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Cost-Effectiveness of Strategies for Diagnosing Pulmonary Embolism Among Emergency Department Patients Presenting with Undifferentiated Symptoms

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Abstract

Objective—Symptoms associated with pulmonary embolism (PE) can be nonspecific and similar to many competing diagnoses, leading to excessive costly testing and treatment as well as missed diagnoses. Objective studies are essential for diagnosis. This study evaluates the cost-effectiveness of different diagnostic strategies in an Emergency Department (ED) for patients presenting with undifferentiated symptoms suggestive of PE.

Methods—Using a probabilistic decision model, we evaluated the incremental costs and effectiveness (quality-adjusted life years (QALYs) gained) of 60 testing strategies for five patient pretest categories (distinguished by Wells score (High, Moderate, or Low) and whether deep venous thrombosis (DVT) is clinically suspected). We performed deterministic and probabilistic sensitivity analyses.

Results—In the base case, for all patient pretest categories, the most cost-effective diagnostic strategy is to use an initial ELISA D-dimer test, followed by compression ultrasound (CUS) of the lower extremities if the D-dimer is above a specified cutoff. The level of the preferred cutoff varies with the Wells pretest category and whether a DVT is clinically suspected. D-dimer cutoffs higher than the current recommended cutoff were often preferred for even Moderate and High Wells category patients. CUS accuracy had to fall below commonly cited levels in the literature before it was not part of a preferred strategy.

Conclusions—When PE is suspected in the ED, use of an ELISA D-dimer assay, often at cutoffs higher than those currently in use (for patients in whom DVT is not clinically suspected), followed by CUS as appropriate, can reduce costs and improve outcomes.

INTRODUCTION

Background

In a typical Emergency Department (ED) setting, pulmonary embolism (PE) is usually one of several competing diagnoses in patients presenting with chest pain, shortness of breath, or a related complaint. If left untreated, PEs have significantly high mortality rates.^{1–13} Typical imaging tests for PE and deep venous thromboses (DVTs) include compression ultrasound (CUS), the ventilation-perfusion scan (VQ), and computed tomographic angiograms (CTAs)

(which have separable pulmonary (CTP) and peripheral venous (CTV) components; the CTV is a CT venogram of the iliofemoral vessels). Several quantitative D-dimer assays are available for evaluating patients with venous thromboembolism (VTE), including the VIDAS™ enzyme-linked immunosorbent assay (ELISA) D-dimer test.^{14–16} Current guidelines commonly assert that a quantitative D-dimer should be used as a precursor to imaging tests only when a normal (low) D-dimer result can establish a posterior probability of PE that is less than 1%.^{17–22} However, accurate estimation of such a probability is difficult, leading to the use of clinical decision rules such as the Wells score.^{21, 23–25}

Importance

Symptoms associated with pulmonary embolism (PE) can be nonspecific and similar to many competing diagnoses, leading to excessive costly testing and treatment, and missed diagnoses. Previous work evaluating the cost-effectiveness of strategies for diagnosing PE in acute care settings has focused on patients specifically undergoing evaluation for a PE. Several studies have analyzed the cost-effectiveness of imaging strategies without considering use of the D-dimer or different cutoffs for the D-dimer test, competing diagnoses, or the breadth of feasible diagnostic strategies.^{26–30}

Goals of the Investigation

We evaluated the cost-effectiveness of different strategies for diagnosing PE in patients presenting to an ED with complaints potentially attributable to a PE. We considered different strategies for the use of the D-dimer test as a precursor to imaging, and a variety of imaging strategies. In addition to VTE, we assumed that the D-dimer test result could be affected by two competing diagnoses, acute coronary syndrome (ACS) and aortic dissection (AD).

METHODS

Overview

Using a sequential decision model (Figure 1), we evaluated the cost-effectiveness of 60 possible testing strategies for patients in five different pretest PE risk categories. We evaluated total incremental costs and benefits (quality-adjusted life years (QALYs) gained) for each strategy in each category of patients. The “Base Case” represents the output of the deterministic analysis with each parameter set at its base value (Table 1). We performed sensitivity analysis on all parameter values (ranges in Table 1). Details of our model and calculations are in the Appendix. The study methodology is exempt from IRB review and approval.

Events and Testing Strategies

We assumed that a patient presenting with complaints potentially attributable to a PE is given an initial clinical evaluation, as described in the Wells decision rule (history, exam, vital signs, 12-lead electrocardiogram (ECG), and chest x-ray) and is then assigned to one of five PE pretest categories based partly on a Wells score: Low Wells, Moderate Wells, and High Wells (a simplified version of the Wells scoring rule is shown in Figure 1).²⁵ We subdivided Moderate and High Wells categories based on the physician’s *a priori* clinical suspicion of DVT (e.g., patient history or clinical findings on extremity exam). Since the known majority of PEs arise from DVTs, and clinical suspicion of DVT is a highly imperfect indicator for the presence of DVT, the probability of PE varies jointly with the clinical suspicion of DVT and the presence of a detectable DVT.^{31–33} Due to the Wells points allotted for a clinically suspected DVT, no patient in the Low Wells risk category can have a clinically suspected DVT.

We considered five cutoffs for the D-dimer assay (Cutoff I - 200, II - 350, III - 500, IV - 650, V - 800 mcg/L), and the use of no D-dimer. For each of these six possibilities, we considered ten imaging strategies (including three different cutoffs for a VQ scan, which we denote as Low, Normal, and Intermediate)³⁰ (Figure 2). Figure 3 depicts the clinician's assessment and decision sequence.

Some patients who present with symptoms potentially attributable to VTE have a seemingly clear non-VTE etiology for their symptoms. Several studies have demonstrated that the probability of PE not only differs if there is an alternative diagnosis, but also varies with the nature of the alternative diagnosis under consideration (i.e., it varies depending upon the clinician's suspicion of anxiety, emphysema, etc.).^{34–36} Two disease processes that cause symptoms potentially attributable to PE and whose impact on ELISA D-dimer results has been quantified are ACS and AD.^{37–44} Pneumonia can lead to symptoms suggestive of PE, but there are often additional signs and symptoms that preclude consideration of PE, and its impact on D-dimer levels has not been quantified at more than one cutoff.^{38, 39, 45, 46} Malignancy^{47–49}, recent surgery, and advanced age⁵⁰ tend to increase D-dimer levels. We consider age in the analysis; malignancy and recent surgery are subsumed as risk factors for VTE.

Primary Data Analysis, Assumptions and Input Parameters

We performed an extensive literature review to obtain values for model parameters (Table 1). When required probabilities were not available in the literature, informed expert judgment (from board-certified emergency physicians) was solicited and the values were validated by joint calibration.

We assumed an average age of presentation of 55 years⁵¹ and an average remaining lifetime of 25 years.⁵²

Base values of probabilities in the model were calibrated to generate a conditional probability of PE by Wells category of 40.5% (High Wells), 16.0% (Moderate Wells), and 1.5% (Low Wells), which match published estimates of PE prevalence among patients suspected of having a PE.^{17, 21, 24, 25, 53–55} We estimated that 15.7% of patients would have ACS^{35, 56–61} and .03% of patients would have AD.^{35, 37, 44, 56, 62} Conditional distributions on the prevalence of DVT for patients with known and suspected PE^{2, 15, 31, 32, 63–74} and mortality rates for patients with treated and untreated PE^{2, 4, 7, 75, 76} were estimated from the literature.

We generated gamma distributions to estimate the performance of the quantitative D-dimer assay in patients with VTE, AD, and ACS (Figure 4). We chose the parameters for the gamma distributions so that the sensitivity and specificity measurements at various D-dimer cutoff values for VTE, AD and ACS match published data. Cutoff III (500 mcg/L) represents the current widely employed cutoff for the VIDASTM ELISA D-dimer (Table 2).^{14, 16, 30, 37, 40–42, 44, 77–80}

We estimated CTV, CUS, and CTP sensitivity and specificity from the literature.^{15, 27, 28, 30, 67, 69, 70, 81–95} VQ scan performance for PE at each VQ cutoff value considered (Low, Normal, Intermediate) has been extensively studied.^{51, 92, 95–98}

Outcome Measures

For each strategy, we calculated net present incremental costs and QALYs using a 3% discount rate.⁹⁹ Incremental costs include monetary costs incurred beyond the initial clinical evaluation including incremental testing and treatment costs, costs of complications, liability payments for missed cases, and indirect costs. Anticoagulation treatment costs were assessed

from the literature.^{5, 9, 100–103} Costs of the D-dimer and imaging tests were estimated based on Medicare data.^{26, 29, 102, 104–107} We used national malpractice databases to estimate the average liability payment for missed cases of PE.^{9, 108–112} We considered a category of indirect costs, based on Medicare data, to account for the time required to execute a diagnostic strategy.^{102, 107, 113}

Quality adjustments for some clinical states were obtained from the literature.^{2–4, 9, 11, 12, 71, 72, 114–121} When published estimates were not available for a given clinical state, we used quality adjustments for an approximately equivalent state.

Model Implementation

For each of the 60 diagnostic strategies in each of the five patient pretest categories, we used the model to evaluate net present incremental cost incurred and QALYs experienced per patient. We evaluated the base case (a 55-year-old patient with 25 years of remaining life expectancy, with all other parameters set at their base value) for each of the 60 diagnostic strategies in each of the five patient pretest categories, and performed sensitivity analyses.

RESULTS

Base Case

In the base case (Table 3, Appendix Figure 2), for all patient pretest categories, the best strategy is to use a D-dimer test, followed by CUS if the D-dimer is above a specified cutoff. A cutoff higher than the current widely used cutoff was preferred or dominant for all pretest categories except High Wells patients with clinically suspected DVT (Cutoff II). We say that a strategy is preferred if it maximizes QALYs at a low incremental cost (less than \$50,000/QALY gained) when compared to the lowest cost strategy or provides high but non-maximal QALY outcomes and moving to the next most cost-effective strategy incurs an incremental cost/QALY gained well above \$50,000. Both Cutoff IV (650 mcg/L), dominant for Moderate Wells category patients with no clinically suspected DVT, and Cutoff V (800 mcg/L), dominant for Low Wells category patients (Table 3, Appendix Figure 2), are higher than the cutoff currently in wide use for the Vidas ELISA assay (500 mcg/L).

Results of Sensitivity Analyses

In deterministic one-way sensitivity analysis (ranges in Table 1), changes in parameters such as patient age, mortality from treated or untreated PE, ACS and AD prevalence, quality-of-life multipliers, exclusion of liability and indirect costs, and high cost assumptions did not substantively change the preferred strategies. We varied the pretest probability of PE and found that D-dimer testing has no value for patients with clinically suspected DVT when the cumulative pretest probability of PE reaches 11% in the base case, 12% in the high-cost scenario, and 30% when liability costs are excluded.

When the sensitivity and specificity of CUS are reduced to 80% and 93%, respectively (values well below those commonly cited in the literature), CUS is not always part of a preferred strategy: when DVT is clinically suspected, CUS/CTP with no D-dimer is the dominant strategy; and when DVT is not clinically suspected, CTA or CTP with D-dimer are the preferred strategies (depending on the patient pretest group). Setting CTP and CTV sensitivity and specificity at the levels documented in the PIOPED II investigation^{91, 93, 122} with all other parameters set at base values did not change the results from the base case. We performed several additional multi-way sensitivity analyses and found no significant changes in the preferred strategies.

In stochastic sensitivity analysis, CUS with D-dimer remained the dominant or preferred strategy for all patient pretest categories (Table 4, Appendix Figure 3), with few changes in D-dimer cutoffs compared to the base case. For Low Wells patients, D-dimer Cutoff III with CUS became the dominant strategy, and for Moderate Wells patients with no DVT clinically suspected, Cutoff V became preferred (but with significant overlap in the 95% confidence interval for Cutoff IV). All other cutoffs remain unchanged.

LIMITATIONS

Our analysis has several limitations. The probabilistic relationship between DVT and PE in our model is based upon our current understanding of the pathogenesis of PE. We did not vary the performance of the D-dimer assay in the presence of malignancy or advanced age. Both tend to raise D-dimer levels,^{47–50} so our analysis is conservative: if a higher cutoff than commonly used is more cost-effective for young patients and patients without malignancy, it will also be cost-effective for older patients or those with malignancy. Due to lack of data, we did not incorporate dependencies between tests and the performance of these tests. The effects of these dependencies (and possibly other unforeseen dependencies) are minimized by the causal model that we used. We handled indeterminate imaging test results in the same manner in which they were handled in the literature cited. We did not incorporate differential risks and detection based upon estimates of clot burden, due to lack of data. We did not include the cost and QALY impact of mistaken treatment for VTE in patients with ACS or AD nor did we consider misdiagnosis of ACS and AD, as our focus is on the diagnosis of PE in a patient with undifferentiated symptoms and not the overall evaluation of a patient with undifferentiated symptoms. If we had assumed higher contrast nephropathy rates for CT angiograms and considered the lifetime malignancy risk for CT angiograms, QALY and incremental cost results would have favored D-dimer and CUS-based strategies even further. In that sense, our analysis is conservative. Lastly, we assumed for each diagnostic strategy that the indicated imaging tests are available. Appendix Figures 2 and 3 show alternative, nearly equivalent strategies that could be chosen when a particular imaging test is unavailable.

DISCUSSION

Our analysis has shown that, for patients who present to the ED with undifferentiated symptoms suggestive of PE, the most cost-effective diagnostic strategy is to use a D-dimer followed by CUS if the D-dimer is above a specified cutoff. Our analysis suggests a D-dimer cutoff higher than the cutoff widely in use (Table 3, 4, Appendix Figures 2, 3) for a broad range of pretest risk categories. Our results were robust over an extensive range of sensitivity analyses. CUS accuracy (specificity in particular) had to fall well below commonly cited levels in the literature before it was not part of a preferred or dominant strategy.

The use of different D-dimer cutoffs for different Wells categories followed, as appropriate, by CUS is an efficient and safe approach reinforced by recent clinical studies.^{123, 124} Our study makes no assumption about the “correct” frequency of D-dimer use. D-dimer use is explicitly considered in the model through the estimation of costs and health outcomes for different D-dimer cutoffs in the setting of different Wells patient categories. The frequency of imaging depends on the cutoff threshold of the D-dimer result that triggers testing. Given that the differences in health outcomes between different top strategies rarely exceeded hundredths of a QALY, it is possible that using a cutoff higher than 500 mcg/L for the VidasTM D-dimer could save money without compromising health outcomes significantly. A retrospective review found that a highly sensitive D-dimer assay increases testing (and, therefore, testing costs) without necessarily increasing the diagnosis rate of PE.¹²⁵

We found that the D-dimer is part of a cost-effective diagnostic strategy for all patient pretest categories until the prevalence of PE in the overall ED population exceeds 11%. While this value is lower than the prevalence of PE (20% or more) noted in most studies of clinical decision rules for diagnosing PE in patients presenting to the ED, those studies deal with populations where PE was the primary process under consideration.^{19, 24, 25, 53, 78, 126–129} Based on data from numerous sources and conservative assumptions, we estimated (Appendix) that the prevalence of PE in patients presenting to the ED with a complaint potentially attributable to PE is less than 2% – well under the 11% threshold identified in our analysis. For the more general ED population, setting the prevalence of PE to the levels cited in the clinical decision rule literature does not properly assess the cost-effectiveness of diagnostic strategies for this patient population.

The recommendations from our analysis represent a significant departure from current practice. Implementing the policies we advocate could result in increased D-dimer testing. However, our analysis indicates that when patients present with signs and symptoms suggestive of PE and warranting a history, exam, vital signs, 12-lead ECG, and chest x-ray, using the D-dimer in accordance with the guidelines from our analysis is part of a cost-effective diagnostic strategy. Moreover, the policies we advocate would likely lead to decreased numbers of imaging tests, particularly in Low and Moderate Wells category patients. Future work will need to validate these results in a prospective clinical trial prior to the delivery of clinical recommendations.

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APPENDIX

Calibration of Data from Multiple Sources

Some probability estimates needed for the model were obtained from the literature and some were obtained from informed expert judgment (as estimated by board-certified emergency physicians). In order to ensure that all probabilities were consistent, we performed a process of joint calibration. In this process, we used Bayes' Rule to ensure that the values obtained were valid probabilities (i.e., between 0 and 1.0) and did not contradict values found in the literature. Similarly, quality adjustments for some clinical states were obtained from the literature, but when published estimates were not available for a given clinical state, we used quality adjustments for an approximately equivalent state. To ensure that we had an internally consistent set of quality adjustments, we ordered the outcomes by preference to confirm that the quality assessments from these heterogeneous sources are consistent with a reasonable preference ordering over the various health states.

Estimation of PE Prevalence

Several studies have questioned the true prevalence of PE in patients presenting to the ED with chest pain or shortness of breath.^{34, 35, 120, 131} This value is difficult to estimate because of the range of complaints associated with PE and the frequency of those complaints in disorders unrelated to PE. Here we develop a conservative estimate of the prevalence of PE among patients presenting to the ED; then, below we describe how we estimated the PE prevalence in the modeled patient population. According to the National Ambulatory Health Statistics (NAHS)¹⁴³, in 2004 there were 110 million visits to EDs. Based on prior studies of common presenting complaints in patients with PE and the NAHS list of presenting complaints^{15, 36, 144–153}, roughly 13 to 15 million of these patient visits

were due to complaints that could be referable to PE (Appendix Table 1). The annual U.S. incidence of PE has been estimated to be approximately 250,000.^{1, 6, 8, 10, 130, 154} Using this incidence, even if we assume that all cases of PE present to the ED, the prevalence of PE among patients presenting to the ED is not likely to exceed 1.9% (= 250,000/13 million). This is likely a gross overestimate since many patients with PE never present to an ED: a large percentage of PEs occur in the post-operative hospitalized patient or they are clinically silent. This approximation is an order of magnitude lower than the prevalence of PE in study populations used to derive and validate clinical decision rules or performance characteristics of imaging tests for diagnosing PE.^{25, 51, 84, 96, 97, 139}

The overall prevalence of PE in the modeled patient population is a function of the prevalence of common presenting conditions and complaints for which PE is part of the differential diagnosis (e.g., pneumonia, “heartburn”, musculoskeletal chest pain, pericarditis, abdominal etiologies for epigastric discomfort, cardiac angina) and risk factors for those disease processes either by history or exam (e.g., cardiac risk factors, history of pulmonary disease, ECG findings, chest x-ray findings, vital signs, oxygen saturation). The variables and their states considered are detailed in Appendix Table 2. We are *not* suggesting that all patients with such complaints should be considered for PE. We are simply recognizing the fact that different combinations of symptoms, signs, and findings will entail different prior probabilities on the presence of PE.

The common disease processes other than PE are sometimes clearly discernable in the course of the base evaluation (history, vitals, exam, ECG, and CXR) and other times are not. We used three main aggregation nodes to capture the effect of other disease processes that do not cause PE and do not affect the outcome of the D-dimer test: “Clear Cause by Imaging or ECG”, “Clear Pulmonary or Musculoskeletal Cause”, and “Clear Abdominal Cause”. Each of these three aggregation nodes was then aggregated into a node labeled “Clear Cause Other than PE”. The simplified sub-graph in Appendix Figure 4 shows the relationship between these aggregation nodes and the distribution of PE. Appendix Table 3 shows the base conditional probability table for the PE node. Based on the joint distribution over various conditional probabilities with marginal distributions calibrated to data obtained from the literature, the overall prevalence of PE was estimated to be 0.79% to 1.96%. Appendix Table 4 shows the conditional probability of pulmonary embolism (PE), as a function of oxygen saturation, whether a clear other cause for signs and symptoms is present, and joint probability of PE. The prevalence of PE in the model was widely ranged in sensitivity analyses.

We note that when a clinician decides that there is a “clear other cause” for the patient’s signs and symptoms (the third column in Appendix Tables 3 and 4), this does not reflect on the state of nature. The state of nature is still uncertain to the clinician. The patient could still have a PE even though the clinician believes that he or she has identified a “clear other cause”. The node “Clear Other Cause” shown in the network in Appendix Figure 1 is an aggregation node that depends upon the findings through various inputs that can be ascertained by history, exam, ECG, or chest x-ray.

Details of Stochastic Sensitivity Analyses

The stochastic sensitivity analyses were designed to evaluate the verisimilitude of the computational model and the impact of multi-directional parameter variation. We varied all parameters probabilistically and independently within the intervals reported in the literature from a constructed probability distribution; as the number of trials increases, all potential combinations of multidirectional sensitivity analysis are effectively performed.

For each D-dimer cutoff d and patient pretest category c , the minimum number of runs needed to achieve 0.5% relative precision on either incremental costs or QALYs with a 95% confidence interval (CI) is

$$n(d, c) = \max_{i \in IS} \left[\max \left(n_i^{QALY}, n_i^{Cost} \right) \right],$$

where IS is the set of all possible imaging strategies, and n_i^{QALY} and n_i^{Cost} are the number of runs needed to achieve the required precision on QALYs and costs, respectively, for strategy $i \in IS$. The quantities n_i^{QALY} and n_i^{Cost} are calculated as:

$$n_i^{QALY} = 1 + Z^2 \frac{\left(\frac{\sigma_i^{QALY}}{m-1} \right)}{\left(\sum_{r=1}^m QALY^{(r)} \right)^p}$$

$$n_i^{Cost} = 1 + Z^2 \frac{\left(\frac{\sigma_i^{Cost}}{m-1} \right)}{\left(\sum_{r=1}^m Cost^{(r)} \right)^p}$$

where m is the number of trial runs and p is the relative precision and Z is the standard normal variate.

The minimum number of runs needed so that 0.5% relative precision on either incremental costs or QALYs is achieved with a 95% confidence interval (CI) for all test strategies is:

$$n^* = \max_{d \in D, c \in C} [n(d, c)]$$

Based on a trial of 100 simulation runs, we calculated $n^* = 4727$. Based on this, we set the simulation run total to 5000. For patient pretest categories where DVT is clinically suspected (Moderate Wells and High Wells with DVT suspected), we used 50,000 total simulation runs to create smaller graphical intervals.

Constructing Gamma Distributions for the D-dimer Assay

We chose gamma distributions to model the range of values found by the D-dimer assay because the gamma distribution is nonnegative, has at most one peak, and allows a fair amount of flexibility in fitting the shape of the probability distribution to observed data (the gamma distribution has two degrees of freedom – a scale parameter and a shape parameter).

We researched the performance of the D-dimer at two or greater different cutoff values for VTE, ACS, and AD from the literature, and constructed a gamma distribution whose shape matched the published performance of the assay at these multiple cutoffs. Since there are two degrees of freedom in a gamma distribution, using the sensitivity and specificity of the D-dimer assay at two different cutoffs allowed us to fully determine the “correct” gamma distribution by iterating over different values for the two different parameters. Through iterative manipulation of the two gamma distribution parameters until we found values that minimized deviation from the published sensitivity and specificity data at the two or more

cutoffs obtained from the literature. In this manner, we constructed gamma distributions for the D-dimer assay in VTE, ACS, and AD.

Modeling Platform

The model was coded in Java JDK 5.0 using the Netica™ Java API and Netica™. LISP expressions were used to represent utility node equations. Netica provides a full set of APIs in multiple languages (<http://www.norsys.com/netica-j.html>). Using their APIs, we wrote a Java application that runs the simulation. The Java API allows one to set various values in utility equations and conditional probability tables directly before calculating the network. While this is useful in the static analysis, it is indispensable for the stochastic analysis because it allows for sampling from distributions, setting the values for various properties based upon this sampling, and repeating this process thousands of times (the number of runs was as determined below). Interested readers may contact Dr. Duriseti (ram1@stanford.edu) for a copy of the code.

Appendix Table 1

Percentage of 2004 emergency department (ED) visits with complaints referable to pulmonary embolism (PE)

Complaint Surveyed	Percentage of 2004 Visits
"Chest pain and related symptoms"	5.4% $\pm$ 0.2% ¹⁴³
"Cough"	2.5% $\pm$ 0.1% ¹⁴³
"Shortness of breath"	2.3% $\pm$ 0.1% ¹⁴³
"Labored or difficult breathing (dyspnea)"	1.2% $\pm$ 0.1% ¹⁴³
"Syncope"	1%–2% ^{152, 153}
Total percentage of visits	11.9% to 13.9%

Appendix Table 2

Clinical variables included in the model outside of PE (pulmonary embolism), DVT (deep venous thrombosis), and D-dimer results

Variable Description	Variable States
Acute coronary syndrome impact on D-dimer results	⟨High, Low⟩
Aortic dissection impact on D-dimer results	⟨High, Low⟩
Pneumonia or bronchitis	⟨Present, Absent⟩
Age	⟨16 to 47, 48 to 63, 64 to 72, older than 72⟩
Congestive heart failure	⟨Present, Absent⟩
Cardiac risk factors	⟨Present, Absent⟩
Acute coronary syndrome	⟨Present, Absent⟩
Pleuritic chest pain	⟨Yes, No⟩
Aortic dissection	⟨Present, Absent⟩
Bronchospasm on exam	⟨Present, Absent⟩
Burning nature of pain	⟨Yes, No⟩
Process that is not otherwise specified	⟨Present, Absent⟩

Variable Description	Variable States
Biliary or pancreatic disease	⟨Present, Absent⟩
Pericarditis or endocarditis	⟨Present, Absent⟩
Dyspepsia or gastritis	⟨Present, Absent⟩
Fever	⟨High, Equivocal, Absent⟩
Radiates to the upper extremities	⟨Yes, No⟩
Response to cocktail	⟨relief, equivocal_or_no_relief⟩
Dull pressure	⟨Yes, No⟩
Symptoms consistent with acute coronary syndrome	⟨Yes, No⟩
Sudden onset	⟨Yes, No⟩
Pneumothorax	⟨Present, Absent⟩
Rales on exam	⟨Present, Absent⟩
Dyspnea or shortness of breath not from pulmonary embolism	⟨Yes, No⟩
Epigastric tenderness to palpation	⟨Mild_to_Moderate_TTP, Severe_TTP, Absent⟩
Cough	⟨Marked, Equivocal⟩
Clear infectious cause from an abdominal etiology	⟨Yes, No⟩
Clear pulmonary or musculoskeletal cause	⟨Yes, No⟩
Respiratory rate	⟨High, Normal⟩
Blood pressure	⟨Markedly_Elevated, Mild_HTN, Normal⟩
Oxyhemoglobin saturation	⟨Low, Within Normal Limits⟩
Simple tachycardia	⟨Yes, No⟩
Clear cause apparent on imaging or on electrocardiogram	⟨Yes, No⟩
Electrocardiogram	⟨Acute MI, Concerning, Equivocal, Normal⟩
Heart rate	⟨Pathologic, Tachycardia, No_Tachycardia⟩
Clear cause on electrocardiogram	⟨Yes, No⟩
Wide mediastinum on chest radiograph	⟨Yes, No⟩
Concerning aortic widening	⟨Yes, No⟩
Tenderness of the chest wall upon palpation	⟨Yes, No⟩
Aortic dissection clinically apparent	⟨Yes, No⟩
Decreased breath sounds unilaterally	⟨Yes, No⟩
Abnormal heart sounds	⟨Yes, No⟩
Electrocardiogram results	⟨Yes, No⟩
Chest radiograph results	⟨Yes, No⟩
Chest radiograph	⟨Yes, No⟩

* The model includes other variables whose primary purpose is as an *aggregation node*, a constant value, or a *rule repository* for computational purposes. Most of these variables are not listed. The aggregation nodes process input from multiple variables to map the combined input into a smaller common output space. Some aggregation nodes are listed in this table. The rule repository nodes hold logical expressions to execute certain functional relationships.

Appendix Table 3

Conditional probability of pulmonary embolism (PE), as a function of oxygen saturation level and whether a clear other cause for signs and symptoms is present

Wells Category	Oxygen Saturation	Clear Other Cause	PE Present	PE Absent	References
Low	low	Yes	.010	.990	34–36, 54, 131, 148, 149, 155–163
Low	low	No	.050	.950	34–36, 54, 131, 148, 149, 155–163
Low	within normal limits	Yes	.001	.999	34–36, 54, 131, 148, 149, 155–163
Low	within normal limits	No	.013	.987	15, 21, 24, 25, 31, 32, 35, 36, 53, 54, 64, 69, 73, 131, 148, 149, 160–163
Moderate	low	Yes	.020	.980	34–36, 54, 131, 148, 149, 155–163
Moderate	low	No	.324	.676	34–36, 54, 131, 148, 149, 155–163
Moderate	within normal limits	Yes	.010	.990	34–36, 54, 131, 148, 149, 155–163
Moderate	within normal limits	No	.162	.838	15, 21, 24, 25, 31, 32, 35, 36, 53, 54, 64, 69, 73, 131, 148, 149, 160–163
High	low	Yes	.040	.960	34–36, 54, 131, 148, 149, 155–163
High	low	No	.800	.200	34–36, 54, 131, 148, 149, 155–163
High	within normal limits	Yes	.020	.980	34–36, 54, 131, 148, 149, 155–163
High	within normal limits	No	.406	.594	15, 21, 24, 25, 31, 32, 35, 36, 53, 54, 64, 69, 73, 131, 148, 149, 160–163

Appendix Table 4

Conditional probability of pulmonary embolism (PE), as a function of oxygen saturation, whether a clear other cause for signs and symptoms is present, and joint probability of PE

						DVT Not Clinically Suspected	DVT Clinically Suspected
Wells Category	Oxygen Saturation	Clear Other Cause	Probability PE is Present	Probability PE is Absent	References	Estimated Joint Probability	Estimated Joint Probability
Low	Low	Yes	.010	.990	34–36, 54, 131, 148, 149, 155–163	0.162	Not Applicable *
Low	Low	No	.050	.950	34–36, 54, 131, 148, 149, 155–163	0.00211	Not Applicable *
Low	Normal *	Yes	.001	.999	34–36, 54, 131, 148, 149, 155–163	0.818	Not Applicable *
Low	Normal	No	.013	.987	15, 21, 24, 25, 31, 32, 35, 36, 53, 54, 64, 69, 73, 131, 148, 149, 160–163	0.0176	Not Applicable *
Moderate	Low	Yes	.020	.980	34–36, 54, 131, 148, 149, 155–163	0.146	0.163
Moderate	Low	No	.324	.676	34–36, 54, 131, 148, 149, 155–163	0.0121	0.00167
Moderate	Normal	Yes	.010	.990	34–36, 54, 131, 148, 149, 155–163	0.7406	0.822
Moderate	Normal	No	.162	.838	15, 21, 24, 25, 31, 32, 35, 36, 53, 54, 64, 69, 73, 131, 148, 149, 160–163	0.10085	0.0139
High	Low	Yes	.040	.960	34–36, 54, 131, 148, 149, 155–163	0.135	0.1507
High	Low	No	.800	.200	34–36, 54, 131, 148, 149, 155–163	0.0194	0.00932
High	Normal	Yes	.020	.980	34–36, 54, 131, 148, 149, 155–163	0.683	0.762
High	Normal	No	.406	.594	15, 21, 24, 25, 31, 32, 35, 36, 53, 54, 64, 69, 73, 131, 148, 149, 160–163	0.163	0.0778

* By construction, in the Wells simplified scoring rule, a patient cannot be in a Low Wells risk category if a DVT is clinically suspected.

Appendix Figure 1.

Simplified influence diagram depicting uncertainties and decisions relevant to the possible diagnostic testing strategies*

* CTP = computed tomographic perfusion. CTV = computed tomographic venography. CUS = compression ultrasound. DVT = deep venous thrombosis. PE = pulmonary embolism. VQ = ventilation perfusion scan. Unshaded circles represent unobserved uncertainties, shaded circles represent observed uncertainties, double circles represent deterministic variables, rectangles represent decisions, the diamond represents a utility node, and arrows represent influences. The choice of a cutoff for the D-dimer test and the cutoff for the VQ scan are subsumed in the respective decision to order the test. Uncertainty nodes that send arrows to decision nodes are observed before these decisions are made. The node labeled *Value Vector* includes an incremental cost component and a quality-adjusted life year (QALY) component. The probability of PE is mediated by the impact of several variables and not just the Wells pretest category. The uncertainty *Other D-dimer Cause* represents the non-VTE disease processes that can raise the D-dimer level. We consider two such disease processes: aortic dissection (AD) and acute coronary syndrome (ACS). The nodes *Clear Other Cause* and *Other D-dimer Cause* are aggregation nodes that represent the joint influence of sets of nodes. They are depicted here as single nodes for diagrammatic simplicity.

Appendix Figure 2a:

Appendix Figure 2b:

Appendix Figure 2c:

Appendix Figure 2d:

Appendix Figure 2e:

Appendix Figure 2. Results under base case assumptions*

Appendix Figure 2a: Base-case results for High Wells Category patients with clinically suspected DVT

Appendix Figure 2b: Base-case results for Moderate Wells Category patients with clinically suspected DVT

Appendix Figure 2c: Base-case results for High Wells Category patients with no clinically suspected DVT

Appendix Figure 2d: Base-case results for Moderate Wells Category patients with no clinically suspected DVT

Appendix Figure 2e: Base-case results for Low Wells Category patients

* Sixty diagnostic strategies were considered for each category of patients. These figures show only the highest performing strategies. D-dimer Cutoff I = 200 mcg/L; D-dimer Cutoff II = 350 mcg/L; D-dimer Cutoff III = 500 mcg/L; D-dimer Cutoff IV = 650 mcg/L; D-dimer Cutoff V = 800 mcg/L. CUS = compression ultrasound. CTP = computed tomographic perfusion. DVT = deep venous thrombosis. ICER = incremental cost-effectiveness ratio. VQ = ventilation perfusion scan.

Appendix Figure 3a:

Appendix Figure 3b:

Appendix Figure 3c:

Appendix Figure 3d:

Appendix Figure 3e:

Appendix Figure 3. Results of stochastic sensitivity analysis***Appendix Figure 3a:** Results for High Wells patients with clinically suspected DVT**Appendix Figure 3b:** Results for Moderate Wells patients with clinically suspected DVT**Appendix Figure 3c:** Results for High Wells patients with no clinically suspected DVT**Appendix Figure 3d:** Results for Moderate Wells patients with no clinically suspected DVT**Appendix Figure 3e:** Results for Low Wells patients

* CTA = computed tomographic angiogram. CTP = computed tomographic perfusion. CUS = compression ultrasound. DVT = deep venous thrombosis. VQ = ventilation perfusion scan. D-dimer Cutoff I = 200 mcg/L; D-dimer Cutoff II = 350 mcg/L; D-dimer Cutoff III = 500 mcg/L; D-dimer Cutoff IV = 650 mcg/L; D-dimer Cutoff V = 800 mcg/L. We performed stochastic sensitivity analysis using Monte Carlo methods, generating 95% confidence intervals (CIs) for estimates. We ranged all parameters within $\pm 10\%$ around the base value while maintaining monotonicity across health states. Each parameter was sampled from a different random number stream. We selected liability payments to be present or absent with a random Boolean operator. When present, we ranged the liability payment $\pm 10\%$ around the base value of \$250,000. We computed the minimum number of trial runs (n^*) required for a relative precision of 0.5% with a 95% CI for each of the 60 diagnostic strategies in each of the five patient pretest categories (details in Appendix). Based on a trial of 100 simulation runs, we calculated $n^* = 4727$, so we set the simulation run total to 5000. For the pretest categories where a DVT is clinically suspected (Moderate Wells and High Wells with DVT suspected), we used 50,000 simulation runs to create smaller graphical intervals. Each testing strategy has nine data points representing the nine possible combinations of the mean, the upper CI, and the lower CI for both costs and QALYs ($[\text{mean, upper CI, lower CI}]^T \times [\text{mean, upper CI, lower CI}]$). Sixty diagnostic strategies were considered for each category of patients. These figures show only the highest performing strategies.

Appendix Figure 4.

Subgraph of the full influence diagram of the model demonstrating the relationship between aggregation nodes that explain away symptoms ("Clear Other Cause") and the pulmonary embolism (PE) node

Appendix Figure 5.

Receiver Operator Characteristic (ROC) curves for D-dimer performance in patients with and without venous thromboembolism (VTE), aortic dissection (AD), and acute coronary syndrome (ACS)

Wells Criteria	
3 points:	DVT (>3cm asymmetry), PE as likely or more likely than an alternative diagnosis
1.5 points:	Heart rate >100, Immobilization (bed rest for 3 consecutive days), Surgery in previous 4 weeks, Previously documented PE
1.0 points:	Hemoptysis, Malignancy
< 2 points →	Low Risk
2-6 points →	Moderate Risk
> 6 points →	High Risk

Figure 1.
Simplified Wells Scoring Rule used in the analysis

- (1) No imaging
- (2) CUS alone
- (3) CUS followed by VQ if negative, and treatment if VQ > Low
- (4) CUS followed by VQ if negative, and treatment if VQ > Normal
- (5) CUS followed by VQ if negative, and treatment if VQ > Intermediate
- (6) VQ and treatment if VQ > Low
- (7) VQ and treatment if VQ > Normal
- (8) VQ and treatment if VQ > Intermediate
- (9) CTA (comprising both a pulmonary portion (CTP) and a peripheral venous portion (CTV)) and treatment if CTA positive
- (10) CUS followed by CTP with treatment if either test is positive

Figure 2.

Imaging strategies considered*

* CUS = compression ultrasound, CTA = computed tomographic angiogram, CTP = computed tomographic perfusion, CTV = computed tomographic venogram, VQ = ventilation perfusion scan

Figure 3.
Diagram of the clinician's decision process*

Figure 4. Estimated gamma distributions for D-dimer performance in patients with and without venous thromboembolism (VTE), aortic dissection (AD), and acute coronary syndrome (ACS)

Table 1Values and sources for key parameters used in the model^{*}

Parameter	Base Value	Range [#]	Source
Demographic Parameters			
Average age of presentation (years)	55	30 – 75	1, 9, 10, 51, 66, 130–133
Average remaining lifetime (years)	25	5 – 50	52
Conditional Probability of PE by Wells category [¶]			
High	40.6%	Not ranged	15, 21, 24, 25, 31, 32, 53, 54, 64, 69, 73
Medium	16.2%	Not ranged	15, 21, 24, 25, 31, 32, 53, 54, 64, 69, 73
Low	1.3%	Not ranged	15, 21, 24, 25, 31, 32, 53, 54, 64, 69, 73
DVT prevalence when PE is present			
DVT clinically suspected	70%	64% – 86%	2, 15, 31, 32, 63–74, 134–138
DVT not clinically suspected	30%	25% – 35%	2, 15, 31, 32, 63–74, 134–136, 138, 139
Mortality with a treated PE	10%	5% – 11.5%	2, 7, 75
Mortality with an untreated PE	25%	20% – 34.5%	2, 7, 75
ACS prevalence	15.7%	5% – 20%	35, 56–61
AD prevalence	0.03%	0.02% – 1%	35, 37, 44, 56, 62
Imaging Test Performance			
CUS performance			
Sensitivity	93%	79% – 99%	15, 67, 70, 81, 85, 93–95
Specificity	98%	84% – 100%	15, 67, 70, 81, 85, 93–95
CTP performance			
Sensitivity	90%	70% – 95%	27, 28, 30, 69, 84, 86–91
Specificity	98%	80% – 100%	27, 28, 30, 69, 84, 86–91
CTV performance			
Sensitivity	80%	70% – 95%	69, 81–85
Specificity	98%	80% – 100%	69, 81–85
Distribution of VQ scan results in patients with PE [£]			
High	40.8%	Not ranged	51, 92, 95–98
Intermediate	41.3%	Not ranged	51, 92, 95–98
Low	15.9%	Not ranged	51, 92, 95–98
Near Normal	2.0%	Not ranged	51, 92, 95–98
Total	100%		
Distribution of VQ scan results in patients without PE [‡]			
High	2.4%	Not ranged	51, 95–98
Intermediate	38.0%	Not ranged	51, 95–98
Low	40.2%	Not ranged	51, 95–98
Near Normal	19.4%	Not ranged	51, 95–98
Total	100.0%		
Costs (\$)			

Parameter	Base Value	Range [#]	Source
Direct test costs			
D-Dimer	20	20 – 100	26, 29, 102, 104–106
CUS	100	100 – 500	26, 29, 102, 104–106
VQ scan	700	700 – 2000	26, 29, 102, 104–106
CTA [§]	400	400 – 2000	26–29, 102, 104–106
Indirect test costs ^{**}			
D-Dimer	200	0 – 200	102, 107, 113
CUS	200	0 – 200	102, 107, 113
VQ scan	800	0 – 800	102, 107, 113
CTA	400	0 – 800	102, 107, 113
Cost of anticoagulation per year ^{##}	1250	1250 – 5000	5, 9, 100–103
Liability costs			
No treatment and PE	250,000	0 – 1,000,000	9, 108–112
Treatment and no VTE	25,000	0 – 100,000	9, 108–112
Quality Adjustments^{¶¶}			
Untreated DVT and live	0.980	0.84 – 1.0	2–4, 9, 71, 114–117
No PE and treated ^{££}	0.980	0.81 – 1.0	114, 117
No DVT and treated ^{££}	0.980	0.81 – 1.0	114, 117
Has DVT and treated ^{££}	0.931	0.79 – 1.0	3, 9, 71, 72, 114–117, 121
Has DVT and not treated	0.914	0.78 – 1.0	3, 4, 9, 71, 72, 114–117, 121
Has PE and treated ^{££}	0.855	0.73 – 0.98	3, 4, 9, 11, 12, 114, 117–120
Has PE and not treated ^{††}	0.651	0.55 – 0.75	2–4, 9, 11, 12, 114, 117–120

* ACS = acute coronary syndrome. AD = aortic dissection. CTA = computed tomographic angiogram. CTP = computed tomographic perfusion. CTV = computed tomographic venography. CUS = compression ultrasound. DVT = deep venous thrombosis. PE = pulmonary embolism. VQ = ventilation perfusion scan.

[#] The range shown represents the value over which the parameter was ranged in one-way, two-way, and (in some cases) three-way sensitivity analyses.

[¶] The overall prevalence of PE in the modeled patient population is 1.96% (see Appendix).

[£] Calculated from data in the PIOPED (Prospective Investigation of Pulmonary Embolism Diagnosis) study: among 252 patients with PE, 103 (40.8%) patients had a High test result, 104 (41.3%) had an Intermediate test result, 40 (15.9%) had a Low test result, and 5 (2.0%) had a Near Normal test result.⁵¹

[†] Calculated from data in the PIOPED (Prospective Investigation of Pulmonary Embolism Diagnosis) study: among 635 patients without PE, 15 (2.4%) had a High test result, 241 (38.0%) had an Intermediate test result, 2560 (40.2%) had a Low test result, and 123 (19.4%) had a Near Normal test result.⁵¹

[§] We estimated that CTA (comprising both CTP and CTV) costs \$400 and CTP alone costs \$200 based on Medicare data.^{104, 105}

^{**} Indirect cost is intended to capture the incremental costs incurred due to increased nursing and physician care associated with different workups. Based on an average Medicare payment of roughly \$400 per ED visit with average length of stay per visit of 2.0 hours in a busy urban ED, we estimated the indirect cost of each test to be \$200 multiplied by the average time to obtain a result from the test (in hours).^{107, 113}

This is the cost of treatment discounted over the duration of therapy. For a lifetime of therapy with an estimated remaining life of 25 years, the net present value at this cost with a 3% discount rate is \$22,419. We assumed that treatment durations for PE and DVT are the same. Insufficient published evidence exists to establish an appropriate duration of treatment for a PE. However, treatment durations beyond six months for DVT have a declining cost-to-benefit ratio.⁹⁵ We considered both lifetime and six-month treatment. Costs of anticoagulation included the costs of treating complications of anticoagulation for VTE including intracranial hemorrhage.^{5, 9, 101, 103, 140, 141}

¶¶ Among the tests considered, CTA is the only one that carries measurable risk (due to the use of injected contrast dye). Based on the expected incidence (0.0008 under base case assumptions) of adverse effects from the contrast injection²⁷, we incorporated a quality adjustment for patients who undergo a CTA. This quality adjustment involves a simple expected value computation involving the incidence of a serious contrast reaction (allergic or renal) and the quality-of-life multiplier associated with these outcomes. Many of these values represent computations over conditional probabilities in the model (e.g., the mortality rate of PE with and without treatment, the probability of PE in the presence of DVT, and the probability of major complications on anticoagulation). Therefore, some ranges are derived by ranging those conditional probabilities. We note that assuming 1% rate of adverse events from contrast injection¹⁴² did not change the preferred diagnostic strategies.

££ The quality adjustment for anticoagulation alone without complications was taken as 0.98. This was extrapolated from patients who are on anticoagulation for a stroke without any residual neurological deficits where anticoagulation usually involves agents and doses of like agents with a lower incidence of bleeding complications than agents commonly used to treat VTE.¹¹⁴ The quality adjustment for anticoagulation used in the paper included risk of significant bleeding complications such as intracranial hemorrhage.^{5, 9, 101, 103, 140, 141}

†† We assumed that the QALY value for a patient with an untreated PE who lives is .93, the QALY value for an untreated patient with PE who dies is 0, and the chance of death from an untreated PE is .30 (ranged in sensitivity analysis). Thus, under base case assumptions, we calculated $(.93)(.70) + (0)(.30) = .651$. This value was ranged up to .744 by including “intermediate states” where some patients with an untreated PE suffer long term cardiopulmonary consequences (e.g., pulmonary hypertension and/or chronic dyspnea) while others do not.

Table 2

Conditional probabilities for the ELISA D-dimer assay performance in the setting of venous thromboembolism (VTE), aortic dissection (AD), and acute coronary syndrome (ACS)*

D-dimer Level	Sensitivity for VTE	Specificity for VTE	Sensitivity for AD	Specificity for AD	Sensitivity for ACS	Specificity for ACS
Cutoff I (200 mcg/L)	99.9%	83.1%	99.9%	5.3%	95.4%	8.3%
Cutoff II (350 mcg/L)	99.8%	30.0%	99.0%	27.5%	76.1%	26.0%
Cutoff III (500 mcg/L)	98.1%	45.8%	93.2%	56.0%	49.9%	45.8%
Cutoff IV (650 mcg/L)	92.1%	63.1%	79.2%	77.6%	28.0%	63.1%
Cutoff V (800 mcg/L)	80.0%	76.1%	14.0%	90.0%	14.0%	76.1%

* Cutoff III (500 mcg/L) represents the current widely employed cutoff for the VIDASTM ELISA D-dimer.³⁰ We also considered values that are 150 mcg/L and 300 mcg/L above and below this value.

Table 3

Summary of results under base case assumptions *

Patient Pretest Category	Best Strategy (Incremental Costs, QALYs)
High Wells; DVT Clinically Suspected	D-dimer, then CUS if D-dimer Cutoff II **
Moderate Wells; DVT Clinically Suspected	D-dimer, then CUS if D-dimer Cutoff III **
High Wells; No DVT Clinically Suspected	D-dimer, then CUS if D-dimer Cutoff III ***
Moderate Wells; No DVT Clinically Suspected	D-dimer, then CUS if D-dimer Cutoff IV ***
Low Wells	D-dimer, then CUS if D-dimer Cutoff V ***

* DVT = deep venous thrombosis. CUS = compression ultrasound. CTP = computed tomographic perfusion. VQ = ventilation perfusion scan. D-dimer Cutoff III = 500 mcg/L; D-dimer Cutoff IV = 650 mcg/L; D-dimer Cutoff V = 800 mcg/L. Incremental costs and QALYs are measured in comparison to the strategy of no testing. The “base case” represents the deterministic analysis results with all parameters set at their “Base Value” as described in Table 1.

** These strategies are preferred: they provide maximum health benefit (QALYs), and cost less than \$50,000 per QALY gained when compared to the next lowest cost strategy.

*** These strategies are dominant: they provide maximum health benefit (QALYs) *and* have the lowest cost of any strategy.

Table 4Summary of results of stochastic sensitivity analysis^{*}

Patient Pretest Category	Best Strategy (Incremental Costs, QALYs)
High Wells; DVT Clinically Suspected	D-dimer, then CUS if D-dimer Cutoff III ^{***}
Moderate Wells; DVT Clinically Suspected	D-dimer, then CUS if D-dimer Cutoff III ^{**}
High Wells; No DVT Clinically Suspected	D-dimer, then CUS if D-dimer Cutoff III ^{**} (with significant overlap in 95% CI with Cutoff IV)
Moderate Wells; No DVT Clinically Suspected	D-dimer, then CUS if D-dimer Cutoff V ^{**} (with significant overlap in 95% CI with Cutoff IV)
Low Wells	D-dimer, then CUS if D-dimer Cutoff V ^{***}

^{*} DVT = deep venous thrombosis. CUS = compression ultrasound. CTP = computed tomographic perfusion. VQ = ventilation perfusion scan. D-dimer Cutoff III = 500 mcg/L; D-dimer Cutoff IV = 650 mcg/L; D-dimer Cutoff V = 800 mcg/L. Incremental costs and QALYs are measured in comparison to the strategy of no testing.

^{**} These strategies are preferred: they provide maximum health benefit (QALYs), and cost less than \$50,000 per QALY gained when compared to the next lowest cost strategy.

^{***} These strategies are dominant: they provide maximum health benefit (QALYs) *and* have the lowest cost of any strategy.