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Using a Machine Learning System to Identify and Prevent Medication Prescribing Errors: A Clinical and Cost Analysis Evaluation

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Background: Clinical decision support (CDS) alerting tools can identify and reduce medication errors. However, they are typically rule-based and can identify only the errors previously programmed into their alerting logic. Machine learning holds promise for improving medication error detection and reducing costs associated with adverse events. This study evaluates the ability of a machine learning system (MedAware) to generate clinically valid alerts and estimates the cost savings associated with potentially prevented adverse events.

Methods: Alerts were generated retrospectively by the MedAware system on outpatient data from two academic medical centers between 2009 and 2013. MedAware alerts were compared to alerts in an existing CDS system. A random sample of 300 alerts was selected for medical record review. Frequency and severity of potential outcomes of alerted medication errors of medium and high clinical value were estimated, along with associated health care costs of these potentially prevented adverse events.

Results: A total of 10,668 alerts were generated. Overall, 68.2% of MedAware alerts would not have been generated by the existing CDS system. Ninety-two percent of a random sample of the chart-reviewed alerts were accurate based on structured data available in the record, and 79.7% were clinically valid. Estimated cost of adverse events potentially prevented in an outpatient setting was more than $60 per drug alert and $1.3 million when extrapolating study findings to the full patient population.

Conclusion: A machine learning system identified clinically valid medication error alerts that might otherwise be missed with existing CDS systems. Estimates show potential for cost savings associated with potentially prevented adverse events.

Patient safety represents a key concern in health care, as medical error continues to be a major issue and a cause of substantial harm.[1] A leading source of harm is prescription drug errors, which result in substantial morbidity, mortality, and excess health care costs, estimated at more than $20 billion annually in the United States.[1–3]

Currently, clinical decision support (CDS) alerting tools are widely used to identify and reduce medication errors.[4–9] However, these CDS systems have a variety of limitations. One limitation is that current CDS systems are rule-based and can thus identify only the medication errors that have been previously identified and programmed into their alerting logic. Further, most have high alerting rates with many false positives, resulting in alert fatigue.[10–12]

Previous studies have assessed the role of software programs related to improving drug safety.[13–17] Examples include assessment of the accuracy of the list of drugs a patient is taking (medication reconciliation),[13,14] identification of the contradictions between the structured and narrative components (providers' notes) of electronic prescriptions (internal prescription discrepancies),[15] and evaluation of the opportunities for enhancing the integration and presentation of drug safety information[16] and improving the quality and consistency of medication reviews performed by pharmacists.[17]

Machine learning capabilities are increasingly applied in health care.[18] Examples of machine learning applications in the health domain include drug discovery and development, diagnosis, disease and outcomes prognosis, and patient management. Machine learning programs may also enhance CDS systems and have the potential to improve the identification and prevention of medication errors and thus, patient safety.

Despite the growing applications of machine learning in medicine, there is a lack of studies assessing the clinical validity and value of these health care interventions. The aims of this study were to further assess the clinical validity and value of one such system (MedAware), and to estimate the health care–related costs associated with medication errors potentially prevented by the system.

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METHODS

Application Evaluated

MedAware (Ra'anana, Israel) is a software system developed for identification and prevention of prescription errors and adverse drug effects.[19] This system identifies medication issues based on machine learning using a set of algorithms with different complexity levels, ranging from statistical analysis to deep learning with neural networks. Different algorithms are used for different types of medication errors. The data elements used by the algorithms include demographics, encounters, lab test results, vital signs, medications, diagnosis, and procedures.

These algorithms generate patient-specific alerts on prescriptions that appear to be outliers that deviate from the conventional prescribing patterns of physicians in similar patient clinical and/or demographic situations.[20] In addition to the standard rule-based alerts of legacy CDS systems, this outlier detection methodology uses information from electronic medical records to identify unusual prescribing decisions in patient care. The system can generate alerts for clinicians at the point of care, as well as monitor post-prescribing events that may render active medications an outlier to the patient's clinical status. The system can also evaluate data retrospectively to produce aggregate alert data about potential medication errors that may be used for a variety of purposes, including population health management and organizational safety and quality improvement efforts. A recent study that evaluated the MedAware system found that it generates novel alerts that might otherwise be missed with existing applications, and it does so with a reasonably high degree of alert usefulness.[21]

The MedAware system analyzes historical electronic medical records and generates a computational model that captures the population that is likely to be prescribed a given medication and the clinical environment in which the medication is likely to be prescribed. The model identifies prescriptions that are statistically significant outliers given a patient's clinical situation; that is, medications that have rarely or never been prescribed before to similar patients with similar clinical conditions. Such prescriptions are flagged by the system as potential medication errors.

A short textual description is automatically generated by the system for each alert generated, to explain why the alert fired. This explanation enables clinicians to understand and track the reasoning underlying the generated alert (for example, an accompanying explanation may read "DIGOXIN is prescribed while patient is an adult or younger, doesn't have cardiac dysrhythmias, ischemic heart disease, congestive heart failure, and similar drug wasn't used before").

The MedAware system generates three distinct types of alerts:

- Clinical outliers. Medication is marked as an outlier to patient's characteristics (for example, prescribing birth control medication to an infant boy, prescribing insulin to a patient without diabetes).
- Time-dependent. Changes in blood test results indicate that a current medication is an outlier to a patient's profile (for example, thrombocytopenia in a patient on anticoagulants).
- Dosage outliers. Medication dosage is an outlier to the machine-learned dosage distribution of the medication in the population and/or to the patient's own history (for example, 180 mg dose of Oxycontin as a high dose outlier).

Study Setting, Patient Population, and Data Collection

The patient population of this study are those who had at least one outpatient encounter with a provider affiliated with Brigham and Women's Hospital (BWH) or Massachusetts General Hospital (MGH) during the two-year period from January 1, 2012, to December 31, 2013. Retrospective clinical and encounter data were collected on these patients for a five-year period: January 1, 2009, to December 31, 2013. Data collected included demographics, diagnoses, problem lists, encounter clinicians, clinician specialties, procedures, medications, allergies, vital signs, and selected blood tests. Patient and clinician names and medical record numbers were removed from the data set, and a random study ID was assigned to each patient and each clinician. The data set was sent to MedAware through a secure transfer system (password-protected and encrypted) for analysis. The MedAware system refined its algorithms using one half of this patient population. The alerts generated for evaluation in this study reflected care provided to the remaining half of the study patients. The overall study, including MedAware access to the data and chart review and analysis conducted by BWH research staff, was approved by the Partners Human Research Committee (Institutional Review Board protocol: 2014P002167).

Comparison of MedAware's System to an Existing CDS Alerting System

We compared alerts generated by the MedAware system with alerts that would have fired in the homegrown CDS system in use at BWH and MGH during the study period to evaluate the value-added role of MedAware's alerts over systems that organizations may already have in place. We compiled a list of the types of alerts that were programmed to fire in our homegrown system in use at the time of the study.

Historical alert data recorded in our homegrown system were incomplete because not all alerts fired were consistently logged. For example, "information only" alerts, which were reminders to providers and did not require them to take any action, were not logged in our electronic

health record (EHR). Other alerts, such as those requiring providers to enter reasons to override the alert, also were not logged consistently. Therefore, we used the institutions' knowledge management system, which catalogues the types of alerts that would have fired, to compare these homegrown alerts to each of the three distinct types of MedAware's alerts: clinical outliers, time-dependent alerts, and dosage outliers.

For clinical outlier alerts, we organized MedAware's alerts by drug and searched the institutions' knowledge management system for alerting rules related to these drugs. MedAware's time-dependent alerts were compared to our drug-lab alerts that would have been generated in our CDS system. To compare MedAware dosage outlier alerts to our CDS system, we identified the different ways our system alerted on high and low doses and determined alert overlap versus where MedAware provided novel alerting not present in the existing CDS system.

Chart Review Analysis

A medical chart review analysis was conducted on the number and types of alerts generated by the MedAware system to assess the accuracy and clinical relevance of these alerts. A random sample of 300 alerts was selected for manual patient chart review. The sample included 100 randomly selected alerts from each alert category (clinical outliers, time-dependent, and dosage outliers).

Patient charts were reviewed to determine the following:

- Whether the alert was *accurate* based on the structured and coded information that was available in the BWH and MGH data provided to MedAware.
- Whether the alert was *valid* based on the clinical data in the patient's EHR (for example, was there additional information from the chart that suggests the alert should not be fired?).
- Whether the alert was clinically *valuable* (that is, contributed potentially useful additional information important to the care of the patient that could influence the caregiver to change the drug or be reminded to consider other important clinical information).

A coding scheme was developed and described in more detail in a prior publication.[21] It was designed to evaluate the accuracy and clinical validity of alerts, given the actual clinical information present in the patients' charts upon manual review (See Appendix 1, available in online article). In brief, alerts were first categorized as eligible for review or ineligible. Eligible cases were then coded as accurate or inaccurate based on structured clinical data available in the medical record. Accurate cases were assessed to determine if they were valid or not clinically valid in reflecting a potential medication error based on all data available in the medical record, including free-text clinical notes. The clinical value of the valid cases was then assessed. Cases were coded as high value when the alert uncovered a situation representing a significant clinical issue that was not otherwise detected based on data available in the medical record. Medium value was assigned to cases that were true clinical outliers but where there was clinical rationale for selecting the medication that was most often documented in the record (hence, an alert would be of questionable value or helpfulness), and less value where it appeared that the alert provided only minimal or no clinically useful information for patient management.

Two premed research assistants [S.M., M.M.] examined charts independently. These reviewers were trained by the principal investigator (PI) and research teams to review and collect specific information from each chart and provide their initial assessment of clinical value based on defined criteria. Quality checks throughout the process were done by reviewing a sample of records. Any questions or issues in identifying and applying criteria to the cases were adjudicated by the physician PI and research team. Following the reviewers' individual examinations, uncertainties were resolved by reviewer consensus discussion and consultation with project physicians and pharmacists. Development of the MedAware alerts system is an iterative process (that is, based on learning from outliers and assessment of their relevance). The chart review and alert coding for this current study was conducted on the alerts produced by the MedAware system based on a more refined algorithm than the one used in our previous study in 2016.[21]

The random sample of 300 charts was selected, representing 100 from each of the alert types. The patient care setting on the date the alert would have fired was reviewed. This study focused on prescription drug alerts generated in the outpatient setting. Hence, cases in which alerts occurred while the patient was at the hospital were excluded and replaced with additional randomly selected cases. Weights were assigned to each alert type to reflect the relative frequency of these alerts in all those generated by the machine learning system to extrapolate results to the entire patient population.

Cost Analysis

We estimated the health care cost associated with the potentially prevented medication errors. Using the result of the stratified random sample of prescription drug alert cases for which we had conducted a detailed chart review, we estimated the related direct health care costs and thus potential savings associated with the potential prevention of drug errors identified by the machine learning medication errors identification system.

The incidence of potential adverse events associated with the prescription medication alerts were extracted from a set of simulated alerts fired by the software for patients who had at least one outpatient encounter during the two-year study period 2012–2013. Five years of clinical data (2009–2013) were collected for these patients.

Table 1. Cost Components*

Cost of a preventable, outpatient adverse drug event[1]	
Average cost	$3,592
Range	$350–$6,834
Pharmacist intervention/call cost	
Pharmacist time cost[2]	$6.67
Physician time cost[3]	$7.57
Total	$14.24

* All costs were adjusted to the year 2017 using the medical care in US city average, all urban consumers, not seasonally adjusted consumer price index (see reference 22 at the end of this article).

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Table 2. Demographics of Patient Population

	Patient Population $N = 747,985$ (%)
Sex	
Female	311,534 (41.6)
Male	436,440 (58.3)
Unknown	11 (0.001)
Age in years	
0–17	81,677 (10.9)
18–29	79,580 (10.6)
30–49	195,442 (26.1)
50–64	177,643 (23.7)
≥ 65	213,643 (28.6)
Race*	
American Indian or Alaska Native	898 (0.1)
Asian	35,314 (4.7)
Black or African American	48,889 (6.5)
Native Hawaiian or other Pacific Islander	349 (0.05)
White	544,173 (72.8)
Other (unknown, declined, two or more races)	118,362 (15.8)
Ethnicity*	
Hispanic or Latino	54,501 (7.3)
Other (not Hispanic or Latino, declined, unknown)	693,484 (92.7)

* Race/ethnicity data based on coded fields in the electronic health record.

All alerts of medium or high value were independently reviewed by a physician [G.S.] and by two clinical pharmacists to identify adverse drug events (ADEs) that could result from potential medication errors and, using clinical resources and their experience, to estimate the severity and likelihood of occurrence of the ADE potentially associated with the alerts identified by the machine learning algorithm. The three study clinicians independently assigned a severity level to each type of potential adverse event (for example, myocardial infarction, dizziness) and classified them as mild, moderate, severe, or no clinical value. Results from the three reviewers were compared and discrepancies reconciled to create a data set with the estimated risk of occurrence and severity of an ADE for each alert.

Direct health care cost estimates from the literature associated with an ADE and the pharmacist/prescriber communications when the drug could not be dispensed as prescribed were included in the analysis (Table 1).

The average cost of an outpatient ADE and the cost of the pharmacist/prescriber communications related with medication alerts were derived from the peer-reviewed literature. The average cost and range were estimated for each type of alert. The labor cost regarding time devoted by prescribers to manage the medication alerts, the cost of false positives, and the cost of developing the MedAware software were not included in the analysis. Direct nonmedical costs and indirect costs also were not included in the analysis. All costs were adjusted to the year 2017 using the medical care in US city average, all urban consumers, not seasonally adjusted consumer price index.[22] Subanalyses were conducted by type of alert and cost component. One-way sensitivity analysis was performed for the percentage of prevented adverse events (50%–150% range for baseline values).

RESULTS

Patient Population

We evaluated 747,985 patients of all ages who had at least one outpatient encounter with a provider affiliated with BWH or MGH during the two-year period from January 1, 2012, to December 31, 2013. Clinical data were collected on these patients for a five-year period: January 1, 2009, to December 31, 2013. The MedAware system developed its algorithms by randomly selecting and analyzing one half of this total patient population, and simulated alerts were generated for the remaining random half of the patient population to support our study evaluation. The characteristics of the patient population are shown in Table 2.

Chart Review Analysis for Clinical Value

A total of 10,668 alerts were generated by the software on the 373,992 patients used for this study. The type of alerts included 9,408 time-dependent, 834 clinical outliers, and 426 dosage outliers. A random sample of 300 alerts was selected for an in-depth review of the clinical records. The sample included 100 randomly selected alerts from each alert category. Figure 1 presents a flow sheet with details of the distribution of the 300 alerts with chart reviews across the different alert assessment codes. A total of 150 alerts

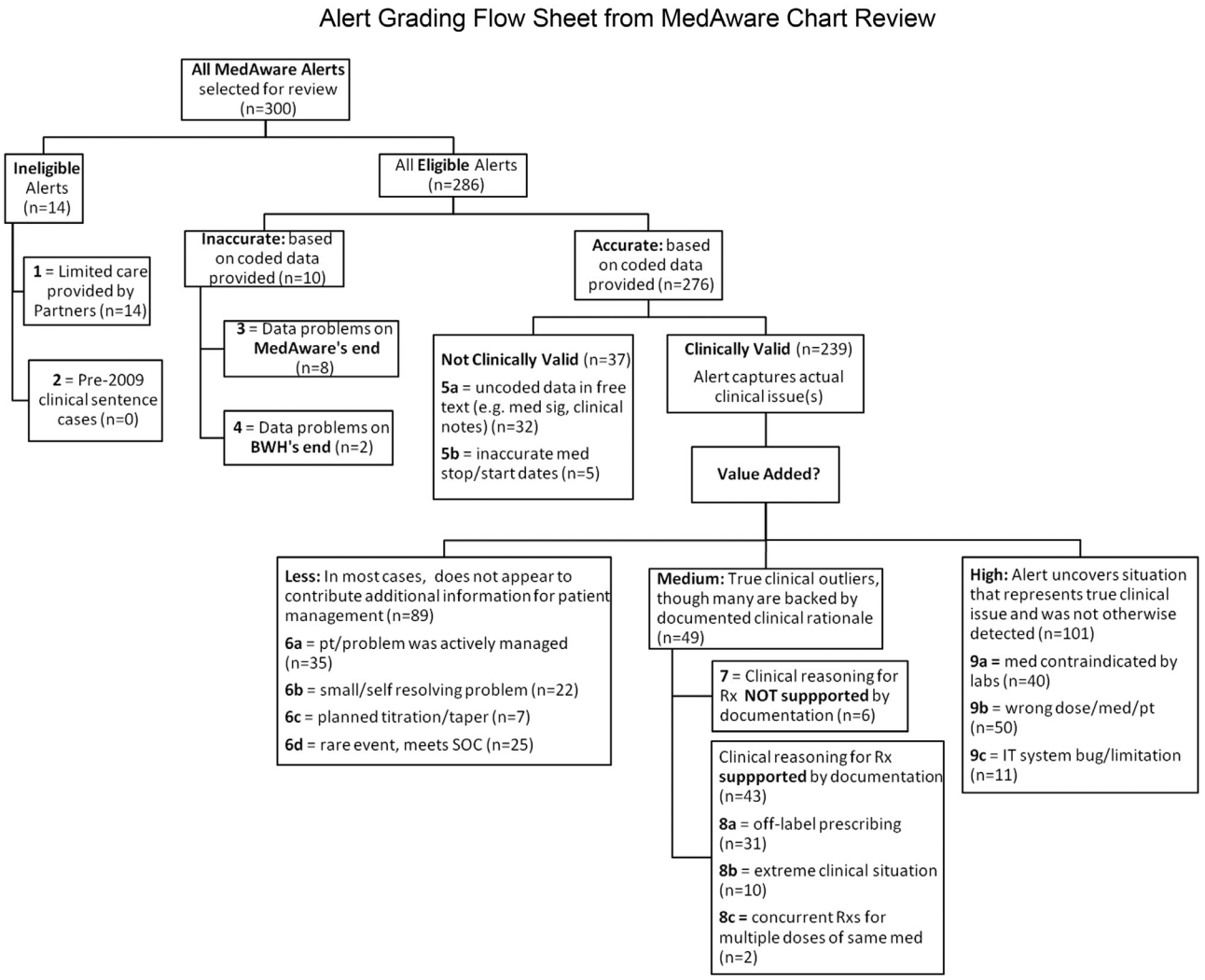

Figure 1: This flow sheet shows the classification of the 300 MedAware alerts selected for chart review by alert grade. BWH, Brigham and Women's Hospital; SOC, standard of care; IT, information technology.

(50.0%) were deemed as having medium or high clinical value (Figure 1).

Evaluation showed that 92.0% of the 300 chart-reviewed alerts generated by the MedAware system were accurate. Of the 300 alerts, 79.7% (86.6% of those that were accurate) were judged to be clinically valid. A total of 37 of the accurate alerts (13.4%) were not clinically valid because of data-related issues, including uncoded data available in free text that could not be evaluated by the MedAware system. Half of the 300 alerts assessed in the chart review (62.8% of the clinically valid alerts) were rated as medium or high value. When these results were weighted to reflect the distribution of different alert types in all alerts generated, approximately 45% of the clinically valid alerts were of medium (3.7%) or high value (41.0%).

Comparison of MedAware's System to an Existing CDS Alerting System

Overall, 68.2% of the alerts generated were unique to the MedAware system and not generated by the institutions' CDS alerting system (Table 3). Clinical outlier alerts were the type least likely to be generated by the institutions' CDS—99.2% of these alerts were unique to the MedAware system. The largest overlap was with dosage alerts, with only 10.6% unique to the MedAware system. Sixty-eight percent of the time-dependent alerts were unique to the MedAware system.

Cost Analysis

The average cost of an adverse event potentially prevented by an alert was $60.67 (range: $5.95–$115.40). The average adverse event cost per type of alert varied from $14.58 (range: $2.99–$26.18) for dosage outliers to $19.14 (range: $1.86–$36.41) for clinical outliers and $66.47 (range: $6.47–$126.47) for time-dependent alerts (Table 4).

Potential savings of $60.67 per alert was mainly derived from the prevention of ADEs. The prevention of ADEs could result in savings of $60.63 per alert, representing 99.93% of the total potential savings. Potential savings

Table 3. Number and Percentage of BWH and MGH Outpatient CDS Alerts That Were Unique to MedAware's System

Alert Type Category	Total MedAware Alerts	MedAware Alerts with Similar BWH and MGH CDS Alerts	% of MedAware Alerts That BWH and MGH CDS Would Generate	% Alerts Unique to MedAware
Time dependent	9,408	3,006	32.0	68.0
Clinical outliers	834	7	0.8	99.2
Dosage outliers	426	381	89.4	10.6
Total	**10,668**	**3,394**	**31.8**	**68.2**

BWH, Brigham and Women's Hospital; MGH, Massachusetts General Hospital; CDS, clinical decision support.

Table 4. Potential Savings per Alert, Baseline Scenario

Alert Type	Average	Min.–Max. Range
Clinical outliers	$19.14	$1.86–$ 36.41
Dosage outliers	$14.58	$2.99–$ 26.18
Time-dependent	$66.47	$6.47–$126.47
Total	**$60.67**	**$5.95–$115.40**

Table 5. Potential Savings per Alert, Sensitivity Analysis

	% Adverse Drug Events Prevented		
Alert Type	50%	Baseline	150%
Clinical outliers	$9.57	$19.14	$28.71
Dosage outliers	$7.29	$14.58	$21.88
Time-dependent	$33.23	$66.47	$99.70
Total	**$30.34**	**$60.67**	**$91.01**

related to averted calls between pharmacists and clinicians could save an average of $0.047 per alert, representing 0.08% of the total potential savings.

The one-way sensitivity analysis, varying the percentage of ADEs potentially prevented by the alerts, showed that the potential savings by alert varied from $30.34 if 50% of the estimated number of preventable ADEs were identified and prevented, to $91.01 if 150% of the estimated number of preventable ADEs were identified and prevented (Table 5).

Extrapolating the results of the analysis to the 747,985 BWH and MGH patients who had at least one outpatient encounter during the two-year study period from 2012 to 2103, the alerts that would have been fired over five years of their clinical care by the machine learning medication errors identification system could have resulted in potential savings of $1,294,457.

DISCUSSION

Machine learning algorithms have the potential to improve identification and prevention of medication errors. We found that 79.7% of the chart-reviewed alerts generated by the MedAware system appeared clinically valid and approximately 45% of the clinically valid alerts were considered of medium or high value when weighted to reflect the entire set of MedAware system alerts generated. We also found that 68.2% of MedAware's alerts generated were unique and would not have been generated by BWH's and MGH's CDS alerting system. These data suggest that many of these errors had the potential for patient harm. This kind of approach can complement traditional rule-based decision support, because it is likely to find additional errors that would not be identified by usual rule-based approaches.

Our overall findings are consistent with previous studies showing that systems that combine clinical knowledge with machine learning data–driven outlier-based monitoring and alerting can identify medication errors that are missed by existing CDS systems.[20,23] For example, one study examined an outlier-based monitoring patient-management decision system in postcardiac surgical patients and found that the true alert rate ranged from 25% to 66% for patient-management actions.[23] A follow-up study focusing on ICU patients found that the overall true positive rate for medication order alerts ranged from 31% to 61%.[24]

Our study confirms and extends findings of our previous study that showed three quarters of the chart-reviewed alerts generated by the MedAware system in the outpatient setting were found to be valid, in that potential medication errors were identified.[21] The results of the current study suggest that the updated MedAware system we tested may have improved its effectiveness over the system tested in our initial study in detecting clinically valid situations. Consistent with these findings, another recent study evaluating the MedAware system in real time at the point of care in a small inpatient unit found that 85% of the alerts generated were clinically valid and 80% were considered clinically useful.[25]

Our study found that the estimated cost of adverse events potentially prevented by applying the system in an outpatient setting is $60.67 per alert, which extrapolates to a total of $1.3 million for a patient cohort with outpatient encounters in a two-year period when they are followed over five years. Studies evaluating cost savings associated with CDS systems are scarce. A review article assessing the literature through January 2011 found that CDS systems had lower treatment costs and total costs compared with control groups and other non-CDS system intervention groups.[26] However, the review also found that the evidence related to

CDS was modest. More data are available for inpatient than outpatient settings.[26]

Limitations

Cost analysis in this study included only the direct health care costs of adverse events and associated pharmacist/prescriber interactions. Including other costs, such as indirect medical and nonmedical costs, might result in different estimates of savings. The cost of the software system and the labor cost of addressing the alerts were not included in this study.

This study also has several other limitations. The study analyzed retrospective data from 2009 to 2013 to evaluate a system that was designed to be primarily used prospectively in real time. Although in theory many of the findings from our retrospective analysis should be applicable to real-time alerting, it is difficult to predict whether some would perform differently or how clinicians would respond to real-time alerts. The study also lacks information about the percentage of alerts that clinicians would actually accept and that would result in appropriate, timely action that would potentially prevent adverse events and patient harm. Furthermore, it is difficult to predict whether patients will fill and take the prescribed medications that would put them at risk of an ADE.

Our analysis was based on CDS available in an earlier homegrown outpatient EHR, which may not be generalizable to current commercial CDS systems. Working with EHR data limitations presents several challenges, all of which might affect study findings. For example, medication start and stop dates may not always accurately reflect when and whether a patient had an active prescription. Medications could be added to the medication list through medication reconciliation even though they were not actually prescribed through the EHR system, making it difficult at times to determine accurate prescription dates. Some diagnoses were discussed in free-text notes, but because providers had not added them to any structured data fields (for example, problem list, International Classification of Diseases [ICD]-9 diagnosis), the MedAware system could generate an alert that was technically accurate but not clinically valid (for example, generating an alert regarding insulin in absence of a diabetes diagnosis, when in fact such a diagnosis was mentioned only in a free-text note).

In addition, information about the incidence of useful alerts was derived from a sample of a simulation study of the MedAware system in a set of BWH and MGH outpatients. The estimation of the risk and severity of the adverse events potentially identified and prevented were derived from the literature and expert opinions, and not actually measured. Information about the cost of an ADE and the cost of the pharmacist/prescriber interaction were derived from the literature. The information about the cost of ADEs is scarce and based on older studies that have not been updated or repeated in recent years. The study that informed our analysis of cost components was focused on older patients, while costs of ADEs in younger patients may be different.

Finally, the frequency and severity of harm from the potential adverse events to which the MedAware system alerted users were subjective estimates by three clinicians (two pharmacists and one physician). Although these estimates used a rigorous approach—looking up drug reference information on the frequency of adverse events—this exercise required subjective judgment on the part of the clinicians to match the alerts to the potential adverse events. We did not assess the actual frequency of harm.

CONCLUSION

We evaluated a machine learning medication errors identification system and found that it appears to generate many clinically valid alerts that might otherwise be missed with existing CDS systems. More than 80% of the alerts were found to be clinically valid, and 62.8% of these were considered of medium or high clinical value. Estimated cost of adverse events potentially prevented in an outpatient setting was more than $60 per drug alert. The true value of such alerts is highly contingent on whether and how clinicians respond to such alerts and their potential to prevent actual patient harm.

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Conflicts of Interest. David Bates consults for EarlySense, which makes patient safety monitoring systems. He receives cash compensation from CDI (Negev), Ltd., a not-for-profit incubator for health information technology startups. He receives equity from ValeraHealth, which makes software to help patients with chronic diseases. He receives equity from Clew, which makes software to support clinical decision making in intensive care. He receives equity from MDClone, which produces deidentified versions of clinical data. His financial interests have been reviewed and are in accordance with his institutional policies. All other authors report no relevant conflicts of interest.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcjq.2019.09.008.

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