Order Indication Solicitation to Assess Clinical Laboratory Test Utilization: D-Dimer Order Patterns as an Illustrative Case

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Abstract

Background: A common challenge in the development of laboratory clinical decision support (CDS) and laboratory utilization management (UM) initiatives stems from the fact that many laboratory tests have multiple potential indications, limiting the ability to develop context-specific alerts. As a potential solution, we designed a CDS alert that asks the ordering clinician to provide the indication for testing, using D-dimer as an exemplar. Using data collected over a nearly 3-year period, we sought to determine whether the indication capture was a useful feature within the CDS alert and whether it provided actionable intelligence to guide the development of an UM strategy. **Methods:** We extracted results and ordering data for D-dimer testing performed in our laboratory over a 35-month period. We analyzed order patterns by clinical indication, hospital service, and length of hospitalization. **Results:** Our final data set included 13,971 result-order combinations and indeed provided actionable intelligence regarding test utilization patterns. For example, pulmonary embolism was the most common emergency department indication (86%), while disseminated intravascular coagulation was the most common inpatient indication (56%). D-dimer positivity rates increased with the duration of hospitalization and our data suggested limited utility for ordering this test in the setting of suspected venous thromboembolic disease in admitted patients. In addition, we found that D-dimer was ordered for unexpected indications including the assessment of stroke, dissection, and extracorporeal membrane oxygenation. **Conclusions:** Indication capture within a CDS alert and correlation with result data can provide insight into order patterns which can be used to develop future CDS strategies to guide appropriate test use by clinical indication.

Keywords: Clinical laboratory information systems, clinical decision support systems, medical order entry systems

INTRODUCTION

Clinical decision support (CDS) is among the most useful tools that clinicians, pathologists, and laboratories can employ to improve laboratory test ordering in the electronic health record (EHR) and manage test utilization.^[1,2] For example, most computerized provider order entry (CPOE) systems can display noninterruptive or interruptive test ordering alerts to advise clinicians of the appropriate indications for testing.^[1,2] Systems may deploy nonspecific alerts that display each time a clinician places an order for a given test and describe the proper indications for the test.^[1,2] Modern CPOE systems also support rule-based alerts that allow for greater specificity; for example, alerts may be developed that only fire on patients meeting certain criteria (e.g., EHR data suggesting that a test order is inappropriate).^[3]

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An important consideration when developing laboratory CDS is that many laboratory tests have multiple potential indications. While a test may be contraindicated in a given patient for one purpose, it may be appropriate for a different indication. In theory, certain rule-based alerts could leverage data within the patient's EHR to either infer the ordering indication or to see if the patient's clinical record suggests that the test could be appropriate for at least one established indication. However, in practice, designing alerts that infer the indication for testing from the EHR is difficult. For example,

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suppose a laboratory wishes to implement a CDS alert to discourage clinicians from ordering prothrombin time (PT) and partial thromboplastin time (PTT) tests as part of routine preoperative workups prior to minor surgery in accordance with the American Society of Clinical Pathology Choosing Wisely Guidelines.^[4] It would likely be too difficult to develop a rule-based approach to reliably discern from structured information in the EHR whether a PT/PTT order is intended for routine preoperative workup or for another reason.

In this article, we focus on CDS for another test with multiple indications: D-dimer. D-dimer is a fibrin degradation product created by the proteolysis of fibrin by plasmin and is a sensitive measure of thrombus formation.^[5] D-dimer assays are clinically useful both in the evaluation of venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE) and in the evaluation of disseminated intravascular coagulation (DIC).^[6,7] Assays for D-dimer facilitate the rapid evaluation and treatment of these serious, progressive, and sometimes fatal conditions.

Exclusion algorithms for VTE which combine clinical probability scoring models with D-dimer have been well validated for outpatients.^[8-12] However, for inpatients, D-dimer has been shown to have low utility for the evaluation of VTE.^[6,13,14] Guidelines do not support the use of D-dimer for the evaluation of VTE in hospitalized patients, and in general, inpatients with suspected VTE should proceed directly to diagnostic imaging studies.^[6] Although D-dimer should almost never be ordered in the inpatient setting for VTE evaluation, this test may be appropriate in some patients as part of a DIC workup. While guidance for the use of D-dimer in the evaluation of DIC is not as well established, a negative D-dimer result may help to rule out DIC.^[15]

Given the limitations of the D-dimer assay and its multiple possible indications, the application of D-dimer in clinical settings is challenging. It is not surprising that studies of provider conformance to guidelines demonstrate significant variation in guideline adherence.^[16-18] The risks created by the inappropriate application of the D-dimer assay include both under- and overdiagnosis.^[16-18] Failing to order a D-dimer when needed may result in a missed diagnosis and subsequent complications, while ordering a D-dimer in an inappropriate clinical context may lead to overdiagnosis, resulting in additional risks associated with the unneeded therapeutic intervention and unnecessary costs.^[16-18]

At our hospital, we observed frequent orders for D-dimer on inpatients. While we suspected that a significant portion of these orders were intended as part of a VTE evaluation and were thus inappropriate, we could not develop a CDS alert that prevented all inpatient orders given the arguably valid inpatient indication of DIC. Instead, we developed a CDS strategy, in which we provided information about the appropriate use of D-dimer in inpatients and captured the indication for testing at the time of order via a CDS alert. We present our work with this D-dimer CDS strategy as an exemplar of a CDS approach that may be generalizable to the wide range of tests that like D-dimer also have multiple indications.

We sought to demonstrate the utility of capturing the indication for a test order within a CPOE system in providing actionable intelligence regarding the use and utility of D-dimer orders. We also sought to evaluate whether solicitation of test ordering indications might provide a practical strategy for development of CDS specific to the selected indication.

We had implemented the CDS tool in our internally developed inpatient and emergency department (ED) POE system beginning in June 2010. We have previously published on the design and implementation of our POE application.^[19] The intent of the D-dimer CDS tool was to inform providers of the limited utility of the D-dimer assay for the assessment of VTE in inpatients, and to not discourage such orders in the outpatient and emergency department population, or to discourage D-dimer orders for DIC which may be appropriate in a variety of care settings. Specifically, providers were presented with the following message: "PLEASE NOTE: Measurement of D-dimer is of limited clinical utility for INPATIENTS with clinically suspected VTE disease. 83% of INPATIENTS undergoing D-dimer testing will test positive with or without DVT/PE. (This note does NOT apply to emergency department patients or outpatients)." The source of our inpatient D-dimer positivity data was an internal analysis of inpatients undergoing D-dimer testing (data not shown). Thus, we discouraged but did not strictly prohibit the use of D-dimer in inpatients.

If a provider chose to continue with the D-dimer order, they were prompted to provide a clinical indication for the order by selecting "DVT," "PE," "DIC," or "other." If "other" was selected, free text entry of the indication was required. The list of appropriate indications was developed by the clinical laboratories in collaboration with the Department of Medicine and was approved by the health system medical policy committee. The provided indication was captured in our POE system database.

We undertook this analysis to identify whether the captured indication information combined with test result data could provide insight into D-dimer use at our institution, both in the emergency department and inpatient care settings. We hoped to answer the following questions related to D-dimer test use: (1) Do providers adhere to clinical guidelines regarding D-dimer orders (e.g. are D-dimer orders placed to assess VTE on inpatient populations where they are not indicated)? (2) What are the positivity rates of D-dimer for various clinical indications in the emergency department and inpatient setting? (3) Do "other" (free text) indications provide insight into utilization patterns which may inform future CDS initiatives?

METHODS

Setting

This study was conducted at the Massachusetts General Hospital (MGH), a 999-bed teaching hospital in Boston,

Massachusetts, United States. MGH provides comprehensive care across acute and ambulatory contexts, including approximately 50,000 inpatient admissions, 110,000 emergency department visits, and 1,500,000 outpatient visits annually. This project was a Quality Improvement Initiative at the MGH, and as such was not formally supervised by the Institutional Review Board per their policies.

D-dimer assay

We used an enzyme-linked immunosorbent assay, Vidas D-dimer Exclusion II (bioMérieux Inc., Durham, North Carolina, United States), for the detection of D-dimer in clinical samples. The reference interval reported with the assay is <500 ng/mL. The Vidas D-dimer assay is approved by the United States Food and Drug Administration for the exclusion of VTE at a cutoff of 500 ng/mL. Low-risk patients, as defined by a VTE scoring system, can be safely be ruled out for VTE using this assay.

Data extraction and analysis

From our custom-developed structured query language server departmental data mart, we extracted D-dimer assay results as well as provider order data.^[20] Order data stored in our system originated from the POE module within our internally developed electronic medical record. Result data present in the datamart originated in our laboratory information system, Sunquest Lab (Sunquest Information Systems, Tucson, Arizona, United States).

The result data extract spanned 35 months (February 1, 2013–December 28, 2015). We chose this date range because we offered a single central laboratory D-dimer assay during this time period (ensuring comparability of result data) and because it preceded the conversion to a new EHR in 2016 (ensuring comparability of our order data).

We included the following result data elements in our extraction for patients receiving a D-dimer test during this 35-month time period: patient medical record number (MRN), sample accession number, result value, sample collection date and time, patient hospital location, and event type. Patient location is stored in our departmental data mart as the patient's location at the time when the result is filed to the electronic medical record. In contrast, event type (e.g., inpatient, outpatient, or emergency department) is stored in our data mart reflecting the clinical context at the time the order is placed.

We excluded outpatient results from our data analysis as providers caring for outpatients would not see this inpatient/ED CDS alert and therefore would not be prompted to provide an indication for the order. We excluded results with a status of refused, canceled, or credited. We classified results as positive or negative based on our established reference interval, with results <500 ng/mL classified as negative, and those 500 ng/mL or greater classified as positive.

Similarly, we extracted laboratory orders data from our department datamart for D-dimer orders occurring during an overlapping time interval to the D-dimer result data. This extract included patient MRN, the date and time at which the provider signed the order, and the order indication provided by the ordering provider. In cases where a patient received more than one order for D-dimer at the same sign date time (<1% of orders), a single order was chosen at random to be included in the data set.

The result data were merged to the orders data via an outer join by patient MRN and nearest order sign date time to specimen collect time occurring within 72 h. We used this matching approach between order and result data because our datamart did not include a unique order and result identifier during this time window with which to link order and result data elements. With the recent implementation of a new EHR, we have made changes to the design of our data mart to include an identifier that facilitates the matching of order and result data.^[20] Some reasons for results unable to be matched to an order include order signing not occurring within 72 h of sample collection, recurring orders where one order may correspond to multiple results over a period of time >72 h, and orders received by paper requisition for which an electronic order would not have been received.

Analysis was performed in Microsoft Access (Microsoft Corporation, Redmond, Washington, United States), and figures were generated with the Python scripting language as implemented in the Anaconda software package (Python 3.6.1 in Anaconda 4.2.1, Continuum Analytics, Austin, Texas, United States). In addition, the WordCloud library, Version 1.3, was employed to assess free-text order indications and create the WordCloud figure [Figure S1].

Statistical analysis

Confidence intervals (CIs) and P values were calculated in R. Binomial CIs around test positivity rates were calculated using the Wilson method as implemented in the R-binom package. CIs describing the fraction of inpatient and emergency department orders by indication were calculated using the Sison–Graz method for multinomial CIs as implemented in the R "multinomial CI" package. The trend in positivity rate by hospital day was tested using univariate logistic regression treating test positivity as a function of hospital day (patients with hospital day 5+ were treated as having the test on day 5).

RESULTS

Our result extract included 17,210 classified D-dimer results. Using the matching logic described in the methods, we were able to match an order to a result for 81% of the results in our result data extract (13,971/17,210). Our final data set, including D-dimer results, joined with provider solicited order indications included 13,971 result-order combinations. This included 6877 (49%) inpatient results and 7094 (51%) emergency department results. We observed similar numbers of results for both female patients, 7310 (52%) and male patients, 6661 (48%). As defined by our established reference interval, 9330 (67% [66%–68%, 95% CI]) of the results were classified as positive.

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Relative order volume by provider supplied indication for D-dimer assays is shown in Figure 1 for patients being cared for in the emergency department [Figure 1a] and for inpatients [Figure 1b]. In emergency department patients, PE was the most commonly provided indication (85.8% [85.7%–86%, 95% CI]), followed by DVT (6.9% [6.8%–7.0%, 95% CI]), other (3.9% [3.8%–4.1%, 95% CI]), and DIC (3.3% [3.2%–3.5%, 95% CI]). For inpatients, DIC was the most commonly provided indication (56.3% [56.1%–56.5%, 95% CI]), followed by PE (20.5% [20.3%–20.7%, 95% CI]), other (14.5% [14.3%–14.8%, 95% CI]), and DVT (8.7% [8.5%–8.9%, 95% CI]). Thus, in the inpatient setting, approximately 30% of results were issued for VTE indications.

The D-dimer positivity rate is plotted in Figure 2 by the indication provided during order entry [Figure 2a] and by hospital service [Figure 2b]. Inpatient D-dimer positivity rates were higher than emergency department positivity rates for all indications. Positivity rates were highest for DIC indications, followed by DVT, other, and PE in both the inpatient and emergency department settings. Positivity rates for D-dimer varied by hospital service [Figure 2b]. General care floor patients exhibited lower rates of positivity (e.g., neurology patients with 44.9% positivity [42.9%–47%, 95% CI]) compared with intensive care unit (ICU) patients (cardiac ICU 98.6% [96.7%–99.4%, 95% CI], medical ICU 96.7% [95.2%–97.8%, 95% CI], neurology ICU 95.5% [90.4%–97.9%, 95% CI], neonatal ICU 95% [88.8%–97.8%, 95% CI], pediatric ICU 90.5% [86.3%– 93.5%, 95% CI]) and oncology patients (97.7% [96.9%–98.4%, 95% CI]), which had >90% D-dimer positivity rates.

D-dimer orders where the provider indication was VTE (i.e., with a DVT or PE indication) are presented in Figure 3. The number of D-dimer orders with a VTE indication by hospital day is shown in Figure 3a (day 1 represents admission duration at time of D-dimer order from 0 to 24 h, day 2 is 24-48 h, etc). The majority of D-dimer orders occur in the first 48 h following admission, though orders continue in later days of hospitalization. The D-dimer positivity rate for VTE indications by hospital day is presented in Figure 3b. Of key importance, the longer the patient had been hospitalized, the higher the likelihood of a positive D-dimer result ($P < 10^{5}$), with a positivity rate of 62% in the first 24 h and 85% for D-dimer assays ordered after the 4th day of hospitalization (logistic regression of positivity rate vs admission day, $P < 10^{-6}$). A review of the subpopulation of patients receiving inpatient D-dimer orders with a VTE indication (DVT or PE) by service reveals general medicine units account for the greatest fraction of orders for these indications (667/2005 orders, 33.3%). Among inpatient services placing more than 30 D-dimer orders for VTE indications during the study period, the highest positivity rates were observed in neurology ICU (33/35 orders, 94.3% [81.4%-98.4%, 95% CI]), oncology (52/57 orders, 91.2% [81.1%-96.2%, 95% CI]), and orthopedics (30/33 orders, 90.9% [76.4%-96.9%, 95% CI]).

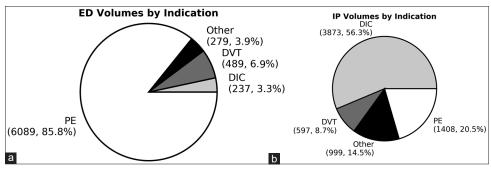


Figure 1: (a) Emergency department D-dimer volumes by indication. Indication (number, percent). (b) Inpatient D-dimer volumes by indication. Indication (number, percent). ED – Emergency department; DVT – Deep venous thrombosis; PE – Pulmonary embolism; DIC – Disseminated intravascular coagulation; IP – Inpatient; DVT – Deep venous thrombosis; PE – Pulmonary embolism; DIC – Disseminated intravascular coagulation

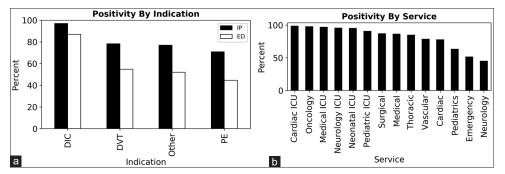


Figure 2: (a) Positivity rate by indication for inpatient and emergency department patients. (b) Positivity rate for clinical services (as defined by order location) with >50 orders during the review window. IP – Inpatient; ED – Emergency department; DVT – Deep venous thrombosis; PE – Pulmonary embolism; DIC – Disseminated intravascular coagulation; ICU – Intensive care unit

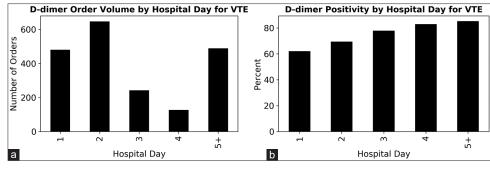


Figure 3: (a) D-dimer order volume by hospital day for orders to assess VTE including deep vein thrombosis and pulmonary embolism. Day 1 is admission duration from 0 to 24 h at the time of sample collection. (b) D-dimer order positivity rate by hospital day for orders to assess VTE including deep vein thrombosis and pulmonary embolism. Day 1 is admission duration from 0 to 24 h at the time of sample collection duration from 0 to 24 h at the time of sample collection. (b) D-dimer order positivity rate by hospital day for orders to assess VTE including deep vein thrombosis and pulmonary embolism. Day 1 is admission duration from 0 to 24 h at the time of sample collection. VTE – Venous thromboembolism

Nine percent of all D-dimer indications were provided as "other." Table 1 includes a grouping and counting of the most frequent word occurrences in the free text indications supplied for the other order indication. The most commonly provided words were "stroke" and "dissection." This data is separately represented in a visual format via a Wordcloud as Figure S1.

Screenshots of our order interface are presented as supplementary figures including the message discouraging orders for VTE in inpatients [Figure S2] and indication solicitation if the provider chooses to place the order [Figure S3].

DISCUSSION

Clinical decision support to assess order appropriateness

Assessing the clinical appropriateness of an individual test order is a difficult challenge given the variation in patient-specific variables that may influence the appropriateness of an order. This challenge is compounded in the setting of assays such as D-dimer that may have multiple possible clinical indications. Applying CDS at the point of the provider order presents one opportunity to guide order practices and encourage appropriate ordering. In our setting, we use a CDS tool during our POE process to display appropriate clinical indications for the use of D-dimer (e.g., DVT, PE, DIC) and discourage its use for inpatients for indications other than DIC. This guidance is based on well-accepted published studies regarding the benefits and limitations of D-dimer in various clinical settings and contexts.^[8,9,14,15]

In addition to providing important guidance at the time of the order, our D-dimer CDS strategy also allows us to leverage the power of the Hawthorne effect. The Hawthorne effect, also called the observer effect, describes the behavior changes observed in participants when those participants are aware that their actions are being tracked. We hypothesize that CDS strategies such as ours, in which user interactions are recorded, may alter user order behavior by an awareness that order decisions are audited in addition to the education provided on order appropriateness.

Our CDS tool provides an important ancillary function in that it allows us to capture and audit provider entered indications to assess patterns of D-dimer order and further understand the clinical practices at our institution. Because we did not previously capture order indications before the initiation of our CDS tool, we are not able to answer the question of whether our tool improved adherence to standard D-dimer guidelines. We can, however, answer questions about how providers indicate they are using the assay and how those answers compare to established guidelines.

General patterns of D-dimer use aligned with our expectations. In the ED setting, D-dimer is overwhelmingly used for the assessment of PE, a condition for which patients are commonly evaluated in that care setting [Figure 1a]. In the inpatient setting, D-dimer is most frequently used for the assessment of DIC [Figure 1b]. This also conforms to our expectations, as DIC is the clinical context in which D-dimer is most likely to be useful for an inpatient.

D-dimer orders not conforming to guidelines suggest an increased role for clinical decision support

Despite the general pattern of D-dimer orders aligning with our expectations, we were surprised to observe the relative abundance of D-dimer orders for the indications of DVT and PE in inpatients, 8.7% and 20.5%, respectively. We had anticipated seeing few inpatient orders for these indications, given the documented low utility of D-dimer in inpatients for these scenarios. However, it is clear that the ordering message informing the user of the lack of utility for inpatient D-dimer for VTE does not eliminate all D-dimer orders in this clinical context. We cannot conclude that all orders placed in this context are clinically inappropriate, but current clinical guidelines would not encourage their routine use. This category of orders is important to identify because patients at high risk for VTE (including all hospitalized patients) should bypass D-dimer and go directly to imaging studies for further assessment. The occurrence of D-dimer orders at our institution for DVT and PE acknowledges the possibility that a limited number of patients with suspected VTE are being managed by D-dimer instead of immediately receiving imaging studies. This could lead to either over or under-diagnosis of VTE in this patient population and possibly delayed care. It is possible that these patients are receiving both D-dimer orders and imaging concurrently which would not delay care; however, the D-dimer result would still be clinically uninformative in this patient cohort.

Table 1: Occurrence of individual words in "other" order indications for words appearing \geq 30 times in the data set

Word	Count
Stroke	144
Dissection	135
Neurology	108
Admit	106
Template	106
Order	106
Thrombosis	57
ECMO	50
Clot	45
Aortic	44
Neonatal	43
Sinus	34
PE	34
Pain	33
Thrombus	33
Rule out	33
?	32
TIA	30

Prepositions such as "for" and "on" are excluded from the data shown. ECMO – Extracorporeal membrane oxygenation; TIA – Transient ischemic attack; PE – Pulmonary embolism, ? - Question mark symbol

Our observations regarding D-dimer orders for VTE in inpatients are likely not unique to our institution. Other authors have noted that providers frequently fail to adhere to guidelines for the appropriate use of D-dimer.^[16-18,21] Despite guideline awareness, ordering providers still fail at times to implement care according to accepted guidelines. This suggests an enhanced role for CDS to prevent lapses in practice. Our CDS tool discouraged but did not strictly prohibit D-dimer orders for the assessment of VTE in inpatients. Our tool may have been made more effective by creating a prohibition against such orders (i.e., an electronic hard stop preventing the order if requested for VTE assessment in inpatients). It also highlights the importance of monitoring and feedback regarding provider ordering patterns. We have previously published on the ability of order auditing and feedback to shift ordering practices.^[22]

Although the specific CDS strategy we employed here did not adapt the CDS alert message to the specific indication selected, our results suggest the possibility of a future CDS strategy that may do just that. Indeed, a clinician indicating that an inpatient D-dimer order is for VTE may benefit from additional context-specific information regarding the lack of utility of this test in this setting. Likewise, the ordering indications our approach captured could identify clinicians frequently misordering this test. Identifying a specific set of clinicians who commonly misutilize a test can be extremely useful, as the hospital or laboratory can focus educational efforts on these individuals or reach out to them for specific discussions.

Our data also confirm the high prevalence of elevated D-dimer in hospital patients. We observe that for inpatients assessed for VTE, the incidence of D-dimer positivity (results above 500 ng/mL cutoff) starts at 60% on day one and rises progressively to over 80% by the 5th day of hospitalization [Figure 3a]. This is consistent with previously published data regarding the utility of D-dimer in the inpatient setting.^[13,14] Given that D-dimer is clinically useful as a tool for exclusion of VTE, such that a negative D-dimer may help to rule out the disease, the observed high positivity rates in inpatients assessed for VTE at our institution further confirms the lack of utility of D-dimer in this specific context. We believe this data would further support using a CDS tool to prohibit D-dimer use for VTE in inpatients, or at least to prohibit such testing in patients hospitalized for more than a short period of time. For patients being assessed for VTE in the emergency department (or possibly even those recently admitted), presenting providers with a calculator, such as those based on the Wells' Criteria, may further increase adherence to guidelines and assure that patients at high risk for VTE proceed directly to imaging.

Order indication solicitation provides insight into emerging patterns of test use

Our CDS tool allows providers to place D-dimer orders for indications other than DVT/PE/DIC as "other" orders. After selecting "other," the provider is required to enter a free text indication that is captured by our CDS tool. We aggregated this free text data and analyzed it for patterns of word use [Table 1 and Figure S1]. Review of this other indication data provides a window into "off label" and emerging uses of D-dimer in our institution.

For example, the most commonly occurring word in our free text order data was "stroke." A small number of studies have been published suggesting a role for D-dimer in assessing stroke, either for the classification of stroke subtypes or the prediction of stroke outcomes.^[23-25] However, the data are limited, and others have suggested that there is not sufficient evidence to warrant the routine use of D-dimer in the evaluation of stroke patients.^[26]

The second most commonly observed word in our other order data was "dissection." Like stroke, a series of studies have been published suggesting D-dimer may be useful in the evaluation of acute aortic dissection, either to rule out low risk outpatients or to predict patient outcomes.^[27-31] However, there is debate here too, as others have noted the use of D-dimer is challenging in this clinical setting and D-dimer may have lower sensitivity for acute aortic dissection than previously thought.^[32,33]

Although further down the frequency list, the relative abundance of the word extracorporeal membrane oxygenation ("ECMO") in our free text order indication data was also of interest. A small number of papers have recently been published regarding the use of D-dimer to predict membrane dysfunction in patients on ECMO.^[34-36] Membrane failure is a common technical problem that necessitates changes to the ECMO circuit. Based on the literature, it appears well established in the ECMO community that D-dimer is a useful marker to help predict membrane oxygenator failure and plan the needed technical intervention to repair the problem.^[34-36]

We also note the similar frequencies of the words "neurology," "admit," "template," and "order." These orders appear on a Neurology admission order template with the "other" indication prepopulated. This explains the common cooccurrence of these words and identifies their origin.

These examples highlight the utility of capturing and analyzing free-text order data to identify emerging trends in order practices. In the first two examples, stroke and dissection, there is mixed literature on the topic and an absence of definitive clinical guidelines to suggest that D-dimer should be routinely used in these clinical contexts. However, our data reveal that some providers are using D-dimer in these "off-label" clinical contexts. This observation suggests that we may need to reach out to our neurology and cardiology departments regarding the use of D-dimer in the context of stroke and dissection. Together we may be able to develop joint policies regarding the use of D-dimer in these clinical contexts and then support the appropriate use of D-dimer in these clinical settings using our CDS tools. In the case of ECMO, the literature clearly supports the use of D-dimer in this clinical context, and we could consider adding a new approved order indication to our decision support tools. These three examples of new order indications suggest that the analysis of order indication by a CDS tool may identify new ordering patterns and that the identified patterns can then be used to both improve the current CDS tool as well as guide future CDS efforts.

It is important to note that while soliciting order indication provides valuable insight into ordering patterns, this information comes at a cost. Significant considerations include provider time and fatigue associated with providing indication level data and the effort to build and deploy such an alert. These factors should be weighed when determining whether to build an interruptive alert such as the one described in this manuscript, as this method may not be appropriate in all cases.

Limitations

Our study is subject to some limitations. Due to the absence of a unique order number in our order and results database tables, we lacked a unique identifier to join orders and results data. We, therefore, had to rely on a "fuzzy" match between orders and results data which may have led to imprecise matching between orders and results in a subset of occasions. Furthermore, it should be noted that the patient location analysis [Figure 2b] reflects the patient location at the time of the result being filed to the medical record. If a patient received a D-dimer order in the emergency department, was admitted, and then received a result, that result would be attributed to the inpatient location for this subanalysis. This may lead to a small subset of patients being misclassified for this subanalysis. We believe that both of these limitations are limited in impact, affecting only a small minority of the test results in the study, although their effect on the study results cannot be entirely excluded.

CONCLUSIONS

CDS tools are commonly used to provide guidance on order practices. These tools can simultaneously be leveraged

to aggregate practice data that increases understanding of current clinical practices and may inform future decision support initiatives. In the current analysis, we describe our experience with a CDS tool designed to both guide providers on appropriate D-dimer use and capture the indications for the intended use of the D-dimer assay. This approach provided a quantifiable view into D-dimer order practices at a large urban academic medical center. It revealed orders not conforming to accepted clinical guidelines in inpatients and new emerging clinical trends in D-dimer assay use, both of which may be amenable to future CDS initiatives.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Baron JM, Dighe AS. The role of informatics and decision support in utilization management. Clin Chim Acta 2014;427:196-201.
- Kim JY, Dzik WH, Dighe AS, Lewandrowski KB. Utilization management in a large urban academic medical center: A 10-year experience. Am J Clin Pathol 2011;135:108-18.
- Procop GW, Yerian LM, Wyllie R, Harrison AM, Kottke-Marchant K. Duplicate laboratory test reduction using a clinical decision support tool. Am J Clin Pathol 2014;141:718-23.
- Choosing Wisely. ABIM Foundation; Available from: http://www.choosingwisely.org/clinician-lists/american society-clinical-pathology-routine-preop-testing-for low-risk-surgeries-without-indication/. [Last accessed on 2019 Jan 20].
- Brill-Edwards P, Lee A. D-dimer testing in the diagnosis of acute venous thromboembolism. Thromb Haemost 1999;82:688-94.
- Wells PS, Ihaddadene R, Reilly A, Forgie MA. Diagnosis of venous thromboembolism: 20 years of progress. Ann Intern Med 2018;168:131-40.
- Wada H, Matsumoto T, Yamashita Y. Diagnosis and treatment of disseminated intravascular coagulation (DIC) according to four DIC guidelines. J Intensive Care 2014;2:15.
- Wells PS, Anderson DR, Rodger M, Stiell I, Dreyer JF, Barnes D, et al. Excluding pulmonary embolism at the bedside without diagnostic imaging: Management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and d-dimer. Ann Intern Med 2001;135:98-107.
- Wells PS, Anderson DR, Rodger M, Forgie M, Kearon C, Dreyer J, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. N Engl J Med 2003;349:1227-35.
- Fancher TL, White RH, Kravitz RL. Combined use of rapid D-dimer testing and estimation of clinical probability in the diagnosis of deep vein thrombosis: Systematic review. BMJ 2004;329:821.
- Crawford F, Andras A, Welch K, Sheares K, Keeling D, Chappell FM. D-dimer test for excluding the diagnosis of pulmonary embolism. Cochrane Database Syst Rev 2016;(8):CD010864. DOI: 10.1002/14651858.CD010864.pub2.
- Harringa JB, Bracken RL, Nagle SK, Schiebler ML, Pulia MS, Svenson JE, *et al.* Negative D-dimer testing excludes pulmonary embolism in non-high risk patients in the emergency department. Emerg Radiol 2017;24:273-80.

- Raimondi P, Bongard O, de Moerloose P, Reber G, Waldvogel F, Bounameaux H, *et al.* D-dimer plasma concentration in various clinical conditions: Implication for the use of this test in the diagnostic approach of venous thromboembolism. Thromb Res 1993;69:125-30.
- Brotman DJ, Segal JB, Jani JT, Petty BG, Kickler TS. Limitations of D-dimer testing in unselected inpatients with suspected venous thromboembolism. Am J Med 2003;114:276-82.
- Bates SM. D-dimer assays in diagnosis and management of thrombotic and bleeding disorders. Semin Thromb Hemost 2012;38:673-82.
- Roy PM, Meyer G, Vielle B, Le Gall C, Verschuren F, Carpentier F, et al. Appropriateness of diagnostic management and outcomes of suspected pulmonary embolism. Ann Intern Med 2006;144:157-64.
- Arnason T, Wells PS, Forster AJ. Appropriateness of diagnostic strategies for evaluating suspected venous thromboembolism. Thromb Haemost 2007;97:195-201.
- 18. Kristoffersen AH, Ajzner E, Rogic D, Sozmen EY, Carraro P, Faria AP, et al. Is D-dimer used according to clinical algorithms in the diagnostic work-up of patients with suspicion of venous thromboembolism? A study in six European countries. Thromb Res 2016;142:1-7.
- Grisson R, Kim JY, Brodsky V, Kamis IK, Singh B, Belkziz SM, *et al.* A novel class of laboratory middleware. Promoting information flow and improving computerized provider order entry. Am J Clin Pathol 2010;133:860-9.
- Kurant DE, Baron JM, Strazimiri G, Lewandrowski KB, Rudolf JW, Dighe AS, *et al.* Creation and use of an electronic health record reporting database to improve a laboratory test utilization program. Appl Clin Inform 2018;9:519-27.
- Thachil J, Fitzmaurice DA, Toh CH. Appropriate use of D-dimer in hospital patients. Am J Med 2010;123:17-9.
- Rudolf JW, Dighe AS, Coley CM, Kamis IK, Wertheim BM, Wright DE, et al. Analysis of daily laboratory orders at a large urban academic center: A multifaceted approach to changing test ordering patterns. Am J Clin Pathol 2017;148:128-35.
- Isenegger J, Meier N, Lämmle B, Alberio L, Fischer U, Nedeltchev K, et al. D-dimers predict stroke subtype when assessed early. Cerebrovasc Dis 2010;29:82-6.
- Zi WJ, Shuai J. Plasma D-dimer levels are associated with stroke subtypes and infarction volume in patients with acute ischemic stroke. PLoS One 2014;9:e86465.
- 25. Yang XY, Gao S, Ding J, Chen Y, Zhou XS, Wang JE, et al. Plasma

http://www.jpathinformatics.org/content/10/1/36

D-dimer predicts short-term poor outcome after acute ischemic stroke. PLoS One 2014;9:e89756.

- Haapaniemi E, Tatlisumak T. Is D-dimer helpful in evaluating stroke patients? A systematic review. Acta Neurol Scand 2009;119:141-50.
- Asha SE, Miers JW. A systematic review and meta-analysis of D-dimer as a rule-out test for suspected acute aortic dissection. Ann Emerg Med 2015;66:368-78.
- Mori K, Tamune H, Tanaka H, Nakamura M. Admission values of D-dimer and C-reactive protein (CRP) predict the long-term outcomes in acute aortic dissection. Intern Med 2016;55:1837-43.
- Watanabe H, Horita N, Shibata Y, Minegishi S, Ota E, Kaneko T, et al. Diagnostic test accuracy of D-dimer for acute aortic syndrome: Systematic review and meta-analysis of 22 studies with 5000 subjects. Sci Rep 2016;6:26893.
- Gorla R, Erbel R, Kahlert P, Tsagakis K, Jakob H, Mahabadi AA, *et al.* Diagnostic role and prognostic implications of D-dimer in different classes of acute aortic syndromes. Eur Heart J Acute Cardiovasc Care 2017;6:379-88.
- Li W, Huang B, Tian L, Yang Y, Zhang W, Wang X, et al. Admission D-dimer testing for differentiating acute aortic dissection from other causes of acute chest pain. Arch Med Sci 2017;13:591-6.
- Dong J, Duan X, Feng R, Zhao Z, Feng X, Lu Q, *et al.* Diagnostic implication of fibrin degradation products and D-dimer in aortic dissection. Sci Rep 2017;7:43957.
- Akutsu K. What are diagnostic implications and limitations of assessing D-dimer and fibrin degradation products levels in the management of patients with acute aortic dissection? J Thorac Dis 2017;9:2214-6.
- Dornia C, Philipp A, Bauer S, Stroszczynski C, Schreyer AG, Müller T, *et al.* D-dimers are a predictor of clot volume inside membrane oxygenators during extracorporeal membrane oxygenation. Artif Organs 2015;39:782-7.
- 35. Di Nardo M, Merli P, Cecchetti C, Pasotti E, Bertaina A, Locatelli F, et al. Progressive increase in D-dimer levels during extracorporeal membrane oxygenation can predict membrane oxygenator failure in children given hematopoietic stem cell transplantation? J Crit Care 2016;31:262-3.
- Lubnow M, Philipp A, Dornia C, Schroll S, Bein T, Creutzenberg M, et al. D-dimers as an early marker for oxygenator exchange in extracorporeal membrane oxygenation. J Crit Care 2014;29:473.e1-5.



Figure S1: Word cloud analysis of free text D-dimer order indications. The frequency of the word in the captured free text order indications is reflected in the size of the word in the visualization. More frequently observed words appear as larger text in the figure

Test Lookup	- 4494	-					
Search for a Test					Tests	Selected	
d-dimer		Search	Double-cl	1 tests found ick to select a test			
Name	Where	TAT		Cost			
D-dimer (MORE) Ordering Message PLEASE NOTE: Measurement (INPATIENTS with clinically suspon INPATIENTS undergoing D-dime DVT/PE. (This note does NOT a	ected venous r testing will t	thromboem test positive	bolic diseas with or with	e. 83% of E			
Collection Instructions				× v			We
	Add				_	Modify Addition	onal Info.
						QK	Cancel
To select a test: double-click on the test n	ame OR single-	-click and ther	n the Add but	ton OR use the arr	ow keys ar	nd then Alt-A	

Figure S2: D-dimer order screen in provider order entry application with ordering message discouraging inpatient D-dimer orders to assess venous thromboembolic disease

Additional information for : D-dimer	And California	
Itest : D-dim	er	
PLEASE NOTE: Measurement of INPATIENTS undergoing D-dimer t	D-dimer is of limited clinical utility for INPATIENTS with clinically suspecte esting will test positive with or without DVT/PE. (This note does NOT appl	d venous thromboembolic disease. 83% of y to emergency department patients or
Additional Information :	* Required fields	Additional Tests for this Specimen
Indication	* Indication for D-dimer testing (REQUIRED):	
Indication	Known or suspected PE Known or suspected DVT DIC evolution Other	
	* Please document other indication:	
	< F	
Click on each Additional Info	rmation item to enter specific information.	QK <u>C</u> ancel

Figure S3: D-dimer order screen in provider order entry application with order indication request for providers choosing to place D-dimer order in emergency department or inpatient clinical settings