Toward Personalized Treatment of Chronic Diseases - the CKD Case Study

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ABSTRACT

Chronic diseases greatly influence the patients' life and incur the bulk of healthcare costs. Medical treatments should be personalized to consider individual variance. In this study, we take a first step toward personalized treatment of chronic kidney disease by formulating two prediction problems. We utilize random forest to learn the prediction models, and the preliminary results look promising.

CCS CONCEPTS

• **Applied computing → Health informatics**;

KEYWORDS

Personalized medicine, chronic kidney disease

1 INTRODUCTION

Chronic diseases are reported to consume 76% of Medicare expenditures in the U.S. [2]. Chronic illness can last for many years and is often accompanied by progressive deterioration. Thus, several healthcare policies aim at slowing deterioration and reducing the cost of care. Chronic kidney disease (CKD) is a chronic disease and notoriously known for having a high risk of developing into end-stage kidney disease (ESKD). The global burden of CKD is growing with the incidence of ESKD more than doubling in the U.S. and Europe during the past two decades [6].

Schork [10] reported that the top ten highest-grossing medications in the U.S. only help less than 25% of the people who take them. This result reveals that physicians need to take individual variability into consideration, and thus personalized medicine has received a lot of attention recently. Nowadays, healthcare organizations widely adopt information technology, thereby making a huge amount of patients' electronic health records (EHRs) available. This valuable data provides a great opportunity to realize personalized medicine by leveraging *big data* and *machine learning*.

To support personalized decision for the use case of diabetes, Neuvirth et al. [8] presented a prototype to predict the patient's future health condition based on three types of features: patient, physician and patient-to-physician. However, they did not consider the type of features characterizing treatments. Moreover, due to the limited power of the employed learning methods, their models only considered much fewer features during the learning process.

Zhang et al. [11] proposed a heterogeneous graph which encodes three relationships: patient similarity, medication similarity and patient-medication prior association. Based on the proposed heterogeneous graph, they performed a label propagation procedure to identify personalized treatments for hypercholesterolemia. Although they considered the characteristics of treatments, the personalized question they deal with is that a single medication is effective for a specific patient, which does not contemplate the usual multi-medication scenario.

As an innovative step toward personalized treatment of chronic disease, the contributions of this work are threefold: First, we formulated the personalized treatment of CKD as two kinds of prediction problems in Section 2. Second, we adopted random forest to learn the prediction models in Section 3. Third, we achieved promising preliminary results and identified several discriminative factors to our problems in Section 4.

2 PROBLEM FORMULATION

In this section, we formulate two kinds of prediction problems to evaluate the effectiveness of CKD treatments based on patients' EHRs. Firstly, we describe the available information which we can retrieve from EHRs in our dataset, followed by the definition of samples who we take into consideration in our prediction problems. Afterwards, we define two kinds of outcome measures to evaluate the effectiveness of CKD treatments and illustrate the input features of our prediction problems. Finally, we establish the notation of our problem formulation.

2.1 Available Contents of EHRs

We used the data provided by Keelung Chang Gung Memorial Hospital, Taiwan to conduct our study under IRB approval[1]. All personal identifiable information in our used data has been removed, and only a hashed unique patient id is available to link them. The data

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[1]This study was approved by the ethics committee of the institutional review board at the Chang Gung Memorial Hospital under the IRB number:105-2541.

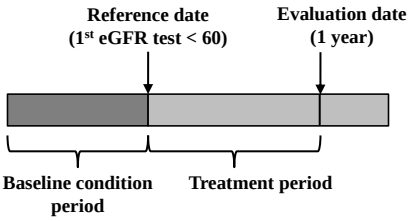

Figure 1: Formulation of a patient's longitudinal data [8]

includes three facility types: inpatient, outpatient and emergency. The available data fields for each patient can be categorized as follows:

(1) Patient Profile: Age, Gender
(2) Claims: Date of Service, Diagnosis Code, Facility Type
(3) Pharmacy: Medication Code, Days of Supply
(4) Lab Tests: Test Name, Date of Test, Test Result, Unit
(5) Clinical Notes: Chief Complaint, Doctor's Order

The diagnosis codes were encoded with ICD9. On the other hand, the medication codes were encoded by using the in-house codebook of the hospital. The clinical notes are free-text and often mixed-language (e.g. Chinese and English) in our data.

2.2 Sample Definition

The glomerular filtration rate (GFR) is a reliable indicator for measuring kidney condition. The lower the GFR measure, the worse the kidney condition. In order to estimate the progression of CKD, practitioners widely utilize the clinical ranges of GFR defined as follows [5]: GFR $\geq$ 90: first stage; 90 > GFR $\geq$ 60: second stage; 60 > GFR $\geq$ 30: third stage; 30 > GFR $\geq$ 15: fourth stage; 15 > GFR: fifth stage. Particularly, the fifth stage of CKD is referred as ESKD. However, the actual GFRs are hard and expensive to obtain for the patients. Therefore, we used the abbreviated Modification of Diet in Renal Disease equation to determine estimated GFR (eGFR).

A patient is considered to have CKD if he/she had any proteinuria and at least one eGFR test result that is less than or equal to 90. However, practitioners will probably not prescribe any aggressive treatment for CKD until the eGFR of a patient is worse than 60. Since our study mainly focuses on the effectiveness of CKD treatments, we only consider the patient who had at least one eGFR test result that is less than 60 as one training sample in our problems. Our dataset contains 7,412 patients that has CKD and 3,616 patients whose eGFRs have ever been lower than 60.

We followed the formulation in [8] to deal with the longitudinal data of our defined samples. For each patient determined to be in worse than the second stage of CKD, we set the day after the earliest eGFR result which is less than 60 as the *reference date* depicted in Figure 1. We regarded the period prior to the reference date as the *baseline condition period* (BCP). On the other hand, we set the day which is one year after the reference date as the *evaluation date*. The period between the reference and evaluation dates is treated as the *treatment period* (TP). The reason we chose one year is that one year is a proper period to assess the effectiveness of the chronic disease treatment, especially for CKD. Thus, in our experiments, we only considered patients whose TPs are more than one year. The records of patients being traced for less than the required period of one year were referred as *censored data*.

2.3 Outcome Measures for Treatment Effectiveness

In this study, we explored two types of outcome measures for the effectiveness of CKD treatments: (1) the occurrence of urgent care (UC) during the treatment period and (2) the control of eGFR after the treatment period. If urgent care does not occur during the treatment period, to some extent, we can interpret this as that the treatment succeeded in avoiding severe complications [8]. Thus, if the patient had no emergency visits during the treatment period, the outcome of the patient's treatment is labeled as "desirable." Otherwise, it is labeled as "undesirable."

For the second measure, the control of eGFR is the prevalent quality metrics in most CKD care. As reported in [6], after the eGFR of a patient is less than 60, it is most likely that the degradation of eGFR is irreversible. Hence, the control of eGFR is a good indicator for the effectiveness of the CKD treatment. We used the criterion whether the eGFR of a patient drops over 50% after the treatment period as the indicator for the good control of eGFR. The logic behind this setting is that if the eGFR of a patient is equal to 60, a 50%-drop means that the eGFR of this patient turns to be 30. This change reflects the stage transition of CKD (thrid to fourth).

In order to acquire the degeneration percentage of eGFRs, it is required for a patient to have an eGFR test result after the evaluation date. The policy for selecting the subsequent eGFR test results is that we choose the eGFR test results that are closest to the evaluation date and is within ±90 days from the evaluation date. If the subsequent eGFR of a patient dropped more than the defined threshold, we label the outcome of the patient's treatment as "undesirable." Otherwise, we label it as "desirable."

2.4 Feature Construction

For each sample defined in Subsection 2.2, we derived two sets of features from BCP and TP, respectively. The feature set of BCP comprises the following sources:

(1) Age and sex
(2) Count of visiting each facility type
(3) Count of codes including disease, medication and test
(4) Various test results

By contrast, the feature set of TP is much simpler and only contains the count of each medication code. Furthermore, since clinical notes are free-text and mixed-language notes, it has been difficult so far for us to extract the harmonized clinical concepts. We will try to resolve this issue in our future work.

As suggested in [8], to extract clinically meaningful features, we applied the respective mapping steps to diagnosis and medication codes. We employed HCUP-US Clinical Classification Software (CCS) for Diagnosis (only single-level form) in mapping our diagnosis codes into diagnostic categorizations. For medication codes, we mapped them into Anatomical Therapeutic Chemical (ATC) codes and took the first five characters as their unique medication class ids. We will show the differences between the feature sets with and without these two mappings in our experiments.

After the entire features are generated, we found several features have too much missing values, i.e. the number of the patients having such features is extremely tiny. Thus, we complied the following criteria which are the common clinical practice to remove them.

(1) The numbers of disease codes or CCS codes (if we apply the mapping) are less than 2%
(2) The numbers of medication codes or ATC codes (if we apply the mapping) are less than 2%
(3) The numbers of test codes and results are less than 25%

The effects of this removal are twofold: Firstly, we can remove the outliers which might be typos. It is hard to avoid artificial typing errors when we are on the track of patients. However, we can rectify the unintentional mistakes by removing the codes which are under the specified thresholds. Secondly, we can improve the generalization of the adopted learning methods. With this removal, we can force the learning method to rely on more generic features rather than special features.

2.5 Notation

To describe the problems we tackled precisely and to ease the following presentation, we establish the notation in this subsection. Consider a training dataset $\{(x^{(1)}, y^{(1)}), \ldots, (x^{(N)}, y^{(N)})\}$, where $x^{(i)} \in \mathcal{X}_1 \times \ldots \times \mathcal{X}_M = \vec{\mathcal{X}}$ is the feature vector defined in Subsection 2.4 for individual i, M is the number of features, N is the number of individuals in the dataset, $y^{(i)}$ is the label of the outcomes we described in Subsection 2.3 ($y = 1$ if the outcome is desirable; otherwise, $y = 0$). Given the training dataset, each of our problems is to learn a prediction function $f : \vec{\mathcal{X}} \to \{0, 1\}$. After the f is learned, we can compute the prediction estimate for an unseen individual u as $\widehat{y^{(u)}} = f(x^{(u)})$.

3 LEARNING MODEL FOR PREDICTION

In order to predict the effectiveness of CKD treatments, we utilized random forest to learn the prediction function f we defined in the previous section. We chose random forest because it often outperforms other standard classifiers, is easy to tune, and is robust to overfitting [3]. In this section, we adopt the notion and explanation in [7] to illustrate random forest in our context. Besides, we introduce the idea of Mean Decrease Impurity (MDI), which is used to examine the importance of the input features of the learned random forests in the subsequent section.

3.1 Random Forest

A random forest comprises several binary decision trees. Every binary decision tree is an input-output model represented by a tree structure T. In our context, T represents f and is a function from $\vec{\mathcal{X}}$ to $\{0, 1\}$. Any node t in T stands for a subset of the space $\vec{\mathcal{X}}$. Among these nodes, the root node is a special node whose space is $\vec{\mathcal{X}}$ itself. Other than the root node, there are two types of nodes in T: internal and terminal. Every internal node t is labeled with a binary test (or split) $s_t = (\mathcal{X}_m) < c$, which divides its original subset into two resultant subsets corresponding to its two child nodes t_L and t_R. On the other hand, every terminal node (or leaf) is labeled with a best guess value of $\{0, 1\}$. For an unseen (or a new) instance, we propagate it through the tree and report the label of the reached leaf as its predicted output $\widehat{y^{(u)}}$.

During the learning process, a tree T is built from a training dataset of size N via algorithms in a top-down fashion. At each node t, these algorithms identify the split $s_t = s^*$ which partitions the N_t node instances into t_L as well as t_R and thereby maximizes

$$\triangle i(s, t) = i(t) - p_L \cdot i(t_L) - p_R \cdot i(t_R), \tag{1}$$

where $i(t)$ represents the impurity measure (e.g., the Gini index, the Shannon entropy, or the variance of output labels [9]), p_L is N_{t_L}/N_t, and p_R is N_{t_R}/N_t. The tree stops growing until nodes become pure in terms of the output labels or all feature are locally constant.

A single tree typically suffers from high variance, which can render its classification result less accurate. Intuitively, we can utilize the randomization-based ensemble methods to simply overcome this flaw. The core idea behind these methods is to introduce random perturbations into the learning process so as to produce several different decision trees from a single training dataset. Then, the predictions of these trees can be derived from by using some aggregation techniques. The random forest algorithm [3], one of such methods, randomly chooses the input features as the candidate features to split at each internal node. That is, instead of looking for the best split s^* among all input features (i.e. $\{\mathcal{X}_1, \ldots, \mathcal{X}_M\}$), random forests select a random subset of input features and then only determine the best split s^* over the selected subset of features.

Table 1: Statistics for our two outcome measures

Outcome	UC	eGFR drop ≥ 50%	Overlap
Desirable	2147	2439	1533
Undesirable	1236	132	79
Censored	233	–	–
Total	3616	2571	1612

3.2 Mean Decrease Impurity

Regarding ensembles of randomized trees, Breiman [3] proposed a metric to evaluate the importance of features for predicting output labels. The metric of a feature $\mathcal{X}_m$ is to add up the weighted impurity decreases $p(t)\triangle i(s_t, t)$ for all internal nodes where $\mathcal{X}_m$ is used in T and then average over all N_T trees in the forest:

$$Imp(\mathcal{X}_m) = \frac{1}{N_T} \sum_{T} \sum_{t \in T : v(s_t) = \mathcal{X}_m} p(t)\triangle i(s_t, t), \tag{2}$$

where $p(t)$ is the proportion N_t/N of training instances reaching t, and $v(s_t)$ is the feature used in the split s_t. For any impurity measure $i(t)$, Equation 2 is referred to the *Mean Decrease Impurity* (MDI) importance. In the next section, our qualitative analysis will use this metric to assess the importance of the input features. Generally, the higher the MDI, the more importance the feature.

4 EXPERIMENTAL RESULTS

In this section, we show our experimental results from quantitative and qualitative aspects. Before elaborating the results, we firstly present the statistics of our dataset.

Table 1 provides detailed counts for the two types of outcomes defined in Subsection 2.3. For the UC context, the desirable outcome is that the patient did not visit emergency care during the treatment period. For this case, we removed censored data defined in Subsection 2.2. Regarding the eGFR drop, the desirable outcome is that the percentage decrease in the selected two eGFRs is less than 50%. Thus, there is no censored data since we have already ruled out the patients who did not have an eGFR test result within ±90 days from the evaluation date. (See Subsection 2.3 for details.)

Table 2: Prediction performance for our two problems

Feature set	Size	UC AUC (std)	eGFR drop ≥ 50% AUC (std)
BCP	690	0.68 (0.024)	0.68 (0.066)
BCP+TP	902	0.78 (0.028)	0.77 (0.044)
BCP (mapped)	391	0.68 (0.022)	0.68 (0.065)
BCP+TP (mapped)	537	0.79 (0.032)	0.81 (0.028)

Table 1 also reports the overlapped samples in the two outcomes in the fourth column. Based on the definition of independent events, we can easily conclude that the desirable events of the two outcomes are independent. For the undesirable events of the two outcomes, the independence can be inferred, too. Thus, there is no significant correlation between the two outcomes, which reflects complementary aspects of the treatment effectiveness.

4.1 Quantitative Results

We utilized random forest to learn the models for the two problems defined in Subsection 2.5. We performed a 10-fold cross-validation for each experiment. The preliminary results are shown in Table 2. The second column of Table 2 shows the size of each feature set. The third and fourth columns present the average area under the receiver operating characteristic curve (AUC) [4] of the two outcomes with the standard deviation. We chose AUC as our evaluation metric because it is invariant to the amount of class imbalance.

The third and fifth rows exhibit the prediction results of the effectiveness of the CKD treatments w and w/o the mapping illustrated in Subsection 2.4. As shown in Table 2, the results with the mapping are slightly better than the results w/o the mapping.

In order to validate our problem formulation, we also carried out two kinds of control experiments where we merely considered the features of BCP. The second and fourth rows demonstrate the results each of which is about 10% worse than its corresponding result. This comparison reveals that the features of TP provide additional discrimination power for the prediction problems.

4.2 Qualitative Analysis

To provide valuable insight into the problems, we also performed some qualitative analysis on the learned models. As elaborated in Subsection 3.2, MDI is a good metric to evaluate the importance of the features of random forest. The average MDI for each feature was computed as follow. Each time we built a random forest, we derived MDIs for all input features. For each experimental setting, we built 100 random forest models to eliminate bias in one model. Based on the average MDI of each feature, we reported the top-5 features for each experimental setting.

Surprisingly, there are close correspondences between the top-5 features and clinical practices. We take the UC context with the mapping as an example to illustrate our observation. As shown in Table 3, the age and gender features are highly correlated to CKD progression since they are the key components of eGFR calculation formula [5]. Moreover, CCS-98 stands for hypertension category, which is a common complication of CKD [1].

Although all the top-5 features in this case come from BCP, we are interested in the features coming from TP. Thus, we listed

Table 3: Top-5 important features for UC with the mapping

Feature name	Average MDI
Top-5 features of BCP+TP	
BCP::outpatient count	0.34 (0.012)
BCP::age	0.34 (0.011)
BCP::gender	0.34 (0.021)
BCP::admission count	0.32 (0.017)
BCP::CCS-98 count	0.31 (0.013)
Top-5 features of TP	
TP::ATC-C09CA count	0.26 (0.011)
TP::ATC-C08CA count	0.24 (0.014)
TP::ATC-C10AA count	0.23 (0.015)
TP::ATC-A02AF count	0.23 (0.015)
TP::ATC-B01AC count	0.22 (0.013)

the top-5 features of TP at the bottom of Table 3. Among the five top-5 features of TP, ATC-C09CA and ATC-C08CA represent "angiotensin II antagonists" (ARBs) and "dihydropyridine derivatives", respectively. These two drugs are suggested to be used for the management of hypertension in CKD patients [1]. Then, ATC-C10AA stands for "HMG CoA reductase inhibitors", which is suggested to be used for the management of hyperlipidemia in CKD patients [1]. These two observations agree with the risk factors for CKD [1]. Please see the following link for the other three analyses: https://research.htc.com/publications-and-talks/.

5 CONCLUSIONS

This paper presents a prototype for predicting the effectiveness of treatments for patients with chronic diseases. We used CKD data where there are more than 2, 500 CKD patients as use case to validate our prototype. The preliminary results are promising and offer insights. As future work, we will perform more qualitative analysis on the learned models and extract the concepts from clinical notes.

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6 APPENDIX

In this appendix, we provide more qualitative analysis of the other experimental settings. Table 4 shows the top-5 features from BCP and TP for the UC context w/o mapping. Table 5 and 6 show the top-5 features from BCP and TP for the eGFR drop scenario w and w/o mapping, respectively.

Table 4: Top-5 important features for UC w/o the mapping

Feature name	Average MDI
Top-5 features of BCP+TP	
BCP::age	0.33 (0.016)
BCP::outpatient count [1]	0.32 (0.016)
BCP::ICD9-4019 count [2]	0.30 (0.014)
BCP::gender	0.3 (0.019)
BCP::Test-347 result [3]	0.29 (0.011)
Top-5 features of TP	
TP::Med-PGC004M count [4]	0.22 (0.013)
TP::Med-PFA008M count [5]	0.22 (0.015)
TP::Med-PFA014M count [6]	0.21 (0.015)
TP::Med-PIC016M count [7]	0.21 (0.014)
TP::Med-PGC020M count [8]	0.21 (0.017)

[1] Facility type count means how many times the patient had visited the facility
[2] "HYPERTENSION NOS" in ICD9-CM code description
[3] test of Estimated GFR
[4] ACETAMINOPHEN 500MG/TAB
[5] AMLODIPINE 5MG/TAB
[6] LOSARTAN POTASSIUM 50MG/TAB(PTP)
[7] FUROSEMIDE 40MG/TAB
[8] COLCHICINE 0.5MG/TAB(PTP)

Table 5: Top-5 important features for eGFR drop $\geq$ 50% w the mapping

Feature name	Average MDI
Top-5 features of BCP+TP	
BCP::CCS-217 count [1]	0.45 (0.329)
BCP::ATC-D05AA count [2]	0.42 (0.316)
BCP::ATC-R03CB count [3]	0.40 (0.320)
BCP::CCS-114 count [4]	0.39 (0.251)
BCP::CCS-145 count [5]	0.38 (0.159)
Top-5 features of TP	
TP::ATC-J01FA count [6]	0.26 (0.011)
TP::ATC-D07CC count [7]	0.24 (0.014)
TP::ATC-C01AA count [8]	0.23 (0.015)
TP::ATC-M01AX count [9]	0.23 (0.015)
TP::ATC-A05BA count [10]	0.22 (0.013)

[1] "Ot cong anom" in CCS category description
[2] Tars
[3] Non-selective beta-adrenoreceptor agonists
[4] "Perip athero" in CCS category description
[5] "Int obstruct" in CCS category description
[6] Macrolides
[7] Corticosteroids, potent, combinations with antibiotics
[8] Digitalis glycosides
[9] Other antiinflammatory and antirheumatic agents, non-steroids
[10] Liver therapy

Table 6: Top-5 important features for eGFR drop $\geq$ 50% w/o the mapping

Feature name	Average MDI
Top-5 features of BCP+TP	
BCP::ICD9-5280 count [1]	0.33 (0.256)
BCP::Med-PED028M count [2]	0.32 (0.306)
BCP::ICD9-37272 count [3]	0.32 (0.196)
BCP::Med-PCD028M count [4]	0.31 (0.304)
BCP::age	0.300 (0.024)
Top-5 features of TP	
TP::Med-PBA016M count [5]	0.21 (0.095)
TP::Med-PGC028M count [6]	0.21 (0.065)
TP::Med-PGC004M count	0.21 (0.025)
TP::Med-PFA008M count	0.21 (0.027)
TP::Med-PCG040M count [7]	0.21 (0.088)

[1] "STOMATITIS" in ICD9-CM code description
[2] drug name for PED028M
[3] "CONJUNCTIVAL HEMORRHAGE" in ICD9-CM code description
[4] drug name for PCD028M
[5] CYPROHEPTADINE HCL 4MG/TAB(PC)
[6] INDOMETHACIN 25MG/CAP
[7] CIPROFLOXACIN HCL 250MG/PC TAB