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## Machine learning approaches to personalize early prediction of asthma exacerbations

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### Abstract

Patient telemonitoring results in an aggregation of significant amounts of information about patient disease trajectory. However, the potential use of this information for early prediction of exacerbations in adult asthma patients has not been systematically evaluated. The aim of this study was to explore the utility of telemonitoring data for building machine learning algorithms that predict asthma exacerbations before they occur. The study dataset comprised daily self-monitoring reports consisting of 7001 records submitted by adult asthma patients during home telemonitoring. Predictive modeling included preparation of stratified training data sets, predictive feature selection, and evaluation of resulting classifiers. Using a 7-day window, a naive Bayesian classifier, adaptive Bayesian network, and support vector machines were able to predict asthma exacerbation occurring on day 8, with sensitivity of 0.80, 1.00, and 0.84; specificity of 0.77, 1.00, and 0.80; and accuracy of 0.77, 1.00, and 0.80, respectively. Our study demonstrated that machine learning techniques have significant potential in developing personalized decision support for chronic disease telemonitoring systems. Future studies may benefit from a comprehensive predictive framework that combines telemonitoring data with other factors affecting the likelihood of developing acute exacerbation. Approaches implemented for advanced asthma exacerbation prediction may be extended to prediction of exacerbations in patients with other chronic health conditions.

### Keywords

personalized medicine; machine learning; asthma exacerbation; prediction

### Introduction

Personalized medicine is a medical model that supports medical decisions, practices, interventions, and technologies that are tailored to individual patients on the basis on their predicted response or risk of disease.<sup>1</sup> Applications of personalized medicine have risen in

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Conflicts of interest

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recent years, given the growth of new diagnostic and informatics approaches.<sup>2</sup> Big Data analytics utilizing a variety of machine learning methodologies play a crucial role in developing analytical foundations of personalized medicine.<sup>3</sup> The broad introduction of electronic algorithms predicting clinical events in real time with the intent to improve patient care and decrease costs has been successfully facilitated by Big Data analytics,<sup>4</sup> and the recent explosion in availability of electronic health data is motivating a rapid expansion of healthcare predictive analytics applications.<sup>5-6</sup>

One of the potentially fruitful areas for further expansion of Big Data analytics is chronic disease management. Chronic health conditions afflict a significant proportion of the population and are particularly prevalent in older adults. Acute exacerbations of chronic health conditions result in emergency room visits or hospitalization, significantly increasing healthcare expenditures.<sup>7</sup> Hospitalizations of older adults, who represent a subgroup of the population with a particularly high prevalence of comorbidities, accounted for one-third of all hospital stays in the United States, totaling nearly \$329 billion in 2006.<sup>8</sup> Many emergency room visits and hospitalizations in people with chronic health conditions may be prevented if incipient exacerbation is diagnosed in advance, allowing timely intervention in ambulatory settings.<sup>9</sup> There is an urgent need for developing efficient approaches to prevent exacerbations in people with chronic health conditions.

Home-based telemonitoring is increasingly used for monitoring patients with chronic health conditions and managing their diseases in ambulatory settings in order to optimize control of chronic disease trajectory and prevent exacerbations.<sup>10</sup> Promising applications of this technology have been described for various conditions such as asthma,<sup>11</sup> hypertension,<sup>12</sup> inflammatory bowel disease,<sup>13</sup> congestive heart failure (CHF),<sup>14</sup> multiple sclerosis,<sup>15</sup> chronic obstructive pulmonary disease (COPD),<sup>16</sup> and depression.<sup>17</sup> However, some recent studies reported limited effectiveness of home telemonitoring interventions in chronic health conditions, owing to a lack of useful early predictors and the poor performance of conventional algorithms for detecting exacerbations.<sup>18</sup> The majority of existing algorithms predict the overall risk of developing exacerbations within a certain time frame, usually 1 month or 1 year. These algorithms are based on various combinations of clinical and billing data and do not account for ongoing alterations in disease severity and day-to-day variations in symptomatology. New approaches in predicting incipient exacerbation, accounting for individual disease trajectory and allowing timely identification of potential deterioration before it occurs, may significantly enhance the usefulness of home-based telemonitoring systems and potentially improve quality of care and reduce healthcare costs.<sup>19</sup>

## Background

Vast amounts of patient-specific information are being continuously aggregated by modern chronic disease telemonitoring systems that uniquely reflect the trajectory of chronic illness.<sup>20</sup> This information usually includes disease-specific symptom diaries reported by patients<sup>21</sup> and physiological parameters obtained from automated monitors,<sup>22</sup> wearable devices,<sup>23</sup> or sensors embedded in the surrounding environment.<sup>24</sup> However, these rich sources of patient-specific information are currently used only in a limited way by telemonitoring systems available in routine clinical practice. In the context of modern

disease management programs, default values or values defined by a case manager are assigned as a threshold for the collected parameters to trigger an alert when significant deterioration in patient status occurs.<sup>25</sup> This approach has several major limitations. First, limited evidence exists for optimal threshold identification; thresholds may differ between patients and may change during the course of a chronic illness. Second, threshold setting and adjustment requires a time commitment from highly trained clinical personnel, who frequently employ professional intuition in alert settings. Third, even with a perfect alert setup, a telemonitoring system identifies exacerbation when it has already occurred. If incipient exacerbation is identified in advance (before a patient experiences it), a timely intervention is more likely to prevent further deterioration of disease severity. The goal of this study was to assess the potential application of machine learning approaches to telemonitoring data for early prediction of chronic disease exacerbation, using predictive modeling of asthma exacerbation.

Asthma is among the most common and costly chronic diseases in United States.<sup>26</sup> Annual U.S. healthcare expenditures for asthma are \$56 billion, with over 50% of direct costs attributable to hospitalizations.<sup>27</sup> About 25 million or 8% of the U.S. population had asthma in 2009 and this number continues to grow.<sup>28</sup> More than half (53%) of people with asthma had an asthma attack in 2008,<sup>29</sup> but the majority of asthma attacks are considered to be preventable.<sup>30</sup> Successful treatment approaches to avoid acute asthma exacerbation have been clearly established in cases where deterioration in asthma control is detected in a timely fashion and appropriate therapeutic options are provided.<sup>31</sup>

Current prediction rules for asthma exacerbations use a variety of predisposing factors, including genes,<sup>32</sup> inflammatory biomarkers,<sup>33-34</sup> airway function,<sup>35-36</sup> symptom scores,<sup>36-37</sup> medication use,<sup>38</sup> urgent-care utilization patterns,<sup>39</sup> and environment factors.<sup>40</sup> However, most of these rules identify who is more likely to experience an asthma attack, rather than when an asthma attack is about to occur. Although identifying individuals with a high risk of developing asthma exacerbations is important because it allows medical care providers to focus on patients who need higher levels of service, it is insufficient for ensuring timely intervention before acute exacerbations occur. This may be one of the reasons that recent randomized controlled trials evaluating telemonitoring of asthma,<sup>41</sup> COPD,<sup>42</sup> and CHF<sup>43</sup> patients were unable to demonstrate a significant decrease in urgent-care utilization despite positive effects on overall patient satisfaction and self-management.

Predictive modeling of biomedical data is characterized by the systematic use of machine learning techniques to develop forecasting or classification algorithms that are used in computer-mediated decision-making processes.<sup>44</sup> Predictive modeling usually operates with a predefined variable of interest (outcome or target) and a set of predictive parameters, called features or attributes.<sup>45</sup> Machine learning methods work by uncovering hidden relationships between the target and features that classify or predict a particular outcome.<sup>46</sup> In the context of telemonitoring, supervised classification algorithms can be used to yield a classifier that distinguishes between a stable disease state and disease trajectory that is indicative of incipient exacerbation on the basis of patient characteristics collected during a predefined time frame. Thus, from a machine learning perspective, telemonitoring data collected on a daily basis may be considered as features and each corresponding day's disposition with

regard to exacerbation status (yes or no) can be considered as an outcome for predictive modeling. Within this framework, an initial predictive model can be continuously improved with increased numbers of cases.

Common machine learning algorithms for supervised learning include artificial neural networks, Bayesian networks, support vector machines, classification and regression trees (CART), k-nearest neighbors, k-means clustering, discriminant analysis, and logistic regression.<sup>47-48</sup> In this study, predictive modeling utilized a subset of these algorithms that were successfully used in previous work to forecast illness trajectory.<sup>49-51</sup> Our main objective in this study was to explore if telemonitoring data can be used in machine learning algorithms to predict the timing of asthma exacerbations before they occur. Furthermore, we evaluated the effect of varying time windows on prediction accuracy and tested the effect of temporal auto-correlation on the performance of the prediction models.

## Methods

### Data collection

The dataset used in this study consisted of 7001 records collected from asthma patients using previously prescribed home telemanagement.<sup>52</sup> The severity of asthma varied from mild persistent to severe persistent.<sup>31</sup> Patients used a laptop computer at home to fill in their asthma diary on a daily basis. The diary included information about respiratory symptoms, sleep disturbances due to asthma, limitation of physical activity, presence of cold, and medication usage (Table 1). The patients also measured peak expiratory flow (PEF) using a peak expiratory flow meter that communicated PEF values to the laptop automatically. The laptop sent the results of patient self-testing to a central server on a daily basis. Once the self-testing results were received, the patient's current asthma status was automatically assigned to one of four levels of asthma severity on the basis of a widely accepted clinical algorithm promulgated by current clinical guidelines<sup>53</sup>—green zone (zone 1): “doing well;” high yellow zone (zone 2): “asthma is getting worse;” low yellow zone (zone 3): “dangerous deterioration;” and red zone (zone 4): “medical alert.” For the purposes of this study, we merged zones 1 and 2 in one class named “no-alert” and merged zones 3 and 4 into another class named “high-alert.” For each day of patient self-testing, our research database included a set of variables from patient asthma diaries and corresponding asthma severity for this day expressed as “no-alert” zone or “high alert” zone.

### Predictive modeling of asthma exacerbation

In the methodology for this study, we have adapted notions from intertransactional association analysis.<sup>54</sup> However, the specific challenge in applying this methodology lies in the fact that we are interested in predicting the rare event of an imminent asthma exacerbation based on a number of features over a preceding time window consisting of several consecutive days. Our methodology consists of the following steps: (1) develop an attribute importance model for ranking the attributes used for predicting the target event; (2) determine a prediction period preceding the target event ( $W_p$ ); (3) create a set of target mega-transactions ( $T_m$ ) by including all attributes from step 1 for the repeat step 1 for  $W_p$ ; (4) repeat step 1 on  $T_m$ , which results in a set of mega-transactions with a reduced subset of

features ( $T_d$ ); (5) group the transaction set  $T_d$ , such that the transactions belonging to each target class belong to the same group; and (6) perform three sets of experiments: train and test a classifier with the original data, train and test classifiers using a stratified sample with equal representation of each class, train a classifier with the training data from the stratified sample and test data from the rest of the dataset.

### Ranking self-reported attributes

The first step in our methodology is to rank attributes based on their ability to discern the class label of an object. The relative importance of an attribute is developed using the minimum description length (MDL) principle.<sup>55</sup> MDL is a global maximum likelihood estimator that compares different selections of models in terms of the stochastic complexity they assign to a given dataset, with the principle that the shorter the stochastic complexity, the better the model. The relative importance of a given attribute is computed in terms of its relative cost, which consists of the cost of the model (stochastic complexity) and the classification error. The stochastic complexity of a model is the shortest code length that it would take to transmit the data over a channel. The classification error ( $E$ ) is given by  $E = 1 - \max [p(i|D)]$ . The attribute with the least cost has the highest importance.

### Classification algorithms

Three classification algorithms were used for building classification models: adaptive Bayesian network, naive Bayesian classifier, and support vector machines. We briefly describe each algorithm and corresponding analytical workflow below.

The naive Bayesian classifier looks at historical data and calculates conditional probabilities for the class values by observing the frequency of attribute values and of combinations of attribute values. For example, suppose A represents “the PEF of a patient is between 250 and 275” and B represents “the patient is in ZONE 3.” The Bayes theorem states that  $Prob (B \text{ given } A) = Prob (A \text{ and } B) / Prob (A)$ . Therefore, to calculate the probability that a patient whose PEF is between 250 and 275 will be in ZONE 3, the algorithm must count the number of cases where A and B occur together as a percentage of all cases (“pairwise” occurrences) and divide that by the number of cases where A occurs as a percentage of all cases (“singleton” occurrences). Generalizing this to multiple attributes,  $Prob (B \text{ given } A_1, A_2 \dots A_n) = [Prob (A_1 \text{ and } B) * Prob (A_2 \text{ and } B) * \dots * Prob (A_n \text{ and } B)] / Prob (A)$ . If there are multiple class values  $B_1 \dots B_m$ , then the probabilities for all the class values are calculated and the one with the highest probability is selected. The naive Bayesian classifier assumes that the attributes are independent. Despite this assumption this classifier has been reported to have a high predictive accuracy in real-life datasets.<sup>45</sup> The naive Bayesian classifier is also very efficient with linear scalability in terms of the number of attributes and instances.<sup>46</sup>

The second algorithm used, adaptive Bayesian network, was based on Bayesian networks, which use a directed acyclic graph consisting of nodes, where each node represents an attribute.<sup>47</sup> Corresponding to each node are instances with conditional probabilities. The conditional probability of an instance is calculated by the relative frequencies of the associated attributes in the training data. The problem of learning Bayesian networks has

two parts: searching through the space of possible networks, and evaluating the networks developed. In this study we used an adaptive Bayesian network model,<sup>56</sup> which starts with a baseline model, such as a naive Bayesian model on the top  $k$  predictive attributes. The network is built starting with the attribute with the best predictive power as the seed and successively adding other attributes until the predictive accuracy cannot be improved. The resulting model is compared with the baseline model, and, if it is not more accurate, the process is repeated with the next best attribute. The algorithm stops either when there are no more seeds left or one of the predefined conditions are met. Specifically, the predefined conditions are met either when the model does not change after a preselected number of iterations or it contains a preselected number of attributes. The models are evaluated using the MDL principle.

The third algorithm we used is a support vector machine algorithm,<sup>57,58</sup> which uses a subset of training data as support vectors. The support vectors are the closest instances to the maximum margin hyperplane, which provides the greatest separation between the classes. The support vectors are determined by constrained quadratic optimization. Support vector machines are useful in instances with nonlinear class boundaries and avoid the problem of overfitting, as the maximum margin hyperplane is fairly stable even in high-dimensional space spanned by nonlinear transformations.

## Evaluation

The results of the experiments were captured in terms of the number of values for true positive (TP), true negative (TN), false negative (FN), and false positive (FP), which subsequently were converted into overall accuracy, sensitivity, and specificity values as follows:

$$\begin{aligned} Accuracy &= \frac{TP + TN}{TP + FP + TN + FN}, \\ Sensitivity &= \frac{TP}{TP + FN}, \quad Specificity = \frac{TN}{TN + FP} \end{aligned}$$

A receiver operating characteristic (ROC) was used to characterize comparative performance of classifying algorithms for asthma exacerbation prediction resulting from different training data sets. The curve was created by plotting the true positive rate against the false positive rate at various threshold settings.

## Results

### Preparation and analysis of experimental data sets

The experiments were run using Oracle data miner as the data mining tool and an Oracle 10-g database server for storing the data. As noted before, the data was preprocessed so that the value of ZONE on the eighth day (ZONE\_8) was discretized to two values: “high-alert” if ZONE\_8 equals 3 or 4, and “no-alert” if it equals 1 or 2. This resulted in a dataset with 148 high-alert records and 2287 no-alert records, which shows that the data is heavily (90%) skewed toward no alert cases. We created a stratified sample from this data, such that the data distribution among the two classes (high-alert and no-alert) was approximately equal.

The resultant dataset had 146 (49%) high-alert records and 152 (51%) no-alert records. The distribution could not be made exactly equal across the two classes because of software limitations.

Three sets of experiments were conducted to evaluate the effect of using a stratified sample to train a classifier as opposed to using only the original skewed data set. In each of these experiments, we divided the data into two disjoint sets for training and testing so that there are no common records in the two sets. Furthermore, about 70% of the data in each set was used for training and the remaining 30% was used for testing. Each set of experiments was conducted on three classification algorithms. The dataset for the first case consisted of the whole dataset with 2435 records, of which 1452 records were used for training and the remaining 983 records were used for testing. The second dataset consisted of a stratified sample of 298 records, of which 205 were used for training and the remaining 93 were used for testing. In the third set of experiments the classifiers were trained using the training data for the stratified sample of 205 records and were tested against the remaining 2230 of the original records. The breakdown of the dataset sizes is provided in Table 2. In each of the abovementioned experimental datasets, three classifiers were trained and tested: adaptive Bayesian network, naive Bayesian classifier, and support vector machines.

Based on a 7-day window with 21 self-report variables generated daily by an asthma patient, there were 147 attributes initially, of which 63 had a positive value in our attribute importance model, which were kept in our subsequent analyses. However, these 63 attributes were spread over 7 days, and, hence, there were nine attributes with values on each of the 7 days prior to the target attribute, namely, the value of *Zone* on the eighth day. The selection of the 7-day preceding window was based on clinical factors. The most important attribute was the value of *Zone* with reduced importance from the seventh day to the first day. This implies that the *Zone* value on the seventh day was the best predictor of the condition of the patient on the eighth day.

### Evaluation of prediction models

The results of the experiments are summarized in Table 3. At a first glance it may seem that the classifiers performed with a high degree of accuracy when trained with the raw data. However, the sensitivity numbers were particularly low across all three classifiers. Since sensitivity in these experiments was the TP rate, this was viewed as problematic because it indicated the percentage of correctly predicted outcomes when the patient was in a high-alert zone. After training the classifiers with a stratified sample, we found that the sensitivity rates increased substantially. As shown in Table 3, the increases were 33% for the adaptive Bayesian network, 16% for the naive Bayesian classifier, and around 40% for support vector machines. In other words, for all of the experiments, we found that the sensitivity was improved substantially with a classifier trained on the stratified sample as compared to a classifier trained on the original data.

The reason for this increase in sensitivity is that the original data are skewed, with 90% of the records in the no-alert class, and hence biased the classifier toward identifying no-alert classes. We validated this conclusion further by creating an ROC curve (Fig. 1), where the areas under the curve are 83.3%, 89.2%, and 87.8% for cases 1, 2, and 3, respectively. This

shows clearly that the classification model built on a stratified sample performed better compared to one that was built on the raw data. It should be noted that the increase in sensitivity was accompanied by a slight decrease in the values of accuracy and specificity. The accuracies of the classifiers were reduced by 2–5% for the naive Bayesian classifier and 14–15% for support vector machines. However, for the adaptive Bayesian network the accuracy increased around 5%. A similar trend can be noticed for the values of specificity. While the specificity increased by 3% for the adaptive Bayesian network, it decreased by 1.5–6.5% for the naive Bayesian classifier, and 18–20% for support vector machines. The drop of accuracy occurred as a result of the drop in specificity. As can be seen from its definition, specificity refers to the true negative rate, which is the ratio of the times where a patient was correctly identified as being in the no-alert zone to the number of true negatives added to the false positives. This indicates that the number of false positives increased as a result of the adjustment made in favor of detecting the true positives for patients in the high-alert zone.

### Impact of varying time windows on effectiveness of prediction model

The purpose of determining the prediction window is to decide the number of previous days that should be included in making the prediction of the *Zone* value. We used two sets of experiments to determine the prediction window. In the first set of experiments we tested the predictive power of each attribute on day  $i$  on the target attribute on day 8, where  $i$  ranged from  $n-1$  to  $n-7$ . We tested the predictive power of the attributes selected in the last step by successively moving backwards, starting with the day prior to the day for which the prediction is to be made and stopping when the measures of prediction fall below a certain threshold. Three measures were used: accuracy, sensitivity, and specificity, as defined above. The results showed that the accuracy of prediction systematically decreased from the day 7 to day 1 for all three algorithms that were used. The sensitivity values showed a similar trend for support vector machines and the naive Bayesian classifier, but showed an inconsistent pattern for the adaptive Bayesian network. Specificity also systematically decreased from day 7 to day 1 for two out of three classifiers.

In the second set of experiments, we compared the three measures (accuracy, sensitivity, and specificity) for windows with varying width. The first window was  $n-1$  with width 0 (meaning only 1 day prior to the target day). Next, we kept the starting point the same ( $n-1$ ) and varied the width from 0 to 6. Thus, we had seven windows, with the largest window having a width of 6. The results showed a slightly decreasing trend in the values of all three measures, except on the fourth window where there was a sudden jump in accuracy and specificity (Fig. 2). One of the reasons for the decrease in the measures could be temporal auto-correlation.

### Impact of temporal auto-correlation on effectiveness of prediction model

In a subsequent set of experiments we tested the temporal auto-correlation for each attribute by examining its correlation between day  $d_i$  with  $d_{i-1}$ . We tested the time series data for each diary answer for temporal auto-correlation, which revealed that all except one attribute had a high degree (70% or above) correlation with its value on the previous day. Hence, we tested whether selecting only uncorrelated parameters would impact the effectiveness of the



prediction model. Thus, all three classification models were created and tested against attributes whose temporal auto-correlation ranged from 0.81 to 0.45 and compared the results with a baseline model where all parameters were included. The results, shown in Figure 3, did not support the hypothesis that uncorrelated parameters would result in a more effective model.

## Discussion

Our study demonstrated significant potential of machine learning approaches using telemonitoring data for early prediction of acute exacerbations of chronic health conditions. A time-series dataset of predictive attributes from telemonitoring records of asthma patients was used to demonstrate that an asthma exacerbation may be predicted before it occurs, using data from preceding telemonitoring reports. Using a 7-day window, the naive Bayesian classifier, adaptive Bayesian network, and support vector machines were able to predict asthma exacerbation occurring on day 8, with the sensitivity of 0.80, 1.00, and 0.84, and specificity of 0.77, 1.00, and 0.80, respectively.

We initially found that the dataset's distribution is highly skewed. Extremely unequal distribution has been found to be challenging in machine learning with a two-class problem.<sup>59</sup> This problem was addressed by rearranging the dataset for three experiments: the first one with all data used for training and testing, the second one with stratified samples for both training and testing, and the last one with a stratified sample for training all remaining data for testing. Then, we built three predictive models using three different algorithms: adaptive Bayesian network, naive Bayesian classifier, and support vector machines, for the purpose of comparison. Predictive models trained from stratified samples yielded better results, as expected. This was confirmed by improved ROC curves (Fig. 1) and significantly improved sensitivity levels (Table 3). One important issue to note is that, in this study, we focused more on better sensitivity measures of the model to improve the number of correctly predicted target events of patients belonging to the high-alert zone.

Evaluation of the effect of windows size on accuracy, sensitivity, and specificity of high-alert prediction supported the initial choice (Fig. 2). Initial choice of the 7-day window for exacerbation prediction was based on pathophysiological underpinnings of asthma exacerbation and its natural history. For chronic lung disease, it has been shown that common symptoms of exacerbation, such as chest tightness, cough, dyspnea, cold, and cough, increase significantly during the prodromal period that lasts approximately 7 days before commencement of exacerbation.<sup>60</sup> In order to validate use of the 7-day window time-series data in the experiments, we investigated the effect of varying time windows on the effectiveness of the prediction model and found some significant results. Attributes collected from day 7 alone tended to have more predictive power than attributes collected from day 1 alone by several performance measures. The most important attribute in correctly predicting the target attribute, *zone\_8*, is *zone\_7*. This indicates the highest importance of attribute nearest the target event and the lowest importance of attribute farthest the target event. When we varied the width of time windows from 0 to 6, the result showed a slightly decreasing trend in the values of all the three measures, except on the fourth window where there was a sudden jump in accuracy and specificity. We suspected that the slight trend could be the

effect of temporal auto-correlation. Therefore, we conducted a subsequent set of experiments to test the temporal auto-correlation for each attribute by examining its correlation between day  $d_i$  and day  $d_{i-1}$ . Even though all but one attribute had a high degree of correlation within its time series, the classification results when selecting only uncorrelated parameters were not improved from a baseline prediction model.

Using 7-day window time-series data in predictive models made sense from the clinical standpoint. However, the attempt to improve the results by selecting uncorrelated parameters was not quite successful. It is possible that the temporal auto-correlation did not play a straightforward role in our predictive models as expected, although the result of varying the time window was encouraging. There might be other types of correlation among variables that caused the exclusion of uncorrelated parameters to jeopardize the result.

Recent studies on using telemonitoring data for exacerbation prediction corroborated our results.<sup>61</sup> Support vector machines, random forest, multiboost with decision stumps, naive Bayes, k-nearest neighbors, and deep learning were applied by Luo *et al.* to the Asthma Symptom Tracker comprising five questions<sup>62</sup> related to asthma control. The study reported sensitivity of 73.8% and specificity of 71.4% in predicting disease control deterioration 1 week in advance in children with asthma. In another study, the CART algorithm was shown to classify telemonitoring data in COPD patients into either a low-risk or high-risk outcome, with 81% specificity and 61% sensitivity.<sup>63</sup> The resulting algorithm identified a high-risk state 1 day prior to worsening of patient condition on the basis of symptom and medication records. Furthermore, Sanchez-Morillo *et al.* used data from an electronic questionnaire to develop an algorithm for early prediction of COPD exacerbations.<sup>64</sup> The resulting k-means clustering algorithm had sensitivity of 75% and specificity of 90% in predicting exacerbation about 4 days prior to its onset. Thus, the promising results of the present study in adult asthma patients correspond to similar reports on the use of telemonitoring data in machine learning algorithms for early exacerbation prediction in pediatric asthma and COPD.

There are several limitations of the present study, including a relatively small data sample containing limited numbers of cases of asthma exacerbations. As the data set was obtained in a real-life setting from adult asthma patients, the low frequency of asthma exacerbations reflected overall population-based prevalence of this rare event. The resulting class imbalance problem may potentially affect classifier performance.<sup>65</sup> To address this challenge, we introduced two stratified samples with approximately equal target class distribution. Using stratified samples for algorithm training resulted in significant improvement of classifier performance (Table 3). Another approach to address the issue of the imbalanced dependent variable is the synthetic minority over-sampling technique (SMOTE) for creating synthetic minority class examples,<sup>66</sup> which was used to balance classes of controlled and uncontrolled asthma.<sup>62</sup> Although several studies expressed concerns about the ability of synthetic data to represent naturally occurring events,<sup>59,67</sup> this approach warrants consideration in future research on exacerbation prediction.

Another potential limitation of our study relates to the use of a single scoring function and a limited number of classifiers. Minimum description length (MDL), Akaike's information

criterion (AIC), Bayesian Dirichlet equivalence score (BDeu), and factorized normalized maximum likelihood (fNML) are among the most popular scoring functions used for model selection.<sup>55-59</sup> Our choice of MDL was based on the findings of a recent study<sup>68</sup> showing that MDL consistently outperformed other scoring functions, such as AIC, BDeu, and fNML. All predictive features were successfully ranked by their relative importance with MDL principle prior to their inclusion in the model. Attributes with negative relative importance value were excluded from the model since their inclusion negatively affects the model performance.

The choice of machine learning algorithms in this study was based on the findings of previous studies reporting that adaptive Bayesian network,<sup>49</sup> naive Bayesian classifier,<sup>50</sup> and support vector machines<sup>51</sup> are effective means for predicting disease trajectories especially in the presence of imbalanced data sets.<sup>59</sup> Consideration of additional machine learning approaches may potentially facilitate our work exacerbation prediction in the future. Among possible approaches, particular attention should be given to recent work on medical temporal-knowledge discovery via temporal abstraction, which may be relevant to prediction of disease trajectories characteristic for acute illness exacerbation.<sup>69</sup> Temporal abstraction of both the time and value dimensions was shown to be effective in transforming multiple types of point-based data into a meaningful, time interval-based data representation, in which significant interval-based temporal patterns can be discovered.<sup>70</sup>

Telemonitoring data used in this study for predictive modeling included asthma symptoms, self-reported medication consumption, asthma trigger exposure, and lung function assessed by PEF. Although using these parameters demonstrated promising results, future predictive models for asthma exacerbation may benefit from multiple data streams that combine telemonitoring data with other potentially relevant predictive factors. These factors can be broadly categorized as genomic, clinical, sociodemographic, behavioral, and environmental. The genomic profile was shown to affect the likelihood for developing acute asthma attacks,<sup>32</sup> as well as individual efficacy of asthma medications.<sup>71</sup> Clinical factors, such as disease history, asthma care utilization, lung function, inflammation indicators, and laboratory and other biomarkers, have been widely used for asthma exacerbation prediction.<sup>72-73</sup> In addition, various sociodemographic factors, such as age, sex, race, ethnicity, income, social support, and proximity and access to quality medical care, were reported to be associated with frequency of asthma exacerbations.<sup>74-75</sup> Behavioral factors, such as self-care skills, health literacy, self-efficacy, medication adherence, depression, anxiety, and stress levels, were shown to contribute to the development of asthma exacerbations,<sup>76-77</sup> and environmental factors, such as indoor and outdoor pollution, exposure to allergens, and weather conditions, have been demonstrated to play an important role in asthma exacerbation prediction.<sup>40</sup>

Future algorithms may benefit from predictive modeling that combines all relevant factors in one predictive framework for asthma exacerbations (Fig. 4). There are several advantages in implementing such a predictive framework. First, since certain parameters (e.g., race, sex) remain constant and certain parameters change more frequently (telemonitoring data) or less frequently (lab data or care utilization), the framework can serve as the foundation for constant update of relevant information in a unified dataset containing all predictive features

in one location. Second, with all relevant features available within such a predictive framework, it is possible to identify the subset of features that is the most relevant for a particular patient in order to predict incipient asthma exacerbations. Third, the proposed framework may be instrumental in developing uniquely personalized prediction algorithms over time (Fig. 5). Initial decision support of patient telemonitoring inevitably has to be based on population-based algorithms ideally matched to patient individual characteristics. However, in the process of telemonitoring, a significant amount of data is accumulated that allows constant retraining of underlying prediction algorithms using personal telemonitoring data and updates from multiple relevant data streams. This will eventually result in implementation of personalized predictive algorithms that are uniquely tailored to individual patient profiles.

## Conclusion

Machine learning approaches have significant potential in prediction of acute exacerbations in asthma patients. Telemonitoring data can be used successfully in predictive modeling. Future steps in developing predictive models for asthma exacerbation will utilize a comprehensive predictive framework combining multiple data streams, and further optimization of feature selection, data set preparation, and machine learning approaches may significantly enhance resulting algorithms. Predictive modeling of asthma exacerbations may be relevant to developing effective predictive frameworks for exacerbations in other chronic health conditions.

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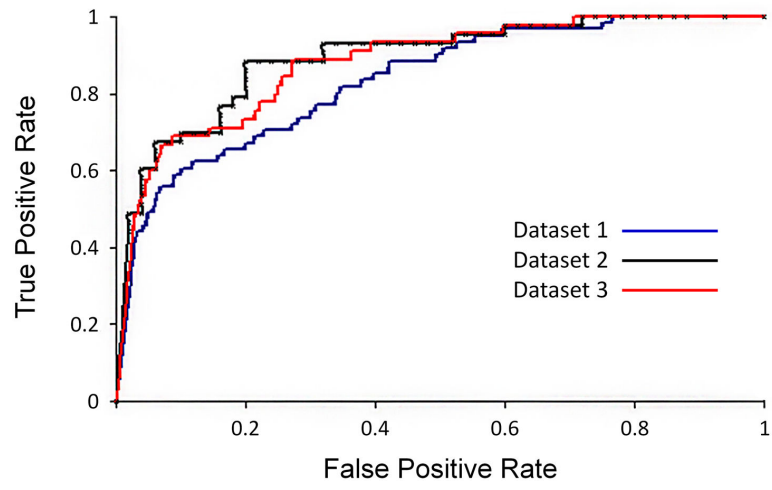
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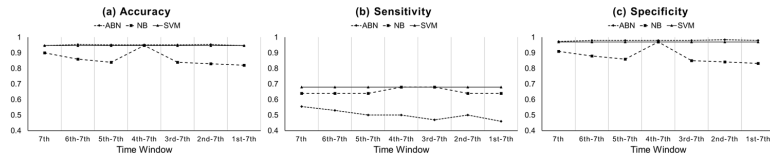
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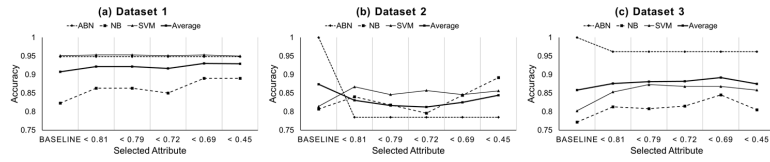




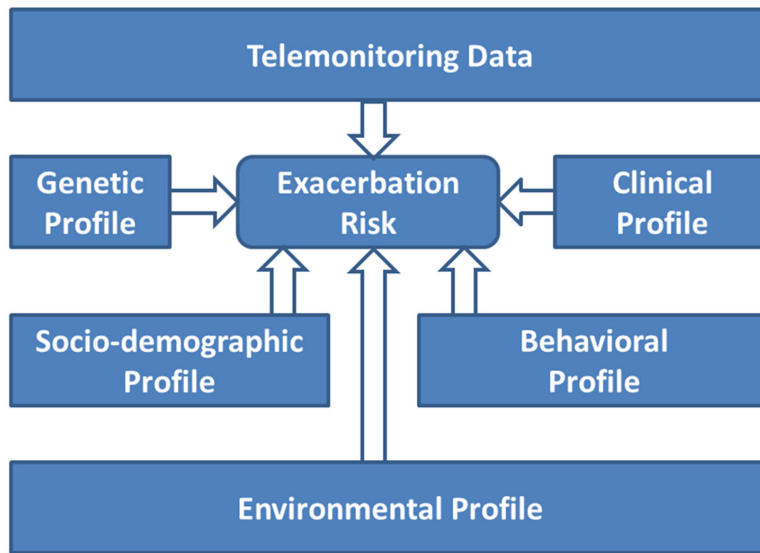
**Figure 1.**  
The receiver operating characteristic (ROC) curve.



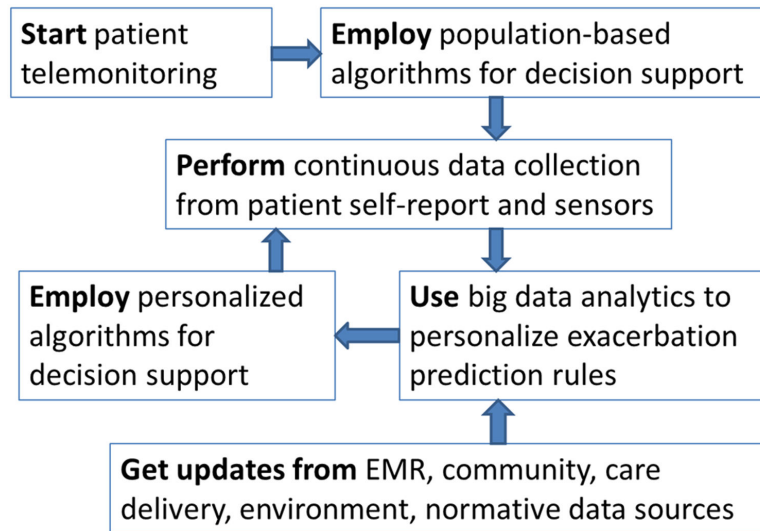
**Figure 2.**  
Impact of varying time windows on effectiveness of prediction model.



**Figure 3.**  
Impact of temporal auto-correlation on effectiveness of prediction model.



**Figure 4.** Comprehensive predictive framework for advanced forecast of asthma exacerbations.



**Figure 5.** Steps to implement personalized decision support for early exacerbation prediction.

**Table 1**

## Daily asthma diary

#	Description
1	Wheeze
2	Cough
3	Sputum production
4	Chest tightness
5	Shortness of breath
6	Limitation of physical activity
7	Overall use of quick-relief inhaler
8	Exposure to your asthma triggers
9	Overall estimate of your asthma today
10	Do you have a cold?
11	How many puffs of quick-relief inhaler did you take during the last 24 hours?
12	How many puffs of preventive medicine did you take during the last 24 hours?
13	Did asthma bother your sleep?
14	How many times did asthma wake you up last night?
15	How many puffs of quick-relief inhaler did you take during the last night?
16	How many times did you use quick-relief inhaler during the last 24 hours?
17	How many tablets of prednisone did you take during the last 24 hours?
18	How many times did you use nebulizer during the last 24 hours?
19	When was the last time you used quick-relief inhaler?
20	How many puffs of the second controller medicine did you take during the last 24 hours?

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**Table 2**

Characteristics of different experimental data sets

<b>Description</b>	<b>Training</b>	<b>Test</b>
Dataset 1: all data used for training and testing	1452	983
Dataset 2: stratified sample for both training and testing	205	93
Dataset 3: stratified sample for training all remaining data for testing	205	2230

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**Table 3**

Evaluation of asthma prediction algorithms

Dataset	Type of classifier								
	Adaptive Bayesian network			Naive Bayesian classifier			Support vector machine		
	1	2	3	1	2	3	1	2	3
<b>Accuracy</b>	0.949	1.000	1.000	0.823	0.807	0.772	0.952	0.817	0.803
<b>Sensitivity</b>	0.672	1.000	1.000	0.639	0.797	0.800	0.455	0.860	0.844
<b>Specificity</b>	0.968	1.000	1.000	0.835	0.820	0.771	0.982	0.780	0.802

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