AI for Patient Support: Predictive Model of Medication Non-Adherence

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Abstract

Adherence in medicine is a measure of how well a patient follows his treatment. Not following the medication plan is actually a major issue as it was underlined in the World Health Organization's reports[2]. They point out that, in developed countries, only about 50% of patients with chronic diseases correctly follow their treatments. This severely compromises the efficiency of long-term therapy and increases the cost of health services. This paper reports our work on modeling patient drug consumption in breast cancer treatments. We compare different approaches to study patient's paths: one drug-phase centered and one patient centered. Different machine-learning solutions are compared to predict medication non-adherence. They show the ability of the AI to estimate a risk score of a patient's non-adherence and thus improve support throughout their care path.

1 Introduction

During the last decades, patient-administered oral medications have become more and more prevalent [Fallowfield et al., 2005, O'neill and Twelves, 2002]. This shift in anticancer treatments has increased the focus on adherence that Osterberg and Blaschke [2005] defined as *"the extent to which patients take their medications as prescribed by their healthcare providers "*. A common solution is to set patient support programs that include, for example, 1) providing patients with information and advice 2) support and coaching sessions delivered by nurses (by phone or face-to-face), and 3) sending information to health professionals treating the patient. These programs have been shown to be effective. For example, pharmacist coaching has improved adherence by 12% [Krolop et al., 2013] and an SMS based recall system showed a 10% improvement in adherence [Spoelstra et al., 2013]. Yet, there are two main limitations to these interventions: 1) The use of human intervention is effective but very expensive thus limiting their reach, 2) The use of digital technologies (e.g. notifications and explanations) is too generic and sometimes too intrusive (e.g. daily reminders) which leads to patients losing interest. To optimize the use of human intervention and improve the use of digital technologies, we propose the use of machine-learning techniques on breast cancer patients' consumption data. These predictive models are trained on the reimbursement data of the French Health Insurance (SNIIRAM - the French National Health System). The goal is to categorize patients into risk classes according to their characteristics. The long-term goal is to know the most appropriate moments to contact them for support. Thus, people will benefit from support adapted to their profile and their needs, and human interventions will be reserved for the situations for which they are really necessary. This paper first reviews previous approaches before introducing the SNIIIRAM database. Then, the different data processing and the applied models are described and discussed.

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[2]http://www.who.int/chp/knowledge/publications/adherence_full_report.pdf

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2 Related work

Given the importance of the phenomenon of non-adherence, many surveys have tried to identify determining factors. This allows us to improve interventions and, therefore, compliance with the treatment. DiMatteo [2004b] and Mann et al. [2010] review many observation-based scientific publications and provide an interesting quantitative assessment of the research conducted on the subject. These meta-analyses emlphasize the impact of factors of non-adherence such as the increasing age of patients, and the treatment complexity level (multiple drugs, injections, ...). Similarly, low education and, more importantly, low income are correlated with lower adherence. DiMatteo et al. [2000] another study highlights the impact of patients' mental health, showing that depressive episodes have a very negative impact on the patient's compliance with the prescriptions of health professionals. DiMatteo [2004a] shows that other factors also influence adherence. For example, they point out that the patient's beliefs influence the level of compliance, and not the actual severity of the condition by distinguishing between the objective severity of the patient's illness and their awareness of the severity of their pathology. This enforces the importance of the role of patient education in strengthening their adherence to their treatment. Similarly, other analyses highlight the effects of modifiable factors in non-adherence. This meta-analysis thus shows the influence of the patient's entourage (support of their spouse, family, relatives and the wider social environment) in the proper monitoring of their treatment.These studies provide apriori indications for detecting risk profiles of non-adherence. At the same time, they highlight the interest of identifying and accompanying these patients in taking their medication. However, Franklin et al. [2016] underline the difficulty to use this information to predict adherence: they evaluate different approaches, using logistic regression and boosted logistic regression, to define three categories of adherence predictors. Hence, they show that using census information or transaction data leads to poor prediction. However, they point out that using adherence observations during the first month significantly increases the accuracy of the results. This nuance on the weight of each adherence prediction variable is confirmed in Lo-Ciganic et al. [2015]. They use random survival forests highlights to find patient specific adherence thresholds to discriminate between hospitalization risks. Here again, the major variables are linked to patient history and previous transactions. Karanasiou et al. [2016] explore Machine Learning approaches to estimate the risk of the non-adherence for a patient with Heart Failure. The database contains general information about the patient, details about each care path, clinical examinations and clean labels based on clinician estimations. They prove the feasibility of this approach using a clean dedicated dataset. This paper proposes to explore these solutions to predict the risk of an illegitimate stop during a treatment. Our models are trained using real reimbursement records data from the French Health System. Our goal is to explore how to use these real, indirect and unlabeled observations to evaluate the risk of non-adherence at key moments of a patient's care path.

3 The SNIIRAM database

SNIIRAM[3] is one of the largest structured databases of health data in the world. It contains reimbursement data of the French Health System, covering 99.8% of the French population ($\simeq$ 66 million persons). Useful data are, for example, hospitalizations, drug purchases or contextual patient information (age, government services, geographic information, ...). The advantage of using this database is that it is very well structured and has no-bias in term of social background due to its universal coverage. More details can be found in Tuppin et al. [2010]. Previous work has already shown the value of massive data mining to aid diagnosis, either by taking all the information for a "static" approach Neumann et al. [2012], or, more recently, by also incorporating dynamic information Morel et al. [2017]. Other studies have been conducted on the determinants of compliance, particularly for breast cancer.Our study focuses on women's breast cancer on part of the SNIIRAM data. The cohort of the study consists of 50%[4] of women (drawn randomly) who met the following criteria: 1-diagnosed with breast cancer; 2- having purchased at least one of the following molecules for the studied period: *Anastrozole*, *Capecitabine*, *Cyclophosphamide*, *Etoposide*, *Everolimus*, *Exemestane*, *Lapatinib*, *Letrozole*, *Megestrol*, *Melphalan*, *Tamoxifen*, *Toremifene* and *Vinorelbine*. Extraction concerns consumption between 2013 and 2015 and is made up of three main categories: 1-Pharmacy transactions (molecule, number of doses, date, ...); 2- Hospitalizations (diagnosis, start date, end

[3] `https://www.ameli.fr/l-assurance-maladie/statistiques-et-publications/sniiram/finalites-du-sniiram.php`

[4] half of the women due to policies for data access set by the French Health System

date, ...); 3-Patient information (age, department, date of the diagnostic of eventual long-term illness (referred as *ALD*) , pathologies, ...). Thanks to the universal coverage of the construction of Sniiram (almost all the French population is part of it), we consider that there is no sociological or geographical bias in its study.

4 Phase analysis

Working with oncologists, we reworked the raw data to show the different phases of the treatment. A phase is a period of continuous intake of a molecule or hospitalization (chemotherapy or radiotherapy), allowing the reconstruction of a patient's care path. A phase of treatment can end with a legitimate stop (i.e. death, change of treatment, a serious cardiac issue, palliative care or right censorship due to data extraction) if this event occurs less than two months after the date of the last theoretical dose. The date of the last theoretical dose is obtained by calculating the median interval between two purchases of the molecule or two hospitalizations of the same type: this median behavior is considered to conform with the drug dose. Thus, the median time is 30 days between two box purchases of 30 doses of Tamoxifen. The end of this period after the last purchased box corresponds to the date of the last theoretical intake. Illegitimate stops are considered if none of the legitimate stops occurred before the date of the last theoretical dose. This method gives us the label for our models. For each phase, the following data is calculated: 1- Start and end dates, number of intakes or hospitalizations, molecule or type of hospitalization; 2- End of treatment type (switch, death, stop, right censorship); 3-Patient information (comorbidities, location, age, ...); 4- Interventions on the breast (mastectomy) during the three months before the studied phase. We first performed survival analyses on these data. Use of Kaplan-Meier estimator[Kaplan and Meier, 1958] roughly characterizes the instantaneous probability of an illegitimate drop-out at time t. Cox models [Cox, 1972] gave us insights for each characteristic of the study phenomena as a Hazard Ratio (results shown in table1). The characteristics highlighted by the literature are found to be influential to the patient's adherence to their treatment, legitimating our approach. We can then evaluate the impact of age, social support, or global patient's care path (psychiatric, mastectomy, ...). The model underlines that the treatment preceding the current phase has a major influence as displayed in Figure2.

These results seem coherent: a lower risk of drop-out is linked with recent hospitalizations in line with the effect of support for adherence: medical staff encountered during these hospitalizations might provide advice and motivation. On the other hand, the high risk with Tamoxifen as a previous treatment reveals that the previous phase might have ended with a certainly-illegitimate drop-out so the model shows the risk of a "relapse". We also tested how multilayer perceptrons (MLP) can use the information available at the beginning of a phase to predict the risk of an illegitimate stop after 3, 6, or 12 months. The data are then composed of, for the 3 months period, 51220 patients with 11.16% non-adherent, for 6 months, 44469 patients with 16.53% non-adherent, for 12 months, 34132 patients with 27.0% non-adherent. We used a 5-fold cross-validation with a 60-20-20 balanced training/validation/testing dataset. Even though we are looking to improve this approach with more complex architecture and fine-tuning parameters, the first results are promising: with only the information at the beginning of a drug phase, we can predict the risk of an illegitimate drop-out in the next months with a 0.65 overall accuracy, which is an improvement compared to a random pick-up, which is the currently used method by the French National Services. These first approaches could already be applied: the caregivers could be notified during the first medical visit and propose

Characteristic	Hazard Ration
CMU-C (financial support)	1.47
ACS (financial support)	1.52
Time since ALD status	1.08
Psychiatric illness	1.19
Recent hospitalization for malignant neoplasms of breast	0.68
Previous treatment: Tamoxifen	2.49
Previous treatment: radiotherapy	0.49
Previous treatment: chemotherapy	0.42

Table 1: Characteristics Hazard Ratio
HR=1: no effect;HR<1: reduction in hazard;HR>1: increase

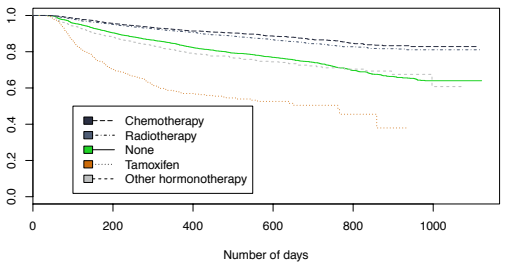

Table 2: previous-treatment dependent Tamoxifen survival functions

more support to the patient at risk. These risk models can also be used to underline the period with more drop-outs according to a patient's profile and trigger an alarm to reach them if needed.

5 Drug transaction analysis

Insights from oncologists and statistical studies [Janssoone et al., 2018] led us to a patient-centered approach focused on all transactions carried out by a patient: every purchase in a pharmacy, every hospitalization,... Indeed, a survival analysis shows that the period between the first and third month has a high risk of illegitimate tamoxifen drop-out for example. Aiming to predict the risk of an illegitimate stop for each pharmacy transaction corresponding to each drug used for treating breast cancer (Tamoxifen, Exemestane, ...), the underlying goal is to evaluate the insights given by the evolution of the last transactions. We use the same 60 days criteria proposed for the phase analysis to determine if a pharmacy transaction precedes an illegitimate stop or not. We obtain 14259 transactions meeting these criteria over a total of 746742. Data are therefore represented as a sequence of events with a set of characteristics, both on the transaction and on the patient. Solutions using Recurrent Neural Networks (RNN) are explored to use temporal information to improve our predictions, especially *Long short-term memory* (LSTM Hochreiter and Schmidhuber [1997]) and *Gated Recurrent Unit* (GRU Cho et al. [2014]). Our ongoing study obtains its best results with the following architecture: 1- a GRU or LSTM network is applied on the "dynamic" information (pharmacy transactions and hospitalizations); 2- an MLP network on the "contextual" information (details about the patient (geographical, financial support, ...)) which are not frequently updated in the SNIIRAM database; 3- both outputs are concatenated and then classified through a fully-connected layer. We tested networks based on this kind of architecture. Inputs are sequences of 10 observations and the output indicates if the current transaction might not be followed by another one (indicating the risk of an illegitimate drop-out). As 10 observations are not always available for each transaction, we also test different padding preprocessing with zeros filling or first observation duplication. We obtain a score that allows targeting efficiently a patient in 82% of the cases. The interest of our model is underlined with the Cumulative accuracy profile (CAP or Lorentz curve) which displays the ability of a model to accurately spot a patient at-risk. Ranking all the surveyed population from the highest to the lowest predicted risk, indicating the ability of a model to accurately spot a patient at-risk. CAP n% is the rate of true positive classifications looking at the n highest ranked predicted risk. Our model gets a CAP 20% of 66% of illegitimate stops and a CAP 50% of 90%. As a point of comparison, French National Services draw randomly patients to provide support to so our approach is twice as effective. As French Health Services has a limited number of hours to call patients for support, our model could double their efficiency. This results could also be applied to notify pharmacists to deliver more support when appropriate or trigger an SMS based system to contact and motivate a high-risk patient.

6 Conclusion and discussion

This paper presents our first studies on how machine-learning can be used to help patients follow their treatment during long-term illness. We explore several approaches applied to real data from the French Health System's reimbursement data to estimate the risk of an illegitimate drug drop-out. The results obtained with simple models on indirect observations from SNIIRAM prove the feasibility of our process. We validate our first results with feedback from oncologists and medical researchers. Our approaches are also willing to be coherent with patients' care-paths. First, we looked at the different drug-phases so we could notify caregivers of the potential risk of a drug drop-out at specific moments of the treatment. This might allow a more efficient support at the appropriate time, also avoiding stress resulting from frequent contact that isn't necessary and limiting the waste of resources for low-risk patients. Our second approach provides a real-time evaluation of the risk. It shows improvement in our classification scores and might lead to a more appropriate support. The ability to compute the risk instantly could notify a pharmacist if a patient is at risk to deliver more support.
These results are the first steps of our studies and there is plenty of room for improvement. However, they validate the ability of AI to estimate the risk of non-adherence. More complex networks should improve our efficiency. For example, we could look at several pathologies and use some kind of domain adaptation methods to detect patterns relevant to non-adherence. The other main challenge concerns the labeling of the data: we plan to explore automatic labeling and anomaly discovery to find more accurate information in our data.

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