Using Association Rule Mining to Detect Adverse Drug Events

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Abstract — **Improving safety for patients is a top priority in health care. However, adverse drug events (ADEs) are estimated to account up to 5% annually of hospitalized patients causing morbidity and mortality. Due to the availability of large amount of medical data, discovering ADE patterns using data mining (DM) techniques becomes a challenge. This paper proposes a framework to mine a large database containing data about previously prescribed drugs and their adverse outcomes. This mining process yields association rules necessary to detect ADEs in future prescriptions. In addition, an Adverse Drug Events Detection Tool (ADEDT) is built to help physicians detect ADE during drug prescription phase.**

Index Terms — **Adverse drug events, association rules, data mining.**

I. INTRODUCTION

Nowadays, hospitalized patients suffer from many adverse drug events (ADEs); this appears to represent an epidemic. An ADE is any adverse outcome that may cause an injury from the use of a drug rather than the underlying condition of the patient. During the past decade, the prevention of adverse drug events has become a major focus of medical institutions and has received the attention of government officials at both state and national levels [25]. Several researches in this area have demonstrated that ADEs account for up to 41% of all hospital admissions that costs more than $2 billion annually in inpatients [23]. There is a difficulty to detect the ADEs in the hospitals because the physicians still use the spontaneous reporting systems (SRS) and the physicians depend only on their own experience to detect ADEs. New various methodologies for detection of ADEs are based on the use of Information Technology and have the potential to significantly detect the ADEs in a timely and cost-effective way using the hospital information system as a base. Moreover many intelligent techniques are used e.g., clinical decision support systems (CDSS) that help physicians in gathering relevant data, making clinical decisions and managing medical actions more effectively. The DM tools and machine learning methods are also available today for use in medical and health care area. Its application in detecting ADEs is relatively new. The main objective of this research is to discover the combination of drugs that might cause ADE.

The paper is organized as follows: Section II presents a review of some related work in the area of detecting ADEs using different techniques. Section III presents a proposed framework to extract association rules used to detect ADE. Section IV depicts a case study which employs the proposed framework to help detecting ADE. In section V, the generated association rules are presented, analyzed and validated. Section VI demonstrates a prototype of an ADE detection tool that might be used to detect ADEs. Finally, this paper is concluded in section VII.

II. REVIEW AND RELATED WORK

The spontaneous reporting system (SRS) is the most important early warning system of ADEs [10]. Most hospitals still rely on SRS. Adverse drug events reported through these reporting systems represent only a small fraction of all adverse events and errors that occur (5–10% of ADEs) [3],[29][4],[21] and [30].

Information technology took the role to enhance the ADEs detection [3] and [7]. Many health care institutions are moving to implement Computerized Physician Order Entry (CPOE) systems [25]. The CPOE system is a computer application that allows physicians to write all orders through the selection from menus. CPOE implementation resulted in significant reductions in harmful medication errors and ADEs [12], [17] and [10]. It has been reported that further enhancements of CPOE should be possible with additional decision support systems [5],[11]and [11].

The ultimate goal of CDSS is to allow physicians to spend more time on complex decisions by reducing routine tasks resulting to improve physicians' performance [22]. A study judged that CPOE with decision support have likely prevented 40% (20/50) of inpatient preventable ADEs and 36% (16/44) of outpatient ADEs [28]. But the development of decision support systems and their integration into hospital information systems require more time and effort by medical experts to create and

maintain knowledge bases [24]. As an example of CDSS is the trigger tools (alerting systems) programs that function continuously, monitoring clinical data as they are stored in the patient's electronic record. They can notify physicians about problems that occur asynchronously as they are designed to test specific types of data against predefined criteria [6].

Artificial Intelligence field is employed in detecting ADEs, including artificial neural network (ANN), fuzzy logic and DM techniques. ANN is used to predict the outcome resulting from prescribed drugs better than expert physicians; so it can be used to learn the prescribing patterns [9]. Fuzzy logic can be utilized to not only represent, interpret and compute imprecise and subjective cases that are commonly encountered in the ADE problem but also to retrieve prior experiences by evaluating the extent of matching between the current situation and a past experience. A study [21] developed the recognition-primed decision (RPD) model that utilizes fuzzy sets, fuzzy rules, and fuzzy reasoning to build an active, multi-agent framework for early detection of ADEs by utilizing electronic patient data distributed across many different sources and locations in real time providing alerts on significant or unexpected ADEs.

As the generating and collecting data have been increasing rapidly in the medicine field, DM is used to discover patterns and extract useful hidden information for medical purposes from medical databases [25]. One of the DM techniques is "Association Rules", which focus on finding relationships (associations) between a certain attribute (target attribute) that the user is interested in, and the remaining attributes in a relational table. Since its introduction in [1], this technique has received great interest by the DM community and a lot of research has been done resulting in the development of many different algorithms. Association rules are defined by level of support and confidence. The support and confidence are the two most important quality measures for evaluating the interestingness of a rule [19]. The support (s) of a rule is represented by the formula: $s(X \rightarrow Y)=|X \cup Y|/n$; where $|X \cup Y|$ is the number of transactions that contain all the items of the rule and n is the total number of transactions. The support is a useful measure to determine whether a set of items occurs frequently in a database or not. The confidence (c) of a rule describes the percentage of transactions containing X which also contain Y. $c(X \rightarrow Y)=|X \cup Y|/|X|$. This is a very important measure to determine whether a rule is interesting or not.

Binary association rules is a special implementation of the association rules, it means that rules can only be derived from data containing binary data, where an item either exists in a transaction or it does not exist [19]. Making only Boolean values (true or false, represented by 1 and 0) possible. Every item in a transaction can thus be defined as a binary attribute with domain {0, 1} [1]. The Apriori algorithm was the first attempt to mine binary association rules from a large dataset. It has been presented in [2]. The algorithm can be used for both, finding frequent patterns and also deriving association rules from them.

More details about using Information Technology in the area of detecting ADEs can be found in [29]. It can be inferred from [29] and this short review that detecting ADEs is very important for medical field and therefore considered as a hot area of research. New methodologies and further works are urgently required in this area.

III. A PROPOSED FRAMEWORK TO DETECT ADE USING ASSOCIATION RULE MINING

This section presents a proposed framework to detect patterns of ADEs using association rule mining. The process of Knowledge Discovery in Databases (KDD) is generally divided into three main steps: data preparation, data mining, and data interpretation [12]. The proposed framework depends mainly on the KDD and applies it in medical field. The framework is designed to work with data mining tools that use association rule mining on medical database constrained by the existence of prescribed drugs and their adverse outcomes. Figure 1 shows the proposed framework architecture and its components.

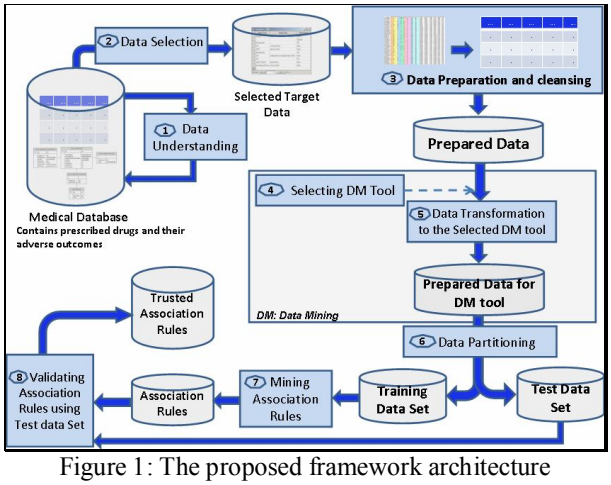

Figure 1: The proposed framework architecture

The proposed framework consists of eight main processes, it starts with the understanding and analysis of the given medical data source. Although the entire data is important, the part of the data which holds the prescribed drugs along with its adverse outcomes is the target data for

the proposed framework. This part of the data source then is selected and new data source is constructed as input for the next processes. The selection process could be done simply by using a SQL statement, or other database query language.

The selected data passes through preparation and cleansing process to improve the quality of the data and consequently the efficiency of the whole framework output. This process aims to eliminate the different sources of errors that could occur in the data source (e.g. data duplication, domain inconsistency or wrong values, and missing values). In the de-duplication process, duplicate data is deleted, leaving only one copy of the data to be stored. Some wrong values are produced when drugs are incorrectly spelled or incorrect information about the adverse outcomes is given. Missing values is another source of problems as this might affect the type of discovered patterns. If the data item is not defined it should be NULL.

The forth process focuses on selecting the DM tool along with its implemented algorithm. DM tool selection depends on its ability to use association rule mining required by the proposed framework. The data transformation process comes to put the prepared data into the structure and format understood by the selected DM tool whereas each tool has its own data format. Data transformation operation produces formatted and smoothed data, ready for being processed by DM tool.

The sixth process in the proposed framework is data partitioning which divides the whole data set D randomly into two non-intersected sets: training data set D_{train} and test data set D_{test} where $D=D_{train} \cup D_{test}$ and $D_{train} \cap D_{test}=\emptyset$. The whole data set is randomly partitioned to help ensure that training and test partitions are minimizing the effects of data discrepancies. The D_{train} and D_{test} sets size depends on the whole data set size. In large data sets, the D_{train} set can be 70% of the whole data set while the D_{test} set is 30%. The proposed framework suggests repeating building D_{train} and D_{test} sets t times (t is a user-specified parameter according to the case study) to achieve basic cross validation and compute averages for extracted rules metrics in the next process. This process generates t independent D_{train} sets and t independent D_{test} sets.

The seventh process in the proposed framework is mining association rules from both D_{train} and D_{test}. The two metrics Support (s) and Confidence (c) are used to define the extracted association rules.

Finally, the proposed framework eighth process is concerned to validate discovered rules. A train/test approach is used to validate the extracted association rules [17]. The D_{train} is used to find interesting patterns while the output of D_{test}, that is a set of rules, is used for validation and estimating the errors of the detected rules. The t sets produce different sets of rules that will have similar rules as well as different rules. The objective of repeating validation on several independent test sets is to get a set of validated association rules. At the end, the DM algorithm finds a validated rule set (R) indicates the existence of ADE that is the intersection of all rule sets (t) from training and test data sets. The metrics (support and confidence) of each rule are computed as averages of the test metrics on the t test sets [26]. Let D_I is the I^{th} test set. Let $X \rightarrow Y$ is a valid rule appearing on all t sets. So:

$$s(X \Rightarrow Y) = \frac{1}{t}\sum_{I=1}^{t} s(X \Rightarrow Y, D_I)$$

$$c(X \Rightarrow Y) = \frac{1}{t}\sum_{I=1}^{t} c(X \Rightarrow Y, D_I)$$

IV. APPLYING THE PROPOSED FRAMEWORK IN A CASE STUDY

To bring our proposed framework to reality, it is applied to a case study. The case study depends on two databases; the first is the Adverse Event Reporting System (AERS) database created by the U.S. Food and Drug Administration (FDA) [15], the second is the database of high alert medications created by the Institute for Safe Medication Practices (ISMP) [20]. The case study uses Waikato Environment for Knowledge Analysis (WEKA) [15] as a data mining tool to generate association rules of ADE of high alert medications using Apriori algorithm.

A. Data Source Description

AERS Database

The AERS is a computerized information database designed to support the FDA's post-marketing safety surveillance program for all approved drugs and therapeutic biologic products. The FDA uses AERS to monitor new adverse events and medication errors that might occur with these marketed products. The reports in AERS are evaluated by clinical reviewers in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) to monitor the safety of products after they are approved by FDA.

The AERS that is used in this case study reflects data from January 2004 to September 2009 which contains more than 1.8 millions of event report and 6.7 millions records of prescribed drugs in generic names and their adverse outcomes. The data are provided into ASCII files in which data elements are separated by a '$' sign ($ delimited). These files are imported to data base tables.

High Alert Medications Database

As there are a huge number of reported drugs in the AERS database, the case study is focused only on the high alert medications (HAM). HAM are drugs that have a high risk of causing significant patient harm when they are used in error either individually or in combination. The high alert medications are used to determine which medications require special safeguards to reduce the risk of errors. ISMP created and periodically updates the list of potential high alert medications, based on error reports submitted to ISMP Medication Errors Reporting Program from practitioners and safety experts.

B. Data Selection

In this process, two tables are selected from the AERS data files and uploaded to a new database: drugs file and outcome file. All records that represent HAM are selected from drugs table using SQL statements. The target fields from drugs table are: *ISR* and *Drug_name* (where *ISR* is the report number and *Drug_name* is the generic drug name). The target fields from *outcome* table are both: *ISR* and *Outc_cod* (where *Outc_cod* is the adverse outcome of the drugs in the specified report). Adverse outcomes ae coded as follow: Death (DE), Life-Threatening (LT), Hospitalized (HO), Disability (DS), Congenital Anomaly (CA) and Required Intervention to Prevent Permanent Impairment/Damage (RI). Finally, a target data set *Drugs_HAM_Out* is created on which discovery process will take place to find out ADEs patterns. It contains the attributes: *ISR* and *Drug_name* from the *drugs* table and *Outc_cod* from *outcome* table.

C. Data Preparation and Cleansing

Data preparation and cleansing processes are used to clean the data before proceeding in further steps. This includes: i) Removing of noise by detecting and removing errors and data inconsistencies in *Drugs_HAM_Out* table, ii) Eliminating the repeated event reports in the *Drugs_HAM_Out* table, and iii) Excluding the reports that fail to spot its adverse outcome.

D. Data Transformation for WEKA Use

The implementation of the case study is done by WEKA using Apriori algorithm [2]. WEKA is an open source data mining and machine learning system which gets widespread acceptance in both academia and business community [14].

The prepared table *(Drugs_HAM_Out)* shows each event report in one or more records, each record contains one prescribed drug and its adverse outcome. In order to get this table ready for mining, all records should be transposed letting the *out_cod* (*status*) and *drug names* appear as attributes. Each record represents one event report in which tow values are possible: NULL, if the drug doesn't exist in this event report whilst, the value takes one if the drug exists in the event report. The resulted table *Drugs_HAM_Out_t* is considered as the data set (*D*) and is transformed to the Attribute-Relation File Format (*arff*) understood by WEKA. Further two steps are done to prepare the *arff* file for WEKA use:

i) Discretization: Apriori algorithm can extract rules from binary data. It can be done simply by discretizing the attributes in the *arff* file, and replacing it with the set of discrete values (0, 1). The value 1 indicates that this drug is taken while the value 0 indicates that this drug is not taken in this event report.

ii) Changing zero values to "?" sign: WEKA doesn't recognize the zero value in the records, instead of leaving them as *0*, the 0 values are replaced by '?' mark understood by WEKA. Finally, the *arff* file, shown in Figure 2, has two distinct sections (Header section and data section) and ready to use by WEKA.

```
% Lines that begin with a % are comments
%This File Created by Ashraf Shawky.
%
@relation 'cleaned data'

@attribute status {DE,CA,DS,HO,LT,OT,RI}
@attribute 'ALTEPLASE' {1,0}
@attribute 'AMIODARONE' {1,0}
@data

HO,?,?,?,?,?,?,?,?,?,?,?,?,?,?,?,?,?,?,?,?,?,?,?,?,?,?,?,1,?,?,?,?,?,?,?,?,?,?,?,?

DS,?,?,?,?,?,?,?,?,?,?,?,?,?,?,?,?,?,?,?,?,?,?,?,?,?,?,?,?,?,?,1,?,?,?,?,?,?,?,?,?
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Figure 2: The prepared ARFF file

E. Data Partitioning

The final prepared data set *Drugs_HAM_Out_t* (*D*) in the previous sub-section, is randomly partitioned to generate a training data set D_{train} representing 70% from the entire data set *D*, and a test data set D_{test} represents the remaining 30%. where $D=D_{train}\cup D_{test}$ and $D_{train}\cap D_{test}=\emptyset$. This process is repeated 5 times generating 5 independent pairs of D_{train} and D_{test}. The average value for every rule metrics is calculated in the next process.

F. Extracting Association Rules

All D_{train} and D_{test} *arff* files are opened in WEKA and the Apriori Algorithm is used to extract rules from each data set. The Apriori algorithm parameters are configured as follows:

- *Car:* it has been set to true to extract the rules based on the "*Status*" class only.
- *ClassIndex*: it has been selected to 1 as the status attribute is the first attribute and it's the interested attribute in our case.
- *Delta*: it has been set to 0.01. The delta value is used to iteratively decrease the maximum support until min support is reached or required number of rules has been generated.
- *LowerBoundMinSupport*: it has been set to 0.0005 as minimum support as it's related to domain sensitivity.
- *MetricType*: the confidence metric type is selected to rank the extracted rules.
- *MinMetric*: it has been set to 0.01. This value considers only rules with confidence higher than this value according to the domain sensitivity.
- *NumRules*: it has been set to 1000, to eliminate the number of rules constraint and to get the maximum number of rules.
- *RemoveAllMissingCols*: it has been set to true to remove columns with all missing values.
- *UpperBoundMinSupport*: it has been set to 1.00 as maximum support in order to obtain the maximum support rules. The algorithm starts iteratively decreasing the selected maximum support from this value until min support is reached or required number of rules has been generated.

The extracted rules are depicted, analyzed and validated in the next section.

V. RESULTS AND RULES VALIDATION

The Apriori algorithm is conducted using WEKA tool on a data set that consists of 60,363 records. 123 rules are extracted from this run. Each extracted rule has one drug or more and can cause one of the adverse outcomes (statuses). One sample rule is explained here:

METOPROLOL POTASSIUM_CHLORIDE ==> Status = HO

As the rule indicates, if the patient takes the drugs "***METOPROLOL***" and "***POTASSIUM_CHLORIDE***"; his/her status will be ***Hospitalization*** with support 0.006 and confidence 0.57 as shown in table 1. In other words, the two mentioned medications were found together 366 times from 60,363 records, 210 records from them point the status as ***Hospitalization***.

To validate the discovered rules, a validation process, shown in Figure 3, is used.

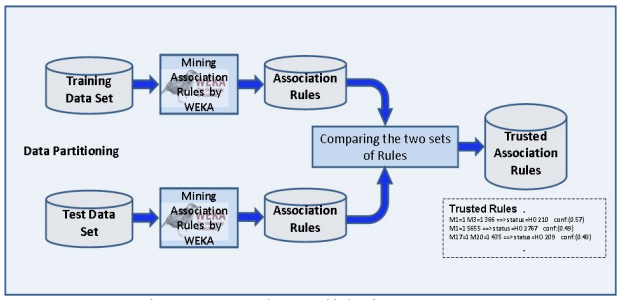

Figure 3: Rules validation process

The validation process consists of three main phases:

Phase1: Dividing the whole data set in two independent segments: the entire data set D which contains 60,363 records is randomly partitioned into two data sets. The first data set is training data set (D_{train}) which represents 70% from the entire data set and it will be used to discover association rules. The second data set is test data set (D_{test}) which represents the remaining 30% and will be used to validate the rules come from the training data set. This process is repeated five times generating 5 pairs of data sets ($D_{train}i$ and $D_{test}i$) where i is the iteration number. These iterations are done to achieve basic cross validation and to eliminate rules that cannot be generalized [26].

Phase 2: Generating rules: Apriori algorithm is applied through WEKA for all pairs of data sets. A pair of results per iteration is obtained ($TR_{Rules}i$, $TS_{Rules}i$) from $D_{train}i$ and $D_{test}i$.

Phase 3: Comparing the extracted rules from the two data sets $D_{train}i$ and $D_{test}i$: through the comparison between the two sets of rules ($TR_{Rules}i$, $TS_{Rules}i$) to get validated rules at the end. Validated rules are the rules that appear in all pairs of results and have a low standard deviation for confidence metric.

Due to the large number of discovered rules, a sample of 20 rules is examined. During this examination, to get validated rules, the missing rules in certain iteration or in test data set of current iteration are excluded from the validated rules. That means rules that are valid on both training and test data sets in all iterations are considered. After the five iterations take place, the average *confidence* of each rule in all iterations is considered to be the *confidence* of the validated rule.

The final comparison of the 20 rules results in 13 validated rules. Table 1 shows the validated rules *R* along with their average confidence.

Table 1: Validated rules

R#	Drug Generic Name		Status	Confidence
1	OPIUM TINCTURE		HO	0.71
2	POTASSIUM_CHLORIDE	PROPOFOL	DE	0.44
3	METOPROLOL	POTASSIUM_CHLORIDE	HO	0.57
4	DIGOXIN	MAGNESIUM SULFATE	HO	0.49
5	COLCHICINE	POTASSIUM_CHLORIDE	HO	0.51
6	INSULIN	METOPROLOL	HO	0.47
7	INSULIN	PROMETHAZINE	HO	0.50
8	COLCHICINE	DIGOXIN	HO	0.51
9	POTASSIUM_CHLORIDE	SODIUM_CHLORIDE	DE	0.37
10	TENECTEPLASE		DE	0.54
11	DIGOXIN	METOPROLOL	HO	0.48
12	PROMETHAZINE		DS	0.05
13	MAGNESIUM SULFATE		CA	0.03

VI. BUILDING A PROTOTYPE TO DETECT ADE USING ASSOCIATION RULES

This section presents a prototype: Adverse Drug Event Detection Tool (ADEDT) to make use of the validated association rules. The prototype is provided by two basic functions: 1- *Check ADE:* this function receives the drugs names (generic names or trade names), check the drugs combination in the rules database and send back the result to the physician informing him/her by the outcome of using these drugs (including the confidence level). *2- Log ADE*: this function receives the physician code, date, time and rule ID and then log these data to a table for security and tracking purposes. The ADEDT architecture is shown in Figure 4.

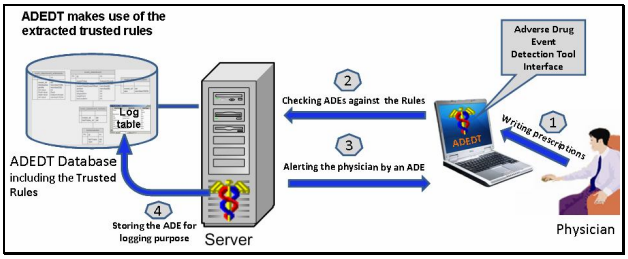

Figure 4: ADEDT architecture

The prototype is provided by a friendly graphical user interface to help the physician to put the basic patient data and prescribe the drugs. When a physician prescribes drugs for a patient, the combination of prescribed drugs is tested against the rules that are stored into the database of the prototype. If there is an ADE, a warning message is displayed containing the expected adverse outcome and level of confidence as shown in Figure 5. If the confidence is minor –from the point of view of the prescriber- the warning can be acknowledged and the prescription is completed. Prescribers do not have to give a reason for overriding warnings but warnings are logged into a log table to track them by more senior prescribers. Explanation can be showed to illustrate how many cases match this combination happened in the AERS database as in Figure 5.

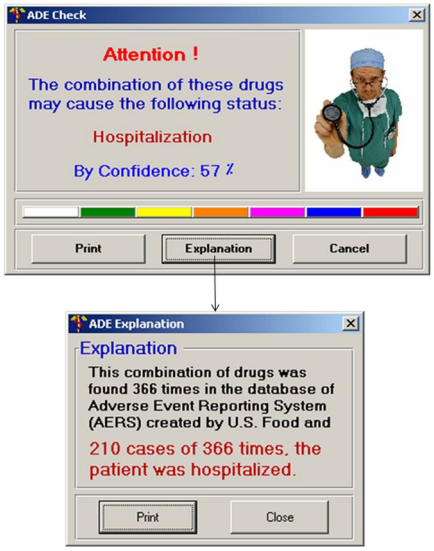

Figure 5: Prototype alert and explanation

CONCLUSIONS AND FUTURE EXTENSIONS

The current approaches used by most organizations to detect ADEs are clearly insufficient. Association rules represent a data mining technique that has a great potential in the medical domain to detect ADEs. This paper presented a proposed framework to detect the patterns of drugs that cause ADEs using association rule mining. The proposed framework gives a general approach to extract validated association rules from medical database containing the prescribed drugs and their adverse outcomes using association rule mining technique. The proposed ADEDT provides physicians by important and critical support information about ADE in the moment of decision making which may result in improvement of the health care quality and patient safety. In the ADEDT, the drug generic names are converted into drug trade names giving it a wide use in hospitals. The proposed prototype is novel in advising the physicians during prescribing critical drugs. The combination of prescribed drugs is tested against the rules that are stored into the database of validated rules providing a warning message containing the expected adverse outcome and level of confidence.

Future extensions include applying other association rules algorithms. We intend to deploy the prototype in life use through implementing new versions for Web-Based applications and mobile devices, to be easily accessible by physicians.

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