors’ observable time span as the number of successive time windows, immediately preceding the current time window, and name it as "Time Step". For example, "Time Step=3" means the predictors (and also ∆) are only observable in \([t-3, t-2, t-1]\) time windows, where \(t\) is the current time window.

For real diabetes EHR data, each time window lasts two years, and the outcomes are obtained from the next time window \(t+1\). We perform all experiments with different setting of Time Step=1,2,3,4 respectively, and compare their performances in subsection 5.3.

For our synthetic data, each time window lasts half a year. Since we have long enough time-series, we can realize further future prediction, and based on larger Time Steps, which is more clinically meaningful than just 1-Time-Step and next-time-window prediction. Here we select the outcomes from the future time window \(t+5\), and three different setting of Time Step=10, 20, 30 (i.e. 5, 10, 15 years) respectively for the experiments.

5.3 Experimental Results.
5.3.1 Results on Real Diabetes EHR Dataset. Table 2 provides the performance of all methods on disease diagnosis prediction task using the real-world diabetes dataset. Each row in the tables represents an individual experiment. The column names indicate the applied methods, and the row names show their predicted labels and different setting of Time Step. The best performing method in each row is typeset in bold font.

We also include similar results for the forecasting of lab or vital outcome in the supplementary file.

We can find that for both tasks, our proposed pre-training RNN method achieved the highest performance in most of the experiments. Specifically, the proposed knowledge-guided learning framework, especially through pre-training, achieved the highest performance in 12 out of 16 disease prediction experiments, and 10 out of 12 lab or vitals forecast experiments.

Looking back additional time windows for predictors (i.e. increasing "time steps") can improve performance. Knowledge-guided learning improves performance regardless of the number of windows, but its impact is higher when the number of windows is lower.

The RNN methods, LSTM in particular, achieved higher performance than the linear models. Also, Δ Augmentation helped the RNN’s more than it helped the linear models.

To more intuitively compare the performance differences, we select one diagnosis outcome (CAD) from Table 2 and depicted the results in a bar-plot in Fig. 6. CAD is a common and important complication of diabetes [30] and among the four diagnoses, it has the largest cohort in our experiments.

5.3.2 Results on the Synthetic EHR Dataset. To generate the synthetic data, we created 10000 patients who can develop at most 10 diseases (Comorbidities 1-10) in 30 years of observation period (60 time windows). Progression of these diseases are measured through 20 lab results, and appropriate medical intervention (of at most 3 lines of medications) is available for each disease. We record lab results, medication prescriptions, and confirmed diagnosis along the timeline, with observation rate = 50%.

For brevity, in synthetic EHR data experiments, we only focus on diagnosis prediction tasks, which is one of the most common applications in EHR data analysis. From the 10 synthetic diseases, we select four late complications, Comorbidities 6, 7, 8, and 9, to display their prediction results in Table 3. Late complication means that the disease only appears in the later half of disease progression. This can allow the causal effects enough time to develop and become significant before the diagnosis is confirmed. We select three different time spans for our synthetic data experiments: Time Step = 10, 20, 30.

![Figure 6: Comparison of CAD prediction performance.](image-url)

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Table 3: Diagnosis Prediction Performance with metric AUC on Synthetic Dataset

| Models   | No $\Delta$ | $\Delta$ Augment | No $\Delta$ | $\Delta$ Augment | No $\Delta$ | $\Delta$ PreTrain | No $\Delta$ | $\Delta$ PreTrain |
|----------|--------------|------------------|--------------|------------------|--------------|-------------------|--------------|-------------------|
|          | GLM          | GLMER            | LSTM         | GRU              | GLM          | GLMER            | LSTM         | GRU              |
| Combd 6  | 0.91138      | 0.92941          | 0.68797      | 0.75994          | 0.98395      | 0.98545          | 0.96650      | 0.97880          |
|          | 0.91324      | 0.92390          | 0.66391      | 0.70550          | 0.99015      | 0.99570          | 0.97640      | 0.98630          |
|          | 0.95273      | 0.95554          | 0.81302      | 0.82381          | 0.99840      | 0.99875          | 0.98870      | 0.99445          |
|          | 0.98395      | 0.98545          | 0.96650      | 0.97880          | 0.96650      | 0.97880          | 0.98870      | 0.99445          |
| Combd 7  | 0.84446      | 0.87259          | 0.66149      | 0.73021          | 0.84795      | 0.87725          | 0.78965      | 0.81145          |
|          | 0.85104      | 0.85542          | 0.58536      | 0.58728          | 0.89330      | 0.94470          | 0.78915      | 0.84680          |
|          | 0.88227      | 0.89797          | 0.61338      | 0.66133          | 0.94970      | 0.95600          | 0.87605      | 0.91930          |
|          | 0.99015      | 0.99570          | 0.97640      | 0.98630          | 0.99015      | 0.99570          | 0.97640      | 0.98630          |
| Combd 8  | 0.85358      | 0.86569          | 0.67232      | 0.71296          | 0.86990      | 0.87744          | 0.78965      | 0.81145          |
|          | 0.87519      | 0.89450          | 0.63996      | 0.70550          | 0.86500      | 0.93340          | 0.85530      | 0.89080          |
|          | 0.89544      | 0.91052          | 0.66501      | 0.72428          | 0.95685      | 0.96450          | 0.92545      | 0.95355          |
|          | 0.95273      | 0.95554          | 0.96650      | 0.97880          | 0.96650      | 0.97880          | 0.98870      | 0.99445          |
| Combd 9  | 0.78437      | 0.79333          | 0.57728      | 0.58417          | 0.80735      | 0.81180          | 0.71890      | 0.76485          |
|          | 0.84665      | 0.86128          | 0.63290      | 0.66652          | 0.81385      | 0.88090          | 0.78850      | 0.81720          |
|          | 0.85759      | 0.88476          | 0.59581      | 0.66309          | 0.87440      | 0.91675          | 0.83420      | 0.88400          |

All experiments were ran 3 times, and the displayed results are the averaged values from all 3 runs. In each run, the same synthetic dataset was randomly re-shuffled into training and test samples.

First, we select Comorbidity 9, the complication that develops last, and display its prediction performances (y axis) as a function of the number of Time Step (x-axis) in Figure 7. Since this disease develops last, we have to longest time to accumulate biases from estimating the effects of medications incorrectly, thus $\Delta$ can be the most impactful. Figure 7 shows that providing $\Delta$ significantly improved the performance of all models with any Time Step.

Table 3 shows the complete results for the remaining diseases. The layout of the table is identical to that of Table 2. Observations from the synthetic data experiments closely mirror those from the real EHR data: (i) the knowledge-guided methods achieved higher performance than “no $\Delta$” methods; (ii) looking back further in time improved performance; and (iii) RNN-LSTM method achieved the highest performance among all models.

Figure 7: Comorbidity 9 prediction performance.

The disadvantage of using real EHR data is that we do not always know whether a newly-added medicine is significantly beneficial based on the existing medication combination, which makes it comparatively harder to evaluate significance of $\Delta$ variables in models. If a $\Delta$ is not significant, it can be because the corresponding drug is not effective for the outcome in the particular combination. However, in synthetic data we designed medications as mostly beneficial, thus we can expect the $\Delta$ variables to be statistically significant in a linear model.

In Figure 8, we collect all p-values of the $\Delta$ variables from GLM and GLMER models in all synthetic data experiments, and display their distribution for different Time Step as a box plot. For GLM, the $\Delta$ variables were mostly significant; however, for the GLMER model they were not. Since the individualized treatment effect, specifically its $E^I$ portion, is a patient-specific (and also drug-specific) random effect, GLMER likely confused $\Delta$ with the random intercept. This is also the likely explanation of why the GLMER models performed much worse than GLM models in our experiments.

Figure 8: P-value Distribution of $\Delta$ in linear models.
6 Conclusion

Based on the comprehensive experiments, we have the following observations: 1) Proper use of the proposed sequential individualized treatment effects (ITE) estimator \( \Delta \) can significantly improve the performance of the prediction models for both tasks for both model families: linear regression models, and well-defined RNN models. 2) We demonstrated that the knowledge-guided methodology, both the augmentation and especially the pre-training methods, is a proper way to utilize \( \Delta \) information for RNN models. 3) Since the addition of \( \Delta \) can improve RNN’s performance, we have verified our hypothesis that the ITE information can not be fully discovered automatically by RNNs.

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Teaching deep learning causal effects improves predictive performance - Supplements

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1 Real Diabetes Dataset - Supplements

1.1 Cohort Details. We used a retrospective cohort of de-identified data from 73,045 primary care patients at Mayo Clinic, Rochester, MN with research consent. Table 1 provides a detailed description of this cohort.

Table 1: Study Cohort Description

| Variable         | Median | Interquartile Range |
|------------------|--------|---------------------|
| Age [years]      | 45     | 31, 59              |
| Male [%]         | 43.4   |                     |
| LDL [mg/dL]      | 105    | 83, 130             |
| TG [mg/dL]       | 130    | 91, 187             |
| HDL [mg/dL]      | 50     | 41, 61              |
| SBP [Hg mm]      | 120    | 108, 132            |
| DBP [Hg mm]      | 70     | 60, 78              |
| FPG [mg/dL]      | 101    | 92, 117             |
| Follow-up [years]| 10     | 6, 12               |

| Number of patients | Percent |
|--------------------|---------|
| Antihypertensive medication | 30968 | 42.4 |
| Antilipemic medication      | 23925 | 32.8 |
| Progressed to DM          | 12367 | 16.9 |
| Progressed to CAD         | 13065 | 17.9 |
| Progressed to CKD         | 5267  | 7.2  |
| Progressed to Stroke      | 779   | 1.1  |

1.1.1 Medication Combination Details. In this dataset, medications for T2DM and related comorbidities are rolled up to National Drug File Reference Terminology NDF-RT pharmaceutical subclasses.

In the process of computing ITE, we need to define the medication combination to separate patients into groups accordingly in each time window. Simply combining all subclasses would produce numerous number of possible medication combinations. Instead, we encode each medication class as a indicator vector with limited length, and form the final medication combination indicator vector $M$ by concatenating the vectors of all classes.

We adopted three medication classes for the encoding: T2DM drugs, Hyperlipidemia (HL) drugs, and Hypertension (HT) drugs. For each class, to limit the length of indicator vector, we perform the encoding based on increasing treatment levels. The higher level denotes the treatment for higher severity of the disease. The Table 2 displays the details of different treatment levels for the three medication classes. For each class, the indicator vector $M$ is defined as binary vector with length equal to the number of treatment levels, and 1 digit per level.

| Treatment Levels | DM | HL | HT |
|------------------|----|----|----|
| Level-1          | 1st non-insulin drug | statin as the 1st drug | 1st drug |
| Level-2          | 2nd or more non-insulin drug | non-statin drug as the 1st drug | 2nd drug |
| Level-3          | insulin added as the 1st drug | non-statin drug added to statin | more drugs |
| Level-4          | insulin added to non-insulin drug(s) | non-statin drug added to non-statin drug(s) | - |
| Level-5          | non-insulin drug added to insulin | - | - |

2 Experimental Results Supplements

2.1 Future Labs and Vitals Forecast Tasks on Real Diabetes EHR dataset. Table 3 provide the performances of all compared methods in the tasks of labs and vitals forecasting, on the real dataset in metric MSE. Each row of the tables represents an individual experiment. The column names indicates the applied methods, and the row names shows their predicted labels and different observable time steps. The best performed method of each row is marked as bold.

To more intuitively compare the performance differences, we select one lab outcome from Table 3, and bar-plot all its results.
Table 3: Lab or Vital Result Forecast Performance with metric MSE on Real Dataset

| Models | MSE Performance | LM | LMER | LSTM | GRU |
|--------|----------------|----|------|------|-----|
|        | Methods        | No ∆ | ∆ Augment | No ∆ | ∆ Augment | No ∆ | ∆ Augment | No ∆ | ∆ Augment | No ∆ |
| LDL    | Step=1         | 969.53 | 908.32 | 991.06 | 932.49 | 1006.04 | 917.85 | **749.58** | 983.1 | 905.26 | 750.38 |
|        | Step=2         | 904.31 | 885.84 | 970.12 | 941.48 | 987.30 | 914.06 | **746.27** | 986.62 | 902.54 | 546.27 |
|        | Step=3         | 940.47 | 972.52 | 958.84 | 918.55 | 1104.61 | 904.83 | **720.29** | 996.01 | 1012.31 | 516.05 |
|        | Step=4         | 827.67 | 681.55 | 827.66 | **681.41** | 866.8 | 836.14 | 689.75 | 1092.29 | 818.17 | 863.58 |
| SBP    | Step=1         | 466.74 | 457.74 | 468.02 | 460.47 | 512.51 | 479.64 | 433.21 | 512.98 | 484.75 | **421.41** |
|        | Step=2         | 432.93 | 418.35 | 430.61 | 418.09 | 488.32 | 458.36 | **396.06** | 488.7 | 473.07 | 418.13 |
|        | Step=3         | 385.72 | 367.77 | 385.2 | 368.41 | 444.67 | 419.25 | **343.38** | 459.5 | 464.11 | 375.98 |
|        | Step=4         | 338.91 | **337.74** | 358.91 | 337.74 | 479.9 | 460.52 | 361.04 | 507.84 | 445.96 | 361.31 |
| TG     | Step=1         | 5292.75 | 4754.95 | 572.52 | 5425.32 | 5466.9 | 4702.7 | 4230.89 | 5428.54 | 4661.68 | **4090.07** |
|        | Step=2         | 5935.08 | 5530.18 | 6556.3 | 5807.74 | 6309.99 | 5366.56 | 4812.45 | 6048.61 | 5301.43 | **4524.19** |
|        | Step=3         | 4571.09 | 3971.84 | 4538.45 | 4026.53 | 4864.27 | 4497.26 | **3487.98** | 4745.23 | 4375.88 | 4478.10 |
|        | Step=4         | 4102.99 | 3342.96 | 4105.74 | 3347.37 | 4761.85 | 4217.16 | **2223.00** | 5694.48 | 5128.49 | 3593.77 |

Figure 1 shows the results of LDL value forecast. Because of the limited number of outcome observations from data, the lab or vital forecasts have comparatively much smaller cohorts than diagnosis predictions, and LDL has the largest one in our experiments, so it’s selected as the approximately most robust one to plot.

Figure 1: Comparison of LDL results forecast performance.