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Early Diagnosis of Pulmonary Embolism: Review and Cost-Effectiveness Analysis

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EARLY DIAGNOSIS OF PULMONARY EMBOLISM:

REVIEW AND COST-EFFECTIVENESS ANALYSIS

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ABSTRACT

EARLY DIAGNOSIS OF PULMONARY EMBOLISM:
REVIEW AND COST-EFFECTIVENESS ANALYSIS

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Pulmonary embolism (PE) is a serious, life-threatening thrombotic disease, which results in considerable health and economic consequences each year for the United States. These consequences include a toll of 83,000 deaths and an economic impact between $1.5 and $5 billion. Approaches to strategy selection by physicians and other health-care specialists are based mainly upon cost, technology availability, and cultural tolerance regarding radiation exposure. The purpose of this study was to determine the most cost-effective diagnostic strategy with patients suspected of PE among several strategies currently used by examining their detection failure rates. This objective was met by (a) assessing parameter estimates and their uncertainty using triangular and γ distributions, (b) conducting a cost-effectiveness analysis, and (c) testing the model for errors using sensitivity analysis.

Cost-effectiveness analysis based upon a decision tree model revealed that among the investigated strategies for patients with suspected PE the most cost-effective strategy appears to be strategy 3, composed of a clinical decision rule (CDR), a D-dimer test (DD), a compression ultrasonography test (CUS), and a computed tomography pulmonary angiography (CT). Strategy 5, composed by a CDR, DD, a CT, a CUS, and an invasive pulmonary angiography (PA) appeared to be a cost-effective method, but it was more expensive than strategy 3 and included an invasive pulmonary angiography (PA).

The results of a Monte Carlo simulation sensitivity analysis were robust over a number of distributions regarding the PE diagnostic test costs, sensitivities, specificities, and strategy effectiveness. Additionally, the results of this investigation were valid over an extensive range of one-way, two-way, and three-way sensitivity analyses regarding PE diagnostic test costs. Overall, the proposed analyses identified uncertainty and eliminated error; thus, it provides a practical approach to help medical professionals estimate uncertainty in the diagnosis of PE. Although this research has broadened the ability to identify uncertainty and eliminate error, further research is needed to validate these findings in a prospective clinical trial before the delivery of a clinical recommendation.

This research is dedicated to my wife, Angeliki Polychronopoulos, M. P. H., and my son, Ioannis Polychronopoulos, M. E. M., whose valuable encouragement and enormous support contributed to pursue this goal. This long lasting journey might have never been accomplished without their love and inestimable assistance. I dedicate this dissertation to my parents Ioannis and Efstathia. My mother, Efstathia Polychronopoulos, has been my inspiration in conducting this research for her courage in rough times and her devotion to helping others. I dedicate this dissertation to individuals who lead accessibility efforts for those in need.

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CHAPTER 1

INTRODUCTION

Pulmonary embolism (PE) is a serious, life-threatening thrombotic disease, which results in considerable health and economic consequences each year for the United States. These consequences include a toll of 83,000 deaths and an economic impact between $1.5 and $5 billion (Anderson et al., 1991; Dobesh, 2009; Eichinger et al., 2004; Goldhaber, 2004; Heit, 2006, 2008; Heit, Mohr, et al., 2000; Kniffin, Baron, Barrett, Birkmeyer, & Anderson, 1994; MacDougall, Feliu, Boccuzzi, & Lin, 2006; Silverstein et al., 1998; Spyropoulos & Lin, 2007; Stein, Kayali, & Olson, 2004a; U.S. Department of Health and Human Services, 2008). PE incidence approximates 207,000 cases per year in the United States, the vast majority of which require hospitalization and expensive treatment (De Lissovoy & Subedi, 2002; Dobesh, 2009; MacDougall et al., 2006; McGarry, Thompson, Weinstein, & Goldhaber, 2004; Ollendorf, Llonch, & Oster, 2002; Silverstein et al., 1998; Spyropoulos & Lin, 2007; U.S. Department of Health and Human Services, 2008). The cost of diagnostic management and treatment of an initial PE episode ranges between $9,500 and $16,700, whereas the diagnostic management and treatment of PE combined with deep vein thrombosis (DVT) costs approximately $25,000 (De Lissovoy & Subedi, 2002; Dobesh, 2009; MacDougall et al., 2006; McGarry et al., 2004; Ollendorf et al., 2002; Silverstein et al., 1998; Spyropoulos & Lin, 2007; U.S. Department of Health and Human Services, 2008). Survivors are affected for the rest of their lives, and those who experience an initial PE episode are at high risk for recurrent PE within 10 years with the highest risk occurring during the first year

(Douketis, Kearon, Bates, Duku, & Ginsberg, 1998; Eichinger et al., 2004; Heit, 2006; Heit, Mohr, et al., 2000; Spencer et al., 2008; Stein, Hull, & Raskob, 2000; White, 2003).

PE diagnostic strategies have been developed based upon combinations of clinical decision rules and available laboratory and imaging PE diagnostic tests such as the (a) D-dimer test, (b) computed tomography pulmonary angiography scan, (c) ventilation-perfusion lung scan, (d) compression ultrasonography test, and (e) invasive pulmonary angiography test (Elias et al., 2004; Gibson et al., 2008; Hudson et al., 1996; Sostman et al., 2008; Stein et al., 2006; Toulon, Lecourvoiser, & Meyniard, 2009; Wells et al., 2000). The costs associated with these tests and rules, implemented as diagnostic strategies, or screenings, are continually being evaluated. Current cost-effectiveness analyses of PE screenings result in variable findings because of several combinations of these tests and rules employed in medical conditions to which they are applied. The factors of cost and effectiveness of each screening present constant challenges to physicians as they decide which diagnostic strategy to select for use with certain conditions (Doyle et al., 2004; Hull, Graham, Stein, Mah, & Butcher, 2001; Paterson & Schwartzman, 2001; Perrier, Mathieu, Francois, Nigel, & Bounameaux, 2003; Quiroz & Schoepf, 2005).

Statement of the Problem

PE is difficult to diagnose. Misdiagnosis or delay in PE detection can be fatal. It is estimated that 10% of all patients with symptomatic PE die within 60 minutes of onset, and 15% of diagnosed patients die within three months after diagnosis (Goldhaber, Visani, & De Rosa, 1999; Kearon, 2003).

Although clinicians are responsible for accurate diagnoses and must use care in the application of the available technologies for PE diagnosis, their selection of

diagnostic strategies varies greatly (Le Gal, Righini, Sanchez, et al., 2006; Nijkeuter et al., 2007; Perrier et al., 2005; Stone et al., 2003; Wells et al., 2001). Approaches to strategy selection by physicians and other health-care specialists are based mainly upon cost, technology availability, and cultural tolerance regarding radiation exposure (Brenner & Hall, 2007; Kline, Courtney, Beam, King, & Steuerward, 2009; Perrier, 2007; Piazza & Goldhaber, 2009; Sodhi & Kaur, 2005). Determining the most cost-effective PE diagnostic screening strategy might ease the challenge to health-care professionals of selecting the most appropriate strategy with which to diagnose a patient with suspected PE and might provide insight regarding the variability among currently available strategies.

Purpose of the Study

The purpose of this study was to determine the most cost-effective diagnostic strategy among several strategies currently used with patients with suspected PE based upon the failure rates of the respective strategies. The ability to identify the most cost-effective strategy may result in wider implementation of a particular strategy for PE detection that is less costly and more effective when compared to alternate strategies.

Factors Influencing the Cost-Effectiveness Analysis (CEA) of Pulmonary Embolism Early Diagnosis

CEA basics.

A cost-effectiveness analysis (CEA) of PE diagnostic strategies is used to compare the cost and effectiveness of a reference strategy with available alternate strategies by assessing the value of each using specific units of cost and effectiveness (e.g., dollars spent per additional life gained, dollars spent per additional PE episode

avoided) (see Doyle et al., 2004; Fenwick, 2009a; Gold, 1996; Hull et al., 2001; Hunink & Krestin, 2002; Jan, 2009; Kaplan, 2006; Kastanioti, 2009; Kuntz, Fleischmann, Hunink, & Douglas, 1999; Muennig, 2008; Paterson & Schwartzman, 2001; Perrier et al., 2003; Quiroz & Schoepf, 2005; Yeh, 2009). There are three very important elements of a CEA for PE diagnostic strategies: *composition*, *costs*, and *effectiveness*. The *composition* of each PE diagnostic strategy includes specific clinical decision rules (CDRs), D-dimer tests, and imaging tests for detecting PE (Doyle et al., 2004; Hull et al., 2001; Paterson & Schwartzman, 2001; Perrier et al., 2003; Quiroz & Schoepf, 2005).

CEA of PE diagnostic strategies can be conducted from a third-party payer *cost* perspective or a societal *cost* perspective, depending upon the particular set of decision-making interests. The third-party payer cost perspective considers the economic impact on the payer, and the societal cost perspective examines the economic impact of costs without regard to who initiates the costs or who finances the costs. Typically, CEAs of PE diagnostic strategies have been conducted with consideration to the third-party payer perspective, which includes only direct costs of PE diagnostic strategies such as laboratory tests or diagnostic tests, treatment, and hospitalization. A CEA from a societal perspective includes indirect costs (e.g., costs due to productivity loss, waiting or travel time, or other economic impact on patients and their families) and opportunity costs (e.g., costs of market competition, income, and taxes). This type of examination is rarely employed (see Doyle et al., 2004; Fenwick, 2009a; Gold, 1996; Hull et al., 2001; Hunink & Krestin, 2002; Jan, 2009; Kaplan, 2006; Kastanioti, 2009; Kuntz et al., 1999; Muennig, 2008; Paterson & Schwartzman, 2001; Perrier et al., 2003; Quiroz & Schoepf, 2005; Yeh, 2009).

Finally, the *effectiveness* of each PE diagnostic strategy reflects the performance of the entire strategy, including failure to detect a PE, which could result in another PE episode that might be fatal. The effectiveness of a PE diagnostic strategy is commonly measured by mortality or survival rates (Doyle et al., 2004; Fenwick, 2009a; Gold, 1996; Hull et al., 2001; Hunink & Krestin, 2002; Jan, 2009; Kaplan, 2006; Kastanioti, 2009; Kuntz et al., 1999; Muennig, 2008; Paterson & Schwartzman, 2001; Perrier et al., 2003; Quiroz & Schoepf, 2005; Yeh, 2009).

Pulmonary embolism diagnostic costs.

A PE diagnostic strategy is a procedure that combines CDR with laboratory tests and imaging tests that surpasses the accuracy of a clinical assessment conducted using only D-dimer or imaging tests (Le Gal, Righini, Sanchez, et al., 2006; Nijkeuter et al., 2007; Perrier et al., 2005; Stone et al., 2003; Wells et al., 2001). PE diagnosis usually begins with a clinical assessment that includes CDR, history, physical examination, and instrumental examination followed by a D-dimer test and other imaging tests, if necessary (Daniel, Courtney, & Kline, 2001; Gibson et al., 2008; Goekoop et al., 2007; Le Gal, Righini, Roy, et al., 2006; Miniati et al., 2003; Nijkeuter et al., 2007; PIOPED Investigators, 1990; Sanson et al., 2000; Söhne, Kamphuisen, Van Mierlo, & Büller, 2005; Stein et al., 2007; Stein & Henry, 1997; Stein et al., 2008; Wells et al., 2000; Wicki et al., 2001).

The high PE incidence, combined with the high average cost for PE diagnostic management and treatment, generates substantial economic cost consequences of as much as $5 billion annually for the U.S. health-care system (De Lissovoy & Subedi, 2002; Dobesh, 2009; Knight et al., 2005; MacDougall et al., 2006; McGarry et al., 2004;

Ollendorf et al., 2002; Spyropoulos & Lin, 2007). In general, the average cost for a PE episode appears to be greater than a DVT episode, mainly due to longer hospitalization and greater treatment and medical costs (Dobesh, 2009). It is estimated that in the United States the cost of a first PE episode ranges between $9,500 and $16,600. The cost of an initial DVT episode ranges between $7,700 and $10,800. Overall, the annual economic impact of VTE for the entire U.S. health care system reaches at least $1.5 billion (Dobesh, 2009).

De Lissovoy and Subedi (2002) estimated median costs of initial PE, DVT, and PE with DVT at $6,424, $3,131, and $6,678, respectively. The median costs of each recurrent VTE event, each bleed event, and each recurrent VTE with bleed event were estimated at $5,736, $4,999, and $10,185, respectively. Applying these estimates to annual PE and DVT incidences in the United States (207,000 and 143,000, respectively) reveals an annual economic cost of $1.33 billion for PE and $0.45 billion for DVT. Thus, the total annual VTE economic cost for the entire nation is approximately $1.8 billion.

According to a 2007 study (Spyropoulos & Lin, 2007), the average annual direct medical costs of a PE episode were $16,644 and about $10,804 for a DVT episode. The cost for a recurrent PE was $14,722 and $11,862 for a recurrent DVT. Applying these estimates to annual PE and DVT incidences in the United States (207,000 and 143,000, respectively) reveals direct medical costs of $3.4 billion for PE and $1.5 billion for DVT. The total annual VTE direct medical costs for the entire nation are approximately $5 billion.

MacDougall et al. (2006) studied a cohort of 26,958 patients to determine that the annual median total reimbursed cost was $18,901 for a PE episode, $17,512 for a DVT

episode, and $25,554 when both PE and DVT were present. Applying these cost amounts to annual PE and DVT incidences in the United States (207,000 and 143,000, respectively) reveals annual direct medical costs of $3.9 billion for PE and $2.5 billion for DVT. The total annual VTE reimbursed cost for the entire nation is approximately $5.4 billion.

The Decision Tree Framework for Assessing Cost-Effectiveness

A common decision-making theoretical framework used in previous studies to assess the cost-effectiveness of PE diagnostic strategies is the decision tree framework (Doyle et al., 2004; Muennig, 2008; Paterson & Schwartzman, 2001; Perrier et al., 2003; Quiroz & Schoepf, 2005). This theoretical framework offers a meaningful presentation of very complex decision-making problems by (a) overcoming the restriction of presenting data in a tabular format and (b) offering the advantages of outlining all potential *actions*, delineating all probable *events*, and demonstrating all possible *outcomes* (Lapin & Whisler, 2002). The decision tree framework is based upon three major concepts—*act*, *event*, and *outcome*—as described by Lapin & Whisler (2002) (see Figure 1).

Act is defined as the decision maker's choices. In each decision, an initial action occurs. For example, when one must choose among four diagnostic strategies to detect a disease, each strategy represents a potential initial action. The decision tree framework demonstrates all actions on the left side of the tree's structure.

An *event* is defined as the component of the decision that contains an element of uncertainty following an initial action. Probability values are assigned to each event in the decision tree structure, the sum of which equals 1.00. For example, with uncertainty regarding diagnostic test results from diagnostic strategy 1 (Action 1), two events can

occur: either the patient receives treatment or another test is administered. If the probability of receiving treatment is p, then the probability of the administration of another test is 1-p.

A new action can follow an event. For example, after selecting the initial action of applying a diagnostic strategy (Action 1) and selecting another test (Event 2), the new action is the administration of another test, which creates a new event that presents a different element of uncertainty. In the decision tree framework, there is a chronological progression of events. Those indicated on the left side are assumed to occur before events indicated on the right side of the decision tree.

Outcome is defined as any component that can be used to measure the investigating condition. A clear measure of an outcome is its payoff value in dollars per life saved. Using an example of disease detection, if the decision maker chooses to apply diagnostic strategy A, then the outcome will be $1.00 per life saved. If he or she selects diagnostic strategy B, then the payoff will be $1.50 per life saved. If diagnostic strategy A results in greater effectiveness but is more expensive than strategy B, then the outcome should be expressed in an incremental cost-effectiveness ratio of dollars per additional life saved. However, calculations that are more complicated follow when expressing an outcome in an incremental cost-effectiveness ratio of dollars spent per additional life saved. The decision tree framework demonstrates the outcomes or the consequences of the events on the right side of the decision tree.

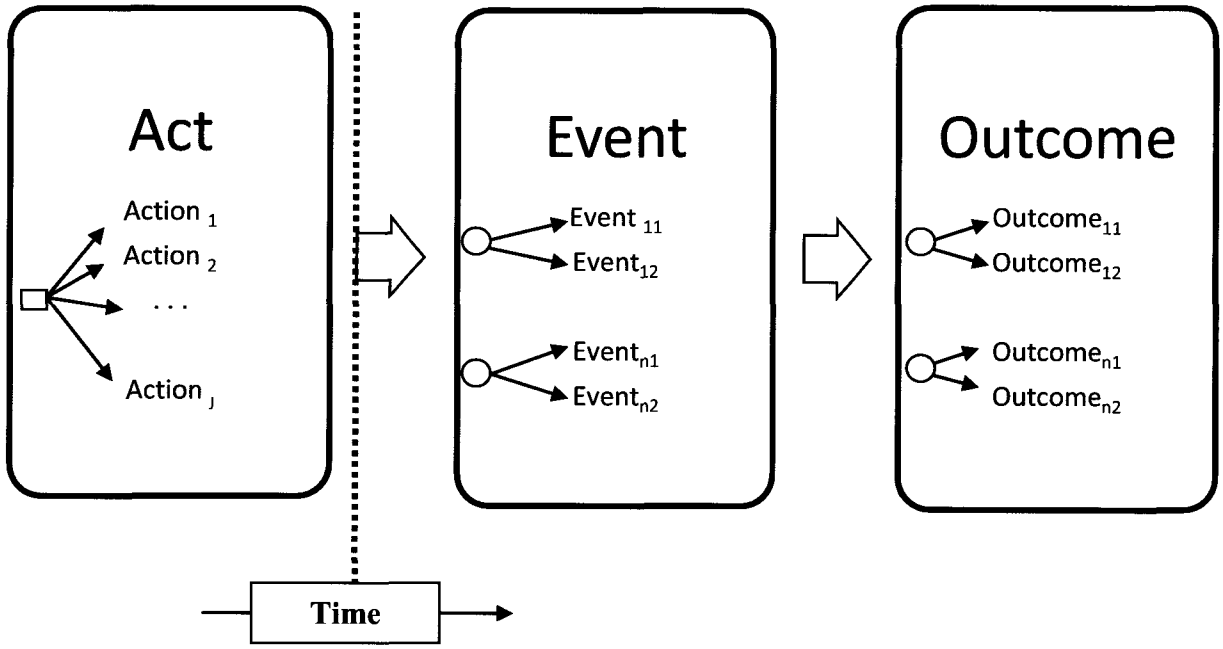


Figure 1. Decision tree framework. A square represents a decision node. A circle represents a chance node. Several events can occur with corresponding outcomes under each action[1]. For example, under Action 1, Events 1-1or 1-2 can occur with corresponding Outcomes 1-1 or 1-2, while under Action j, Events n-1 or n-2 can occur with corresponding Outcomes n-1 or n-2.

Significance of the Study

At the time of this dissertation limited research was available to identify the most cost-effective diagnostic strategy currently in use that detects PE. This study assessed the cost and effectiveness of several diagnostic strategies currently in use for patients with suspected PE. Specifically, this research attempted to determine the most cost-effective diagnostic strategy, particularly with attention to its screening value (i.e., screening failure rate).

[1] The decision tree framework for assessing cost-effectiveness is based upon the decision tree framework as described by Lapin and Whisler (2002).

The individual cost and effectiveness components of PE detection, though significant, do not describe the combined effect of the performance and the economic impact of a PE diagnostic strategy compared to alternate strategies. When a PE diagnostic strategy results in better effectiveness, but costs more than an alternate strategy, the incremental cost-to-incremental effectiveness ratio (ICER) should be calculated. Therefore, this study examined the combined effect of performance and economic impact of costs and effectiveness with particular attention to the failure rates of each diagnostic strategy for detecting PE.

This study is one of only a few studies, which have investigated factors influencing PE diagnostic strategies from a cost-effectiveness perspective. This study is the only study that has addressed these strategies using a CEA in combination with triangular distributions, γ distributions, and Monte Carlo Simulation to evaluate which PE diagnostic strategy is more cost-effective based upon the failure rates for PE detection.

Assumptions

A few assumptions were made about diagnostic tests, treatment, and utilization of secondary data. First, if PE is ruled out, then patients will not receive treatment or further tests. Additionally, if PE is confirmed, then patients will receive treatment, and no further tests will be performed. Also, if PE is not ruled out or confirmed, then further imaging test(s) will follow. Finally, it was assumed that the secondary data identified in literature are true and unbiased.

Limitations

Several limitations can be applied to this study. First, this research is based upon data collected solely from the literature cited, which limits the applicability of the data to

the design and methodology presented in the original research. In addition, it is assumed that all tests included in the investigated strategies are available and that any strategy could be selected based upon the cost-effectiveness analysis (CEA). This analysis approached the implementation of treatment and the nondiagnostic imaging test results in the same manner that they were approached in the cited literature. Further, this study did not distinguish between different types of the same imaging test because it is focused upon early PE diagnosis in patients, in general, and not upon an evaluation of each of the available types of imaging tests.

CHAPTER 2

LITERATURE REVIEW

This chapter reviews the literature that addressed this study's components: a theoretical decision-making framework, individual screening tools for diagnosing pulmonary embolism (PE), their combinations into distinct diagnostic strategies, and cost-effectiveness analysis (CEA) studies of these strategies. The decision tree framework (Lapin & Whisler, 2002) is described, and its application to a CEA for assessing PE diagnostic strategies is presented.

PE is a serious disease. It is difficult to diagnose and it has considerable health and economic impacts on a community (Dobesh, 2009; U.S. Department of Health and Human Services, 2008). Diagnostic challenges are mainly associated with the implementation of clinical decision rules, the availability of diagnostic laboratory and imaging tests, and the medical costs associated with them (Brenner & Hall, 2007; Kline, Courtney, Beam, King, & Steuerward, 2009; Perrier, 2007; Piazza & Goldhaber, 2009; Sodhi & Kaur, 2005). The application of cost-effective diagnostic strategies could reduce costs and decrease mortality and recurrence rates of the disease in patients with suspected PE (Horlander, Mannino, & Leeper, 2003; Perrier, 2007; Stein, Kayali, & Olson, 2004a).

Theoretical Framework: The Decision Tree Framework

The theoretical framework for this study is based upon the comprehensive decision tree framework, as described by Lapin & Whisler (2002). It was selected for its flexibility in combining three constructs—*Actions*, *Events*, and *Outcomes*—of a decision and for its use in previous studies that evaluated the cost- effectiveness of PE diagnostic strategies (Doyle et al., 2004; Paterson & Schwartzman, 2001; Perrier, Mathieu, Francois,

Nigel, & Bounameaux, 2003; Quiroz & Schoepf, 2005). The PE diagnostic strategies were assigned to the *Actions* construct. The components of these strategies (i.e., the diagnostic tools that include clinical decision rules, laboratory tests, and imaging tests) were assigned to the *Events* construct. A probability value that the event will occur was assigned to each *Events* construct. The supposition of a payoff was assigned to the *Outcomes* construct.

The *Actions* construct includes the PE diagnostic strategies investigated in this study. Diagnostic strategy is defined as a series of diagnostic procedures based upon a combination of clinical decision rules (CDR), laboratory tests, and imaging tests that can maximize the accuracy of a stand-alone clinical decision rule, D-dimer test, or imaging test performed to detect a disease. First, patients are evaluated for PE by a clinical decision rule. If PE is not excluded, then a D-dimer test is administered. If PE still is not excluded, then an imaging test or tests are performed to rule out or confirm PE (see Doyle et al., 2004; Hull, Graham, Stein, Mah, & Butcher, 2001; Paterson & Schwartzman, 2001; Perrier et al., 2003; Quiroz & Schoepf, 2005).

The *Events* construct includes clinical decision rules (CDR) used to detect a disease. A CDR is defined as "an instrument containing variables obtained from history, physical examination, and simple diagnostic tests, quantifying the likelihood of a diagnosis, prognosis, or likely response to treatment in an individual patient" (Klok et al., 2008, p. 2131). The *Events* construct also includes the diagnostic tests performed to detect a disease. A diagnostic test is defined as the laboratory or imaging test applied to detect a disease (Elias, Colombier, et al., 2004; Hudson et al., 1996; Sostman, Stein, et al., 2008; Stein, Fowler, et al., 2006; Toulon et al., 2009). The D-dimer test (DD) is a

laboratory blood test used to exclude PE and to eliminate the need for imaging testing (Hogg et al., 2005; Kline, Runyon, Webb, Jones, & Mitchell, 2006; Stein, 2007a; Stein, Hull, et al., 2004). Imaging tests are diagnostic tests based upon a range of imaging modalities to diagnose a disease (Elias, Colombier, et al., 2004; Hudson et al., 1996; Perrier, 2007; Perrier et al., 2005; Sostman, Stein, et al., 2008; Stein, Fowler, et al., 2006; Toulon et al., 2009). Several different imaging tests can be performed to detect PE. These include a computed tomography pulmonary angiography (CT), a ventilation-perfusion lung scan (VQ), a compression ultrasonography (CUS), and an invasive pulmonary angiography (PA). Also included in this construct is the probability that a test will exclude (rule out) or confirm PE and the probability that a new (i.e., additional) test will follow (Doyle et al., 2004; Hull et al., 2001; Paterson & Schwartzman, 2001; Perrier et al., 2003; Quiroz & Schoepf, 2005).

The *Outcomes* construct includes any payoff for each event. The payoff in this study was defined as the combined cost and effectiveness of each event (Doyle et al., 2004; Hull et al., 2001; Paterson & Schwartzman, 2001; Perrier et al., 2003; Quiroz & Schoepf, 2005). Accordingly, direct costs are defined as "Costs associated with goods and services consumed", and effectiveness is defined as "The performance of health intervention in the real world" (Muennig, 2008, p. 250).

The basic tenet of the decision tree framework, also well-known as decision tree model, is that events are presented in a chronological sequence. Events indicated on the left side of the framework occur before events on the right side of the framework, beginning with the event node at the furthest left (Doyle et al., 2004; Ishwaran & Rao, 2009; Lapin & Whisler, 2002; Paterson & Schwartzman, 2001; Perrier et al., 2003;

Sonnenberg & Hagerty, 2009). The initial component of the decision tree framework is the decision node, usually depicted by a small square with at least two lines originating from it that represent possible options. In this study, the lines beginning at the decision node symbolized the available PE diagnostic strategies as options.

The next component of a decision tree framework is the chance node, usually depicted by a small circle. Several lines originate from each chance node, which represents the possible events that cannot be controlled by the decision maker, for example, laboratory test results. Assume that the implementation of strategy 1 included a D-dimer test. If the test results are negative, then no treatment will be administered; if the test results are positive, then a CT will be performed. Regardless, the decision maker has no control or foreknowledge of the event's results.

The probabilities for a single event in this study are (a) the probability of a test to rule out or confirm PE *and* (b) the probability of a new (i.e., additional) test to follow. For example, if the probability that a D-dimer test is negative is 0.30, then the probability that an additional test will follow is 0.70 because the summing of the event's probabilities must equal 1.00. The last component of a decision tree framework is the payoff, the triangle at the far right side of the decision tree, which began at a decision node that was followed by a chance node in the *Actions* and *Events* constructs. Payoffs are the consequences of the events. In this study, a payoff was described as the 3-month follow-up mortality rates and the VTE (i. e., PE and/or DVT) recurrence rates occurring among patients with suspected PE after the implementation of a certain diagnostic test or a series of tests with their corresponding costs. Figure 2 depicts a decision tree framework for selecting diagnostic strategies to detect PE among patients with suspected PE.

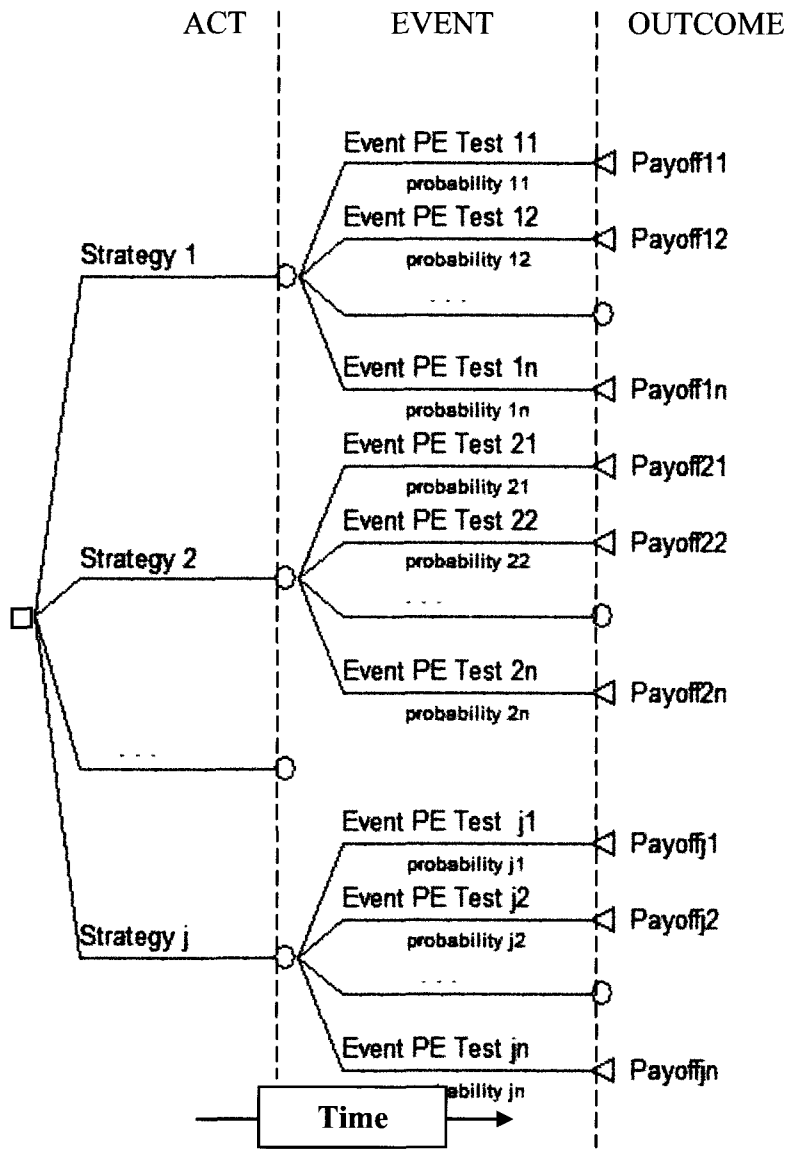


Figure 2. Decision tree framework for PE diagnostic strategies. A square represents a decision node. A circle represents a chance node. A triangle represents a terminal node. Several events can occur with corresponding probabilities and outcomes under each action[2]. For example, under *Action* PE diagnostic strategy 1, *Event* PE test 1_1 or $1_2 \ldots 1_n$ can occur with corresponding Probabilities 1_1 or $1_2 \ldots 1_n$ and *Outcomes* payoff 1_1 or $1_2 \ldots 1_n$, while under *Action* PE diagnostic strategy j, *Event* PE test j_1 or $j_2 \ldots j_n$ can occur with corresponding Probabilities j_1 or $j_2 \ldots j_n$ and *Outcomes* payoff j_1 or $j_2 \ldots j_n$.

[2] The decision tree framework for PE diagnostic strategies is based upon the decision tree framework as described by Lapin and Whisler (2002).

Pulmonary Embolism Diagnostic Tools

A review of the literature was conducted to identify diagnostic tools for PE screening currently in use. Identified diagnostic tools included clinical decision rules, D-dimer tests, and imaging tests such as computed tomography pulmonary angiography (CT), ultrasonography (CUS), ventilation-perfusion lung scan (VQ) and invasive pulmonary angiography (PA). This review highlights CDR scoring systems as well as D-dimer and imaging test sensitivity and specificity values to detect PE in patients with suspected PE.

In this study, sensitivity was defined as the percentage of patients with PE who obtained a positive test result. Conversely, specificity was defined as the percentage of patients without PE who obtained a negative test result. Additionally, five sensitivity and specificity levels were established: very low with a value of less than 60%, low with a value between 60 and 79.99%, moderate with a value between 80 and 89.99%, high with a value between 90 and 95.99%, and very high with a value between 96 and 100%. A test with very high sensitivity/low specificity or low sensitivity/very high specificity values was considered a poorly performing test. Only a test demonstrating both very high sensitivity and very high specificity values was considered an excellent test.

Clinical decision rules.

Historically, PE detection has been empirically based upon the patient's medical history and a physical examination. However, during the past decade several clinical decision rules (CDRs) have been introduced that use a scoring system, which measures the pretest probability of PE with certain clinical variables (Klok et al., 2008). In particular, during the past decade, seven CDRs for PE detection currently in use have

been identified and discussed in the literature: (a) the extended Wells CDR (Wells et al., 2000); (b) the simplified Wells CDR (Gibson et al., 2008); (c) the original Geneva CDR (Wicki et al., 2001); (d) the revised Geneva CDR (Le Gal et al., 2006); (e) the Pisa CDR (Miniati et al., 2003); (f) the Pennsylvania CDR (Aujesky et al 2005); and (g) the Charlotte CDR (Kline et al., 2002). A brief presentation of each CDR follows.

Extended and simplified Wells CDRs. The extended Wells CDR and the simplified Wells CDR are Canadian clinical models (Gibson, Söhne, et al., 2008; Wells et al., 2000) based upon standardized scores, the maximum of which are 12.5 and 7, respectively. Wells CDRs include the following seven clinical variables: clinical signs and symptoms of DVT, heart rate higher than 100 beats per minute, immobilization or surgery in the past four weeks, previous PE or DVT episode, hemoptysis, cancer, and an alternative diagnosis is less likely than a PE diagnosis. There are two main differences between the extended and simplified Wells CDRs. First, in the extended CDR, a score of 3 is assigned for two variables; a score of 1.5 is assigned for three variables; and a score of 1 is assigned for two variables resulting in a maximum score of 12.5. In the simplified CDR, the same score of 1 is assigned to all seven variables resulting in a maximum score of 7. Second, PE is considered unlikely if the total score is 4 or less in the extended CDR and 1 or less in the simplified CDR. In the extended Wells CDR, a total score of less than 2 represents a low clinical probability of PE, while a score between 2 and 6 signifies a moderate clinical probability of PE, and a score greater than 6 indicates a high clinical probability of PE.

Original and revised Geneva CDRs. The original Geneva CDR is a clinical model based upon a scoring system of clinical variables combined with an arterial blood

gas analysis, while the revised Geneva CDR is a scoring system with clinical variables without a blood gas analysis (Le Gal, Righini, Roy, et al., 2006; Wicki et al., 2001). The level of probability for PE in the original Geneva CDR is based upon a total score achieved by combining scores assigned to clinical variables and blood gas analysis. A score of 0 to 4 indicates a low clinical probability of PE; a score of 5 to 8 signified a moderate clinical probability of PE; and a score of 9 or higher represents a high clinical probability of PE (Wicki, Perneger, Junod, Bounameaux, & Perrier, 2001). Similarly, in the revised Geneva CDR, a score of 0 to 3 indicates a low clinical probability of PE; a score of 4 to 10 represents a moderate clinical probability of PE; and a score of 11 or higher denotes a high clinical probability of PE (Le Gal, Righini, Roy, et al., 2006). Clinical probability levels for PE for the extended Wells, simplified Wells, original Geneva, and revised Geneva CDRs are presented in Table 1.

Table 1

Clinical Probability Levels for PE of the Wells and Geneva CDR Scoring Systems

Clinical Probability Levels for PE		Study
Low, moderate, high	Unlikely, Likely	First Author & Year
Extended Wells CDR	Extended Wells CDR	Wells, 2000
Simplified Wells CDR	Simplified Wells CDR	Gibson, 2008
Original Geneva CDR		Wicki, 2001
Revised Geneva CDR		Le Gal, 2006

Note. PE = pulmonary embolism; CDR = clinical decision rule.

Pisa, Pennsylvania, and Charlotte CDRs. In 2003, Miniati, Monti, and Bottai proposed a clinical model to predict PE (Pisa CDR) that included 10 variables associated

with a high risk of PE and five variables associated with a low risk of PE (Miniati, Monti, & Bottai, 2003). High-risk indicators include, but are not limited to, male gender, older age, sudden-onset dyspnea, chest pain, and hemoptysis. According to the Pisa CDR, the clinical probability of PE is classified into four distinct categories: low (score of less than or equal to 10%), intermediate (score of greater than 10% to less than or equal to 50%), moderate (score of greater than 50% to less than or equal to 90%), and high (score of greater than 90%). The implementation of this model demonstrated excellent accuracy in predicting PE, specifically, the classification into the high-risk group of 28% of the patients, 98% of whom were accurately diagnosed with PE. Although the Pisa CDR revealed excellent results, it has the major disadvantage of difficult implementation (Miniati et al., 2003; Stein, 2007b).

In 2005, Aujesky and colleagues conducted an analysis of 15,531 hospital discharges of PE patients from 186 Pennsylvania hospitals that used a PE diagnosis CDR of 11 variables, which categorized patients into five risk classes (Aujesky et al., 2005). According to this CDR, a score of less than or equal to 65 indicates very low risk (Class I); a score of 66 to 85 inclusive suggests low risk (Class II); a score of 86 to 105 inclusive denotes intermediate risk (Class III); a score of 106 to 125 inclusive signifies high risk (Class IV); and a score above 125 represents very high risk (Class V). In a follow-up study, the researchers concluded that this CDR is useful in identifying low-risk patients with PE (Aujesky et al., 2006).

The Charlotte CDR proposed by Kline and colleagues (2002) is a flow protocol to rule out PE based upon specific criteria in combination with the use of a D-dimer test (Kline, Nelson, Jackson, & Courtney, 2002). The criteria include (a) suspicion for PE; (b)

the shock index (heart rate divided by systolic blood pressure) greater than 1 or the patient age is greater than 50; (c) non-smoker, no asthma, no COPD, or unexplained hypoxemia (SaO_2 less than 95%); (d) unilateral leg swelling; (e) recent surgery; and (f) hemoptysis (Kline et al., 2002; Kline & Wells, 2003). Although accurate, the Charlotte CDR is disadvantaged by the complexity of its variables, scoring, classifications, and its D-dimer test requirement (Kline et al., 2002; Kline, Webb, Jones, & Hernandez-Nino, 2004; Kline & Wells, 2003; Runyon, Webb, Jones, & Kline, 2005).

D-dimer tests.

There are several types of D-dimer tests (DD) available, including (a) enzyme linked immuno-sorbent assay (ELISA), (b) ELISA rapid quantitative, (c) ELISA rapid semi-quantitative, (d) latex quantitative agglutination assay, (e) latex semi-quantitative agglutination assay, (f) whole-blood agglutination assay, and (g) simplify D-dimer assay. The time-to-results for these tests are approximately 8 hours, 35 minutes, less than 10 minutes, 7 to 15 minutes, 3 to 4 minutes, 2 minutes, and about 10 minutes, respectively (Bruinstroop, van de Ree, & Huisman, 2009; De Moerloose et al., 2008; Di Nisio et al., 2007; Ghanima & Sandset, 2007; Hogg et al., 2005; Kline et al., 2006; Parent et al., 2007; Stein, 2007a; Than et al., 2009; Toulon et al., 2009; van Belle et al., 2006).

Although D-dimer tests have been used since the 1980s, their contribution to PE diagnosis is controversial, particularly regarding their sensitivity and specificity values. A negative D-dimer test for patients with either low or moderate clinical probability of PE safely rules out PE, while a positive D-dimer test is nonspecific (Stein, 2007a).

The sensitivity and specificity levels of several D-dimer assays derived from studies published between 2004 and 2009 are presented in Table 2.

Table 2

Sensitivity and Specificity Levels of D-dimer Assays

D-dimer Assay	Sensitivity Level	Specificity Level	Study First Author & Year
ELISA	H	VL	Stein, 2004
standard	H	VL	Di Nisio, 2007
	VH	VL	Than, 2009
ELISA rapid	H	VL	Stein, 2004
quantitative	VH	VL	Parent, 2007
ELISA rapid	H	VL	Stein, 2004
semi-quantitative			
Latex	M	VL	Stein, 2004
Quantitative	VH	VL	Di Nisio, 2007
	VH	VL	Than, 2009
Latex	H	VL	Stein, 2004
semi-quantitative	M	L	Di Nisio, 2007
Simplify	M	L	Hogg, 2005
	M	L	Kline, 2006
	VH	VL	Toulon, 2009
VIDAS	VH	VL	Ghanima, 2007
	VH	VL	De Moerloose, 2008
	VH	VL	Toulon, 2009
STA-Liatest	VH	VL	Ghanima, 2007
	VH	VL	Toulon, 2009

Note. ELISA = enzyme linked immuno-sorbent assay; Simplify = whole-blood agglutination D-dimer assay; VIDAS = rapid quantitative ELISA D-dimer assay; STA-Liatest = Diagnostica Stago Liatest latex rapid quantitative agglutination D-dimer assay. M = moderate sensitivity level with a value between 80 and 89.99%; H = high sensitivity level with a value between 90 and 95.99%; VH = very high sensitivity level with a value between 96 and 100%; VL= very low specificity level with a value less than 60%; L = low specificity level with a value between 60 and 79.99%.

Computed tomography pulmonary angiography.

Computed tomography pulmonary angiography (CT) is a combination of X-ray and computer images providing cross-sectional views of organs and tissues of a patient (Brenner et al., 2007; Odle, 2006). "In helical CT, which is commonly used for body scans, the table moves continuously as the x-ray source and detectors rotate, producing a spiral or helical scan" (Brenner et al., 2007, p. 2279). CT scanning systems currently in use are single or multiple-row (also called multiple-slice) systems.

Early in the 1990s, the noninvasive and quick CT emerged with great potential for PE detection. Since then, as the number and speed of CT detectors have increased and the sensitivity and specificity values have improved, CT has become the imaging technique of choice for PE diagnosis (Perrier et al., 2005). Several systematic reviews have collectively chronicled the technological improvements in CT (Eng et al., 2004; Rathbun, Whitsett, Vesely, & Raskob, 2004; Roy et al., 2005; van Beek, Brouwers, Bing, Bongaerts, & Oudkerk, 2001; Van Rossum et al., 1996). In 2002, a sensitivity of 91% and a specificity of 94% were reported for CT (Nilsson et al., 2002).

According to reviews and meta-analyses published between 2000 and 2006, CT demonstrated summary sensitivities ranging from 79 to 89% and summary specificities ranging from 89 to 95% (Cueto, Cavanaugh, Benenson, & Redclift, 2001; Harvey, Gefter, Hrung, & Langlotz, 2000; Hayashino, Goto, Noguchi, & Fukui, 2005; Hogg, Brown, et al., 2006; van Beek et al., 2001). The investigators in the large PIOPED II study, which used 4-, 8-, and 16-multidetector-row CT scanners, reported a sensitivity of 83% and a specificity of 96% for PE (Stein, Fowler, et al., 2006). In 2009, Wang and colleagues established a sensitivity of 91.7% and a specificity of 100% with 16- or 64-

multidetector-row CT for PE (Wang et al., 2009). CT is an adequate test and is considered by several researchers as the new, diagnostic gold standard for PE detection, despite the challenges of detecting pulmonary embolisms at the small vessel level, a common hurdle for all PE diagnostic tests (Goodman & van Beek, 2009; Mos et al., 2009; Quiroz et al., 2005).

Compression ultrasonography.

Compression ultrasonography (CUS) is an imaging test appropriate for PE detection. Its diagnostic validity is based upon the lack of compressibility of a venous segment. There are three CUS techniques: (a) segmental compression CUS of the common femoral and popliteal veins; (b) extended compression CUS of the complete deep thigh and popliteal veins; and (c) complete compression CUS of all segments of the deep thigh and calf veins (Beyer et al., 2007).

CUS of the veins in the lower limbs is usually performed following a D-dimer test or a VQ lung scan to detect indirectly PE in patients with suspected PE. The CUS is performed because PE and DVT in a lower limb (i.e., leg) are considered conditions related to the same disease, and DVT is present in about 30% of all patients with PE (Elias et al., 2005; Elias, Colombier, et al., 2004; Galle et al., 2001; Kalva, Jagannathan, Hahn, & Wicky, 2008; Kearon & Ginsberg, 1998; Le Gal, Righini, Sanchez, et al., 2006; Michiels et al., 2005; Paterson & Schwartzman, 2001; Perrier, 2007; Perrier et al., 2003; Perrier et al., 2004; Quiroz et al., 2005; Righini et al., 2008; Righini et al., 2009; Turkstra et al., 1997).

CUS sensitivity levels have been reported as low as 50% with a range of 30 to 60% and a specificity of 95 to 100% (Perrier, 2007; Perrier et al., 2003) to as high as

82.4% with a range of 50 to 90% and a specificity of 86 to 100% (Paterson & Schwartzman, 2001). A sensitivity of 93% and a specificity of 84% were reported for a CUS of proximal and distal veins to detect PE (Elias, Colombier, et al., 2004). In 2006, Le Gal and colleagues determined a sensitivity of 39% and a specificity of 99% for CUS investigating the presence of PE (Le Gal, Righini, Sanchez, et al., 2006). More recently, Righini and colleagues revealed a poor sensitivity of 22% and a high specificity of 94% for CUS in PE detection (Righini et al., 2009).

Although studies of CUS sensitivity and specificity have indicated variability within those two determinants, CUS presents some advantages for PE detection (Elias et al., 2005; Galle et al., 2001; Michiels et al., 2005; Perrier et al., 2004; PIOPED Investigators, 1990; Quiroz et al., 2005). First, CUS is useful as a diagnostic tool subsequent to a nondiagnostic VQ lung scan or nondiagnostic CT (PIOPED Investigators, 1990). For instance, a positive CUS subsequent to a nondiagnostic VQ lung scan can confirm PE (PIOPED Investigators, 1990). Also, the combination of a negative CUS and a negative CT can rule out PE (Elias et al., 2005; Perrier et al., 2004; Quiroz et al., 2005). Second, CUS can help reduce the total number of patients requiring additional imaging tests (Elias et al., 2005; Michiels et al., 2005; Perrier et al., 2004; Quiroz et al., 2005). Third, an advantage of its ease of use, practicality, and accessibility is its application as a bedside test with intensive care patients (Galle et al., 2001).

Ventilation-perfusion lung scan.

A ventilation-perfusion lung scan (VQ) comprises two imaging procedures: perfusion and ventilation. Perfusion evaluates the blood flow in the lungs, and ventilation

assesses the air space distribution in the lungs (Dutton et al., 2009). There are two main VQ techniques in use, the traditional PLANAR VQ and the SPECT VQ.

During the 1980s and 1990s, VQ lung scan was the dominant diagnostic tool for suspected PE (see Bajc & Jonson, 2009; Bajc et al., 2009a; Bajc, Olsson, Olsson, Palmer, & Jonson, 2004; Cook & Kyriou, 2005; De Geeter, Reinartz, & Buell, 2005; Douma, Kamphuisen, Rijnders, Ten Wolde, & Büller, 2009; Einstein, Henzlova, & Rajagopalan, 2007; Freeman & Haramati, 2009; Freeman, Stein, Sprayregen, Chamarthy, & Haramati, 2008; Gutte et al., 2010; Gutte et al., 2009; Hull, Raskob, Coates, & Panju, 1990; Itti et al., 2002; Meignan, 2002; Parker et al., 2005; Perrier, 2007; Reinartz et al., 2004; Roach, Thomas, Bajc, & Jonson, 2008; Scarsbrook, Bradley, & Gleeson, 2007; Sostman, Miniati, et al., 2008; Sostman, Stein, et al., 2008; Stein et al., 2009; Stein, Kayali, & Olson, 2004b; Stein, Woodard, et al., 2006; Uren, 2009; Zöphel, Bacher-Stier, Pinkert, & Kropp, 2009). However, after the publication of the PIOPED I (Prospective Investigation of Pulmonary Embolism Diagnosis I) in 1990, a controversy ignited about the accuracy of the VQ lung scan due to low sensitivity and substantial numbers of nondiagnostic results.

This controversy continued after the publication of the PIOPED II (Prospective Investigation of Pulmonary Embolism Diagnosis II) in 1996, and although significant improvements were made in the interpretation of VQ lung scans, this controversy continues (Bajc et al., 2004; De Geeter et al., 2005; Douma, Kamphuisen, et al., 2009; Freeman et al., 2008; Gutte et al., 2010; Meignan, 2002; Perrier, 2007; Reinartz et al., 2004; Roach et al., 2008; Sostman, Stein, et al., 2008; Stein et al., 2009; Uren, 2009).

A high-probability VQ lung scan indicates the presence of PE; normal- or low-probability results indicate the absence of PE. Using the results of the PIOPED I study, Perrier (2007) reported a sensitivity of 99% for normal-probability VQ lung scans and a specificity of 91% for high-probability VQ lung scans for PE. From the PIOPED II study results, Sostman, Stein, and colleagues (2008) reported a sensitivity of 77.4% for high-probability VQ lung scans and a specificity of 97.7% for normal- or low-probability VQ lung scans. None of the VQ lung scans was nondiagnostic.

Comparisons of the tomographic ventilation-perfusion lung imaging (SPECT VQ) to traditional planar ventilation-perfusion lung imaging (Planar VQ) indicated that the SPECT VQ is a more accurate tool for diagnosing PE (Bajc et al., 2004; De Geeter et al., 2005; Douma, Kamphuisen, et al., 2009; Freeman et al., 2008; Gutte et al., 2010; Meignan, 2002; Perrier, 2007; Reinartz et al., 2004; Roach et al., 2008; Sostman, Stein, et al., 2008; Stein et al., 2009; Uren, 2009). In 2004, greater sensitivity and specificity for the SPECT VQ than for the Planar VQ in PE detection were reported (Bajc et al., 2004; Reinartz et al., 2004). More recently, it was corroborated that the SPECT VQ had a greater sensitivity (100%) and specificity (87%) than did the Planar VQ (64% and 72%, respectively) (Gutte et al., 2010).

Invasive pulmonary angiography.

Invasive pulmonary angiography (PA) is the most accurate procedure for diagnosing PE and served as the diagnostic gold standard for many decades. It has a very high sensitivity of 96% and a very high specificity of 97%, but it is no longer widely used by physicians because of its expense and, more importantly, its invasiveness, which has associated risks with complications at a rate of 1 to 5% and mortality at a rate of up to

0.5%, inclusive (Hudson et al., 1996; Paterson & Schwartzman, 2001; Perrier, 2007; PIOPED Investigators, 1990; Stein et al., 1992; van Loveren, van Beek, & Oudkerk, 2009).

PA complications during the 1960s, 1970s, and 1980s occurred at an average rate of 2.1% (see Mills, Jackson, Older, Heaston, & Moore, 1980; Nilsson, Carlsson, & Måre, 1998; Oudkerk et al., 2002; van Beek, Brouwers, Song, Stein, & Oudkerk, 2001; van Loveren et al., 2009). Complication rates dropped in the 1990s to an average of 0.62%, due to technological advances such as the development of a safer catheter and rapid imaging equipment improvements (see Hudson et al., 1996; Nilsson et al., 1998; Stein et al., 1992; Stein, Sostman, et al., 2008; van Beek, Reekers, Batchelor, Brandjes, & Büller, 1996; van Loveren et al., 2009). Currently, non-fatal complication rates have dropped as low as 0.3 to 0.5% and as low as 0.03% for fatal complications (see Nilsson et al., 1998; Stein, Sostman, et al., 2008; van Loveren et al., 2009).

Today, PA remains important as the final diagnostic tool for specific categories of patients with suspected PE for whom noninvasive methods produce nondiagnostic results or for whom interventions are under consideration (see Hudson et al., 1996; Paterson & Schwartzman, 2001; Perrier, 2007; PIOPED Investigators, 1990; Qanadli et al., 2000; Stein et al., 1992; van Loveren et al., 2009; Winer-Muram et al., 2004).

Pulmonary Embolism Diagnostic Strategies

Various PE diagnostic strategies that combine the diagnostic components of CDR, DD, CT, VQ, CUS, and/or PA were identified in the literature. Each of the PE diagnostic strategies identified in this review includes a CDR as well as a DD. Each strategy was identified either as independent or as a branch of a strategy that could be subsumed into

one of five categories. The composition of the 14 identified diagnostic strategies is presented in Table 3.

Table 3

Composition of PE Diagnostic Strategies

Category	Strategy	Clinical Assessment	Imaging Tests		
			First	Second	Third
I	1	CDR, DD			
II	2	CDR, DD	CT		
	3	CDR, DD	PA		
III	4	CDR, DD	CT	CUS	
	5	CDR, DD	CT	CUS	VQ
	6	CDR, DD	CT	CUS	PA
IV	7	CDR, DD	CUS	CT	
	8	CDR, DD	CUS	PA	
	9	CDR, DD	CUS	CT	PA
	10	CDR, DD	CUS	VQ	PA
V	11	CDR, DD	VQ	CUS	
	12	CDR, DD	VQ	CUS	CT
	13	CDR, DD	VQ	CUS	PA
	14	CDR, DD	VQ	CT	PA

Note. PE = pulmonary embolism; CDR = clinical decision rule; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS = compression ultrasonography; VQ = ventilation-perfusion lung scan; PA = invasive pulmonary angiography.

Clinical decision rule and D-dimer test.

Strategy 1 comprises a combination of the clinical decision rule (CDR) and the D-dimer test (DD) as components for assessing pulmonary embolism in patients. Patients are evaluated first with a CDR followed by a DD. Studies suggest that PE can be safely ruled out in patients with a low clinical probability of PE and a negative DD, which is the outcome in 24 to 47% of the patients with suspected PE. Patients with a moderate or high clinical probability of PE and a positive DD usually undergo further diagnostic tests (see Carrier et al., 2009; Corwin, Donohoo, Partridge, Egglin, & Mayo-Smith, 2009; Djurabi et al., 2009; Gibson, Söhne, Gerdes, et al., 2008; Gupta, Kakarla, Kirshenbaum, & Tapson, 2009; Hammond & Hassan, 2005; Kabrhel et al., 2009; Kearon et al., 2006; Kruip, Slob, Schijen, van der Heul, & Büller, 2002; Pasha et al., 2009; Perrier et al., 2005; Righini et al., 2006; Rodger et al., 2006; Segal, Eng, Tamariz, & Bass, 2007; Söderberg, Brohult, Jorfeldt, & Lärfars, 2009; Stein, Hull, et al., 2004; Teismann, Cheung, & Frazee, 2009; van Belle et al., 2006; Wells et al., 2000; Wells et al., 2001).

There are concerns regarding the accuracy of this diagnostic strategy for the elderly, mostly because DD levels increase with age (Righini, Goehring, Bounameaux, & Perrier, 2000). There are also concerns regarding its accuracy with pregnant women because DD levels are higher in pregnancy and overlap the normal values of the test for PE diagnosis (Damodaram, Kaladindi, Luckit, & Yoong, 2009). However, pregnant women with suspected PE undergo additional testing such as a ventilation-perfusion (VQ) lung scan or CT with the former being conducted more frequently than the latter (Cahill, Stout, Macones, & Bhalla, 2009).

A summary of the percentages of patients for whom PE was excluded by a low or intermediate clinical probability or PE unlikely CDR and a negative DD by study are presented in Table 4.

Table 4

Percentages of Patients Excluded by CDR and DD Combined by Study

Study First Author & Year	CDR Probability Level for PE	D-dimer Results	% Patients with PE Excluded by CDR & DD
Wells, 2001	Low	N	47.0
Kruip, 2002	Low	N	25.6
Perrier, 2005	Low/Intermediate	N	30.7
Hammond, 2005	Low	N	24.2
Righini, 2006	Low	N	31.8
Kearon, 2006	Low	N	32.6
van Belle, 2006	Unlikely	N	31.0
Gibson, 2008	Unlikely	N	27.7
Söderberg, 2009	Low	N	42.0
Kabrhel, 2009	Low	N	25.3
Corwin, 2009	Low	N	42.8
Djurabi, 2009	Unlikely	N	46.6
Gupta, 2009	Low/Intermediate	N	27.4
Teismann, 2009	Not Reported	N	41.4
Carrier, 2009	Low/Intermediate/Unlikely	N	40.0
Pasha, 2009	Unlikely	N	33.8

Note. PE = pulmonary embolism; CDR = clinical decision rule; DD = D-dimer test; N = negative.

Clinical decision rule, D-dimer test, and computed tomography pulmonary angiography or invasive pulmonary angiography.

The CT and the PA are used in PE diagnostic strategies as the only imaging tests following a CDR and a DD in Strategy 2 and Strategy 3. The components of Strategy 2 include the CDR, the DD, and a CT as the only imaging test (Anderson et al., 2007; Eng, Wansaicheong, Goh, Earnest, & Sum, 2009; Ghanima et al., 2005; Ghaye & Dondelinger, 2008; Huisman & Klok, 2009; Kamphuisen & Agnelli, 2005; Nijkeuter et al., 2007; Perrier et al., 2005; Righini et al., 2008; Sohns, Amarteifio, Sossalla, Heuser, & Obenauer, 2008; Stein, Woodard, et al., 2006; van Belle et al., 2006).

The use of single or multidetector-row CT following the evaluation of a CDR and a DD was strongly indicated by several researchers who suggested that there is not enough evidence to withhold anticoagulation treatment from a patient after only a negative CT without involving a CDR and/or a DD (Anderson et al., 2007; British Thoracic Society, 2003; Eng et al., 2009; Ghanima et al., 2005; Ghaye & Dondelinger, 2008; Hogg, Brown, et al., 2006; Huisman & Klok, 2009; Kamphuisen & Agnelli, 2005; Kruip, Leclercq, Heul, Prins, & Büller, 2003; Musset et al., 2002; Nijkeuter et al., 2007; Nijkeuter, Ginsberg, & Huisman, 2006; Perrier et al., 2005; Rathbun et al., 2004; Righini et al., 2008; Schoepf, Goldhaber, & Costello, 2004; Sohns et al., 2008; Stein, Woodard, et al., 2006; Trowbridge, Araoz, Gotway, Bailey, & Auerbach, 2004; van Belle et al., 2006; Wells, 2007).

In the Christopher study (see van Belle et al., 2006), 3,306 patients with suspected PE were examined. Upon examination, 2,206 patients were classified with a PE unlikely CDR. Of those, 1,057 obtained negative DD results and 1,149 obtained positive DD results. DDs were not performed for the other 1,100 patients who were classified with a

PE likely CDR. In the same study, CTs were ordered for 2,249 of the 3,306 patients: 1,149 PE unlikely patients with positive DD results and the 1,100 PE likely patients. CTs were not performed for the 1,057 patients with PE unlikely CDRs and negative results for a DD assay. Of the 2,249 patients scheduled for either a single- or multidetector-row CT, PE was confirmed in 674, ruled out in 1,505, and was inconclusive for 20. Fifty of the scheduled CTs were not performed. The 3-month follow-up VTE rate was 1.3% (van Belle et al., 2006).

A 4-multidetector-row CT was used to diagnose 432 patients with suspected PE who also were evaluated in conjunction with a DD and a CDR (Ghanima et al., 2005). PE was ruled out in 103 patients with a negative DD and a low or intermediate clinical probability of PE. Among the 329 patients with a positive DD, the CT confirmed PE in 93, ruled out PE in 221, and was inconclusive for 15.

The combination of a CDR, a DD, and a CT was investigated in a study of 408 patients with suspected PE (Hogg, Dawson, et al., 2006). Among the 403 patients who completed follow-up, PE was detected in 22 patients and excluded in 381 patients, with a 3-month follow-up VTE rate of 0.8%. Nijkeuter and colleagues (2007) evaluated the combination CDR, DD, and CT in a study of inpatients and outpatients with suspected PE. Among the 190 patients who were indicated as having a previous PE episode, likely clinical probability of PE, and/or a positive DD, results from CTs excluded recurrent PE in 127 and confirmed recurrent PE in 63 of these patients, with a 3-month follow-up VTE rate of 0.8%, indicating that this combination safely ruled out PE in patients with a history of PE.

From a population of 1,693 patients with suspected PE, Righini and colleagues (2008) evaluated the combination of a CDR, a DD, and a CT using a randomly selected sample of 815 patients. The CT confirmed PE in 160 and excluded PE in 361 of the sample patients with a PE low or intermediate CDR and a positive DD. The CT was inconclusive for 14 patients. PE was excluded in 280 sample patients who obtained a negative DD and a PE low or intermediate CDR.

Results from 200 patients with suspected PE who were tested using the combination of a CDR, a DD, and a 64-multidetector-row CT were analyzed. Each of the 200 patients was assessed with a high clinical probability of PE. Each achieved positive results from a DD. Then, each patient underwent a 64-multidetector-row CT. PE was confirmed in 60 patients; PE was ruled out for 140 patients. It was determined that the 64-multidetector-row CT has an increased ability to detect conditions that mimic PE, including pneumonia, pneumothorax, and cardiovascular diseases. A total of 120 incidental findings of these conditions were reported (Sohns et al., 2008).

A follow-up of 219 cases of patients with suspected PE revealed that the multidetector-row CT confirmed PE in 42 patients with high clinical probability of PE and a positive DD. Results from this CT ruled out PE in 177 patients, including 49 who had a negative DD (Eng et al., 2009).

An examination of the findings for 5,344 cases of emergency department patients was conducted in 2009 by Corwin and associates. They evaluated the results from the combination of a CDR, a DD, and a CT that used a 4- or 16-detector-row CT. PE was ruled out in 4,580 patients, and of those, 3,091 obtained a PE low CDR in combination with DD and CT tests, while 1,489 obtained a PE high CDR and a negative CT without a

DD test. Of the remaining 764 cases, PE was confirmed in 159 patients. Of those, 20 obtained a PE low CDR in combination with DD and CT tests and 139 obtained a PE high CDR with a positive CT without a DD test. CTs were not performed in 605 patients who obtained a PE low CDR with positive DD and discharged for diagnoses other than PE (Corwin et al., 2009).

Strategy 3 combines the testing components of a CDR, a DD, and a PA as the sole imaging test (Söderberg et al., 2009; van Beek et al., 2001; Winer-Muram et al., 2004). Using the combination of a CDR, a DD, and PA to determine PE in patients with suspected PE was evaluated in a study of 120 outpatients. PA confirmed PE in 34 (28.3%) of the outpatients (Söderberg et al., 2009). Winer-Muram and colleagues (2004) ascertained that the combination of CDR and PA ruled out PE in 75 (80.6%) and confirmed PE in 18 (19.4%) of the 93 patients. Conversely, with the same patients, the combination of CDR and a 4-multidetector-row CT ruled out PE in 67 (72%) and confirmed PE in 26 (28%) of them; the use of DD was unspecified in this study (Winer-Muram et al., 2004). A review of eight studies conducted between 1978 and 1999 investigating the validity of PA in patients with suspected PE revealed that the test ruled out PE in 1,050 patients and that the recurrence rate was 1.7% (see van Beek et al., 2001). The use of CDR and DD was unspecified in this review.

Clinical decision rule, D-dimer test, computed tomography pulmonary angiography, and other imaging tests.

The CT has been used in several PE diagnostic strategies as the first imaging test that follows a CDR and a DD. This sequence of diagnostic components is used in Strategies 4, 5, and 6.

Strategy 4 comprises the following sequence of diagnostic components: CDR, a DD, a CT as the first imaging test, and a CUS. In a cohort study of 858 patients with suspected PE, Anderson and colleagues used a CDR, a DD, a CT, and a CUS sequence to diagnose PE. The main results of this study follows (Anderson et al., 2005). PE was ruled out in 469 and confirmed in 10 patients who obtained a PE low CDR in combination with DD, CT, and CUS tests. PE was ruled out in 280 and confirmed in 44 patients who obtained a PE moderate CDR in combination with DD, CT, and CUS tests. PE was ruled out in 29 and confirmed in 26 patients who obtained a PE high CDR in combination with DD, CT and CUS tests.

The sequence of diagnostic components that comprise Strategy 5 is the CDR, the DD, a CT, a CUS, and a VQ lung scan. The CT remains the first imaging test performed with patients with suspected PE. Perrier and colleagues (2005) evaluated Strategy 5 in a study of 674 patients in which 193 PE cases were detected by a CT, CUS, or VQ lung scan: 187 by a multidetector-row CT, 4 by a CUS, and 2 by a VQ lung scan (Perrier et al., 2005).

The CT is also the first imaging test used in Strategy 6. The diagnostic components sequence of this strategy begins with a CDR followed by the DD, a CT, a CUS, and a PA. Perrier and colleagues (2005) used Strategy 6 to confirm PE in patients with a high clinical probability of PE. They were evaluated with a CDR and experienced a testing battery (DD, a multidetector-row CT, and CUS) followed by a PA. PE was confirmed in 82 patients by the CT and ruled out by PA for 3 patients. No VTE episodes occurred during the 3-month follow-up among patients for whom PE was excluded.

Clinical decision rule, D-dimer test, compression ultrasonography, and other imaging tests.

The CUS is used in four PE diagnostic strategies as the first imaging test following a CDR and a DD: Strategies 7, 8, 9, and 10. In Strategy 7 (CDR, DD, CUS, and CT), the CUS precedes the CT. It is important to note that CUS is used to detect DVT, and it can indirectly detect PE in patients with suspected PE because DVT is present in about 30% of the patients with PE (Righini et al., 2008).

Michiels and colleagues (2005) noted that the combination of a moderate or high clinical probability of PE, a positive DD, and a positive CUS detect DVT in 20 to 25% of patients. Michiels et al. (2005) also asserted that the use of CDR, a DD, and a CUS could reduce the need for CTs by 40 to 50%. The combination of CDR, a DD, and CUS was investigated by Elias and colleagues (2005) in a study of 274 patients with suspected PE (Elias et al., 2005). PE was ruled out in 165 patients and confirmed in 109 patients. CUSs were performed on all 274 patients: 102 were positive (i.e., PE diagnosis confirmation) and 64 were negative (i.e., PE excluded). The other 108 were followed by a CT, indicating a potential reduction of 166 (60.6%) additional imaging tests.

In a study of 828 patients with suspected PE, Righini and colleagues (2008) investigated the combination of CDR, a DD, and a CUS. PE was ruled out for 660 patients, confirmed for 150 patients, and inconclusive for 18 patients with an overall 3-month follow-up risk of developing VTE of 0.3% (Righini et al., 2008). Of the 547 CUS tests performed, 38 were positive (i.e., PE diagnosis confirmation), 397 were negative (i.e., PE excluded), and 112 were false negative, indicating a potential reduction of 435 (52.5%) additional imaging tests. Perrier and colleagues (1999) investigated the

combination of CDR, a DD, CUS, and VQ lung scans with 918 patients and found that CUS reduced the need for VQ lung scans in 393 (42.8%) of the patients.

In Strategy 8 (CDR, DD, CUS, and PA), the first imaging test in the diagnostic tool sequence is the CUS. If necessary, then it is followed by a PA. The use of CUS was evaluated in an investigation of the combination of a CDR, a DD, CUS, and PA in 234 patients with suspected PE. PE was ruled out in 182 patients and confirmed in 52 patients with a 3-month follow-up VTE risk for the entire strategy of 1%. Of the 174 CUSs performed, 27 were positive (i.e., PE confirmation) and 122 were negative (i.e., PE excluded), with 25 being false negatives, indicating a potential reduction of 149 (63.7%) additional imaging tests (Kruip et al., 2002). Reducing the need for additional imaging tests with the use of CUS as indicated by Strategies 7 and 8 is presented in Table 5.

Table 5

Percent Reduction in Use of Additional Imaging Tests Following a CUS

Study First Author & Year	Patient Category	% Reduction in Use of Additional Imaging Tests Following CUS
Perrier, 1999	Outpatient	42.8
Kruip, 2002	Outpatient and Inpatient	63.7
Elias, 2005	Outpatient	60.6
Righini, 2008	Outpatient	52.5

Note. CUS = compression ultrasonography.

In Strategy 9, the CDR, DD, and CUS are followed by a CT and a PA. This strategy was evaluated by Perrier and colleagues (2004) in a study that included 965 patients with suspected PE. Of those 965, 685 patients obtained positive DDs (Perrier et

al., 2004). Among those patients, DVT was excluded by CUS in 593 and confirmed in 92. A subsequent CT (of the 593 patients in which DVT was excluded by CUS) excluded PE in 450 patients with low or intermediate clinical probability of PE, confirmed PE in 124 patients, and was nondiagnostic in 11 patients. Among the eight patients who were assessed as having a high clinical probability of PE, PA excluded PE in six and confirmed it in two individuals.

In Strategy 10 (CDR, DD, CUS, VQ lung scan, and PA), the first imaging test in the diagnostic tool sequence is a CUS, followed by a VQ lung scan and a PA, if necessary. Perrier and colleagues (1999) evaluated this strategy with 918 patients. A DD ruled out PE/DVT in 286 of the patients (Perrier et al., 1999). Of the 632 CUS performed, 393 ruled out PE/DVT, 2 confirmed DVT, and 237 were followed by a VQ lung scan. Of the 237 VQ lung scans performed, 37 obtained normal-probability results (i.e., PE excluded), 43 obtained high-probability results (i.e., PE diagnosis confirmation), and 157 were nondiagnostic. Of the 157 nondiagnostic VQ lung scans performed, 107 ruled out PE in combination with a low probability for PE, a positive DD, and a negative CUS, and the 50 VQ lung scans followed by a PA obtain negative results for 37 tests and positive results for 13 of the PAs.

Clinical decision rule, D-dimer test, ventilation-perfusion lung scan, and other imaging tests.

The ventilation-perfusion (VQ) lung scan has been used in the following PE diagnostic strategies as the first imaging test after a CDR and a DD: Strategies 11, 12, 13, and 14. In Strategy 11 (CDR, DD, VQ lung scan, and CUS), the imaging test sequence is a VQ lung scan followed by a CUS. Patients may repeat CUS in one week if necessary (Kearon et al., 2006; Perrier et al., 2000; Ten Wolde et al., 2004; Wells et al., 2001).

The performance of this strategy was evaluated in a randomized control trial involving 712 patients. The use of VQ lung scans confirmed VTE in 75 patients, ruled out VTE in 247 patients, and produced nondiagnostic readings in 386 patients. VQ lung scans were not performed with four patients. The use of CUS following the nondiagnostic VQ lung scans among the 386 patients resulted in 15 positive CUS (i.e., VTE diagnosis confirmation), 360 negative CUS (i.e., VTE excluded), and 11 false negative CUS tests. Also, CUS was repeated in one week for 78 patients obtaining negative results from the first CUS test (Anderson et al., 2007).

This strategy was also evaluated by Kearon and colleagues (2006) using two groups of randomly selected patients with suspected PE. Group 1 comprised 670 patients with a low probability of PE, a negative or positive DD, and a VQ lung scan. Group 2 comprised 456 patients with a moderate or high clinical probability of PE and a VQ lung scan. The VQ lung scan in 186 Group 1 patients (low clinical probability of PE and negative DD) excluded PE in 97 patients and produced nondiagnostic VQ lung scans in 86 patients. Three VQ lung scans were not performed. Among the 456 Group 2 patients (moderate or high clinical probability of PE, without performing a DD), 241 attained a nondiagnostic VQ lung scan. A CUS confirmed PE in 15 of these patients and ruled out PE for the remaining 226. A serial CUS was performed in 41 of the 226 patients with a negative DD for whom PE was excluded. Results excluded PE in 40 patients.

Ten Wolde et al. (2004) examined this strategy through a study of 631 patients with suspected PE. The use of serial CUS in 224 patients with moderate or high clinical probability of PE, a positive DD, and a nondiagnostic VQ lung scan excluded PE in 210 patients and confirmed PE in 14 patients. Wells et al. (2001) used a cohort study

composed of 930 patients with suspected PE to investigate Strategy 11. PE was excluded in 437 patients with a PE low probability CDR and a negative DD; 471 patients underwent a VQ lung scan. Among the remaining 22 patients, a DD was not performed with 1 patient and 21 did not receive VQ lung scans. The use of VQ lung scans among 471 patients confirmed PE in 64 patients, ruled out PE in 183 patients, and produced nondiagnostic readings in 224. This study also determined that of the ordered 173 CUSs, which followed a nondiagnostic VQ lung scan combined or not combined with a DD, PE was excluded for 148 patients and confirmed for one patient. Twenty-four (24) scheduled CUSs were not performed. Perrier and colleagues (2000) assessed this strategy using the results from 837 patients with suspected PE. Of the 180 patients with a low clinical probability of PE and an inconclusive VQ lung scan, a follow-up CUS excluded PE in 175 (20.9%) and confirmed DVT in 5 (0.6%) of these patients. A 3-month follow-up revealed a VTE rate of 1.7%. The probability levels for diagnosing PE with VQ lung scans after a CDR and DD is presented in Table 6.

Table 6

Probability Levels of Diagnosing PE with VQ Lung Scan in Patients with Suspected PE

Study's First Author and Year	CDR Probability Level	D-dimer Test	VQ Lung Scan % Probability of PE		
			Normal	High	Nondiagnostic
Ten Wolde, 2004	Moderate or High	Positive	30.2	18.6	51.2
Kearon, 2006	Moderate or High	Positive	21.5	25.1	53.4
Anderson, 2007	Moderate or High	Positive	34.9	10.6	54.5

Note. PE = pulmonary embolism; VQ = ventilation-perfusion lung scan; CDR = clinical decision rule.

In Strategy 12 (CDR, DD, VQ lung scan, CUS, and CT), the VQ lung scan is the first imaging test performed in this diagnostic tool sequence. If necessary, it is followed by a CUS, then a CT. In a randomized control trial, Anderson et al. (2007) evaluated the performance of Strategy 12 with 712 patients. The use of CT following a nondiagnostic VQ lung scan and a positive CUS, confirmed PE in 6 additional patients and ruled out PE in 17 patients.

In Strategy 13 (CDR, DD, VQ lung scan, CUS, and PA), the VQ lung scan is the first imaging test performed in this diagnostic tool sequence. It is followed by a CUS, then a PA, if necessary (Perrier et al., 1996; Quinn et al., 1994). In the Anderson and colleagues (2007) study cited with strategy 12, a PA following the VQ lung scan-CUS sequence and performed independently of the CT tests confirmed PE in 3 patients and ruled out PE in 3 additional patients. Perrier and colleagues (1996) investigated this strategy in 308 patients with suspected PE. VQ lung scan ruled out PE in 43 patients, confirmed PE in 63 patients, and was nondiagnostic in 202 patients. The use of CUS indicated no DVT in 77 patients and confirmed DVT in 22 patients with a nondiagnostic VQ lung scan, a PE moderate CDR, and a positive DD. Among these 77 patients, testing with a follow-up PA ruled out PE in 55 patients and confirmed PE in 22. The 6-month follow-up VTE risk rate for the entire strategy was 1%.

An investigation of 36 patients with suspected PE indicated intermediate-probability VQ lung scan results for PE in all 36 patients. PE was confirmed by a follow-up CUS in 7 patients and by a follow-up PA in 15 patients (Quinn et al., 1994).

As in the previous three strategies, Strategy 14 (CDR, DD, VQ lung scan, and CT or PA) incorporates a VQ lung scan as the first imaging test conducted on patients with

suspected PE. It is followed by a CT or a PA. This strategy was suggested by Bajc and colleagues (2009b) in the guidelines of the European Association of Nuclear Medicine.

Review of PE Diagnostic Strategy CEA Studies

CEA studies published in the 1990s and 2000s.

In an early application of a cost-effectiveness analysis (CEA) for PE diagnostic strategies Oudkerk, van Beek, van Putten, and Büller (1993) classified nine diagnostic strategies that did not employ clinical decision rules (CDR) or D-dimer tests (DD) into three categories (CEA 1). Oudkerk and colleagues concluded that the most cost-effective strategy should include PA and that the use of VQ lung scan and CUS can reduce the need for PA from 40 to 50%.

Hull, Feldstein, Stein, and Pineo (1996) also evaluated three diagnostic strategies that did not include a CDR or DD (CEA 2). The first strategy included VQ lung scan and PA; the second strategy included VQ lung scan, CUS, and PA; the third strategy employed a VQ lung scan, serial CUS, and PA. The average cost per patient by strategy was assessed at $14,421, $14,407, and $13,842, respectively. Hull et al. concluded that the combination of a VQ lung scan, serial CUS, and PA was the most cost-effective method of diagnosing a pulmonary embolism.

In their examination of diagnostic strategies using a VQ lung scan, a CDR, a DD, a PA, and a CUS, Michel, Seerden, Rutten, van Beek, and Büller (1996) analyzed assigned CDR cut-off points and DD cut-off values (CEA 3). They identified a PE diagnosis cost-per-patient for 12 strategies between $4,118 and $4,339 with 6-month survival rates between 97.05% and 97.42%. The strategy that emerged as the most cost-

effective commenced with a VQ lung scan followed by a CDR with an assigned cut-off value of 0.075, a DD with an assigned cut-off value of 300, a PA, and a CUS.

Twelve PE diagnostic strategies evaluated by van Erkel, van Rossum, Bloem, Kievit, and Pattynama (1996) comprised a single or a combination of as many as five PE diagnostic tools. Four (4) of the 12 diagnostic strategies employed the PA as the final test, and 8 incorporated CT as the final test (CEA 4). The researchers determined that the strategy that combined a CUS with a subsequent CT was the most cost effective with a cost of $20,562 per life saved. This evaluation demonstrated that the use of CT in PE diagnostic strategies could reduce mortality rates and achieve more cost-effective results.

Perrier and associates investigated six PE diagnostic strategies that included combinations of VQ lung scan, DD, CUS, and/or PA (CEA 5) (Perrier et al., 1997). Each of the six strategies included a VQ scan, and five strategies employed PA as the final test. The research concluded that strategies with a DD and a CUS preceding or following a VQ lung scan are cost effective given that they resulted in a 37 to 47% decrease in the need for PA tests.

A CEA conducted by Larcos, Chi, Shiell, and Berry (2000) investigated three PE diagnostic strategies. The first employed a CT only. The second included a CT with CUS and PA. The third was composed of a VQ lung scan, CUS, and PA (CEA 6). The third diagnostic strategy was assessed as the most cost-effective with a cost of $940 per life saved.

Hull et al. (2001) also examined three PE diagnostic strategies with data extrapolated from the Prospective Investigation of Pulmonary Embolism (PIOPED I) study of 662 patients with suspected PE (CEA 7). All three strategies included the VQ

lung scan as the first test. The first strategy combined the VQ lung scan and a subsequent PA. The second strategy combined the VQ lung scan with a subsequent CUS and PA. The third strategy combined the VQ lung scan with subsequent serial CUS and PA. The cost per patient for the first, second, and third strategies was $10,761, $10,364, and $8,915 (Canadian dollars), respectively. This study revealed that the third strategy is the most cost-effective method of PE diagnosis among patients with suspected PE.

Combinations of VQ lung scan, CUS, CT, and PA were included in a CEA of PE diagnostic strategies conducted by Paterson and Schwartzman (2001). They investigated seven different strategies (CEA 8), three of which involved the PA as the final test. Three other strategies employed the CT as the final procedure, and one strategy used the CUS as the last test performed. This analysis revealed two of the seven strategies examined as cost-effective. The more cost-effective strategy of the two identified as such combined a VQ lung scan, a CUS, and the CT that produced a survival rate of 953.4 per 1,000 patients at a cost-per-patient of $1,391 (Canadian dollars).

Perrier and Bounameaux (2001) reviewed the performance of several diagnostic strategies in patients with suspected PE (CEA 9). The first strategy combined the CDR and DD with a subsequent CUS, VQ lung scan, and PA. The five strategies resulted in a savings per additional QALY (quality-adjusted life year) of $2,467, $2,447, $2,700, $3,202, and $3,439, respectively. Overall, this study revealed that the first strategy was the most cost-effective with 38 lives saved per 1,000 patients and a savings per additional QALY of $2,467.

Low, intermediate, or high clinical probability of PE patient classifications as well as CT in eight PE diagnostic strategies was the basis for a CEA conducted by Perrier et

al. (2003) (CEA 10). For patients with a low clinical probability of PE, the most cost-effective strategy employed the DD, CUS, and VQ lung scan at a cost of $845 per patient. For patients with an intermediate clinical probability of PE, this analysis demonstrated that the most cost-effective strategy included a DD, CUS, VQ lung scan, and CT at a cost of $2,674 per patient. For those in the high clinical probability of PE group, the strategy that included a DD, CUS, and PA was the most cost-effective at a cost of $4,598 per patient because it required a subsequent PA in 25% of the cases.

An evaluation of the cost effectiveness of three PE diagnostic strategies in pregnant women with suspected PE was conducted by Doyle and colleagues (2004) (CEA 11). The first strategy commenced with a CUS followed by a VQ lung scan, a CT, or a PA. The second strategy used a VQ lung scan as the primary test in a combination of diagnostic tools, and the third strategy employed the CT as the first procedure in a combination with other diagnostic tools. Doyle et al. revealed that the CT scan as the primary test (i.e., third strategy) resulted in the most cost-effective diagnostic strategy with a cost of $17,208 per life saved compared to a cost of $24,004 per life saved for the first strategy and a cost of $35,906 per life saved for the second strategy.

The cost-effectiveness of CUS as a diagnostic tool for determining PE was investigated (Elias, Molinier, et al., 2004) in a CEA, which includes nine separate diagnostic strategies (CEA 12) that comprised various combinations of CDR, DD, CUS, CT, VQ lung scan, and PA. Three strategies emerged as cost effective. One such strategy included a DD, extensive CUS, and CT with a cost of $3,679 per patient and a survival rate of 95.11%. A second cost-effective strategy included a DD, CUS, and CT with a cost of $3,719 and a survival rate of 95.53%. The third diagnostic strategy that emerged as

cost effective included a CUS and CT with a cost of $3,804 per patient and a survival rate of 95.89%. Of these three, the most cost-effective strategy was that which included the CUS and CT with an ICER of $23,649 per additional life saved.

Ten imaging strategies for diagnosing PE were investigated by Duriseti, Shachter, and Brandeau (2006) by examining the assigned values of five different cut-off points for DD and the level of clinical probability of PE (CEA 13). The researchers concluded that the DD with CUS as the pulmonary imaging test has utility, but when a CT is available, the DD does not result in a cost-effective strategy.

The influence of age was evaluated by Righini, Nendaz, Le Gal, Bounameaux, and Perrier (2007) in a study of four strategies used to diagnose patients with suspected PE (CEA 14). One diagnostic strategy commenced with a CDR and DD followed by CUS and CT. Another commenced with a CDR and DD in combination with only a subsequent CT. The strategy employing a CUS was more expensive than strategies not using a CUS. The strategy that included a CDR, a DD, and CT was the most economical with a 3-month VTE risk of less than 1%.

Costs.

The expense of diagnosing PE involves several costs, including laboratory and imaging tests as well as those associated with treating patients, which, in addition to prescribed treatment, may include treatment for any complications and hospital stays. Each is a very significant element in a CEA and represents the direct costs related to PE screening under a third-party payer perspective.

However, none of the CEAs published in the 1990s as well as in the past decade calculated indirect costs such as productivity loses in PE patients due to hospitalization or

the costs of long-term effects of PE in patients (see Cox, Carson, & Biddle, 2003; Doyle et al., 2004; Elias, Molinier, et al., 2004; Hull et al., 1996; Hull et al., 2001; Larcos et al., 2000; Michel et al., 1996; Paterson & Schwartzman, 2001; Perrier et al., 1997; Perrier et al., 2003; Righini et al., 2007; van Erkel et al., 1996).

In the 1990s, direct costs associated with diagnostic tests, patient treatment, and patient hospitalization were assessed by Hull and colleagues (1996), Michel and colleagues (1996), Perrier and colleagues (1997), and van Erkel and colleagues (1996). Hull and colleagues used the average costs of $510 for a VQ lung scan, $300 for CUS, $1,500 for serial CUS, and $2,553 for PA in their CEA. The average cost-per-patient of treatment of $6,522 was classified as costs related to anticoagulant treatment, including the medications, laboratory tests performed to monitor anticoagulant treatment, and physicians' fees, as well as costs of complications and side effects. The average hospitalization cost was $575 per day and included the hospital stay, laundry charges, and meals (Hull et al., 1996). In their systematic examination of extrapolated data retrieved from published studies, van Erkel and colleagues determined that the most expensive imaging test was the PA with an associated cost of $660 (van Erkel et al., 1996). Direct costs also were studied by Michel and colleagues (1996). These costs included medical expenses such as hospital stays, diagnostic tests, and treatment. Indirect costs such as productivity losses were not calculated. It was determined that the most expensive test was the PA with an associated cost of $765 (Michel et al., 1996). Only direct costs were estimated in the Perrier et al. (1997) CEA, which included costs for diagnostic tests, treatments, and major complications. The average costs of a VQ lung scan and PA were calculated at $301 and $1,038, respectively.

As in the previous decade, CEA studies published in first decade of the 21st century used only direct costs in their analyses (see Cox et al., 2003; Doyle et al., 2004; Elias, Molinier, et al., 2004; Hull et al., 2001; Larcos et al., 2000; Paterson & Schwartzman, 2001; Perrier et al., 2003; Righini et al., 2007). A study conducted in Australia calculated average costs for hospital stays and treatment derived from the country's Medicare benefits schedule for diagnostic tests and from groups monitoring hospital admissions. The average hospitalization cost for a PE patient per day was $325, and the average cost for PE treatment per day was $1,977 (Larcos et al., 2000).

The CEA by Hull and colleagues (2001) considered the costs of the diagnostic tests performed as well as the costs of the treatment, including therapy, hospitalization, and medical side effects. Specifically, therapy costs included the price of drugs, laboratory tests used to monitor treatment, and corresponding physicians' fees. Hospitalization costs were composed of room and laundry charges with an average cost-per-patient of $604 (Canadian dollars) per day. The costs of side effects, which averaged $4,644 (Canadian dollars) per patient per day, were those associated with medical side effects and complications from the anticoagulant therapy (Hull et al., 2001). In their CEA, Paterson and Schwartzman (2001) determined average direct costs derived from Canadian financial services monitoring hospital costs and physicians' fees. Expenditures for PE diagnostic tests included technical, professional, and capital costs. An average cost for a PE hospital stay was calculated using several categories of costs, including diagnostic tests, physician and nursing fees, prescription drugs, and hospital bed/room with an average hospitalization cost of $7,798 (U.S. dollars).

Direct costs were retrieved from a hospital database by Perrier et al. (2003) for their CEA; they did not calculate indirect costs. An overall average cost for PE treatment of $5,982 per patient was reported. This amount included costs for diagnostic tests, hospital stays, treatment and monitoring, and those related to major bleeding episodes. The D-dimer test was the most economical ($33), and the PA was the most expensive ($1,038).

Direct costs retrieved from the literature were used in a CEA that indicated an average cost of $7,839 per PE episode, ranging from $5,252 to $10,426 inclusive, as well as an average cost of $807 per day for hospitalization, ranging from $505 to $1,009 (Cox et al., 2003). Direct costs retrieved from previous CEA studies were used by Doyle and colleagues (2004) to determine average costs for diagnostic tests and treatment. An average cost of $200 was assigned to CUS and an average cost of $5,982 per patient was assigned for treatment (Doyle et al., 2004). Direct costs also were examined in the Righini and colleagues (2007) CEA; indirect costs were not. An average cost of $184 was assigned to CUS, and an average cost of $5,982 was assigned for treatment (Righini et al., 2007).

In any presentation of costs associated with PE diagnostic tools, costs of tests and treatment may differ widely among countries and even among hospitals within a particular country. These differences may seriously affect the accuracy of a CEA to determine the most cost-effective PE diagnostic strategy. Most CEAs investigating the diagnosis and treatment of PE were conducted in North America (i.e., USA and Canada) and in northern European countries (e.g., the Netherlands and Switzerland) (see Cox et al., 2003; Doyle et al., 2004; Elias, Molinier, et al., 2004; Hull et al., 1996; Hull et al.,

2001; Larcos et al., 2000; Michel et al., 1996; Paterson & Schwartzman, 2001; Perrier et al., 1997; Perrier et al., 2003; Righini et al., 2007; van Erkel et al., 1996). A study of costs among six countries, Austria, France, Great Britain, Switzerland, The Netherlands, and the United States (van Erkel, van Den Hout, & Pattynama, 1999), revealed that the most economical diagnostic test for PE detection is the D-dimer test. The average cost of its administration was cited as $19 U.S. dollars. The study also revealed that the most expensive diagnostic test is the PA; its average cost was cited as $432, ranging from $190 in France to $797 in the Netherlands. The average cost of treating PE ranges widely among the six countries with a low of $1,385 in Great Britain and a high of $21,182 in the United States (van Erkel et al., 1999).

Effectiveness.

Defining and measuring effectiveness are essential components of a CEA. How effectiveness is defined varies among CEAs published in the 1990s and 2000s (see Cox et al., 2003; Doyle et al., 2004; Elias, Molinier, et al., 2004; Hull et al., 1996; Hull et al., 2001; Larcos et al., 2000; Michel et al., 1996; Paterson & Schwartzman, 2001; Perrier et al., 1997; Perrier et al., 2003; Righini et al., 2007; van Erkel et al., 1996). CEA studies published in the 1990s measured effectiveness by (a) establishing criteria for the correct (accurate) detection of PE and the correct (appropriate) withholding of treatment or (b) the 3-month mortality and morbidity rates as well as the 6-month survival rate (Hull et al., 1996; Michel et al., 1996; Perrier et al., 1997; van Erkel et al., 1996). To measure effectiveness, Hull and colleagues established two criteria: (a) the accuracy of PE detection in conjunction with the costs associated with a correctly treated patient and (b) the number of patients with suspected PE for whom treatment was accurately withheld in

conjunction with the costs associated with establishing that these patients did not require any treatment (i.e., diagnostic strategy implemented) (Hull et al., 1996). Three-month mortality and morbidity rates were used to measure effectiveness in the van Erkel CEA. The marginal effectiveness of a diagnostic strategy was calculated based upon the costs associated with each additional life saved. The diagnostic strategy with the lowest marginal effectiveness was the most cost-effective (van Erkel et al., 1996). Effectiveness was estimated using 6-month survival rates, mortality rates retrieved from CEA data, and mortality rates subsequent to a PA retrieved from the literature by Michel et al. (1996). In the Perrier and colleagues (1997) CEA, effectiveness was measured using parameters that included mortality rates of treated PE, untreated PE, and treatment subsequent to PA results (Perrier et al., 1997).

CEA studies published during the first decade of the 21st century measure effectiveness using several methodologies. The ratio of average costs per life-year was used by the Larcos and colleagues (2000) CEA in which the total cost of each diagnostic strategy was calculated and then divided by the life-years experienced in each group of patients (Larcos et al., 2000). The Hull and colleagues (2001) CEA applied the two criteria used in Hull et al. (1996): the accurate detection of VTE followed by the accurate identification of patients in which treatment was withheld. This study identified 194, 195, and 169 patients who correctly received treatment, and 468, 467, and 493 patients who were correctly left untreated based upon the first, second, and the third evaluated strategies, respectively (Hull et al., 1996). Paterson and Schwartzman (2001) measured effectiveness with a 3-month survival rate following an initial PE episode, 3-month mortality rates for untreated PE (31%), and for treated PE (6.5%) from both older and

more recent studies of PE diagnostic strategies they examined. Effectiveness was measured in a CEA using the 3-month quality-adjusted expected survival rate (Perrier et al., 2003). In this study, calculations of the 3-month survival rate involved parameters, such as treated PE or untreated PE, mortality rate of treated PE (based upon older studies), and anticoagulant therapy. In the Doyle and colleagues (2004) CEA, effectiveness was measured by mortality rates for untreated and treated PE retrieved from previous CEA studies. Effectiveness in the Elias, Molinier, et al. (2004) CEA was measured by the 3-month survival rates from the literature that were based upon mortality rates associated with a CT, PA, and PE treatment (see Barritt & Jordan, 1960; Carson et al., 1992; Dalen & Alpert, 1975; Douketis, Kearon, Bates, Duku, & Ginsberg, 1998; Elias, Molinier, et al., 2004; Giuntini, Di Ricco, Marini, Melillo, & Palla, 1995; Levine, Raskob, Beyth, Kearon, & Schulman, 2004; Perrier et al., 2003; Stein et al., 1992). Righini and colleagues (2007) used the 3-month quality adjusted expected survival rate as it was described in the Perrier CEA (Perrier et al., 2003) to measure effectiveness. Righini et al. used mortality rates for CT, PA, and treatment protocols retrieved from the literature. Concerns were expressed by Rosen (1999) that the mortality rate for untreated PE of 25% used in the van Erkel CEA was very high (see Barritt & Jordan, 1960; Dalen & Alpert, 1975; Rosen, 1999; van Erkel et al., 1996). This mortality rate continued to be used in later CEA studies (see Elias, Molinier, et al., 2004; Perrier et al., 2003). Concerns also were expressed by Lipchik et al. (2004) regarding the lack of CT venography inclusion in the 2003 Perrier CEA. Additional concerns were expressed by Sodhi and Kaur (2005) about the findings in the 2004 Doyle CEA regarding the use of CT during pregnancy.

Summary

Pulmonary embolism diagnosis continues to challenge physicians who must select a diagnostic strategy from a variety of adequate diagnostic tools that includes CDRs, D-dimer tests, and imaging tests. Clinical decision rules (CDRs) can exclude PE in 10% of the patients and can assign a high clinical probability of PE in 14 to 23% of patients with suspected PE. Both the exclusion of PE in some patients and the assignment of a high clinical probability of PE in others contributes to the reduction of diagnostic costs by eliminating the need for further diagnostic procedures (Chagnon et al., 2002;Gibson, Söhne, Kruip, et al., 2008; Klok et al., 2008; Laupacis, Sekar, & Stiell, 1997; Le Gal, Righini, Roy, et al., 2006; Miniati et al., 2003; Shapiro, 2006; Stein, 2007b; Wells et al., 2000; Wicki et al., 2001). D-dimer tests (DD) are blood tests with a sensitivity ranging from 82 to 100%, but a specificity ranging from 36 to 58%, which allows physicians to rule out PE in a significant proportion of the patients with negative DD, thereby reducing the need for additional costly diagnostic imaging tests (see Bruinstroop et al., 2009; De Moerloose et al., 2008; Di Nisio et al., 2007; Ghanima & Sandset, 2007; Hogg et al., 2005; Kline et al., 2006; Parent et al., 2007; Stein, 2007a; Than et al., 2009; Toulon et al., 2009; van Belle et al., 2006). Normal- and high-probability VQ lung scans have excellent sensitivity and specificity for PE diagnosis. The use of VQ lung scans can reduce the cost of PE diagnosis by eliminating the need for further imaging tests; unfortunately, most (50 to 70%) of these scans are nondiagnostic and necessitate further diagnostic procedures (see Bajc & Jonson, 2009; Bajc et al., 2009a; Bajc et al., 2004; Cook & Kyriou, 2005; De Geeter et al., 2005; Douma, Kamphuisen, et al., 2009; Einstein et al., 2007; Freeman & Haramati, 2009; Freeman et al., 2008; Gutte et al., 2010; Gutte et al., 2009; Hull et al.,

1990; Itti et al., 2002; Meignan, 2002; Parker et al., 2005; Perrier, 2007; Reinartz et al., 2004; Roach et al., 2008; Scarsbrook et al., 2007; Sostman, Miniati, et al., 2008; Sostman, Stein, et al., 2008; Stein et al., 2009; Stein, Kayali, et al., 2004b; Stein, Woodard, et al., 2006; Uren, 2009; Zöphel, et al., 2009). Compression ultrasonography (CUS) of the lower limb veins is a noninvasive test that can be performed in a hospital's intensive care unit and detects PE indirectly by diagnosing DVT. However, only about 30% of the patients with confirmed PE have DVT detected by compression ultrasonography (see Elias et al., 2005; Elias, Colombier, et al., 2004; Galle et al., 2001; Kalva et al., 2008; Kearon & Ginsberg, 1998; Le Gal, Righini, Sanchez, et al., 2006; Michiels et al., 2005; Paterson & Schwartzman, 2001; Perrier, 2007; Perrier et al., 2003; Perrier et al., 2004; Quiroz et al., 2005; Righini et al., 2009; Righini et al., 2008; Turkstra et al., 1997). Computed tomography pulmonary angiography (CT) is a noninvasive, quick test that has been the first-line imaging test for PE detection during the past 10 years. A negative CT can exclude PE in about 98% of patients with suspected PE, while approximately 3% of CT scans are nondiagnostic (see Brenner & Hall, 2007; De Monaco et al., 2008; Ghaye & Dondelinger, 2008; Goodman & Lipchik, 1996; Goodman & van Beek, 2009; Kalva et al., 2008; Mos et al., 2009; Perrier et al., 2005; PIOPED Investigators, 1990; Quiroz et al., 2005; Remy-Jardin et al., 1996; Remy-Jardin et al., 1992; Revel et al., 2005; Schoepf & Costello, 2005; Stein, Fowler, et al., 2006; Stein, Kayali, et al., 2004b; Stone et al., 2003; Turkstra et al., 1997; van Belle et al., 2006; Van Rossum et al., 1996; Vigo et al., 2006; Wang et al., 2009). Invasive pulmonary angiography (PA) was the gold standard procedure of PE diagnosis for many decades, but despite its excellent accuracy with a very high sensitivity of 96% and a very high

specificity of 97%, physicians resort to it as the last procedure because it is invasive, not available in all hospitals, and expensive (see Brenner & Hall, 2007; De Monaco et al., 2008; Ghaye & Dondelinger, 2008; Goodman & Lipchik, 1996; Goodman & van Beek, 2009; Kalva et al., 2008; Mos et al., 2009; Perrier et al., 2005; PIOPED Investigators, 1990; Quiroz et al., 2005; Remy-Jardin et al., 1996; Remy-Jardin et al., 1992; Revel et al., 2005; Schoepf & Costello, 2005; Stein, Fowler, et al., 2006; Stein, Kayali, et al., 2004b; Stone et al., 2003; Turkstra et al., 1997; van Belle et al., 2006; Van Rossum et al., 1996; Vigo et al., 2006; Wang et al., 2009).

Diagnostic tools such as the D-dimer tests and the multidetector-row CT, continue to improve as research innovations are tested. However, Balas and Boren (2000) noted that clinical research findings enter daily practice after about 17 years, which represents a considerable lag between research and practice, which affects all aspects of diagnosis, including costs and effectiveness.

Combinations of certain diagnostic criteria that match the level of clinical probability of PE and the findings of DD and imaging tests can safely rule out or confirm PE in patients with suspected PE. Studies have demonstrated that the combination of low clinical probability of PE and a negative D-dimer test can safely rule out PE without further imaging tests in 24 to 47% of the patients with suspected PE. Also, certain studies have revealed that PE can be detected in a significant segment of patients with suspected PE by using a simple diagnostic tool combination of a CDR, a DD, and CT or PA (see Anderson et al., 2007; Eng et al., 2009; Ghanima et al., 2005; Ghaye & Dondelinger, 2008; Huisman & Klok, 2009; Kamphuisen & Agnelli, 2005; Nijkeuter et al., 2007; Perrier et al., 2005; Righini et al., 2008; Sohns et al., 2008; Stein, Woodard, et al., 2006;

van Belle et al., 2006). Findings from other studies have indicated that PE can be detected in a large portion of patients with suspected PE by using more complex diagnostic strategies of CDR and DD with various combinations of CT, CUS, VQ lung scan, and PA (see Anderson et al., 2007; Anderson et al., 2005; Elias et al., 2005; Hammond & Hassan, 2005; Kearon et al., 2006; Kruip et al., 2002; Perrier et al., 2004; Perrier et al., 2005; Righini et al., 2008; Wells et al., 2001). As Table 7 demonstrates, triangular distributions, γ distributions, and Monte Carlo Simulation analysis were not applied in previous CEA studies. A list of studies summarizing the CEA methodology of PE diagnostic strategies is presented in Table 7.

Table 7

Summary of CEA Methodology of PE Diagnostic Strategies

Study First Author & Year	Decision Tree Model Applied to CEA	Triangular and γ Distributions Applied to Parameter Estimates	Deterministic Sensitivity Analysis	Monte Carlo Simulation Sensitivity Analysis
Larcos, 2000	X		X	
Paterson, 2001	X		X	
Perrier, 2003	X		X	
Doyle, 2004	X		X	
Elias, 2004	X		X	
Righini, 2007	X		X	
Polychronopoulos, 2011	X	X	X	X

Note. PE = pulmonary embolism; CEA = cost-effectiveness analysis.

Gap in the Literature

The literature review demonstrated that a substantial amount of research examined PE clinical decision rules (CDR); evaluated PE diagnostic tests such as the D-dimer test (DD), the computed tomography pulmonary angiography (CT), the compression ultrasonography (CUS), the ventilation-perfusion (VQ) lung scan, and the invasive pulmonary angiography (PA); and appraised the performance of PE diagnostic strategies to detect PE in patients with suspected PE. The literature also suggested that a cost-effectiveness analysis (CEA) might be a valuable technique for assessing the performance of these strategies; however, as Table 7 indicates, there is a dearth of research regarding CEA of PE diagnostic strategies. No research was discovered regarding a CEA in conjunction with triangular distributions, γ distributions, and Monte Carlo Simulation as a methodology for evaluating the performance of PE diagnostic strategies. Hence, there exists a need for a CEA that applies the triangular and γ distributions as well as the Monte Carlo Simulation as a method by which the cost-effectiveness of PE diagnostic strategies can be assessed when examining PE detection failure rates. Such an approach may prove to be a valuable addition to the literature regarding decisions about diagnostic strategy selection for pulmonary embolism diagnosis.

CHAPTHER 3

METHOD

Overview

The purpose of this study was to assess the most cost-effective diagnostic strategy among several strategies currently in use for patients with suspected PE based upon their screening failure rates. Diagnostic strategy selection directly influences the cost and effectiveness of a PE diagnosis. The identification of cost-effective strategies and/or the most cost-effective strategy is significant to the medical decision making process (PE early diagnosis) and for the delivery of health services (PE treatment). Such discovery can result in a broader use of a particular strategy or strategies that are less expensive and more effective than alternate strategies (Cox et al., 2003; Doyle et al., 2004; Elias, Molinier, et al., 2004; Hull et al., 1996; Hull et al., 2001; Larcos et al, 2000; Michel et al., 1996; Paterson & Schwartzman, 2001; Perrier et al., 1997; Perrier et al., 2003; Righini et al., 2007; van Erkel et al., 1996).

Human Subjects Review

Secondary aggregated data were used for this study and retrieved from published studies in the literature. Thus, there was no need to obtain consent from the subjects who participated in the original studies analysed for this research. Therefore, an approval for exemption was obtained from Old Dominion University's College of Health Sciences Human Subjects Review Committee.

Target Population

The population of this study was patients with suspected PE who were either outpatients in hospital emergency departments or inpatients following a hospital

admission. The study population consisted of patients with suspected PE who participated in studies published from January 2000 to December 2010, as either an outpatient or inpatient, of all adult age groups, without restrictions to race or gender or socioeconomic status.

Definitions of Input Variables

PE diagnostic strategy tests and treatment, the three constructs of the decision tree model, the statistical methods that comprise this research, the measurement tools applied, and the variables tested were identified, operationally defined, and described from the literature (see Beyer & Scellong, 2007; Brenner & Hall, 2007; De Milto & Odle, 2006; Dutton et al., 2009; Fenwick, 2009b; Ford-Martin, 2006; Jekel et al., 2001; Klok et al., 2008; Lapin & Whisler, 2002; Mazur, 2009; Miller, 2009; Muennig, 2008; Odle, 2006; Petitti, 2000; Sonnenberg, 2009; van Loveren et al., 2009; Wells, 2007a, 2007b). PE diagnosis consisted of the following terms: strategy, treatment, CDR, D-dimer test, CT, VQ lung scan, CUS, and PA. The decision tree model constructs were act, event, and outcome. The analytical methods that comprise the design of the study include parameter estimation, a decision tree model applied to a cost-effectiveness analysis (CEA), Monte Carlo Simulation as well as one-way, two way, and three-way sensitivity analyses. Measurement terms included prior probability, posterior probability, dominant strategy, and dominated strategy. The variables that were examined were the direct costs and effectiveness of PE diagnosis and treatment as well as the incremental cost-effectiveness ratio. Each of these terms is defined in Table 8.

Table 8

Definitions and Descriptions of the Study Terms

Theoretical Definition/ General Description	Operational Definition/ Operational Description	Decision, Diagnostic, and Measuring Tools
Act Action chosen by the decision maker (Lapin & Whisler, 2002)	Act PE diagnostic strategies representing initial actions	Act All actions on the left side of the decision tree structure (Lapin & Whisler, 2002)
Clinical decision rule (CDR) Decision tool based upon clinical variables assessing the probability of a disease diagnosis in a patient (Klok et al., 2008)	CDR Scoring system measuring the pretest probability of PE based upon clinical variables	CDR Pretest probability of PE is expressed in numbers in two categories (PE unlikely or PE likely) or in three categories (low, intermediate or high)
Compression ultrasonography (CUS) Three CUS techniques: "(a) segmental CUS, examining the common femoral vein and the popliteal vein; (b) extended CUS, examining the complete deep thigh veins and popliteal vein; (c) complete CUS, of all segments of the deep thigh and calf veins (Beyer & Scellong, 2007)	CUS Imaging test to detect DVT and an essential test to indirectly detect PE using the two-point compression ultrasound (2-CUS), the extended compression ultrasound (E-CUS), or the complete compression ultrasound (C-CUS)	CUS Results are read as negative, positive, or nondiagnostic for PE

Table 8 (continued)

Theoretical Definition/ General Description	Operational Definition/ Operational Description	Decision, Diagnostic, and Measuring Tools
Computed tomography pulmonary angiography (CT)	CT	CT
Combination of X-ray and computer images providing cross-sectional views of patient organs and tissues (Brenner & Hall, 2007; Odle, 2006)	Fast, noninvasive PE diagnostic test able to directly image a clot as the X-ray source and detectors rotate, producing a spiral or helical scan	Results are read as negative, positive, or nondiagnostic for PE
Cost-effectiveness analysis (CEA)	CEA	CEA
Method of comparing two or more strategies in terms of their costs and effectiveness (Muennig, 2008)	Comparison of cost and effectiveness of a PE strategy with other available alternative PE strategies	Assessing the value of each PE diagnostic strategy under specific units of cost and effectiveness
D-dimer test (DD)	DD	DD
By-product of the breakdown of fibrin found in blood clots (Wells, 2007a)	Blood tests that allow physicians to rule out PE in patients with suspected PE	Results are read as negative, positive, or nondiagnostic for PE
Decision tree model (DTM)	DTM	DTM
A decision-making model combining three constructs, action, event, and outcome (Lapin & Whisler, 2002)	The action construct includes PE diagnostic strategies. The event construct includes CDRs, diagnostic tests, and probabilities. The outcome construct includes any payoff.	Triangular and γ distributions of costs and effectiveness as well as event probabilities

Table 8 (continued)

Theoretical Definition/ General Description	Operational Definition/ Operational Description	Decision, Diagnostic, and Measuring Tools
Direct costs The use of services and goods (Petitti, 2000)	Direct costs PE diagnostic tests costs, PE treatment costs, and PE hospitalization costs	Direct costs Laboratory and imaging tests costs, treatment costs, and hospitalization costs
Diagnostic strategy Diagnostic procedure based upon combinations of clinical decision rules, diagnostic laboratory tests, and imaging tests	Diagnostic strategy Combinations of PE clinical decision rules, D-dimer tests, and PE imaging tests to detect PE	Diagnostic strategy PE diagnostic strategy composition
Dominant strategy Strategy that demonstrates greater effectiveness and lower cost than one competing strategy (Miller, 2009)	Dominant strategy Strategy considered the dominant strategy if it is more effective and less expensive compared to an alternative strategy	Dominant strategy Effectiveness and cost units
Dominated strategy Strategy that demonstrates less effectiveness and higher cost than one competing strategy (Miller, 2009)	Dominated strategy Strategy dominated if it is less effective and more expensive than an alternative strategy	Dominated strategy Effectiveness and cost units
Effectiveness Measure of an intervention's performance (Muenning, 2008)	Effectiveness Performance of an entire PE diagnostic strategy	Effectiveness Includes the failure rate to Detect PE after implementing a strategy

Table 8 (continued)

Theoretical Definition/ General Description	Operational Definition/ Operational Description	Decision, Diagnostic, and Measuring Tools
Event	Event	Event
Component of the decision under uncertainty that follows an initial action (Lapin & Whisler, 2002)	PE diagnostic tests or treatment, representing potential events	A chronological progression with events on the left side assumed to occur before events on the right (Lapin & Whisler, 2002)
Incremental cost-effectiveness ratio (ICER)	ICER	ICER
Incremental cost divided by incremental effectiveness (Fenwick, 2009b)	Incremental cost divided by incremental effectiveness of two PE diagnostic strategies	Cost of strategy A minus cost of strategy B divided by effectiveness of strategy A minus effectiveness of strategy B
Invasive pulmonary angiography (PA)	PA	PA
Imaging procedure that displays the blood vessels and organs and uses an injection of a radio contrast agent, X-ray techniques and a catheter inserted into the vein, the heart, and pulmonary artery (Ford-Martin, 2006; van Loveren et al., 2009)	Invasive test that examines blood circulation to the lungs using radio contrast material, X-ray imaging, and catheter inserted into the vein, the heart, and the pulmonary artery	The most accurate PE diagnostic test with very high sensitivity and specificity

Table 8 (continued)

Theoretical Definition/ General Description	Operational Definition/ Operational Description	Decision, Diagnostic, and Measuring Tools
Monte Carlo Simulation (MCS) Sensitivity analysis involving probability distributions for each variable in the decision model (Mazur, 2009)	MCS Sensitivity analysis involving repeated random sampling from input distributions assigned for each variable in the PE decision model	MCS Input: Probability distributions Output: Distribution of samples; mean incremental cost-effectiveness ratio (ICER)
One-way, two-way and three-way sensitivity analyses Test of the impact on a decision model's outputs by varying the values of a variable, or two variables or three variables of interest in a range of plausible values, while holding all other variables constant (Sonnenberg, 2009)	One-way, two-way and three-way sensitivity analyses Test of the effect on the PE decision tree model results by varying values of an uncertain variable or two variables or three variables with a range of plausible values and holding all other variables in the model constant	One-way, two-way and three-way sensitivity analyses Input: Range of plausible values and a baseline value Output: Error in the model results and findings based upon the baseline value
Outcome Measurement of the evaluating condition (Lapin & Whisler, 2002)	Outcome Cost and effectiveness of PE diagnostic strategies, e.g., dollars per life saved	Outcome Outcomes or the consequences of the events

Table 8 (continued)

Theoretical Definition/ General Description	Operational Definition/ Operational Description	Decision, Diagnostic, and Measuring Tools
Parameter estimates Determination of parameter estimates for variables with uncertainty to use them as inputs in the decision tree model to conduct a CEA	Parameter estimates Determination of estimates by applying triangular and γ distributions to address variability to resolve uncertainty and eliminate error	Parameter estimates Estimation of diagnostic tests' costs, sensitivities, probabilities, and PE diagnostic strategy failure rates.
Posterior probability Likelihood of disease estimated after a test is conducted (Jekel et al., 2001)	Posterior probability Estimation of the presence of PE after performing PE laboratory or imaging tests	Posterior probability Measured using Bayes's theorem
Prior probability Likelihood of disease estimated before a test is conducted (Jekel et al., 2001)	Prior probability Estimation of the presence of PE before the performance of PE diagnostic laboratory or imaging tests	Prior probability Measured by the prevalence of PE among patients with suspected PE
Pulmonary embolism (PE) PE is the condition in which clots block the pulmonary artery (U. S. DHHS, 2008; Virchow, 1860/2009)	PE Diagnostic strategies for early diagnosis of PE in patients with suspected PE	PE CDR, DD, CT, CUS, VQ, PA

Table 8 (continued)

Theoretical Definition/ General Description	Operational Definition/ Operational Description	Decision, Diagnostic, and Measuring Tools
Strategy failure rate (SFR) The performance of the entire strategy	SFR The performance of the five investigated PE diagnostic strategies	SFR Three-month follow-up mortality rates and three-month follow-up VTE (i. e. PE and/or DVT) recurrence rates.
Treatment (Tr) Thrombolytic therapy to dissolve blood clots (De Milto & Odle, 2006)	Tr Anticoagulant treatment received by patients with PE to dissolve and/or prevent clot formation	Tr Treatment cost
Ventilation-perfusion (VQ) Two imaging procedures: perfusion lung scan evaluates blood flow in the lungs; ventilation study assesses the air space distribution in the lungs (Dutton et al., 2009)	VQ Noninvasive imaging diagnostic test for detecting PE using two imaging procedures: ventilation and perfusion scanning of PE	VQ Results are read as negative, positive, or nondiagnostic for PE
Venous thromboembolism (VTE) VTE can be described as the condition in which blood clots exist in a remote vein (U. S. DHHS, 2008)	VTE VTE includes the medical conditions of pulmonary embolism (PE) and deep vein thrombosis (DVT)	VTE CDR, DD, CT, CUS, VQ, PA

Data Collection

Data parameter.

The purpose of triangular and γ distribution in this dissertation was to determine appropriate summary estimates for variables with uncertainty and to use them as inputs in the decision tree model for conducting a cost-effectiveness analysis. Specific inclusion criteria were established for selecting and retaining a study for determining parameter estimates by employing triangular and γ distributions. They included (a) a publication date from January 2000 to December 2010 inclusive, (b) at least one criterion from the performance criteria 1 through 5, and (c) criterion 6:

1. PE CDR, D-dimer test, and CT.
2. PE CDR, D-dimer test, CT, and CUS.
3. PE CDR, D-dimer test, CUS, and CT.
4. PE CDR, D-dimer test, VQ lung scan, and CUS.
5. PE CDR, D-dimer test, CT, CUS, and PA.
6. Sufficient information about PE diagnostic strategy failure rates to detect PE is provided.

With regard to sensitivity, specificity, cost, and effectiveness values, a study must have satisfied either criterion 7 or 8 or both criteria to be selected for and retained in determining parameter estimates by employing triangular and γ distributions.

7. Sufficient information about PE diagnostic test sensitivity and/or specificity values was provided.
8. Sufficient information about costs of a PE diagnostic test or treatment or about effectiveness (i. e. strategy failure rates) was provided.

There were no restrictions on the type of CDR or PE diagnostic test, hospital location, outpatient or inpatient status, gender, age, or total number of patients.

CEA data.

Data for direct costs (diagnostic test and treatment) was entered in the decision tree model to conduct a CEA. Indirect costs were not included in this study, such as costs due to productivity lost, waiting or travelling, or other economic impact on the patients and their families as well as the opportunity costs of market competition, income, and taxes. Inclusion of indirect costs was unnecessary since this study did not examine the well-being of PE patients (i.e., a societal perspective) to assess social welfare maximization. Rather, this study focused upon direct costs by examining certain variables that affect medical decision-making, not societal decision-making.

Direct costs data was identified from the literature for the following components of PE screening: (a) diagnostic test costs, including laboratory tests costs, imaging tests costs, and physician fees for D-dimer test, CT, CUS, VQ lung scan, PA and (b) treatment costs, including drugs, laboratory tests performed for monitoring the anticoagulant treatment, and physician fees.

Effectiveness data was entered into the proposed CEA decision tree model to detect PE after implementing a strategy. These data included PE detection failure rates, which could result in a new PE episode or a fatality. Effectiveness data was identified from the literature or was calculated using (a) the three-month follow-up mortality rates and (b) the three-month follow-up VTE (i. e. PE and/or DVT) recurrence rates.

Probabilities data was entered into the proposed CEA decision tree model. These probabilities were calculated from several events related to PE diagnostic procedures: (a)

ruling out PE after performing a PE diagnostic test, (b) administering treatment after performing a PE diagnostic test, and (c) performing an additional PE diagnostic test following negative or nondiagnostic results from the previous diagnostic test.

Research Question and Hypothesis

Research question.

To assess the most cost-effective PE diagnostic strategy among five strategies currently in use, the following research question was established based upon the CEA decision tree model and review of the literature: Which strategy offers the best possible effectiveness at the lowest or most acceptable cost?

Hypothesis.

The null and alternate hypotheses for this CEA were derived from the five PE diagnostic strategies investigated. The composition of each strategy involved a CDR and a D-dimer test as initial diagnostic procedures followed by one or more imaging tests in the described sequence.

Strategy 1: CDR, D-dimer test, with or without CT;

Strategy 2: CDR, D-dimer test, CT, with or without CUS;

Strategy 3: CDR, D-dimer test, CUS, with or without CT;

Strategy 4: CDR, D-dimer test, VQ lung scan, with or without CUS; and

Strategy 5: CDR, D-dimer test, CUS, with or without PA; and

The following null and alternative hypotheses were investigated.

Ho: There is no difference in cost-effectiveness among the five PE diagnostic strategies investigated.

Ha: At least one strategy is more cost-effective among the five PE diagnostic strategies investigated.

The following alternative decisions (Da_n) based upon the study's hypothesis were evaluated:

Da_1: At least strategy 1 is more cost-effective than strategy 2, strategy 3, strategy 4 and strategy 5.

Da_2: At least strategy 2 is more cost-effective than strategy 1, strategy 3, strategy 4 and strategy 5.

Da_3: At least strategy 3 is more cost-effective than strategy 1, strategy 2, strategy 4 and strategy 5.

Da_4: At least strategy 4 is more cost-effective than strategy 1, strategy 2, strategy 3 and strategy 5.

Da_5: At least strategy 5 is more cost-effective than strategy 1, strategy 2, strategy 3 and strategy 4.

Data Analysis

Parameter estimates.

Triangular and γ distributions were powerful statistical methods that were appropriate for determining parameter estimates for this study. They increased the power and precision of the earlier, individual studies that investigated the performance of PE diagnostic tests or PE diagnostic strategies. This research suggested that applying triangular and γ distributions in a CEA to assess parameter estimates of pulmonary embolism diagnostic tests' cost, sensitivity and specificity, and effectiveness addressed variability in data retrieved from the literature. Additionally, it resolved the uncertainty

surrounding the values of cost, effectiveness, and sensitivity and specificity, and it eliminated error in the assigned baseline values in the CEA model. For a more detailed discussion of triangular and γ distributions see Mendenhall and Sincich as well as TreeAge Software (Mendenhall & Sincich, 2007; TreeAge Software, 2009).

CEA methodology.

CEA techniques mainly were developed during the past four decades, with significant research pertaining to cost, effectiveness, incremental cost-effectiveness ratio, probabilities, sensitivity analysis, and Monte Carlo Simulation. During the same period, CEA techniques concentrating on health issues have been discussed by several authors (see Alemi & Gustafson, 2007; Briggs, Goeree, Blackhouse, & O'Brien, 2002; Detsky & Naglie, 1990; Drummond, O'Brien, Stoddart, & Torrance, 1997; Gold, 1996; Manly, 2007; Muennig, 2002, 2008; Pauker & Kassirer, 1978; Porzsolt & Kaplan, 2006; Thompson & Nixon, 2005; TreeAge Software, 2009; Willan & Briggs, 2006).

Cost. Cost data for this study retrieved from the literature are dated and each requires an adjustment for inflation (see Drummond et al., 1997; Muennig, 2008; Petitti, 2000 for a discussion of costs and inflation adjustments). It is assumed that the cost in any given year for any PE laboratory test and/or the cost of any PE imaging test can be determined and, consequently, adjusted for inflation using information retrieved from the medical section of the Consumer Price Index (U. S. Department of Labor, 2011). When calculating adjusted costs in years with the inflation rate remaining constant, the equation $C_n = C_o (1+i)^n$ was appropriate. However, if the rate of inflation fluctuates, the equation $C_n = C_{n-1} (1+i_n)$ has been found to be more effective in evaluating adjusted cost, where C

is the cost and i is the inflation rate for years 1, 2, 3, . . . and n. Therefore, the adjusted for inflation costs for years 1, 2, 3, . . . and n were determined by the following equations:

$$\text{year 1: } C_1 = C_0 (1+i_1)$$

$$\text{year 2: } C_2 = C_1 (1+i_2)$$

$$\text{year 3: } C_3 = C_3 (1+i_3)$$

$$\ldots$$

$$\text{year n: } C_n = C_{n-1} (1+i_n)$$

Cost data usually has highly skewed distributions; thus, several techniques are available for transforming data to produce normality in skewed distributions (see Cohen, Cohen, West, & Aiken, 2003; Darren, Mallery, & Briggs, 2003; Field, 2003; Keppel & Wickens, 2004; Leech, Barrett, & Morgan, 2008; Maindonald & Braun, 2007; Maxwell & Delaney, 2004; Mertler & Vannatta, 2002; Stevens, 2002; Tabachnick & Fidell, 2001; Willan & Briggs, 2006).

Effectiveness. The effectiveness of a given PE diagnostic strategy is typically measured by mortality and survival rates (Drummond et al., 1997; Muennig, 2008; Petitti, 2000). Several authors offered comprehensive mathematical presentation of various methods that have been developed to estimate effectiveness (see Drummond et al., 1997; Howard, 2009; Muennig, 2008; Petitti, 2000; Willan & Briggs, 2006). Effectiveness in this study reflected the performance of each PE diagnostic strategy, including failure rates to detect a PE. Strategy failure rates represented 3-month follow-up mortality rates and 3-month follow-up VTE (i. e. PE or DVT) recurrence rates after implementing a specific PE diagnostic strategy in patients with suspected PE.

Incremental cost-effectiveness ratio (ICER). CEA using the decision tree model is a powerful statistical tool that supports complex calculations (see Detsky & Naglie, 1990; Fenwick, 2009a; Jekel et al., 2001; Miller, 2009; Muennig, 2008; Pauker & Kassirer, 1978; Petitti, 2000; van den Hout, 2009). A PE diagnostic strategy was considered cost-effective if it meets the general criteria for a cost-effective intervention: (a) less expensive and at least as effective; (b) more effective and more expensive, with the additional benefit worth the additional cost; (c) less effective and less expensive, with the additional benefit of the alternative not worth the additional cost; or (d) cost reduction with an equal or improved outcome (Petitti, 2000).

When PE diagnostic strategy A is more effective but costs more than alternate strategy B, the incremental cost-to-incremental effectiveness ratio (ICER) should be calculated (Detsky & Naglie, 1990; Fenwick, 2009b; Petitti, 2000). The ICER is computed with the following formula:

$$\text{Incremental cost} - \text{effectiveness} = \frac{\text{Cost}_{\text{strategy A}} - \text{Cost}_{\text{strategy B}}}{\text{Effectiveness}_{\text{strategy A}} - \text{Effectiveness}_{\text{strategy B}}}$$

PE strategy A is considered the dominant strategy if it is more effective and less expensive than alternate strategy B (Muennig, 2008; van den Hout, 2009). This relationship is expressed by the following formulas:

$$\text{Effectiveness}_{\text{strategy A}} \geq \text{Effectiveness}_{\text{strategy B}}$$

$$\text{Cost}_{\text{strategy A}} \leq \text{Cost}_{\text{strategy B}}$$

PE strategy B is considered the dominated strategy if it is less effective and more expensive than alternate strategy A (Muennig, 2008; van den Hout, 2009). This relationship is expressed by the following formulas:

$$\text{Effectiveness}_{\text{strategy B}} \leq \text{Effectiveness}_{\text{strategy A}}$$

$$\text{Cost}_{\text{strategy B}} \geq \text{Cost}_{\text{strategy A}}$$

Event probabilities. Determining event probabilities was essential in CEA that incorporates the decision tree model. Probabilities for each possible event and outcome not retrieved from the literature were calculated. Two statistical concepts were associated with calculating probabilities. For this research, prior probability of PE was an estimate of the presence of PE before laboratory or imaging tests were performed. It was derived from the estimate of the prevalence of PE among patients with suspected PE (Jekel et al., 2001; Pauker & Kassirer, 1978). Posterior probability of PE was the estimate of the presence of PE after laboratory or imaging tests were performed or after intervention (Jekel et al., 2001; Pauker & Kassirer, 1978). Posterior probability estimations for the first, second, and further tests were calculated based upon Bayes's theorem (see Bayes, 1763; Daniel, 2000; Jekel et al., 2001; Pagano & Gauvreau, 2000). Bayes's theorem is considered "the foundation for managing and manipulating uncertainty using probability theory in expert systems" (Bondi, 2007, p. 32).

Within the context of the decision tree model, Bayes's theorem can be used to answer the following two questions: (a) What is the probability that a patient with a positive diagnostic test result has a disease? and (b) What is the probability that the patient with a negative diagnostic test result does not have the disease? These questions are not answered by either the sensitivity or specificity values of a diagnostic test. Assuming that PE+ is an event in which a patient has PE and PE- is an event in which a patient does not have PE, then the posterior probability for a positive PE diagnostic test is established using the following formula,

$$p(PE+/T+) = [p(T+/PE+)p(PE+)]/[p(T+/PE+)p(PE+)+p(T+/PE-)p(PE-)].$$

The posterior probability for a negative PE diagnostic test is determined using this formula:

$$p(PE-/T-) = [p(T-/PE-)p(PE-)]/[p(T-/PE-)p(PE-)+p(T-/PE+)p(PE+)].$$

The letter p indicates probability, T+ indicates that a specific PE diagnostic test is positive, T- indicates that the specific PE diagnostic test is negative, and the diagonal line (/) indicates conditional upon that which follows.

Monte Carlo Simulation Sensitivity Analysis: A Probabilistic Approach

A sensitivity analysis was conducted using a probabilistic approach through a Monte Carlo simulation (see Bondi, 2007; Manly, 2007; Muennig, 2008; TreeAge Software, 2009). This method, which was named for the European gambling establishment, considered probability distributions for each variable in the decision tree model. A mean and 95% CI for the variable of interest was obtained by sampling each distribution repeatedly for the overall cost, effectiveness, and incremental cost-effectiveness ratio by diagnostic strategy. Available software (TreeAge Software, 2009) that applies a Monte Carlo simulation offers the option to select the input distribution for each variable from a large number of distributions. As a result, the simulation provided the final distribution of each variable as well as the final distribution of incremental cost-effectiveness values on a normal distribution, one of the most commonly used distributions in probability theory and statistics (see Daniel, 2000; Howell, 2002; Kuzma & Bohnenblust, 2001; Pagano & Gauvreau, 2000; TreeAge Software, 2009).

In the Monte Carlo simulation, the inputs in the decision tree model function as variables that can indicate a wide range of values, instead of fixed numbers and can allow

all variable uncertainties to be included in the analysis while reproducing the model multiple times. The advantages of this simulation included testing all variables simultaneously, providing the mean and standard deviation, and generating a confidence interval for the expected outcomes (i.e., cost, effectiveness, and cost-effectiveness ratio). A Monte Carlo simulation significant at α (alpha) level of .05 required a minimum of 1,000 sets of simulated data, and a simulation significant at α level of .01 required a minimum of 5,000 sets of simulated data (Manly, 2007). The α level for this research was set at .05.

The software used in this study (TreeAge Software, 2009) performs CEAs using the decision tree model. It allowed the researcher to conduct Monte Carlo Simulations as well as one-way, two-way, and three-way sensitivity analyses. It exported to Microsoft Excel and allowed the production of several charts for the input distributions, the distribution of outcomes, and the distribution of the incremental outcomes.

One-Way, Two-Way, and Three-Way Sensitivity Analyses: A Deterministic Approach

In this research, the CEA combined effectiveness data and cost data of PE diagnostic strategies retrieved from studies identified in the literature. Inferential uncertainty due to possible errors within the data was addressed using a one-way, two-way and three-way sensitivity analysis that assessed the effect of varying model assumptions on the findings (Muennig, 2008; Petitti, 2000; Willan & Briggs, 2006). The decision tree CEA model was tested using this sensitivity analysis.

In a one-way, two-way, and three-way sensitivity analysis, a single variable, or a pair of variables or a group of three variables, respectively, was tested within a range of

reasonable values while all other variables were held constant. Variables for which there was uncertainty were tested using a wide range of values from much lower to much higher than the baseline estimate. Variables for which there was less uncertainty, hence more confidence, were tested using a narrower range of values. If a PE diagnostic strategy remained dominant within a range of plausible values for inputs involving uncertainty, then the model was robust.

CHAPTER 4

RESULTS

Overview

The purpose of this study was to assess the most cost-effective diagnostic strategy, among several strategies currently in use for patients with suspected pulmonary embolism (PE), based upon strategy failure rates. This chapter examines the parameter estimates, the comparisons of decision's alternative, and the sensitivity analysis results. First, parameter estimates were assessed based upon data retrieved from the literature with regards to PE diagnostic test direct costs, effectiveness of PE diagnostic strategies as well as PE diagnostic tests' sensitivity and specificity. Second, alternative decisions addressing PE diagnostic strategies were evaluated to determine which strategy exerted influence on the medical decision-making process. Third, Monte Carlo probabilistic sensitivity analyses and one-way, two-way, and three-way deterministic sensitivity analyses were conducted to assess the impact of uncertainty on the cost-effectiveness analysis (CEA) model. Finally, it was determined that Strategy 3, comprising a clinical decision rule (CDR), a D-dimer test (DD), a compression ultrasonography (CUS), and a computed tomography pulmonary angiography (CT), was the most cost effective. This strategy was compared to alternate strategy 1, comprising a CDR, a DD, and a CT; alternate strategy 2, comprising a CDR, a DD, a CT, and a CUS; alternate strategy 4, comprising a CDR, a DD, a VQ lung scan, and a CUS; and alternate strategy 5, comprising a CDR, a DD, a CT, a CUS, and a PA.

Parameter Estimates Results

Pulmonary embolism diagnostic tests and treatment direct costs.

A literature review was conducted to obtain PE diagnostic tests and treatment direct costs. The predetermined inclusion criteria were met only by five studies appropriate for inclusion in the analysis. Of them, three are cost-effectiveness analysis (CEA) studies, one is a management study, and one is an economic review. A list of studies included in the analysis is presented in Table 9.

Table 9

Studies Included in the Analysis to Obtain PE Diagnostic Tests and Treatment Direct Costs

Study First author	Year	Diagnostic Test					
		DD	CT	CUS	VQ	PA	Tr
Van Erkel	1999	X	X	X	X	X	X
Paterson	2001		X	X	X	X	
Doyle	2004		X	X	X	X	
Duriseti	2006	X	X	X	X		X
Stein	2006	X	X	X	X	X	

Note. PE = pulmonary embolism; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS = compression ultrasonography; VQ = ventilation-perfusion lung scan; PA = invasive pulmonary angiography; Tr = treatment for PE.

Since the annual inflation rates differ, substantially among the years between 1998 and 2010 the direct costs, adjusted for inflation, were determined by the equation $C_n = C_{n-1}(1+i_n)$, where C is the cost and i is the inflation rate for years 1, 2, 3, . . . , and n.

Estimations were based upon the studies included in the analysis, while the Bureau of Labor Statistics within the U.S. Department of Labor provided the Consumer Price Index for hospital and related services (U. S. Department of Labor, 2011). Comparisons among the adjusted-for-inflation PE diagnostic testing cost during the period from 1998 through 2010 are presented in Figures 3 through 8. The trend line equations and r^2 values for the PE diagnostic testing costs adjusted for inflation are presented in Tables 10 through 15.

D-dimer test (DD) adjusted costs increased linearly during the years 1998-2010 with trend line equation R^2 values of more than 98% (see Table 10). The range from the lowest to the highest DD adjusted cost was $8 (see Figure 3).

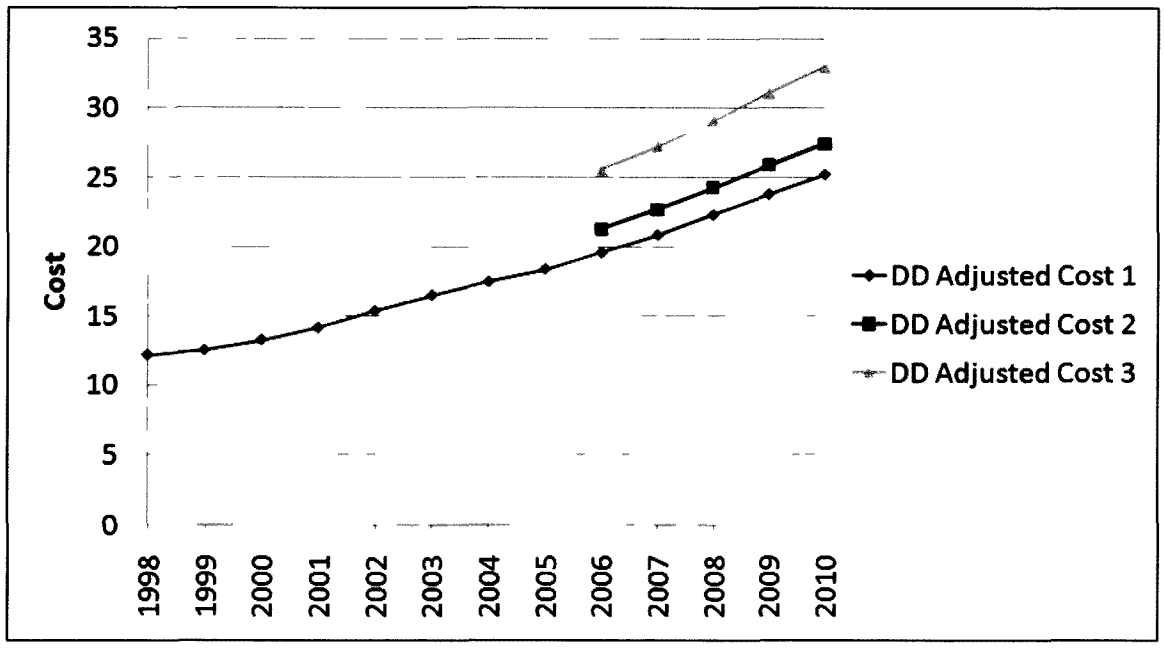


Figure 3. Comparisons of D-dimer test (DD) direct cost for the years 1998-2010 adjusted for inflation.

Table 10

Trend Line Equations and R^2 Values of DD Cost Adjusted for Inflation

	Adjusted Cost		Study of Unadjusted Cost	
D-dimer (DD)	Equation	R^2	First Author	Year
Adjusted Cost 1	Y_{DD1}=1.1062x+10.069	R_{DD1}=0.9872	Van Erkel	1999
Adjusted Cost 2	Y_{DD2}=1.559x+7.2024	R_{DD2}=0.9994	Duriseti	2006
Adjusted Cost 3	Y_{DD3} =1.867x+8.6429	R_{DD3}=0.9994	Stein	2006

Note. Y = adjusted cost; x = time.

Computed tomography pulmonary angiography (CT) adjusted costs increased linearly during the years 1998-2010 with trend line equation R^2 values of more than 98% (see Table 11). The lowest-to-highest CT adjusted cost range was $2,112 (see Figure 4).

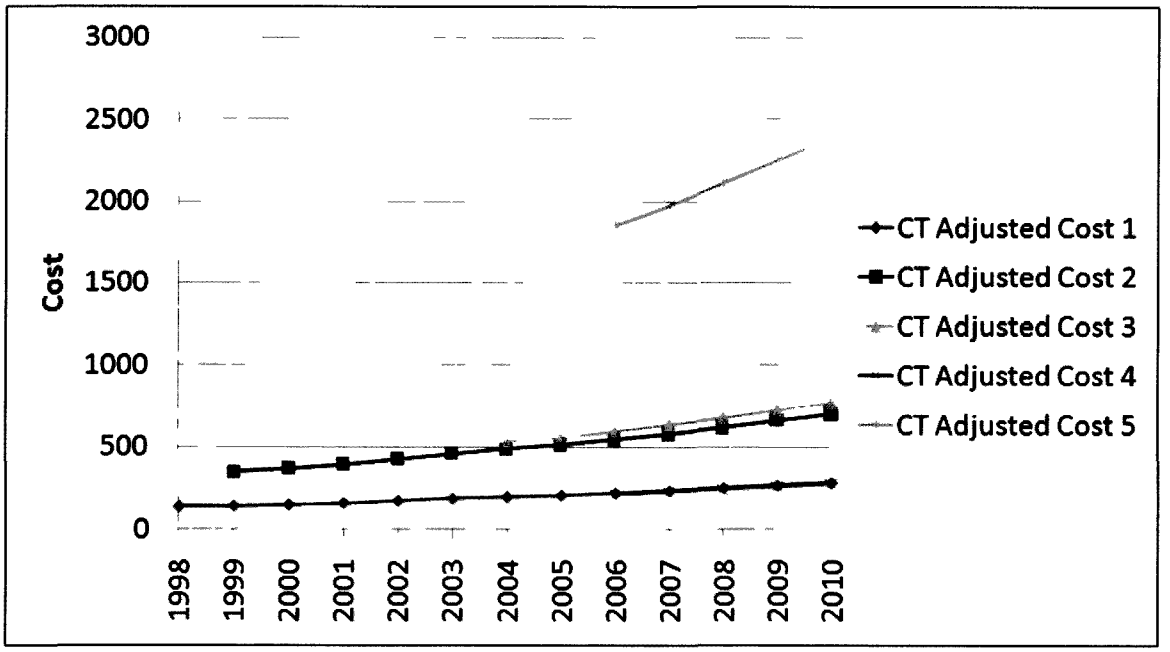


Figure 4. Comparisons of computed tomography pulmonary angiography (CT) direct cost for the years 1998-2010 adjusted for inflation.

Table 11

Trend Line Equations and R^2 Values of CT Cost Adjusted for Inflation

	Adjusted Cost		Study of Unadjusted Cost	
CT	Equation	R^2	First Author	Year
Adjusted Cost 1	Y_{CT1}=12.445x+113.28	R_{CT1}=0.9872	Van Erkel	1999
Adjusted Cost 2	Y_{CT2}=32.044x+267.99	R_{CT2}=0.9924	Paterson	2001
Adjusted Cost 3	Y_{CT3}=39.993x+239.61	R_{CT3}=0.9946	Doyle	2004
Adjusted Cost 4	Y_{CT4}=15.559x+72.024	R_{CT4}=0.9994	Duriseti	2006
Adjusted Cost 5	Y_{CT5}=135.29x+626.25	R_{CT5}=0.9994	Stein	2006

Note. CT = computed tomography pulmonary angiography; Y = adjusted cost; x = time.

Compression ultrasonography (CUS) adjusted costs increased linearly during the years 1998-2010 with trend line equation R^2 values of more than 98% (see Table 12). The range from the lowest-to-highest CUS adjusted cost range was $295 (see Figure 5).

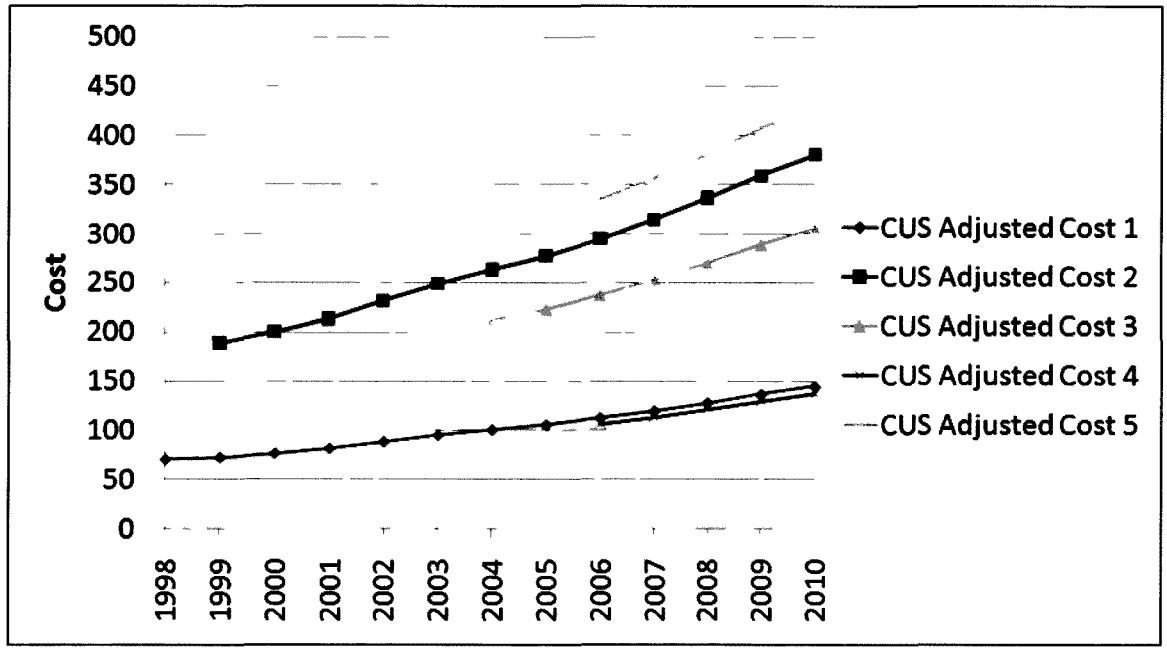


Figure 5. Comparisons of compression ultrasonography (CUS) direct cost for the years 1998-2010 adjusted for inflation.

Table 12

Trend Line Equations and R^2 Values of CUS Cost Adjusted for Inflation

	Adjusted Cost		Study of Unadjusted Cost	
CUS	Equation	R^2	First Author	Year
Adjusted Cost 1	Y_{CUS1}=6.3609x+26.095	R_{CUS1}=0.9872	Van Erkel	1999
Adjusted Cost 2	Y_{CUS2}=17.392x+58.497	R_{CUS2}=0.9924	Paterson	2001
Adjusted Cost 3	Y_{CUS3}=15.997x+15.857	R_{CUS3}=0.9946	Doyle	2004
Adjusted Cost 4	Y_{CUS4}=7.7796x-2.8862	R_{CUS4}=0.9994	Duriseti	2006
Adjusted Cost 5	Y_{CUS5}=24.506+113.44	R_{CUS5}=0.9994	Stein	2006

Note. CUS = compression ultrasonography; Y = adjusted cost; x = time.

Ventilation-perfusion lung scan (VQ) adjusted costs increased linearly during the years 1998-2010 with trend line equation R^2 values of more than 98% (see Table 13). The range from the lowest-to-highest VQ adjusted cost range was $824 (see Figure 6).

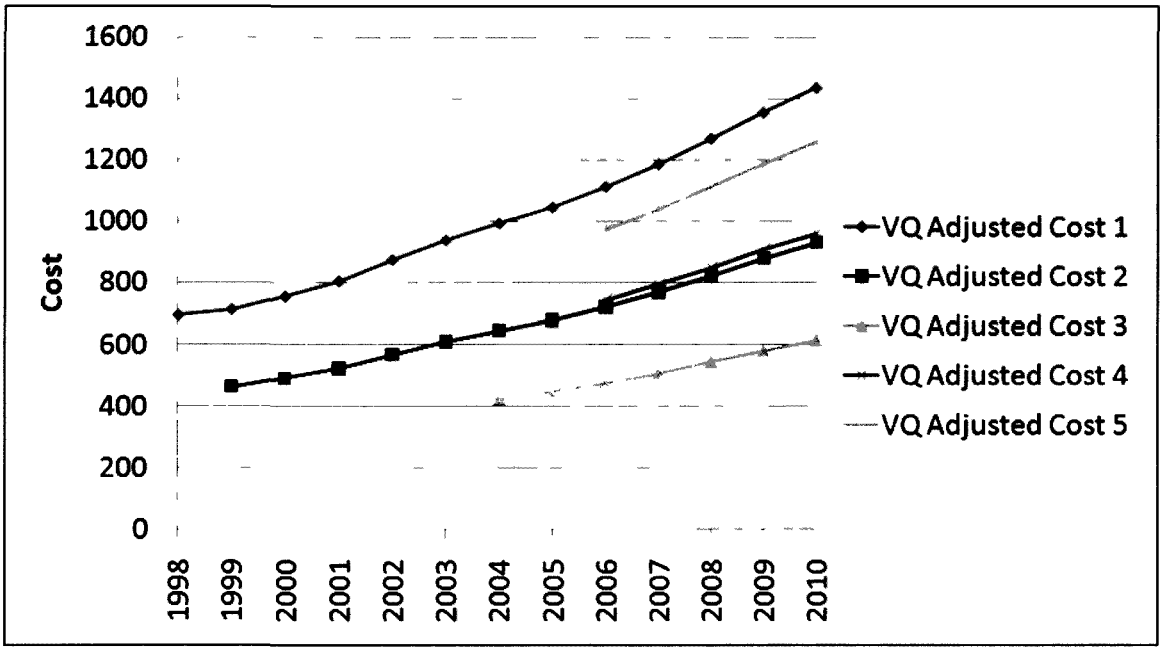


Figure 6. Comparisons of ventilation-perfusion lung scan (VQ) direct cost for the years 1998-2010 adjusted for inflation.

Table 13

Trend Line Equations and R^2 Values of VQ Cost Adjusted for Inflation

	Adjusted Cost		Study of Unadjusted Cost	
VQ	Equation	R^2	First Author	Year
Adjusted Cost 1	$Y_{VQ1}=62.963x+258.3$	$R_{VQ1}=0.9872$	Van Erkel	1999
Adjusted Cost 2	$Y_{VQ2}=42.536x+143.06$	$R_{VQ2}=0.9924$	Paterson	2001
Adjusted Cost 3	$Y_{VQ3}=31.994x+31.714$	$R_{VQ3}=0.9946$	Doyle	2004
Adjusted Cost 4	$Y_{VQ4}=54.458x-20.204$	$R_{VQ4}=0.9994$	Duriseti	2006
Adjusted Cost 5	$Y_{VQ5}=71.339x-26.467$	$R_{VQ5}=0.9994$	Stein	2006

Note. VQ = ventilation-perfusion lung scan; y = adjusted cost; x = time.

Invasive pulmonary angiography (PA) adjusted costs increased linearly during the years 1998-2010 with trend line equation R^2 values of more than 98% (see Table 14). The range from the lowest-to-highest PA adjusted cost range was $7,319 (see Figure 7).

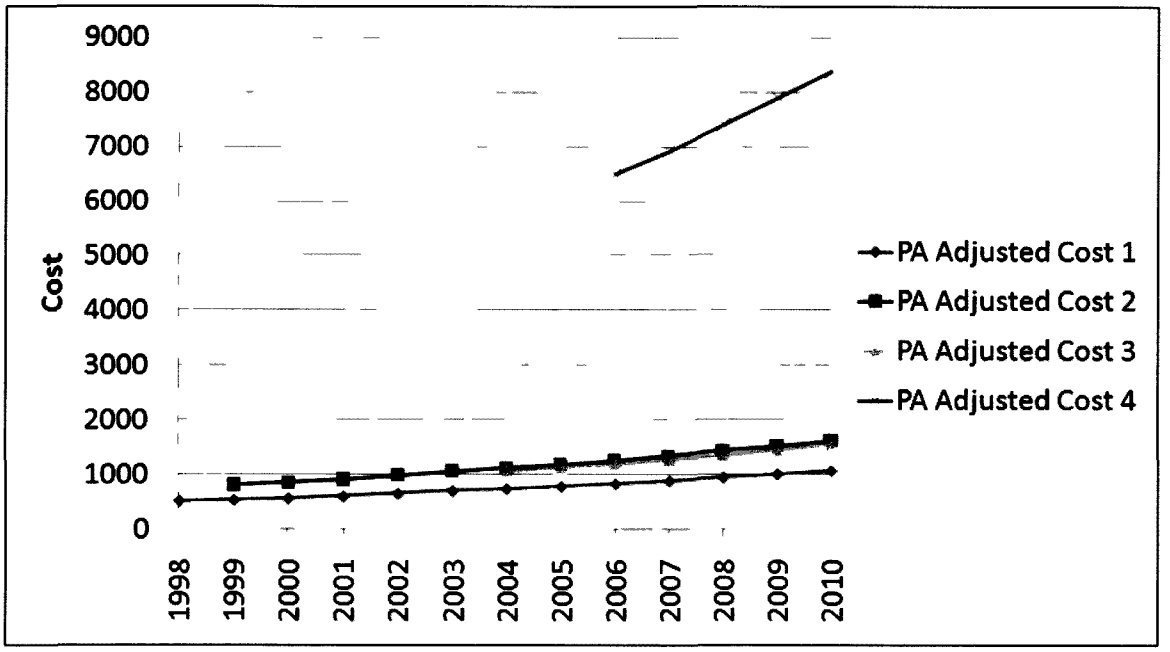


Figure 7. Comparisons of invasive pulmonary angiography (PA) direct cost for the years 1998-2010 adjusted for inflation.

Table 14

Trend Line Equations and R^2 Values of PA Cost Adjusted for Inflation

	Adjusted Cost		Study of Unadjusted cost	
PA	Equation	R^2	First Author	Year
Adjusted Cost 1	Y_{PA1}=47.015x+192.87	R_{PA1}=0.9872	Van Erkel	1999
Adjusted Cost 2	Y_{PA2}=74.012x+248.93	R_{PA2}=0.9924	Paterson	2001
Adjusted Cost 3	Y_{PA3}=79.985x+79.286	R_{PA3}=0.9946	Doyle	2004
Adjusted Cost 4	Y_{PA4}=475.03x-176.23	R_{PA4}=0.9994	Stein	2006

Note. PA = invasive pulmonary angiography test; Y = adjusted cost; x = time.

PE treatment adjusted costs increased linearly during the years 1998-2010 with trend line equation R^2 values of more than 99% (see Table 15). The range from the lowest-to-highest treatment adjusted cost range was $191 (see Figure 8).

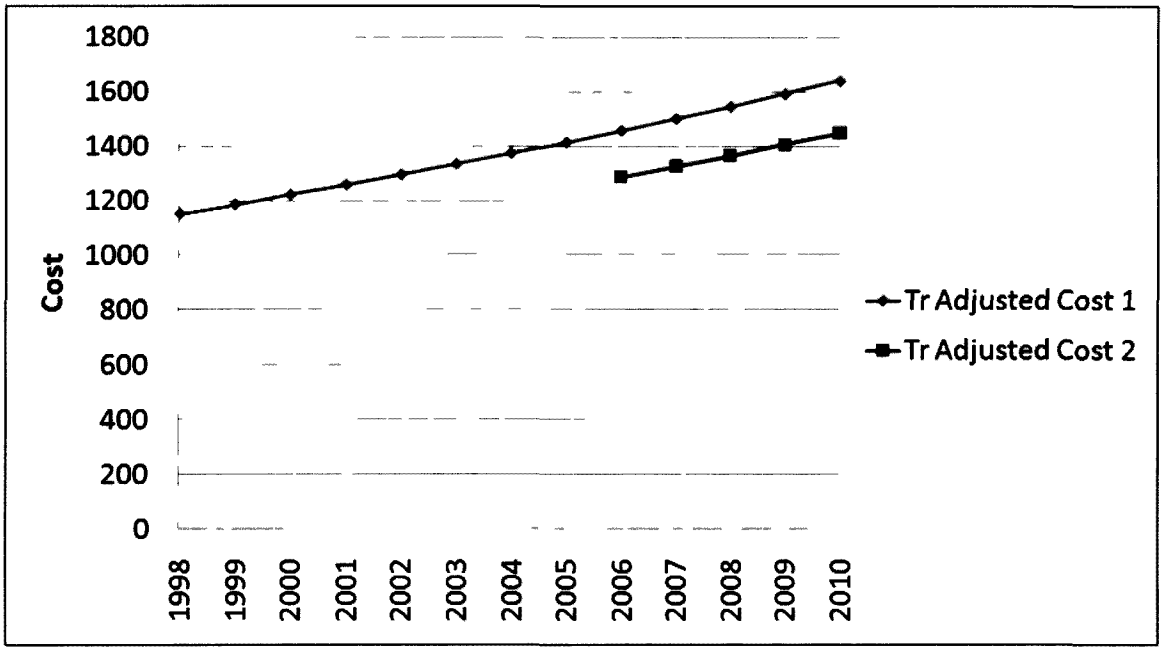


Figure 8. Comparisons of PE treatment (Tr) direct cost for the years 1998-2010 adjusted for inflation.

Table 15

Trend Line Equations and R^2 Values of Treatment Cost Adjusted for Inflation

	Adjusted Cost		Study of Unadjusted cost	
Treatment (Tr)	Equation	R^2	First Author	Year
Adjusted Cost 1	$Y_{Tr1} = 40.755+1096.9$	$R_{PA1}=0.9976$	Van Erkel	1999
Adjusted Cost 2	$Y_{Tr2} = 0.395+922.76$	$R_{PA2}=0.9997$	Durisetı	2006

Note. Y = adjusted cost; x = time.

In general, considerable differences among PE diagnostic testing costs were identified in the literature. Therefore, to resolve the uncertainty surrounding the costs of these tests, triangular distributions were applied based upon the adjusted cost estimations presented. D-dimer test direct costs ranged from $25 to $33 with an expected value of $28.3 (see Figure 9). The cumulative probability within the first 10th percentile indicated DD costs at approximately $26.3 or less. At the 50th percentile, the median DD cost was approximately $28.1, while at or above the 90th percentile DD costs were approximately $30.8 or greater (see Figure 10).

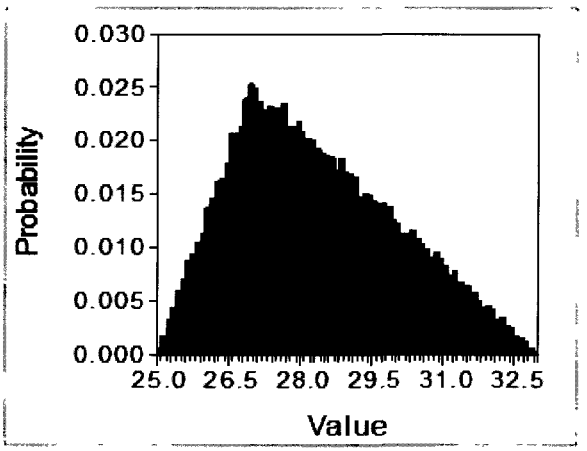


Figure 9. D-dimer test (DD) direct cost triangular distribution.

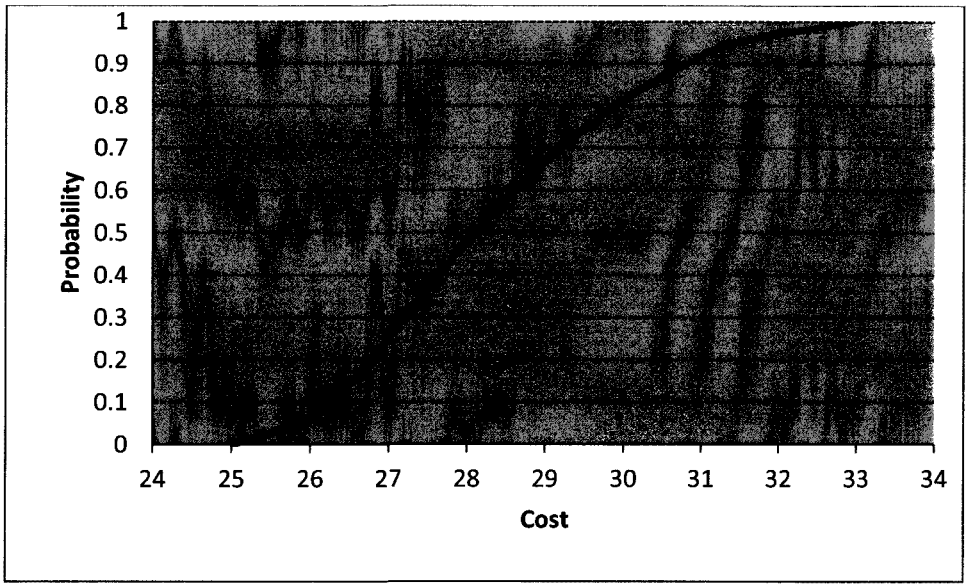


Figure 10. D-dimer test (DD) direct cost cumulative probability.

The computed tomography pulmonary angiography (CT) direct costs ranged from $275 to $2,387, with an expected value of $1,121 (see Figure 11). The cumulative probability within the 10th percentile revealed that CT direct costs were approximately $572.5 or less. At the 50th percentile, the median CT cost was about $1,051.6, while at and above the 90th percentile CT costs were $1,792.2 or greater (see Figure 12).

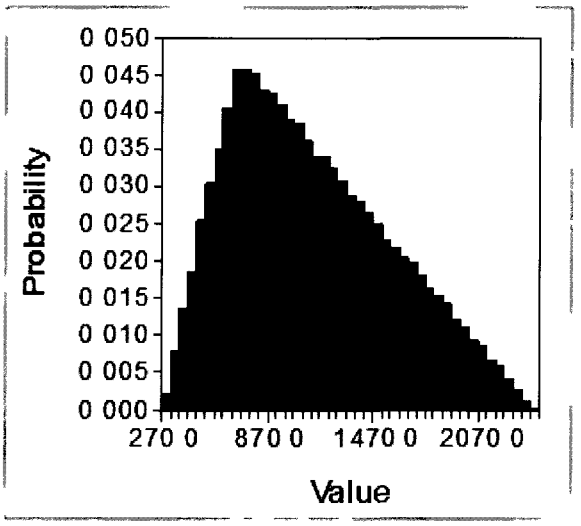


Figure 11. Computed tomography pulmonary angiography (CT) direct cost triangular distribution.

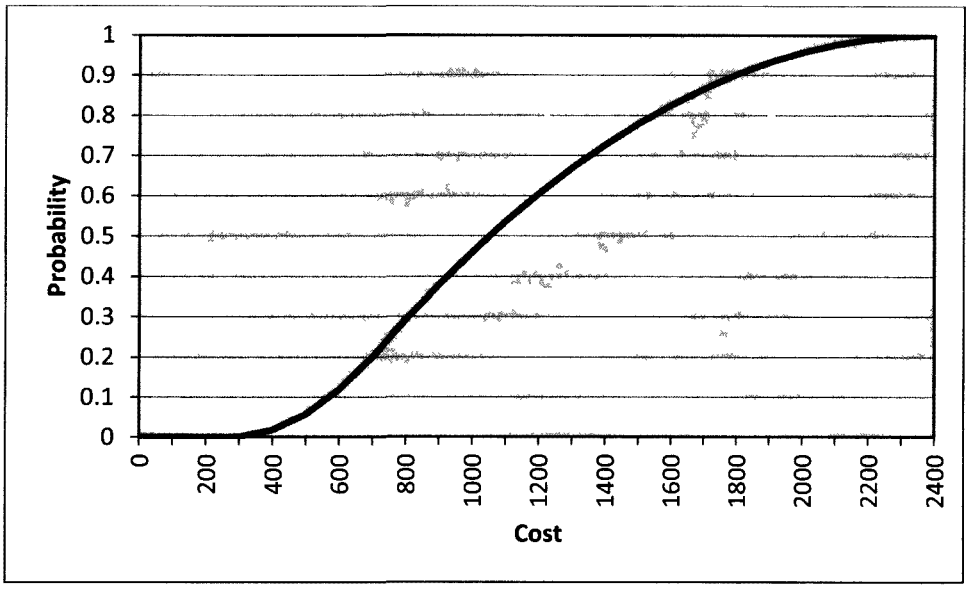


Figure 12. Computed tomography pulmonary angiography (CT) direct cost cumulative probability.

The compression ultrasonography (CUS) direct cost values ranged from $137 to $432 with an expected value of $292 (see Figure 13). The cumulative probability within the 10th percentile indicated that CUS direct costs were approximately $207.8 or less. At the 50th percentile, the median CUS cost was $294.8 while at and above the 90th percentile the CUS cost values were approximately $371.1 or greater (see Figure 14).

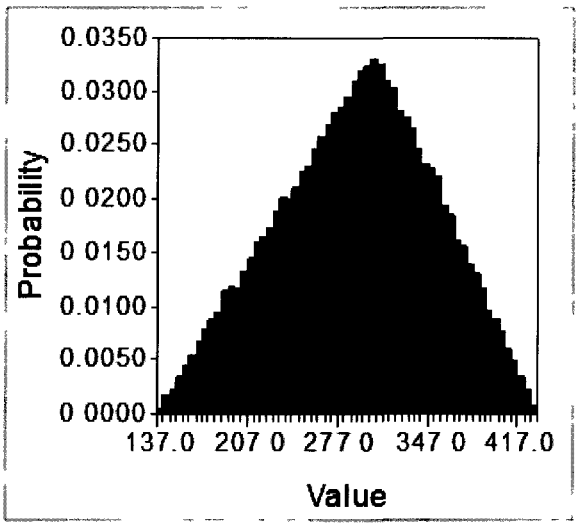


Figure 13. Compression ultrasonography (CUS) direct cost triangular distribution.

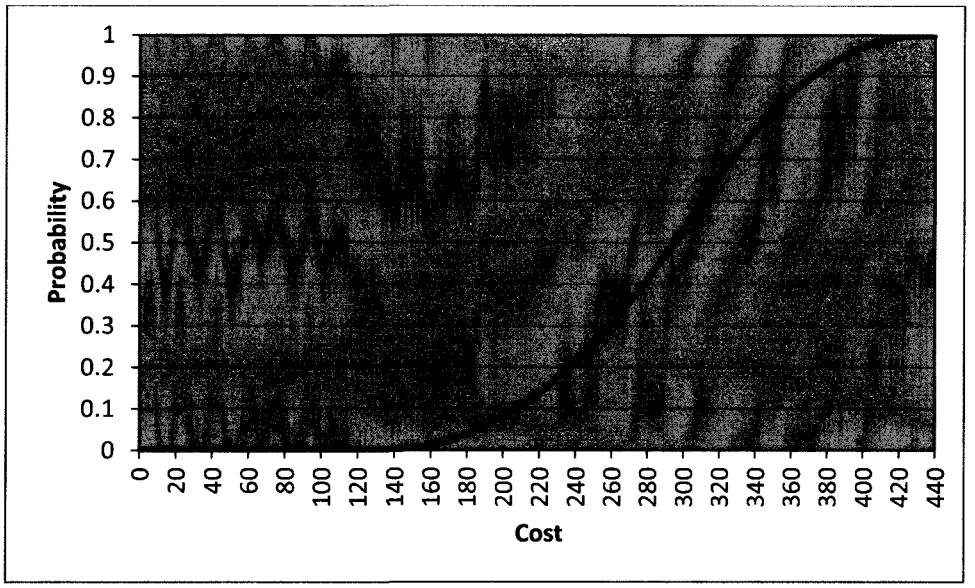


Figure 14. Compression ultrasonography (CUS) direct cost cumulative probability.

The ventilation-perfusion lung scan (VQ) direct costs ranged from $612 to $1,436 with an expected value of $1,003 (see Figure 15). The cumulative probability within the 10th percentile revealed that VQ costs were approximately $782.4 or less. At the 50th percentile, the median VQ cost was about $994.7, while at or above the 90th percentile the VQ costs were approximately $1,237.6 or greater (see Figure 16).

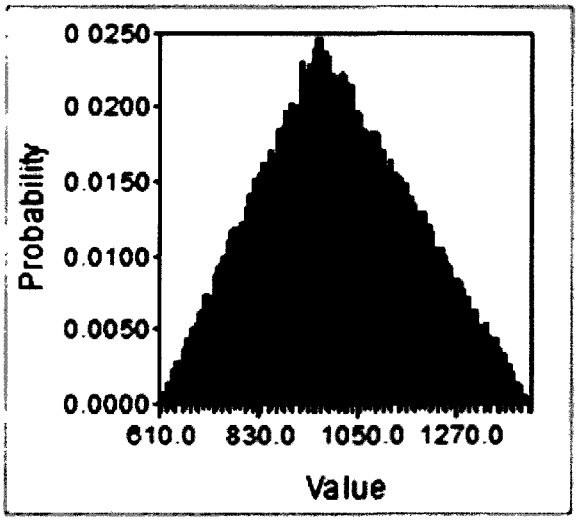


Figure 15. Ventilation-perfusion lung scan (VQ) direct cost triangular distribution.

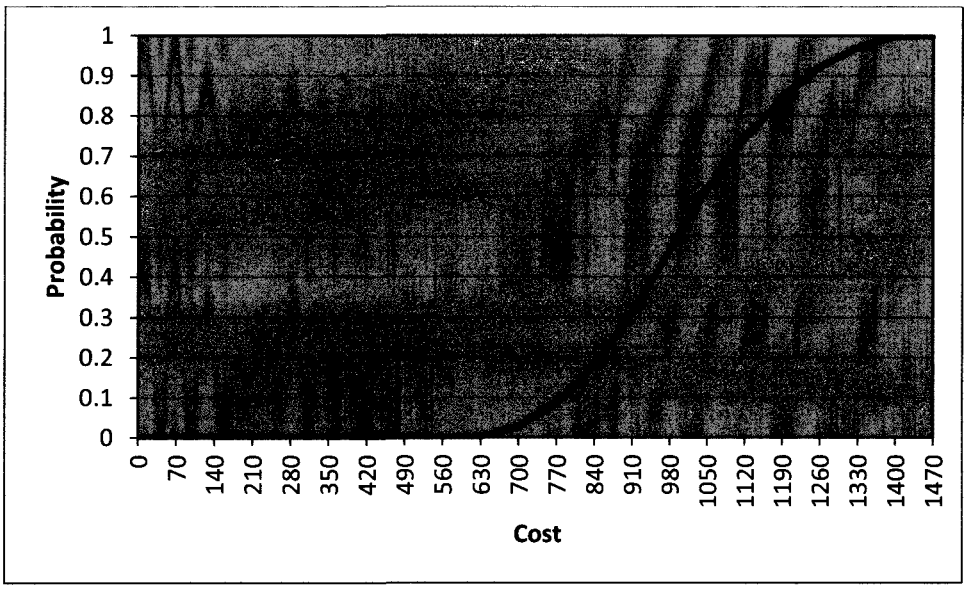


Figure 16. Ventilation-perfusion lung scan (VQ) direct cost cumulative probability.

The invasive pulmonary angiography (PA) direct costs ranged from $1,072 to $8,381 with an expected value of $3,676 (see Figure 17). The cumulative probability at the first 10th percentile revealed that the costs were approximately $1,689.02 or less. At the 50th percentile, the median PA cost was about $3,383.0, while at and above the 90th percentile the PA cost values were $6,158.3 or greater (see Figure 18).

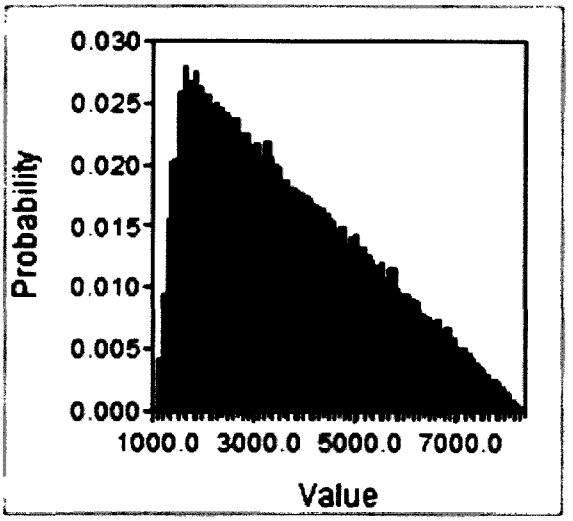


Figure 17. Invasive pulmonary angiography (PA) direct cost triangular distribution.

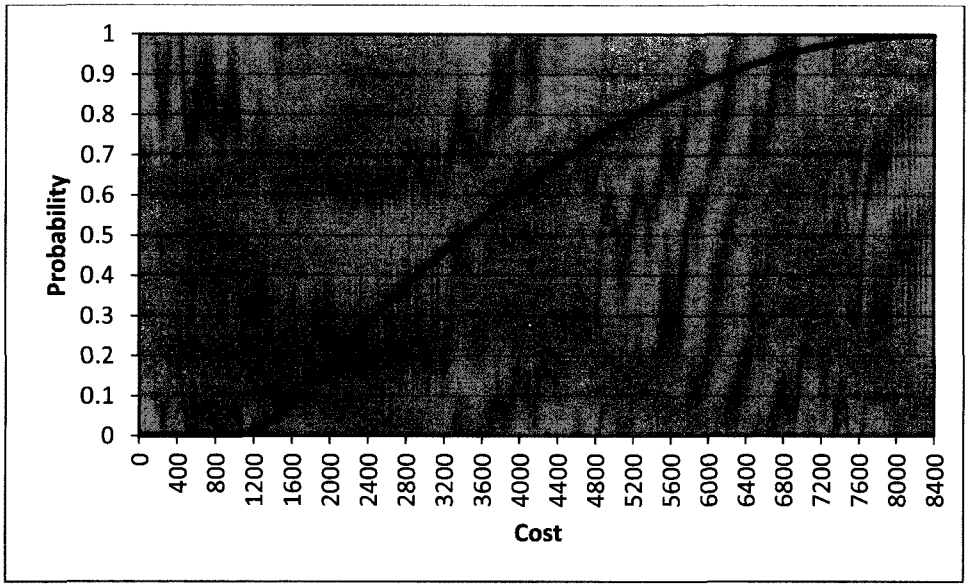


Figure 18. Invasive pulmonary angiography (PA) direct cost cumulative probability.

The direct costs of PE treatment ranged from $1,449 to $1,640 with an expected value of $1,545 (see Figure 19). The cumulative probability at the first 10th percentile indicated that PE treatment cost was $1,491.8 or less. At the 50th percentile, the median cost of treatment was $1,544.7, while at or above the 90th percentile treatment cost values were roughly $1,597.4 or greater (see Figure 20).

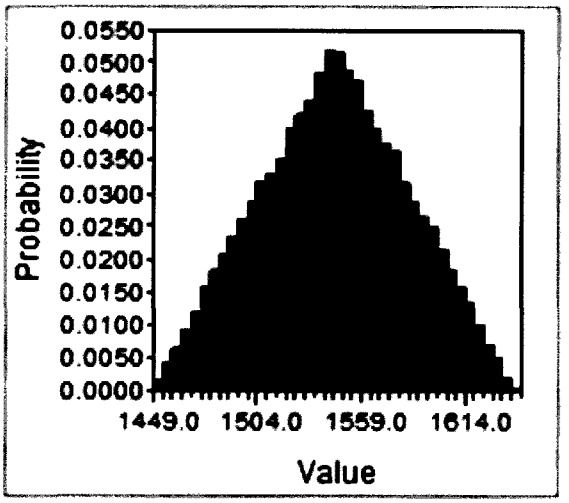


Figure 19. PE treatment (Tr) direct cost triangular distribution.

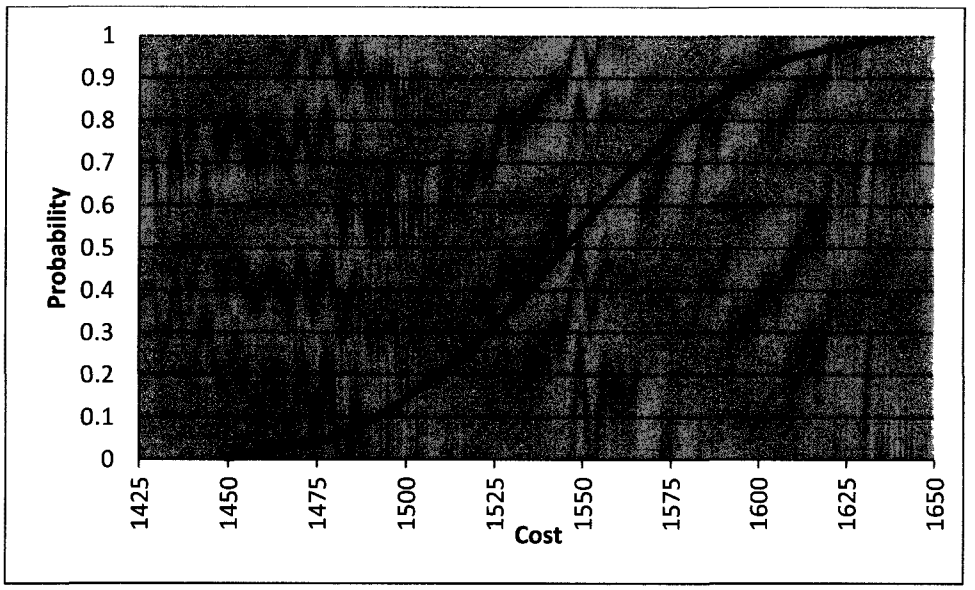


Figure 20. PE treatment (Tr) direct cost cumulative probability.

Table 16 presents a summary of the results of the triangular distribution expected values and statistics of PE diagnostic testing direct costs adjusted for inflation.

Table 16

Expected Values and Statistics of Triangular Distribution of PE Diagnostic Direct Costs

PE Diagnostic Test	Expected Value	Percentiles	
		2.5^{th}	97.5^{th}
DD	28.3	25.6	31.9
CT	1121.3	422.5	2092.0
CUS	291.7	172.5	401.7
VQ	1003.0	698.2	1337.6
PA	3676.3	1376.4	7270.2
Tr	1544.7	1470.6	1639.3

Note. PE = pulmonary embolism; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS = compression ultrasonography; VQ = ventilation-perfusion lung scan; PA = invasive pulmonary angiography; Tr = treatment. Costs are in dollars.

Effectiveness of pulmonary embolism diagnostic strategies.

A literature review of the research regarding the effectiveness of the strategies employed to diagnose PE was conducted. Of the studies identified, 233 had potential relevance for strategy 1, 99 had potential relevance for strategy 2, 97 for strategy 3, 47 for strategy 4, and 7 articles had potential relevance for strategy 5. The predetermined inclusion criteria were met by six studies addressing strategy 1, two studies discussing strategy 2, three studies concerning strategy 3, four studies examining strategy 4, and two studies reviewing strategy 5. A summary of the numbers of articles included in the process to obtain PE diagnostic strategy effectiveness values is presented in Table 17.

Table 17

Summary of Articles Evaluated for Inclusion in the Review of PE Diagnostic Strategy Effectiveness

Categories of Evaluation	Strategy 1		Strategy 2		Strategy 3		Strategy 4		Strategy 5	
Potentially Relevant Articles Identified	233		99		97		47		7	
Articles not Related to PE Test for PE Diagnosis	202		78		74		29		2	
Articles Related to PE Test for PE Diagnosis	31		21		23		18		5	
	In	Ex	In	Ex	In	Ex	In	Ex	In	Ex
	6	25	2	19	3	20	4	14	2	3

Note. PE = pulmonary embolism; Strategy 1 = a CDR, a D-dimer test, and a CT; Strategy 2 = a CDR, a D-dimer test, a CT, and a CUS; Strategy 3 = a CDR, a D-dimer test, a CUS, and a CT; Strategy 4 = a CDR, a D-dimer test, a VQ, and a CUS; Strategy 5 = a CDR, a D-dimer test, a CT, a CUS, and a PA. CDR = clinical decision rule; CT = computed tomography pulmonary angiography; CUS= compression ultrasonography; VQ = ventilation-perfusion lung scan; PA = invasive pulmonary angiograph. In = included articles related to PE test for PE diagnosis that met inclusion criteria; Ex = excluded articles related to PE test for PE diagnosis that did not meet inclusion criteria.

Studies used in the analysis of PE diagnostic strategy effectiveness, including the total number of participants as well as effectiveness levels expressed as failure rates, are presented in Table 18. Differences in the PE diagnostic strategy failure rates were identified in the literature. To resolve the uncertainty surrounding those failure rates, γ distributions were applied based upon failure rate estimations (see Table 18). The γ distribution expected values of the strategy failure rates to detect PE demonstrated very small differences expressed within a .553329 range between a high of 1.099999 and a low of 0.546667. Specifically, strategy 3 achieved the lowest expected failure rate of

0.546667. A summary of the γ distribution strategy failure rates statistics for the studies included in this analysis is presented in Table 19.

Table 18

Studies Included in the Analysis to Obtain PE Diagnostic Strategy Failure Rates

Study First Author and Year	Strategy	Patients Total *n*	Strategy Failure rates (%)		
			Level 1 Rate < 0.50	Level 2 0.50 ≤ Rate ≤ 1.00	Level 3 1.00 <Rat e
Ghanima, 2005	1	432		SFR 2	
Hogg, 2006	1	408		SFR 2	
van Belle, 2006	1	3306		SFR 2	
Nijkeuter, 2007	1	3306		SFR 2	
Righini, 2008	1	838	SFR 1		
Eng, 2009	1	219	SFR 1		
Anderson, 2005	2 & 5	858	SFR 1		
Perrier, 2005	2 & 5	756			SFR 3
Elias, 2005	3	274		SFR 2	
Perrier 2004	3	965		SFR 2	
Righini, 2008	3	855	SFR 1		
Wells, 2001	4	930		SFR 2	
ten Wolde, 2004	4	631			SFR 3
Kearon, 2006	4	1126			SFR 3
Anderson, 2007	4	712		SFR 2	
Anderson, 2005	5 & 2	858	SFR 1		
Perrier, 2005	5 & 2	756		SFR 2	

Note. PE = pulmonary embolism; SFR 1 = strategy failure rate level 1 < 0.50%; SFR 2 = 0.50 % ≤ strategy failure rate level 2 ≤ 1.00%; SFR 3 = 1.00% < strategy failure rate level 3.

Table 19

Expected γ Distribution Values and Statistics of PE Diagnostic Strategies Failure Rates (in Percentage)

Statistic	Strategy 1	Strategy 2	Strategy 3	Strategy 4	Strategy 5
Expected	0.576667	1.099999	0.546667	1.004999	0.725000
Mean	0.576674	1.100821	0.547071	1.005474	0.724849
Standard Deviation	0.142124	0.612938	0.122665	0.152025	0.235165
Median	0.564553	0.989058	0.538462	0.997995	0.699498
Minimum	0.159337	0.020879	0.178322	0.524694	0.062979
Maximum	1.393475	6.052246	1.222180	1.782201	2.113984
Percentiles					
2.5^{th}	0.333015	0.247525	0.332183	0.728888	0.338600
10^{th}	0.404102	0.425513	0.396809	0.815425	0.444665
90^{th}	0.765901	1.921855	0.709004	1.204917	1.038356
97.5^{th}	0.887872	2.596096	0.811244	1.324990	1.255302

Note. PE = pulmonary embolism; Strategy 1 = a CDR, a D-dimer test, and a CT; Strategy 2 = a CDR, a D-dimer test, a CT, and a CUS; Strategy 3 = a CDR, a D-dimer test, a CUS, and a CT; Strategy 4 = a CDR, a D-dimer test, a VQ, and a CUS; Strategy 5 = a CDR, a D-dimer test, a CT, a CUS, and a PA. CDR = clinical decision rule; CT = computed tomography pulmonary angiography; CUS= compression ultrasonography; VQ = ventilation-perfusion lung scan; PA = invasive pulmonary angiography.

Sensitivity and specificity of pulmonary embolism diagnostic tests.

A literature review of articles investigating sensitivity and specificity values of tests to diagnose PE was conducted. Of the 354 articles examining the D-dimer test, 55 addressed sensitivity and specificity values. Of the 517 articles addressing the CT, 28 reviewed sensitivity and specificity. The VQ lung scan diagnostic test was examined in 203 articles: 14 addressed specificity and sensitivity. Six of the 270 CUS studies addressed sensitivity and specificity, and four of the 119 articles presenting PA as a PE

diagnostic tool examined these values. A summary of the articles considered for inclusion in the review process for obtaining sensitivity and specificity values is presented in Table 20. A list of studies analyzed to obtain PE diagnostic test sensitivity and specificity values is presented in Table 21.

Table 20

Summary of Articles Evaluated for Inclusion in the Review of PE Test Sensitivity and Specificity

Categories of Evaluation	DD		CT		VQ		CUS		PA	
Potentially Relevant Articles Identified	354		517		203		270		119	
Articles not Related to PE Test for PE Diagnosis	193		403		133		226		108	
Articles Related to PE Test for PE Diagnosis	161		114		70		44		11	
	In	Ex	In	Ex	In	Ex	In	Ex	In	Ex
	55	106	28	86	14	56	6	38	4	7

Note. PE = pulmonary embolism; DD = D-dimer test; CT = computed tomography pulmonary angiography; VQ = ventilation-perfusion lung scan; CUS= compression ultrasonography; PA = invasive pulmonary angiography. In = included articles related to PE test for PE diagnosis that met inclusion criteria; Ex = excluded articles related to PE test for PE diagnosis that did not meet inclusion criteria.

Table 21

Studies Included in the Analysis to Obtain PE Diagnostic Test Sensitivity and Specificity

Study First Author	Year	Type	Study First Author	Year	Type	Study First Author	Year	Type
D-dimer Test (DD)								
Lucassen	2010	M	Ghanima	2006	M	Chunilal	2002	M
Corwin	2009	R	Grant	2006	R	De Monye	2002	M
Djurabi	2009	R	Kline	2006	M	Dunn	2002	M
Eng	2009	R	Righini	2006	M	Gosselin	2002	M
Gupta	2009	M	Von Lode	2006	R	Reber	2002	M
Kabrhel	2009	M	Bosson	2005	M	Bucek	2001	M
Legnani	2009	M	Di Nisio	2005	M	Castro	2001	R
Than	2009	M	Hogg	2005	R	Kline	2001	M
Toulon	2009	M	Sohne	2005	M	Kovacs	2001	M
De Moerloose	2008	R	Steeghs	2005	M	Reber	2001	M
Ghys	2008	M	Curtin	2004	M	Rodger	2001	R
Gibson	2008	M	Kulstad	2004	R	Gosselin	2000	M
Mitchell	2008	M	Reber	2004	M	Kollef	2000	R
Runyon	2008	M	Righini	2004	M	LaCapra	2000	R
Di Nisio	2007	M	Stein	2004	R	Sijens	2000	M
Froehling	2007	M	Aujesky	2003	M			
Ghanima	2007	M	Brotman	2003	R			
Parent	2007	M	Brown	2003	M			
Aujesky	2006	R	Hainaut	2003	M			
Duriseti	2006	M	Brown	2002	M			

Table 21 (continued)

Study First Author	Year	Type	Study First Author	Year	Type	Study First Author	Year	Type
Computed Tomography Pulmonary Angiography (CT)								
Gutte	2009	M	Russo	2005	R	Nilsson	2002	M
Reichelt	2009	M	Van Strijen	2005	M	Safriel	2002	Meta
Wang	2009	M	White	2005	M	Adams	2001	M
Brader	2008	M	Eng	2004	M	Coche	2001	M
MacKenzie	2007	M	Reinartz	2004	R	Perrier	2001	M
Stein	2007	R	Righini	2004	M	Velmahos	2001	M
Stein	2007	R	Winer	2004	M	Harvey	2000	R
Heuschmid	2006	M	Coche	2003	M	Rathbum	2000	R
Hayashino	2005	R	Ruiz	2003	M			
Katsouda	2005	M	Herold	2002	R			
Compression Ultrasonography (CUS)								
Shiver	2010	M	Segal	2007	M	Rozycki	2004	M
Aywak	2007	M	Elias	2004		Theodorou	2003	M
Ventilation-Perfusion Lung Scan (VQ)								
Gutte	2010	M	Thieme	2008	M	Bajc	2002	M
Gutte	2009	N	Katsouda	2005	M	Cueto	2001	M
Stein	2009	R	Marini	2005	M	Reinartz	2001	M
Sostman	2008	M	Reinartz	2004	M	Blachere	2000	M
Sostman	2008	M	Coche	2003	M			
Invasive Pulmonary Angiography (PA)								
Perrier	2003	CEA	Van Erkel	1999	E			
Larcos	2000	CEA	Stein	1992	M			

Note. PE = pulmonary embolism; M = diagnostic management; R = review; Meta = meta-analysis; CEA = cost-effectiveness analysis; E = economical study.

The sensitivity and specificity values identified in the literature for the various PE diagnostic tests reveal significant differences. To resolve the uncertainty surrounding the values, γ distributions were applied based upon data retrieved from the cited studies. The γ distribution expected values for the PE diagnostic tests illustrated a very high sensitivity and a very low specificity level for the D-dimer test; a moderate sensitivity and a high specificity level for the CT, the CUS, and the VQ lung scan; and very high sensitivity and specificity levels for the PA. The PA demonstrated the highest sensitivity and specificity values of all the diagnostic tests. Table 22 presents a summary of the results of the γ distribution sensitivity and specificity expected values from the PE diagnostic test studies included in this analysis.

Table 22

Expected γ Distribution Sensitivity and Specificity Values of PE Diagnostic Tests (in Percentage)

PE Diagnostic Test	Expected Sensitivity	Expected Specificity
DD	95.17436	47.77547
CT	88.11154	94.56923
CUS	89.95000	94.90000
VQ	82.77500	90.49999
PA	97.24999	97.00000

Note. PE = pulmonary embolism; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS= compression ultrasonography; VQ = ventilation-perfusion lung scan; PA = invasive pulmonary angiography. Five sensitivity and specificity levels were established: very low with a value less than 60%, low with a value between 60 and 79.99%, moderate with a value between 80 and 89.99%, high with a value between 90 and 95.99%, and very high with a value between 96 and 100%.

The γ distribution mean sensitivity values of the PE diagnostic tests illustrated the lowest sensitivity level for the VQ lung scan followed by the CT, the CUS, and the DD, while the PA demonstrated the highest sensitivity level. Table 23 presents a summary of the results of the sensitivity γ distribution statistics for studies included in this analysis.

Table 23

Sensitivity γ Distribution Statistics of PE Diagnostic Tests (in Percentage)

Statistic	DD	CT	CUS	VQ	PA
Mean	95.17372	88.10945	89.95211	82.77985	97.24905
Standard Deviation	0.605346	1.702001	1.082319	3.060102	0.477765
Minimum	92.54764	81.01011	85.37590	71.27853	95.14016
Maximum	98.42711	96.44676	94.46894	97.73141	99.27941
Quartiles					
1st	94.76501	86.95498	89.21584	80.69633	96.92572
2nd	95.17191	88.09015	89.95053	82.73046	97.24823
3rd	95.58067	89.25084	90.68287	84.82823	97.57306
Percentiles					
2.5th	94.00338	84.81504	87.84398	76.89480	96.31592
10th	94.40088	85.93493	88.56492	78.89455	96.63695
90th	95.95058	90.31270	91.34198	86.72416	97.86229
97.5th	96.36435	91.46800	92.07793	88.85643	98.18110

Note. PE = pulmonary embolism; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS = compression ultrasonography; VQ = ventilation-perfusion lung scan; PA = invasive pulmonary angiography.

The γ distribution mean specificity values of the PE diagnostic tests illustrated the lowest specificity level for the DD followed by the VQ lung scan, the CT, and the CUS. The PA test demonstrated the highest specificity level. Table 24 presents a summary of the results of the specificity γ distribution statistics of the studies included in this analysis.

Table 24

Specificity γ Distribution Statistics of PE Diagnostic Tests (in Percentage)

Statistic	DD	CT	CUS	VQ	PA
Mean	47.77661	94.56998	94.90292	90.49730	96.99722
Standard Deviation	1.96198	0.863097	2.497489	2.465599	0.409109
Minimum	40.04181	91.03230	83.93758	79.77953	95.28446
Maximum	55.92826	99.04141	108.8677	100.9065	98.94585
Quartiles					
1st	46.43802	93.98669	93.21365	88.82344	96.72200
2nd	47.75553	94.56723	94.88306	90.48401	96.99653
3rd	49.08395	95.14589	96.56493	92.1506	97.27361
Percentiles					
2.5th	44.00549	92.87477	90.05558	85.71871	96.19148
10th	45.28254	93.46866	91.70814	87.35149	96.47117
90th	50.31514	95.68185	98.13173	93.66573	97.51936
97.5th	51.69914	96.26664	99.8654	95.40051	97.80146

Note. PE = pulmonary embolism; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS = compression ultrasonography; VQ = ventilation-perfusion lung scan; PA = invasive pulmonary angiography.

Evaluation of Alternative Decisions (Da_n)

The cost-effectiveness analysis (CEA) revealed that alternative decision 3 (Da_3) was accepted, while all other alternatives were rejected. Alternative decision 3 stated that at least strategy 3, composed by a CDR, a DD, a CUS, and a CT, would be more cost-effective than strategy 1, strategy 2, strategy 4, or strategy 5. The results of this evaluation are summarized in Table 25.

Table 25

Summary of Alternative Decisions Evaluation

Alternative Decision	Strategies Compared	Type of Analysis	Results
Da_1	Strategy 1 vs. all other strategies	CEA	Rejected
Da_2	Strategy 2 vs. all other strategies	CEA	Rejected
Da_3	Strategy 3 vs. all other strategies	CEA	**Accepted**
Da_4	Strategy 4 vs. all other strategies	CEA	Rejected
Da_5	Strategy 5 vs. all other strategies	CEA	Rejected

Note. Strategy 1 = a CDR, a DD and a CT; Strategy 2 = a CDR, a DD, a CT, and a CUS; Strategy 3 = a CDR, a DD, a CUS, and a CT; Strategy 4 = a CDR, a DD, a VQ, and a CUS; Strategy 5 = a CDR, a DD, a CT, a CUS, and a PA. CDR = clinical decision rule; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS = compression ultrasonography; VQ = ventilation–perfusion lung scan; PA = invasive pulmonary angiography; CEA = cost-effectiveness analysis; Da_n = alternative decision.

Detailed evaluation.

The CEA model was applied to a decision tree, and all five strategies were analyzed (see Figure 21).

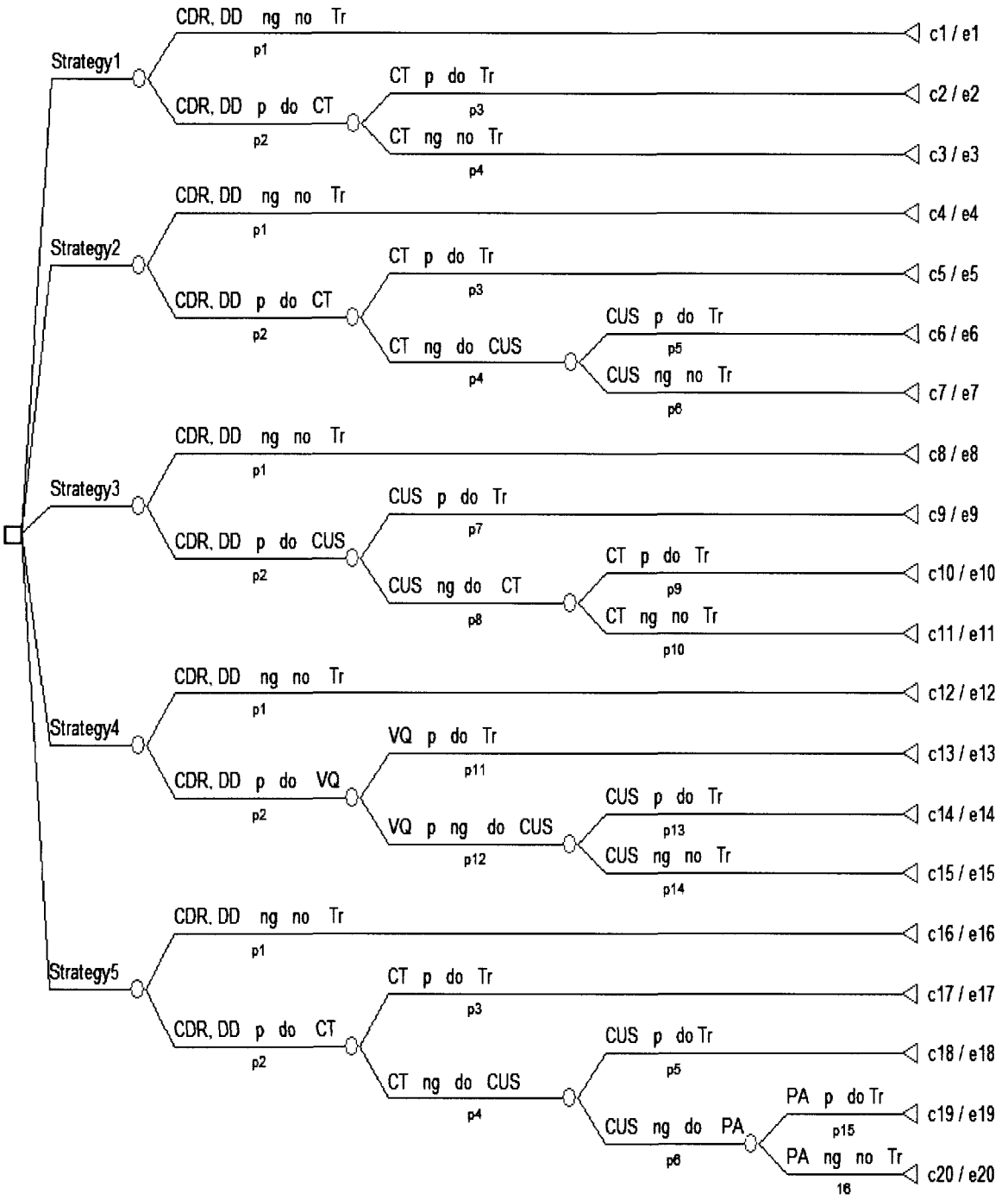


Figure 21. Decision tree CEA model of five PE diagnostic strategies. CEA = cost-effectiveness analysis; PE = pulmonary embolism; Strategy 1 = a CDR, a DD, and a CT; Strategy 2 = a CDR, a DD, a CT, and a CUS; Strategy 3 = a CDR, a DD, a CUS, and a CT; Strategy 4 = a CDR, a DD, a VQ, and a CUS; Strategy 5 = a CDR, a DD, a CT, a CUS, and a PA. CDR = clinical decision rule; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS = compression ultrasonography; VQ = ventilation–perfusion lung scan; PA = invasive pulmonary angiography; Tr = treatment; ng = negative; p = positive; pn = probability; c = cost payoffs; e = effectiveness payoffs.

Strategy 1, comprising a CDR, a DD, and a CT, appeared in the first arm of the decision tree. The costs associated with strategy 1 were defined by appropriate triangular distributions (i.e., c1, c2, and c3). The effectiveness associated with strategy 1 was defined by appropriate γ distributions (i.e., e1, e2, and e3). The event probabilities for strategy 1 were defined by appropriate Bayes's applications (i.e., p1, p2, p3, and p4). Strategy 2, comprising a CDR, a DD, a CT, and a CUS, appeared in the second arm of the decision tree. The costs associated with strategy 2 were defined by appropriate triangular distributions (i.e., c4, c5, c6, and c7). The effectiveness associated with strategy 2 was defined by appropriate γ distributions (i.e., e4, e5, e6, and e7). The event probabilities for strategy 2 were defined by appropriate Bayes's applications (i.e., p1, p2, p3, p4, p5, and p6). Strategy 3, comprising a CDR, a DD, a CUS, and a CT, appeared in the third arm of the decision tree. The costs associated with strategy 3 were defined by appropriate triangular distributions (i.e., c8, c9, c10, and c11). The effectiveness associated with strategy 3 was defined by appropriate γ distributions (i.e., e8, e9, e10, and e11). The event probabilities for strategy 3 were defined by appropriate Bayes's applications (i.e., p1, p2, p7, p8, p9, and p10). Strategy 4, comprising a CDR, a DD, a VQ, and a CUS, appeared in the fourth arm of the decision tree. The costs associated with strategy 4 were defined by appropriate triangular distributions (i.e., c12, c13, c14, and c15). The effectiveness associated with strategy 4 was defined by appropriate γ distributions (i.e., e12, e13, e14, and e15). The event probabilities for strategy 4 were defined by appropriate Bayes's applications (i.e., p1, p2, p11, p12, p13, and p14). Strategy 5, comprising a CDR, a DD, a CT, a CUS, and a PA, appeared in the last arm of the decision tree. The costs associated with strategy 5 were defined by appropriate

triangular distributions (i.e., c16, c17, c18, c19, and c20). The effectiveness associated with strategy 5 was defined by appropriate γ distributions (i.e., e16, e17, e18, e19, and e20). The event probabilities for this strategy were defined by appropriate Bayes's applications (i.e., p1, p2, p3, p4, p5, p6, p15, and p16).

CEA results revealed that strategy 3 was the most cost-effective of the strategies. Strategy 5 was cost-effective; however, strategies 1, 2 and 4 were not cost-effective and were dominated by strategy 3. The lowest cost was demonstrated by strategy 3, followed by strategies 1, 4, 2, and 5, respectively. Conversely, the highest effectiveness was demonstrated by strategy 5, followed by strategies 3, 4, 2, and 1, in that order. The lowest cost-effectiveness ratio was demonstrated by strategy 3, followed in order by strategies 1, 4, 2, and 5. Table 26 summarizes cost-effectiveness analysis results.

Table 26

Summary of Cost-effectiveness Analysis (CEA) Results

Strategy	Cost $	Incremental Cost	Effectiveness ALS	Incremental Effectiveness	C/E $/ALS	Type of Strategy
Strategy 3	1922.396		99.91767		19.23980	Most C-E
Strategy 1	1952.982	30.5861	99.78456	-0.13310	19.57198	Dominated
Strategy 4	2281.085	358.6892	99.91518	-0.00248	22.83021	Dominated
Strategy 2	2441.230	518.8345	99.91172	-0.00594	24.43387	Dominated
Strategy 5	2483.821	561.4250	99.91999	0.00232	24.85810	C-E

Note. Strategy 1 = a CDR, a DD and a CT; Strategy 2 = a CDR, a DD, a CT, and a CUS; Strategy 3 = a CDR, a DD, a CUS, and a CT; Strategy 4 = a CDR, a DD, a VQ, and a CUS; Strategy 5 = a CDR, a DD, a CT, a CUS, and a PA. CDR = clinical decision rule; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS = compression ultrasonography; VQ = ventilation–perfusion lung scan; PA = invasive pulmonary angiography; C/E = cost-effectiveness ratio; C-E = cost-effective strategy; ALS = additional lives saved.

The CEA of the five PE diagnostic strategies revealed that strategies 3 and 5 formed a cost-effectiveness frontier. Strategies 1, 2, and 4 were to the left of this frontier line with higher costs and lower effectiveness levels, indicating domination by strategy 3. The CEA results are illustrated in Figure 22.

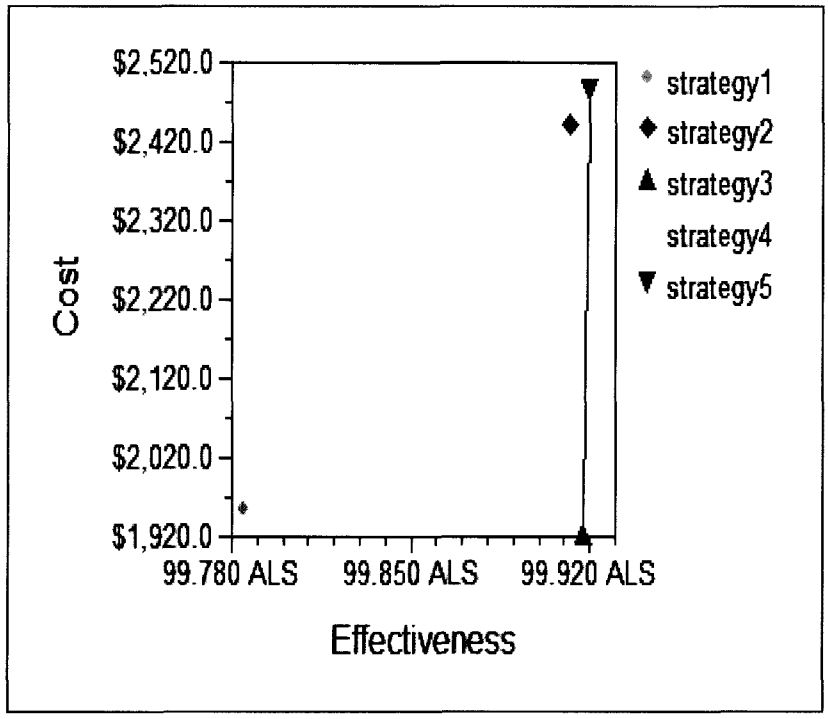


Figure 22. Cost-effectiveness analysis for five PE diagnostic strategies. Strategy 1 = a CDR, a DD and a CT; Strategy 2 = a CDR, a DD, a CT, and a CUS; Strategy 3 = a CDR, a DD, a CUS, and a CT; Strategy 4 = a CDR, a DD, a VQ, and a CUS; Strategy 5 = a CDR, a DD, a CT, a CUS, and a PA. CDR = clinical decision rule; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS = compression ultrasonography; VQ = ventilation–perfusion lung scan; PA = invasive pulmonary angiography; ALS = additional lives saved.

Individual cost and effectiveness pairs for each recalculation of the model are presented in the cost-effectiveness scatter plot with a different color representing each strategy (see Figure 23). Strategy 1 cost-effectiveness dots formed an area similar to a rectangle, indicating a wide range of both costs and effectiveness values. Strategy 2 dots

formed an area similar to a rectangle, indicating a wide range of costs and a narrow range of effectiveness values. Strategy 3 and 4 dots were concentrated in a small area similar to a circle, indicating a narrow range of both costs and effectiveness values. Strategy 5 dots formed an area similar to a rectangle, indicating a wide range of costs and a narrow range of effectiveness values.

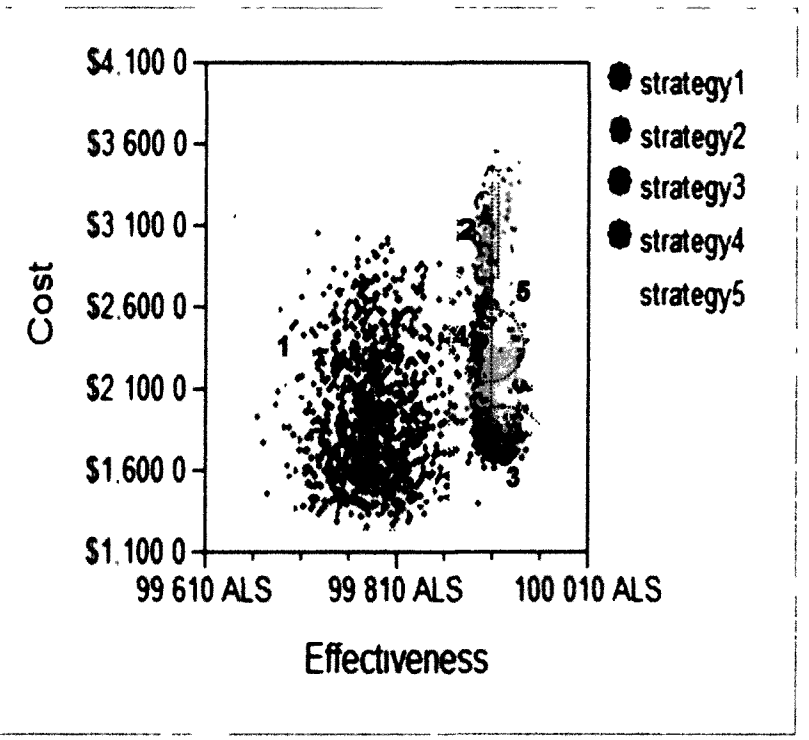


Figure 23. Cost and effectiveness scatter plot by strategy. 1 = strategy 1; 2 = strategy 2; 3 = strategy 3; 4 = strategy 4; 5 = strategy 5; Strategy 1 = a CDR, a DD and a CT; Strategy 2 = a CDR, a DD, a CT, and a CUS; Strategy 3 = a CDR, a DD, a CUS, and a CT; Strategy 4 = a CDR, a DD, a VQ, and a CUS; Strategy 5 = a CDR, a DD, a CT, a CUS, and a PA. CDR= clinical decision rule; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS = compression ultrasonography; VQ = ventilation–perfusion lung scan; PA = invasive pulmonary angiography; ALS = additional lives saved.

Results by alternative decision (Da_n).

Da_1: At least strategy 1 will be more cost-effective than strategy 2, strategy 3, strategy 4, or strategy 5.

This alternative decision is rejected. Strategy 1, comprising a CDR, a DD, and a CT, with a cost of about $1,952.98 and an effectiveness level of 99.78456 was dominated by strategy 3 (see Table 26). Results for the costs, effectiveness, and cost-effectiveness ratio of PE diagnostic strategy 1 are presented in Table 27.

Table 27

Statistics of PE Diagnostic Strategy 1 Cost and Effectiveness

	Cost	Effectiveness	C/E
Statistic	$	ALS	$/ALS
Mean	1952.982	99.78456	19.57198
Standard Deviation	401.039	0.03935	4.01903
Median	1893.733	99.89000	18.97709
2.5th percentile	1338.345	99.70730	13.41204
97.5th percentile	2800.714	99.86173	28.06723

Note. PE = pulmonary embolism; Strategy 1 = a CDR, a DD and a CT. CDR = clinical decision rule; DD = D-dimer test; CT = computed tomography pulmonary angiography; ALS = additional lives saved.

In strategy 1, the lowest cost was associated with a negative DD not requiring treatment, while the most expensive cost was associated with the combination of a positive DD and a positive CT requiring treatment. Specifically, the overall cost of a negative DD not requiring treatment was $28 (c1). The overall cost of a positive DD followed by a positive CT requiring treatment was $2,694 (c2). The overall cost of a

positive DD and a negative CT was $1,150 (c3). The DD and CT branches of strategy 1 are presented in Figure 24.

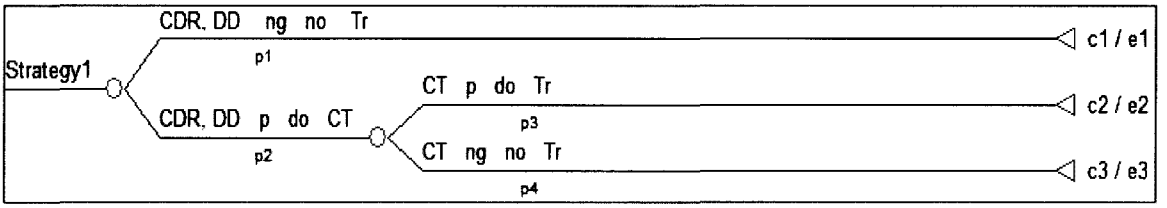
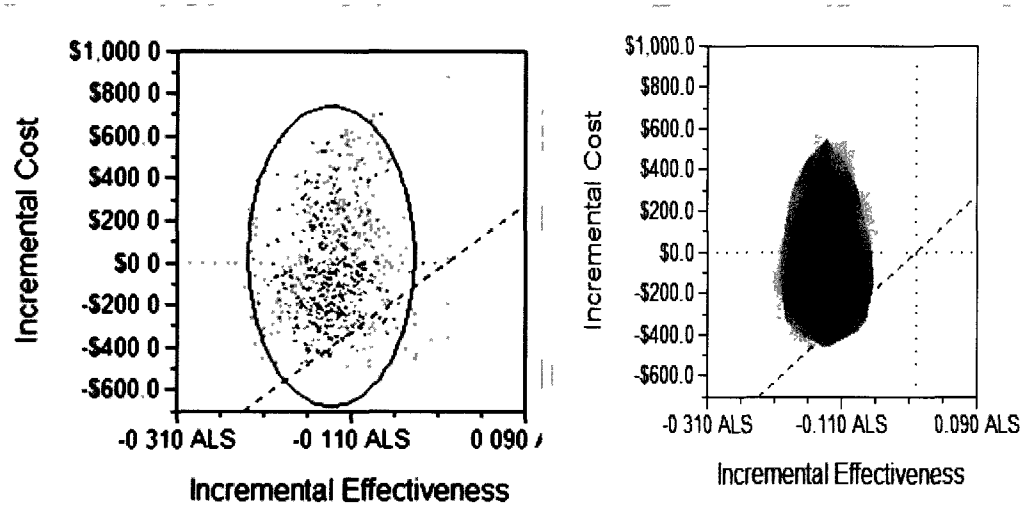


Figure 24. Decision tree CEA model arm for PE diagnostic strategy 1. CEA = cost-effectiveness analysis; PE = pulmonary embolism; Strategy 1 = a CDR, a DD and a CT. CDR = clinical decision rule; DD = D-dimer test; CT = computed tomography pulmonary angiography; Tr = treatment; ng = negative; p = positive; pn = probability; c = cost payoffs; e = effectiveness payoffs.

The confidence ellipse on the cost-effectiveness plane in Figure 25a illustrates the region that contains 95% uncertainty surrounding cost and effectiveness comparators of strategy 1 vs. strategy 3. The dots in the confidence ellipse represent the individual incremental cost and incremental effectiveness pairs for each recalculation of the model. The dots in the confidence ellipse in the upper left (north-west) quadrant of the cost-effectiveness plane demonstrate that strategy 1 was less effective and more costly than strategy 3. Thus, strategy 3 dominates strategy 1. The dots of the confidence ellipse in the lower left (south-west) quadrant of the cost-effectiveness plane indicate that strategy 1 was less effective and less costly than strategy 3. Thus, strategy 3 is optimal. The lower and upper 95% confidence interval limits of the ICER were -5909 and 4015, respectively, based upon the 2.5^{th} and 97.5^{th} probability distribution percentiles.

The isocontours in Figure 25b illustrate the regions that correspond to 10 regions of similar frequency of incremental cost and incremental effectiveness of strategy 1 vs. strategy 3. When the lines are close together, the magnitude of the slope is large,

indicating steep variation. The willingness-to-pay line intersects the x and y axes at the origin of the plot, (x, y = 0, 0).



a) (b)

Figure 25. Incremental cost and effectiveness (ICE) scatter plot and isocontours graphs of strategy 1 vs. strategy 3. Strategy 1 = a CDR, a DD and a CT; Strategy 3 = a CDR, a DD, a CUS, and a CT. CDR = clinical decision rule; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS = compression ultrasonography; ALS = additional lives saved.

Da_2: At least strategy 2 will be more cost-effective than strategy 1, strategy 3, strategy 4, or strategy 5.

This alternative decision is rejected. Strategy 2, comprising a CDR, DD, a CT, and a CUS, with a cost of $2,441.23 and an effectiveness level of 99.91172 was dominated by strategy 3 (see Table 26). Results for the costs, effectiveness, and cost-effectiveness ratio of PE diagnostic strategy 2 are presented in Table 28.

Table 28

Statistics of PE Diagnostic Strategy 2 Cost and Effectiveness

	Cost	Effectiveness	C/E
Statistic	$	ALS	$/ALS
Mean	2441.2300	99.91172	24.43387
Standard Deviation	402.0882	0.01112	4.02443
Median	2381.8910	99.91174	23.83954
2.5^{th} percentile	1823.9910	99.88986	18.25482
97.5^{th} percentile	3289.8910	99.93346	32.92609

Note. PE = pulmonary embolism; Strategy 2 = a CDR, a DD, a CT, and a CUS. CDR = clinical decision rule; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS = compression ultrasonography; C/E = cost-effectiveness ratio; ALS = additional lives saved.

In strategy 2, the lowest cost was associated with a negative DD not requiring treatment. The most expensive cost was associated with the combination of a positive DD, a negative CT, and a positive CUS requiring treatment. The overall cost of a negative DD was $28 (c4). The overall cost of a positive DD followed by a positive CT requiring treatment was $2,694 (c5). The overall cost of a positive DD, a negative CT, and a positive CUS requiring treatment was $2,986 (c6). The overall cost of a positive DD, a negative CT, and a negative CUS was $1,441 (c7). The DD, CT, and CUS branches of strategy 2 are presented in Figure 26.

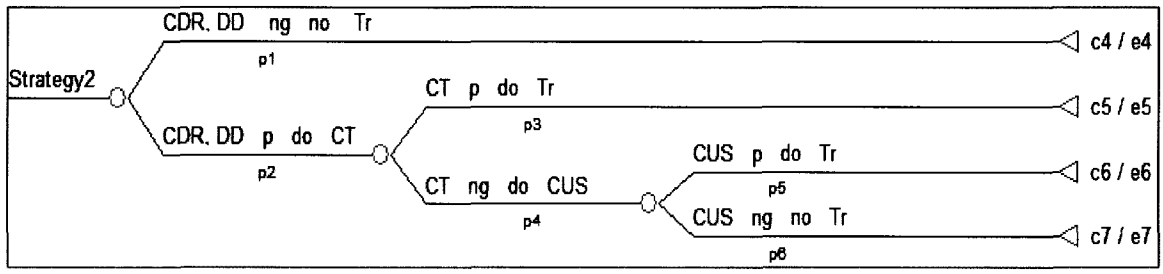


Figure 26. Decision tree CEA model arm for PE diagnostic strategy 2. CEA = cost-effectiveness analysis; PE = pulmonary embolism; Strategy 2 = a CDR, a DD, a CT, and a CUS. CDR= clinical decision rule; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS= compression ultrasonography; Tr = treatment; ng = negative; p = positive; pn = probability; c = cost payoffs; e = effectiveness payoffs.

The confidence ellipse on the cost-effectiveness plane in Figure 27a illustrates the region that contains 95% uncertainty surrounding cost and effectiveness comparators of strategy 2 vs. strategy 3. The dots in the confidence ellipse are located in the upper left (north-west) quadrant of the cost-effectiveness plane. This indicates that strategy 2 was less effective and more costly than strategy 3. Thus, strategy 3 dominates strategy 2. The lower and upper 95% confidence interval limits of the ICER were -877755 and 716385, respectively, based upon the 2.5^{th} and 97.5^{th} probability distribution percentiles.

The isocontours in Figure 27b illustrate the regions that correspond to 10 regions of similar frequency of incremental cost and incremental effectiveness of strategy 2 vs. strategy 3. When the lines are close together, the magnitude of the slope is large, indicating steep variation. The willingness-to-pay line intersects the x and y axes at the origin of the plot, (x, y = 0, 0). (x, y = 0, 0).

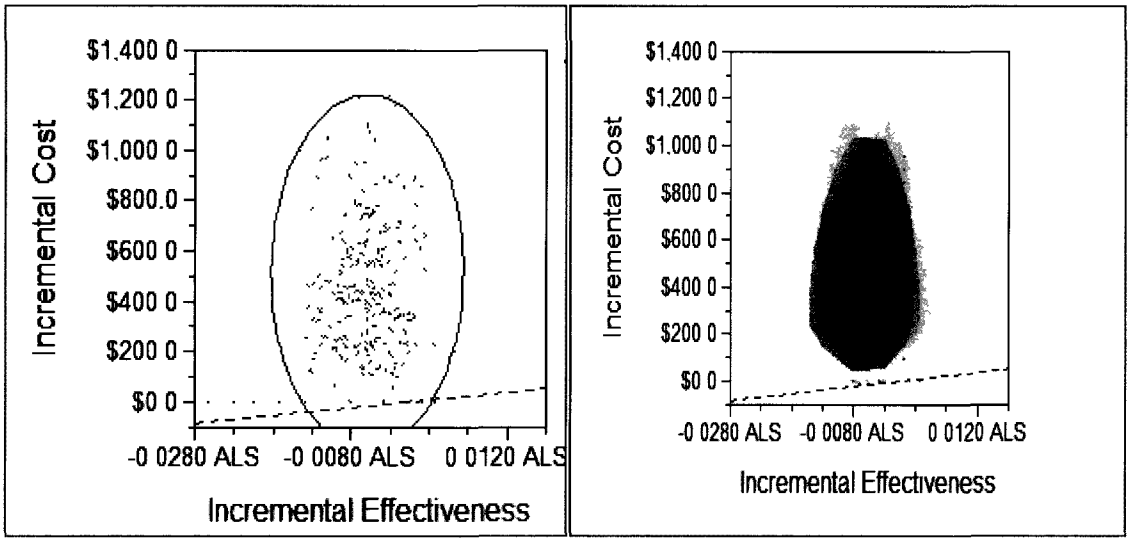


Figure 27. Incremental cost and effectiveness (ICE) scatter plot and isocontours graphs of strategy 2 vs. strategy 3. Strategy 2 = a CDR, a DD, a CT, and a CUS; Strategy 3 = a CDR, a DD, a CUS, and a CT. CDR = clinical decision rule; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS = compression ultrasonography; ALS = additional lives saved.

Da_3: At least strategy 3 will be more cost-effective than strategy 1, strategy 2, strategy 4, or strategy 5.

This alternative decision is accepted. Strategy 3, comprising a CDR, a DD, a CUS, and a CT, with a cost of about $1,922.396 and an effectiveness level of 99.91767 was the most cost-effective strategy (see Table 26). Additionally, strategy 3 dominates strategies 1, 2, and 4. Statistical results for the costs, effectiveness, and cost-effectiveness ratio of PE diagnostic strategy 3 are presented in Table 29. The DD, CUS, and CT branches of strategy 3 are presented in Figure 28.

Table 29

Statistics of PE Diagnostic Strategy 3 Cost and Effectiveness

	Cost	Effectiveness	C/E
Statistic	$	ALS	$/ALS
Mean	1922.396	99.91767	19.23980
Standard Deviation	132.182	0.00997	1.32290
Median	1911.065	99.91767	19.12639
2.5^{th} percentile	1693.861	99.89809	16.95223
97.5^{th} percentile	2196.657	99.93722	21.98656

Note. PE = pulmonary embolism; Strategy 3 = a CDR, a DD, a CUS, and a CT. CDR = clinical decision rule; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS = compression ultrasonography; C/E = cost-effectiveness ratio; ALS = additional lives saved.

In strategy 3, the lowest cost was associated with a negative DD not requiring treatment, while the most expensive cost was incurred by the combination of a positive DD, a negative CUS, and a positive CT requiring treatment. The overall cost of a negative DD was $28 (c8). The overall cost of a positive DD followed by a positive CUS requiring treatment was $1,865 (c9). The overall cost of a positive DD, a negative CUS, and a positive CT requiring treatment was $2,986 (c10). The overall cost of a positive DD, a negative CUS, and a negative CT was $1,441 (c11). The DD, CUS, and CT branches of strategy 3 are presented in Figure 28.

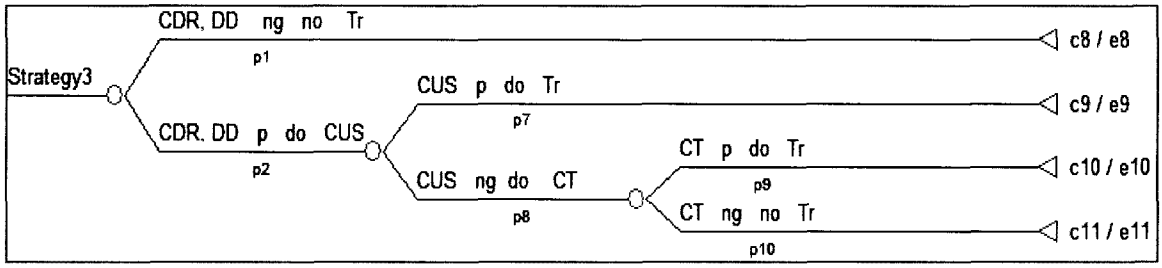


Figure 28. Decision tree CEA model arm for PE diagnostic strategy 3. CEA = cost-effectiveness analysis; PE = pulmonary embolism; Strategy 3 = a CDR, a CDR, a DD, a CUS, and a CT. CDR = clinical decision rule; DD = D-dimer test; CUS= compression ultrasonography; CT = computed tomography pulmonary angiography; Tr = treatment; ng = negative; p = positive; pn = probability; c = cost payoffs; e = effectiveness payoffs.

Da_4: At least strategy 4 will be more cost-effective than strategy 1, strategy 2, strategy 3, or strategy 5.

This alternative decision is rejected. Strategy 4, comprising a CDR, a DD, a VQ, and a CUS, with a cost of $2,281.085 and an effectiveness level of 99.91518 was dominated by strategy 3 (see Table 26). Results for the costs, effectiveness, and cost-effectiveness ratio of PE diagnostic strategy 4 are presented in Table 30.

Table 30

Statistics of PE Diagnostic Strategy 4 Cost and Effectiveness

	Cost	Effectiveness	C/E
Statistic	$	ALS	$/ALS
Mean	2281.085	99.91518	22.83021
Standard Deviation	152.315	0.00997	1.52445
Median	2273.688	99.91519	22.75634
2.5th percentile	2003.943	99.89559	20.05730
97.5th percentile	2583.258	99.93480	25.85495

Note. PE = pulmonary embolism; Strategy 4 = a CDR, a DD, a VQ, and a CUS. CDR = clinical decision rule; DD = D-dimer test; VQ = ventilation–perfusion lung scan; CUS = compression ultrasonography; C/E = cost-effectiveness ratio; ALS = additional lives saved.

In strategy 4, the lowest cost was associated with a negative DD not requiring treatment, while the most expensive cost was incurred by a positive DD, a negative VQ, and a positive CUS requiring treatment. The overall cost of a negative DD was $28 (c12). The overall cost of a positive DD followed by a positive VQ requiring treatment was $2,576 (c13). The overall cost of a positive DD, a negative VQ, and a positive CUS requiring treatment was $2,868 (c14). The overall cost of a positive DD, a negative VQ, and a negative CUS was $1,353 (c15). The DD, VQ, and CUS branches of strategy 4 are presented in Figure 29.

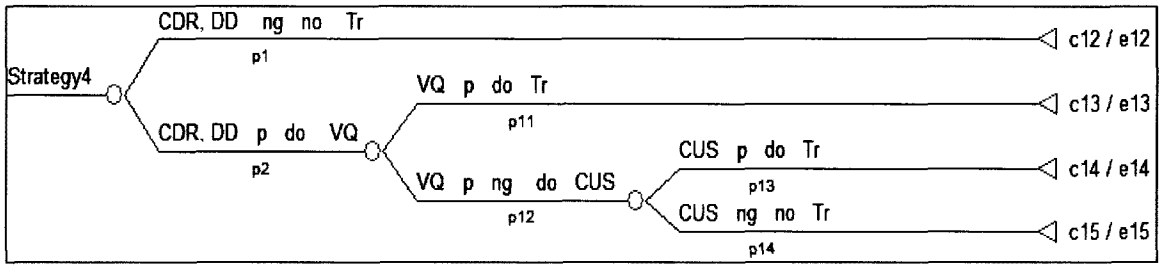
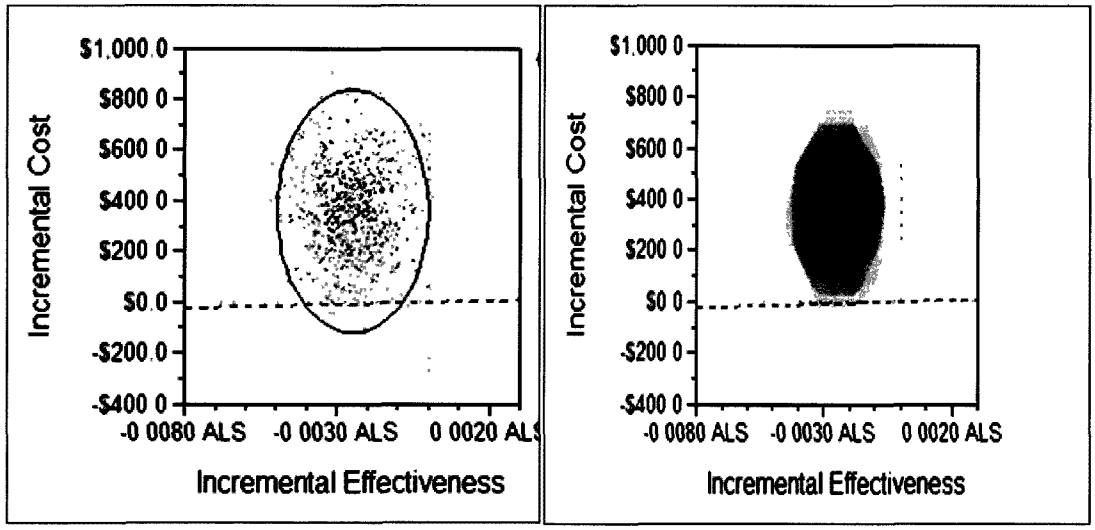


Figure 29. Decision tree CEA model arm for PE diagnostic strategy 4. CEA = cost-effectiveness analysis; PE = pulmonary embolism; Strategy 4 = a CDR, a DD, a VQ, and a CUS. CDR = clinical decision rule; DD = D-dimer test; VQ = ventilation-perfusion lung scan; CUS= compression ultrasonography; Tr = treatment; ng = negative; p = positive; pn = probability; c = cost payoffs; e = effectiveness payoffs.

The confidence ellipse on the cost-effectiveness plane in Figure 30a illustrates the region that contains 95% uncertainty surrounding cost and effectiveness comparators of strategy 4 vs. strategy 3. The dots in the confidence ellipse are located in the upper left (north-west) quadrant of the cost-effectiveness plane. This demonstrates that strategy 4 was less effective and more costly than strategy 3. Thus, strategy 3 dominates strategy 4.The lower and upper 95% confidence interval limits of the ICER were -665274 and 19926, respectively, based upon the 2.5^{th} and 97.5^{th} probability distribution percentiles.

The isocontours in Figure 30b illustrate the regions that correspond to 10 regions of similar frequency of incremental cost and incremental effectiveness of strategy 4 vs. strategy 3. When the lines are close together, the magnitude of the slope is large, indicating steep variation. The willingness-to-pay line intersects the x and y axes at the origin of the plot, (x, y = 0, 0).



(a) (b)

Figure 30. Incremental cost and effectiveness (ICE) scatter plot and isocontours graphs of strategy 4 vs. strategy 3. Strategy 3 = a CDR, a DD, a CUS, and a CT; Strategy 4 = a CDR, a DD, a VQ, and a CUS. CDR = clinical decision rule; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS = compression ultrasonography; VQ = ventilation–perfusion lung scan; ALS = additional lives saved.

Da_5: At least strategy 5 will be more cost-effective than strategy 1, strategy 2, strategy 3, or strategy 4.

This alternative decision is rejected. Strategy 5, comprising a CDR, a DD, a CT, a CUS, and a PA, with a cost of approximately $2,483.82 and an effectiveness level of 99.91999 was a cost-effective strategy, while strategy 3 was the most cost-effective strategy (see Table 26). Results for the costs, effectiveness, and cost-effectiveness ratio of PE diagnostic strategy 5 are presented in Table 31.

Table 31

Statistics of PE Diagnostic Strategy 5 Cost and Effectiveness

	Cost	Effectiveness	C/E
Statistic	$	ALS	$/ALS
Mean	2483.821	99.91999	24.85810
Standard Deviation	402.333	0.01000	4.02655
Median	2423.890	99.92000	24.25726
2.5th percentile	1866.426	99.90036	18.67782
97.5th percentile	3332.686	99.93961	33.35305

Note. PE = pulmonary embolism; Strategy 5 = a CDR, a DD, a CT, a CUS, and a PA. CDR = clinical decision rule; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS = compression ultrasonography; PA = invasive pulmonary angiography; C/E = cost-effectiveness ratio; ALS = additional lives saved.

In strategy 5, the lowest cost was associated with a negative DD not requiring treatment, while the most expensive cost was associated with a positive DD, a negative CT, a negative CUS, and a positive PA requiring treatment. The overall cost of a negative DD was $28 (c16). The overall cost of a positive DD followed by a positive CT requiring treatment was $2,694 (c17). The overall cost of a positive DD, a negative CT, and a positive CUS requiring treatment was $2,986 (c18). The overall cost of a positive DD, a negative CT, a negative CUS, and a positive PA requiring treatment was $6,662 (c19). The overall cost of a positive DD, a negative CT, a negative CUS, and a negative PA was $5,118 (c20). The DD, CT, CUS, and PA branches of strategy 5 are presented in Figure 31.

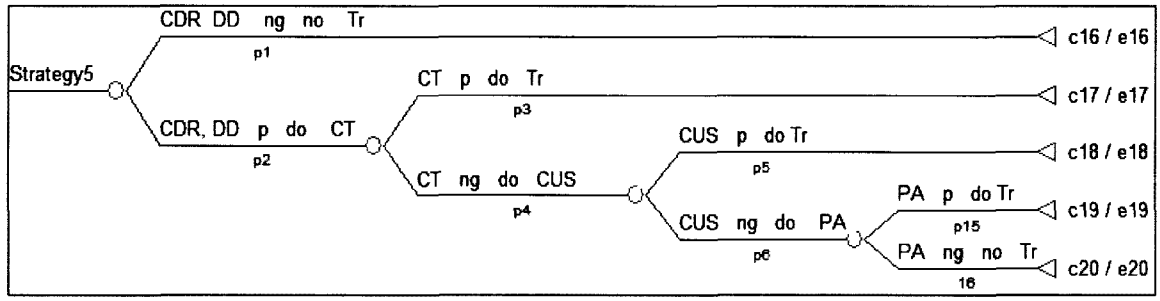
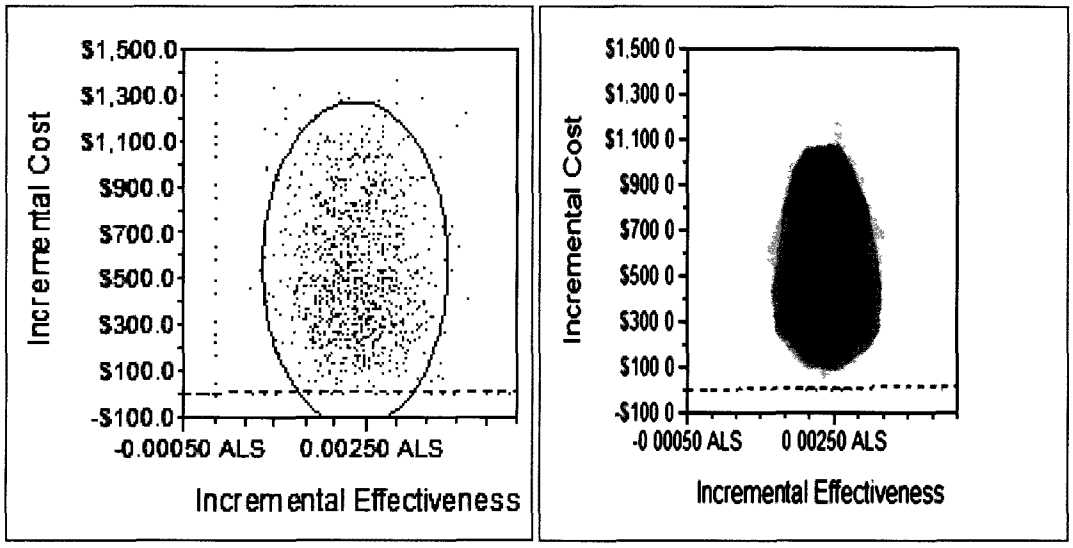


Figure 31. Decision tree CEA model arm for PE diagnostic strategy 5. CEA = cost-effectiveness analysis; PE = pulmonary embolism; Strategy 5 = a CDR, a DD, a CT, a CUS, and a PA. CDR = clinical decision rule; D-dimer test; CT = computed tomography pulmonary angiography; CUS= compression ultrasonography; PA = invasive pulmonary angiography; Tr = treatment; ng = negative; p = positive; pn = probability; c = cost payoffs; e = effectiveness payoffs.

The confidence ellipse on the cost-effectiveness plane in Figure 32a illustrates the region that contains 95% uncertainty surrounding costs and effectiveness comparators of strategy 5 vs. strategy 3. The dots in the confidence ellipse are located in the upper right (north-east) quadrant of the cost-effectiveness plane. This indicates that strategy 5 was more effective and more costly than strategy 3, but its ICER was greater than the willingness-to-pay. Thus, strategy 3 is optimal. Overall, strategy 5 was a cost-effective strategy. The lower and upper 95% confidence interval limits of the ICER were 48523 and 681970, respectively, based upon the 2.5^{th} and 97.5^{th} probability distribution percentiles.

The isocontours in Figure 32b illustrate the regions that correspond to 10 regions of similar frequency of incremental cost and incremental effectiveness of strategy 5 vs. strategy 3. When the lines are close together, the magnitude of the slope is large, indicating steep variation. The willingness-to-pay line intersects the x and y axes at the origin of the plot, (x, y = 0, 0).



(a) (b)

Figure 32. Incremental cost and effectiveness (ICE) scatter plot and isocontours graphs of strategy 5 vs. strategy 3. Strategy 3 = a CDR, a DD, a CUS, and a CT; Strategy 5 = a CDR, a DD, a CT, a CUS, and a PA. CDR = clinical decision rule; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS = compression ultrasonography; PA = invasive pulmonary angiography; ALS = additional lives saved.

Monte Carlo Simulation CEA Model Sensitivity Analysis Results

Summary of Monte Carlo simulation sensitivity analysis results.

Strategy 3 statistics were used as baseline data with a willingness-to-pay ranging from $.01 to $3,000 in a Monte Carlo simulation probabilistic sensitivity analysis within the CEA model. Figure 33 presents the results of this analysis as acceptability curves. Acceptability curves provide the uncertainty around cost-effectiveness and illustrate the probability that a strategy is cost-effective when compared with alternate strategies. The acceptability curve representing the optimal strategy demonstrates that the cost-effectiveness probability of strategy 3 increased as the willingness-to-pay increased.

The cost-effectiveness probability ranges determined for each strategy are as follows: (a) strategy 1, 0.0674 to 0.51006; (b) strategy 2, 0 to 0.00023; (c) strategy 3, 0.45675 to 0.90172; (d) strategy 4, 0.03062 to 0.03322; and (e) strategy 5, 0 to 0.00003.

The sum of the cost-effective probabilities at each interval, i.e., the willing-to-pay amount, for the five PE diagnostic strategies is 1.00. The corresponding results at the willingness-to-pay intervals are presented in Table 32.

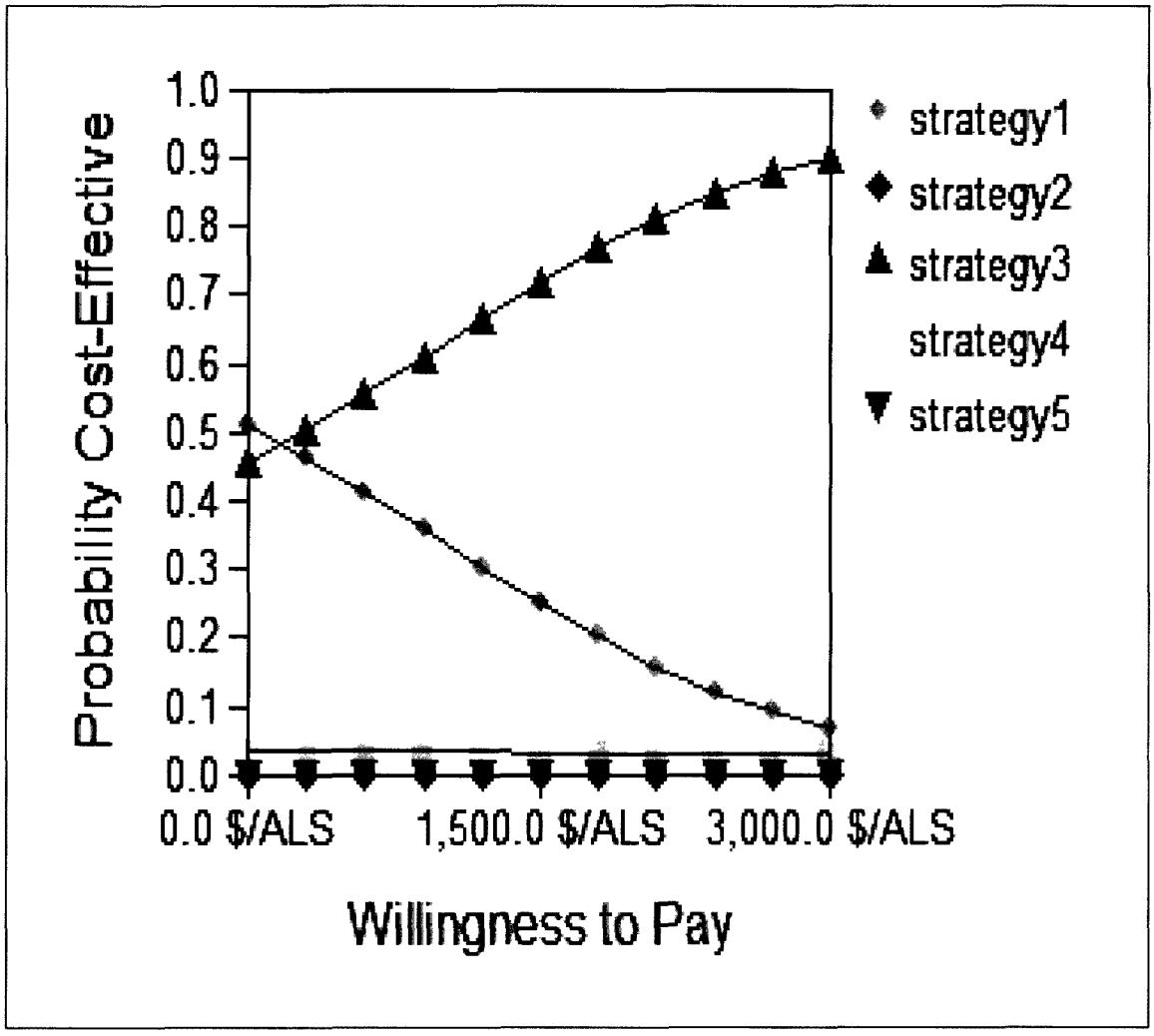


Figure 33. Acceptability curves with a willingness-to-pay from $.01 to $3,000. Strategy 1 = a CDR, a DD and a CT; Strategy 2 = a CDR, a DD, a CT, and a CUS; Strategy 3 = a CDR, a DD, a CUS, and a CT; Strategy 4 = a CDR, a DD, a VQ, and a CUS; Strategy 5 = a CDR, a DD, a CT, a CUS, and a PA. CDR = clinical decision rule; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS= compression ultrasonography; VQ = ventilation-perfusion lung scan; PA = invasive pulmonary angiography; ALS = additional lives saved.

Table 32

Acceptability Curves with a Willingness-to-Pay from $.01 to $3,000

W-T-P $	Strategy 1	Strategy 2	Strategy 3	Strategy 4	Strategy 5	Total
0.01	0.51006	0	0.45672	0.03322	0	1
300	0.46282	0	0.50417	0.03301	0	1
600	0.41140	0	0.55577	0.03283	0	1
900	0.35723	0	0.61013	0.03264	0	1
1200	0.30264	0	0.66498	0.03238	0	1
1500	0.24932	0	0.71850	0.03218	0	1
1800	0.19942	0	0.76873	0.03185	0	1
2100	0.15592	0	0.81256	0.03152	0	1
2400	0.11961	0	0.84908	0.03131	0	1
2700	0.09037	0.00007	0.8786	0.03096	0	1
3000	0.06740	0.00023	0.90172	0.03062	0.00003	1

Notes. Strategy 1 = a CDR, a DD and a CT; Strategy 2 = a CDR, a DD, a CT, and a CUS; Strategy 3 = a CDR, a DD, a CUS, and a CT; Strategy 4 = a CDR, a DD, a VQ, and a CUS; Strategy 5 = a CDR, a DD, a CT, a CUS, and a PA. DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS= compression ultrasonography; VQ = ventilation-perfusion lung scan; PA = invasive pulmonary angiography.

Monte Carlo simulation of cost by strategy.

Monte Carlo simulation (MCS) revealed strategy 1 cost values ranging from about $1,169.74 to $3,107.04. Within the first 10th percentile, the cost values were $1,472.47 or less, the median cost value was $1,893.73, and at or above the 90th percentile, the cost values were $2,538.44 or greater (see Figure 34).

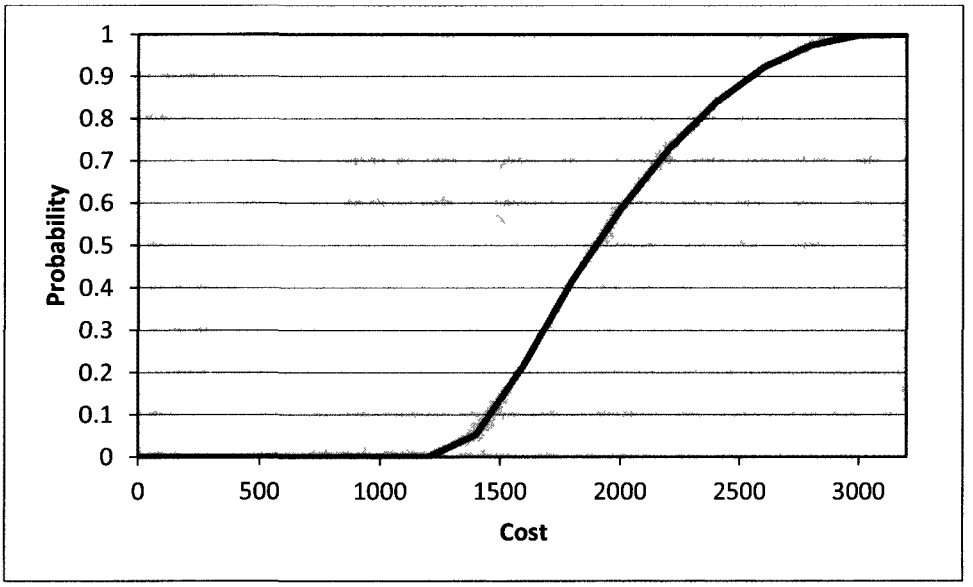


Figure 34. MCS of cost cumulative probability for strategy 1. Strategy 1 = a CDR, a DD and a CT; CDR = clinical decision rule; DD = D-dimer test; CT = computed tomography pulmonary angiography.

MCS revealed strategy 2 cost values ranging from about $1,633.05 to $3,632.07. Within the first 10th percentile, the cost values was $1,959.52 or less, the median cost value was $2381.89, and at or above the 90th percentile, the cost values were $3028.56 or greater (see Figure 35).

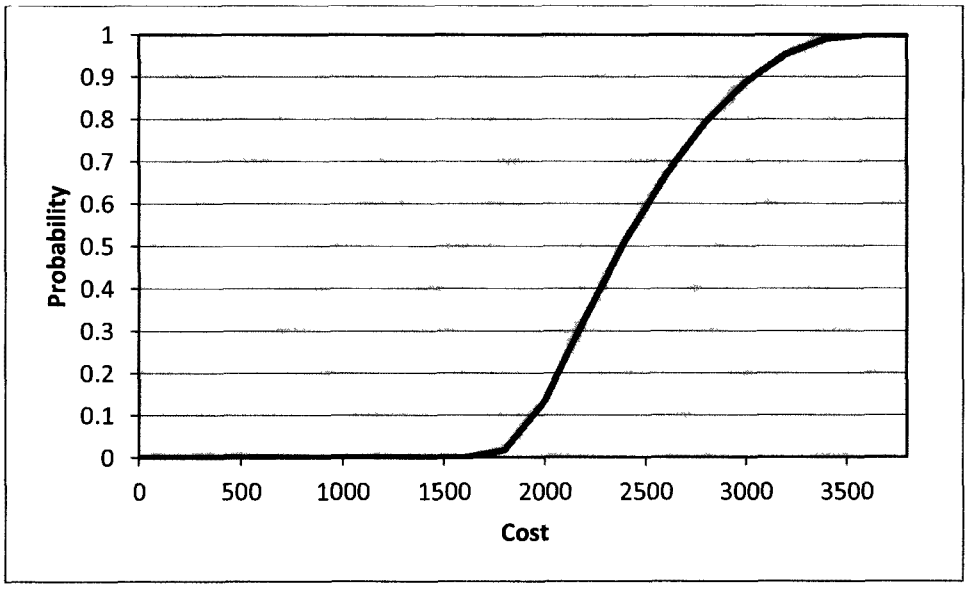


Figure 35. MCS of cost cumulative probability for strategy 2. Strategy 2 = a CDR, a DD, a CT, and a CUS; CDR = clinical decision rule; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS = compression ultrasonography.

MCS revealed strategy 3 cost values ranging from about $1,543.20 to $2,392.84. Within the first 10th percentile, the cost values was $1,759.13 or less, the median cost value was $1,911.07, and at or above the 90th percentile, the cost values were $2,106.78 or greater (see Figure 36).

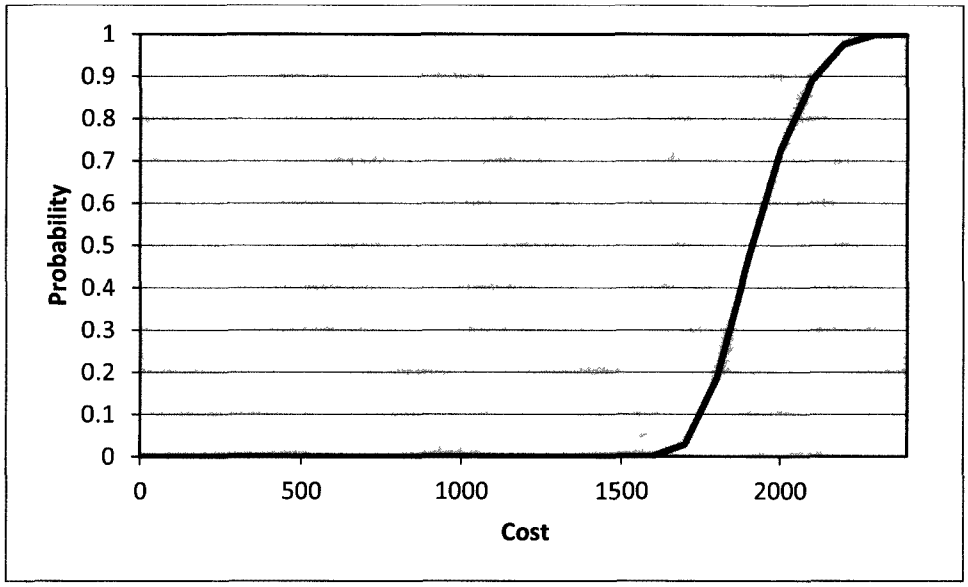


Figure 36. MCS of cost cumulative probability for strategy 3. Strategy 3 = a CDR, a DD, a CUS, and a CT; CDR = clinical decision rule; DD = D-dimer test; CUS = compression ultrasonography; CT = computed tomography pulmonary angiography.

MCS identified strategy 4 cost values ranging from about $1,870.05 to $2,725.04. Within the first 10th percentile, the cost values was $2,082.96 or less, the median cost value was $2,273.69, and at or above the 90th percentile, the cost values were $2,490.71 or greater (see Figure 37).

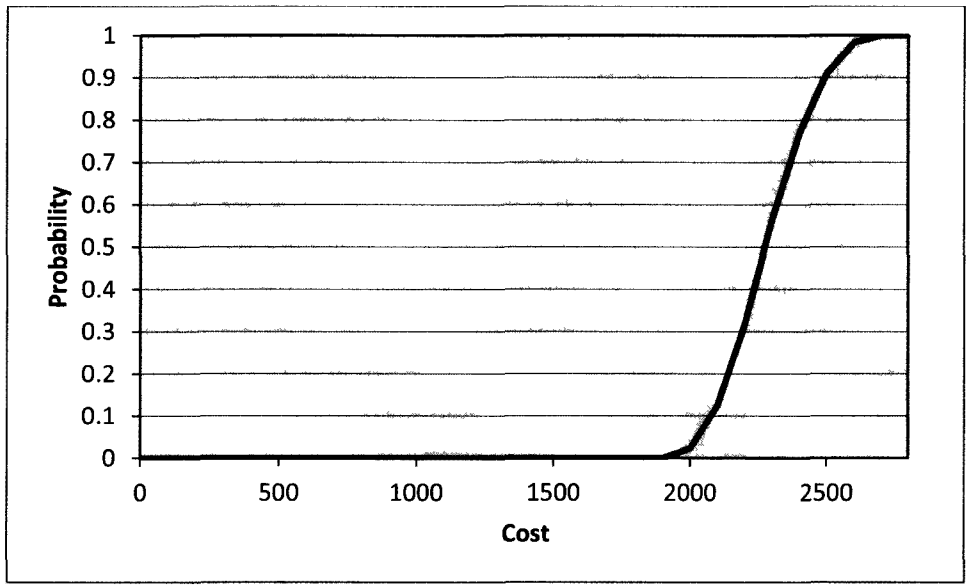


Figure 37. MCS of cost cumulative probability for strategy 4. Strategy 4 = a CDR, a DD, a VQ, and a CUS; CDR = clinical decision rule; DD = D-dimer test; CT = computed tomography pulmonary angiography; VQ = ventilation–perfusion lung scan; CUS = compression ultrasonography.

MCS identified strategy 5 cost values ranging from about $1,667.69 to $3,671.55. Within the first 10th percentile, the cost values was $2,001.67 or less, the median cost value was $2,423.89, and at or above the 90th percentile, the cost values were $3,071.55 or greater (see Figure 38).

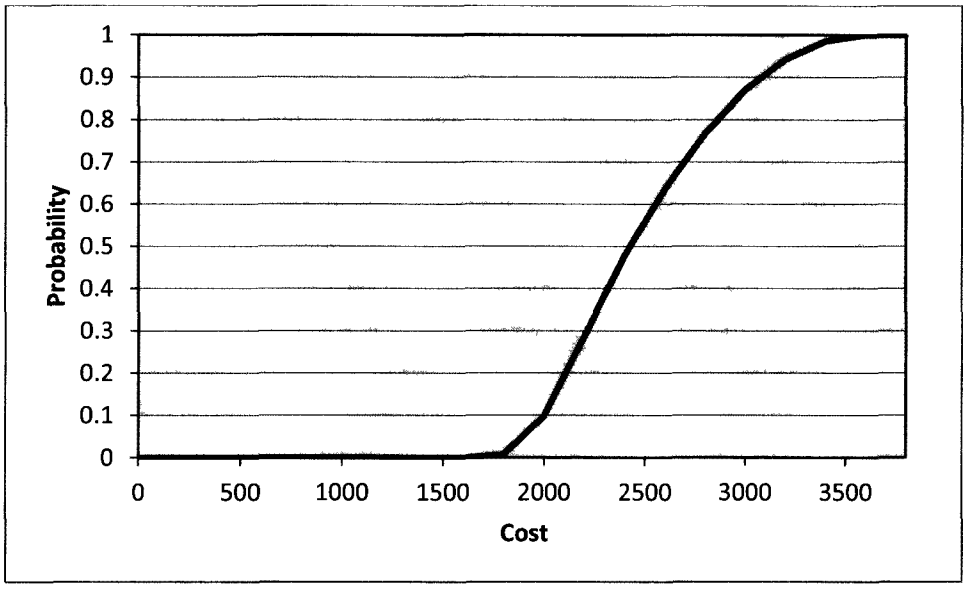


Figure 38. MCS of cost cumulative probability for strategy 5. Strategy 5 = a CDR, a DD, a CT, a CUS, and a PA; CDR = clinical decision rule; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS = compression ultrasonography; PA = invasive pulmonary angiography.

Monte Carlo simulation of incremental cost and effectiveness by strategy.

Incremental cost values were generated from a Monte Carlo simulation (MCS) independently comparing the strategy 3 statistical data set against the data set of each other strategy. The incremental cost values generated when PE strategy 1 was compared to PE strategy 3, ranged (in dollars) from -614.82 to 919.34. Probability levels increased as incremental dollar cost increased with the highest attained probability achieved at .11181 (-$140), after which probability decreased. The probability of attaining incremental cost values (in dollars) of -614, -300, -220, 100, 260, 340, 420, 580, 740, and 919 was .07082, .10170, .08630, .07047, .06074, .05129, .03165, .01319, and .00005, respectively (see Figure 39).

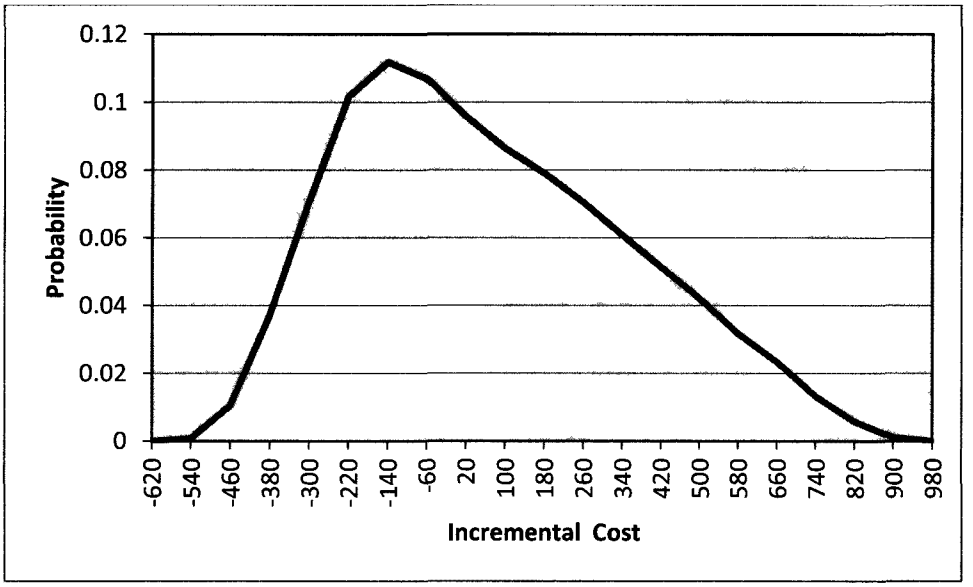


Figure 39. MCS incremental cost probability of strategy 1 vs. strategy 3. Strategy 1 = a CDR, a DD and a CT; Strategy 3 = a CDR, a DD, a CUS, and a CT. CDR = clinical decision rule; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS = compression ultrasonography.

As Figure 40 indicates, the incremental cost values generated when PE strategy 2 was compared to PE strategy 3, ranged (in dollars) from -74.66 to 1,374.52. Probability levels increased as incremental dollar cost increased with the highest attained probability achieved at .10002 ($340), after which probability decreased. The probability of attaining incremental cost values (in dollars) of 74, 130, 270, 410, 550, 690, 900, 1,180 and 1,374 were .00001, .04101, .09414, .09578, .07914, .0682, .04451, .01678, and .00033, respectively.

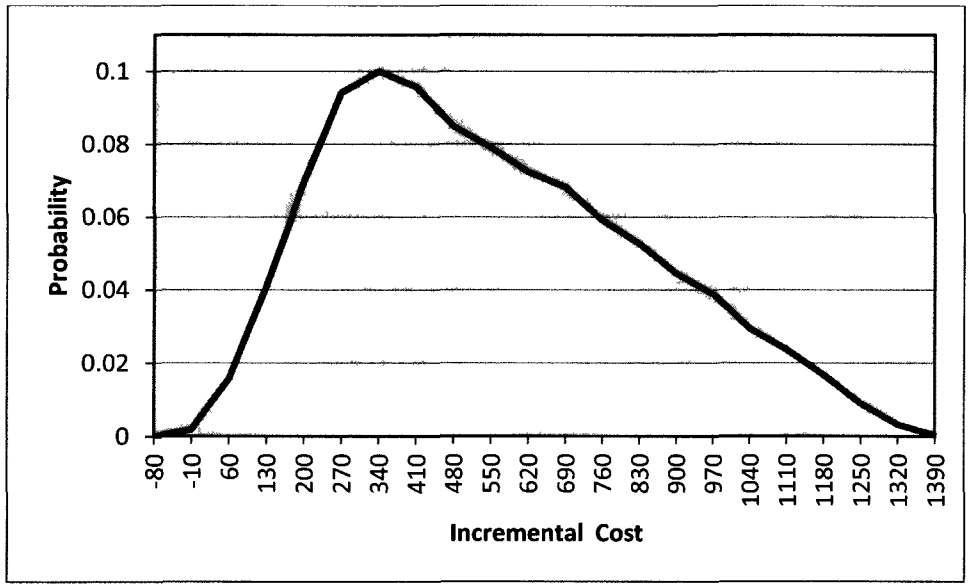


Figure 40. MCS incremental cost probability of strategy 2 vs. strategy 3. Strategy 2 = a CDR, a DD, a CT, and a CUS; Strategy 3 = a CDR, a DD, a CUS, and a CT. CDR = clinical decision rule; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS = compression ultrasonography.

The incremental cost values generated when PE strategy 4 was compared to PE strategy 3, ranged (in dollars) from -384.36 to 979.89. Probability levels increased as incremental costs increased with the highest attained probability achieved at .13889 ($380), after which probability decreased. The probability of attaining incremental cost values (in dollars) of -384, 100, 170, 310, 450, 590, 730, 870, and 979 were .00001, .04987, .07469, .12732, .13527, .08657, .03631, .00669, and .00017, respectively (see Figure 41).

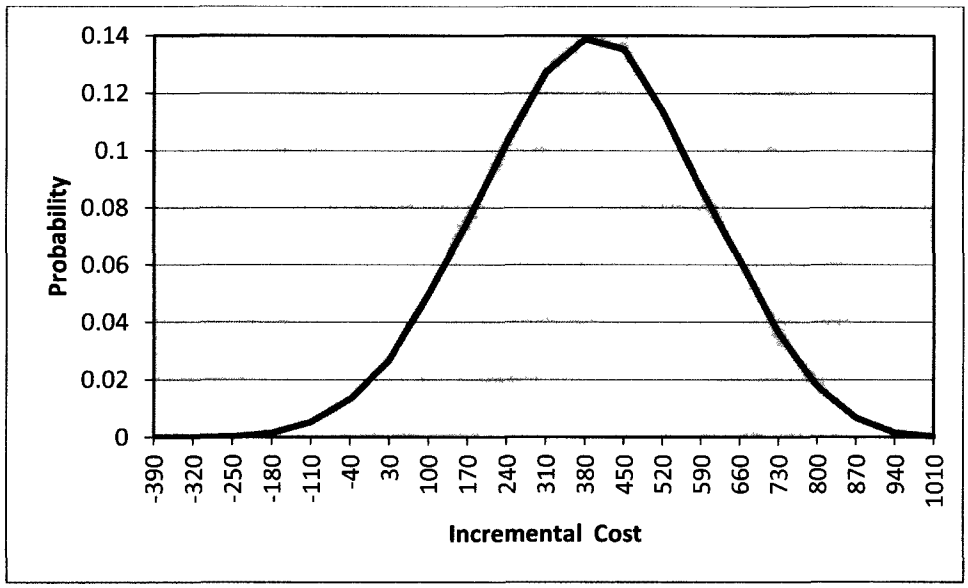


Figure 41. MCS incremental cost probability of strategy 4 vs. strategy 3. Strategy 3 = a CDR, a DD, a CUS, and a CT; Strategy 4 = a CDR, a DD, a VQ, and a CUS. CDR = clinical decision rule; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS = compression ultrasonography; VQ = ventilation–perfusion lung scan.

The incremental cost values generated when PE strategy 5 was compared to PE strategy 3, ranged (in dollars) from -40.35 to 1,414.90. Probability levels increased as incremental costs increased with the highest attained probability achieved at .10020 ($370), after which probability decreased. The probability of attaining incremental cost values (in dollars) of -40, 160, 230, 510, 580, 790, 1,000, 1,280 and 1,414 were .00001, .03627, .06449, .08767, .07978, .06095, .03997, .01041 and .00068, respectively (see Figure 42).

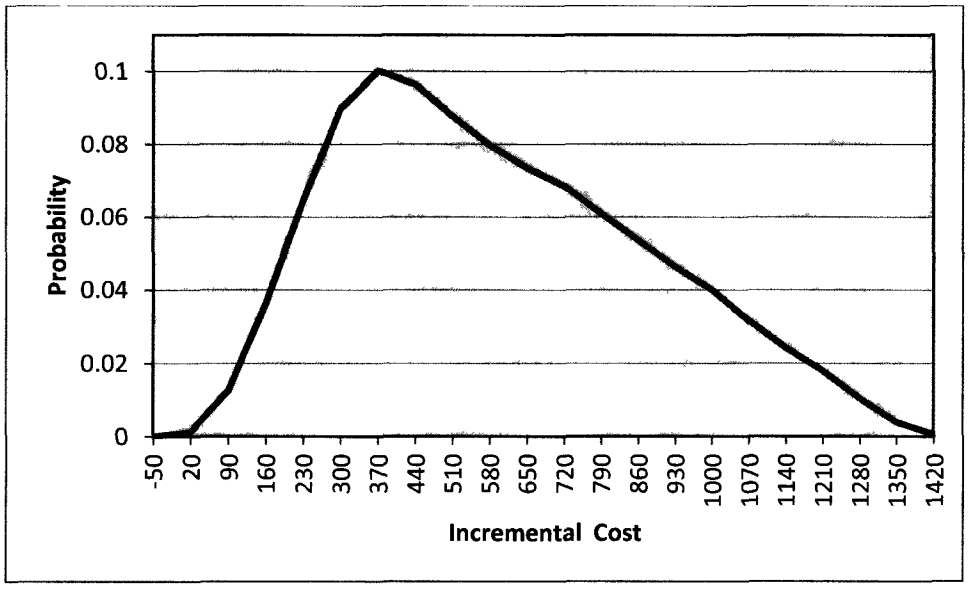


Figure 42. MCS incremental cost probability of strategy 5 vs. strategy 3. Strategy 3 = a CDR, a DD, a CUS, and a CT; Strategy 5 = a CDR, a DD, a CT, a CUS, and a PA. CDR = clinical decision rule; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS = compression ultrasonography; PA = invasive pulmonary angiography.

An MCS generated incremental effectiveness values when PE strategy 1 was compared to PE strategy 3. Effectiveness, which is measured as additional lives saved (ALS), ranged from -.30351 to .02074. Probability increased as incremental effectiveness increased, with the highest attained probability of .20034 and effectiveness value of -.13, after which probability decreased. The probabilities of attaining incremental effectiveness values of -0.31, -0.25, -0.23, -0.15, -0.09, -0.05, -0.01, 0.01, and 0.02 were .00001, .00099, .00525, .16204, .14292, .03521, .00314, .00072, and .00012, respectively (see Figure 43).

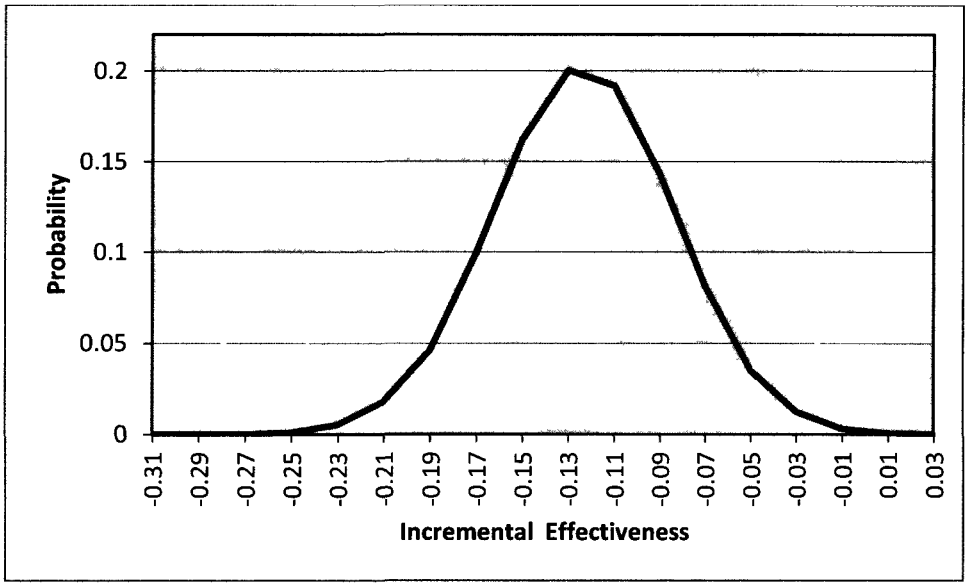


Figure 43. MCS incremental effectiveness probability of strategy 1 vs. strategy 3. Strategy 1 = a CDR, a DD and a CT; Strategy 3 = a CDR, a DD, a CUS, and a CT. CDR = clinical decision rule; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS = compression ultrasonography.

An MCS generated incremental effectiveness values when PE strategy 2 and 3 were analyzed. Effectiveness, which is measured as additional lives saved (ALS), ranged from -0.02783 to 0.016424. Probability increased as effectiveness increased, with the highest attained probability of .15370 and incremental effectiveness value of -0.006, after which probability decreased. The probabilities of attaining incremental effectiveness values of -.028, -.016, -.012, -.01, -.004, .01, .012, .014, and .018 were .00001, .01472, .06008, .09594, .15366, .00216, .0007, .00014 and .00002, respectively (see Figure 44).

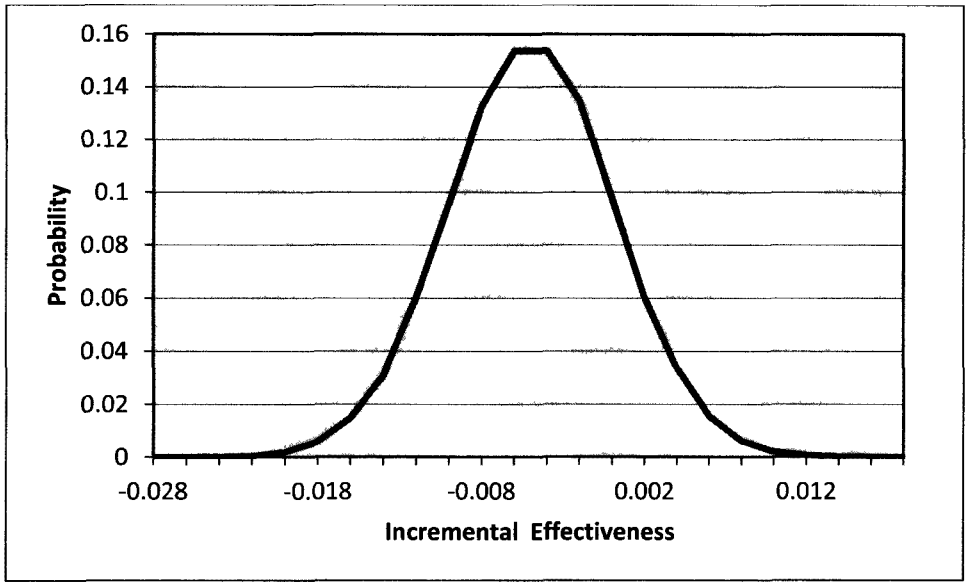


Figure 44. MCS incremental effectiveness probability of strategy 2 vs. strategy 3. Strategy 2 = a CDR, a DD, a CT, and a CUS; Strategy 3 = a CDR, a DD, a CUS, and a CT. CDR = clinical decision rule; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS = compression ultrasonography.

An MCS generated incremental effectiveness values when PE strategies 4 and 3 were analyzed for effectiveness. Effectiveness, which is measured as additional lives saved (ALS), ranged from -0.00719 to 0.001929. Probability increased as incremental effectiveness increased, with the highest attained probability of .19576 and incremental effectiveness value of .0022, after which probability decreased. The probabilities of attaining incremental effectiveness values of .00719, -.0052, -.0047, -.0037, -.0012, -.0007, .0008, .0018, and .001929 were .00001, .00312, .01098, .0691, .11702, .06513, .00257, .00009 and .00001, respectively (see Figure 45).

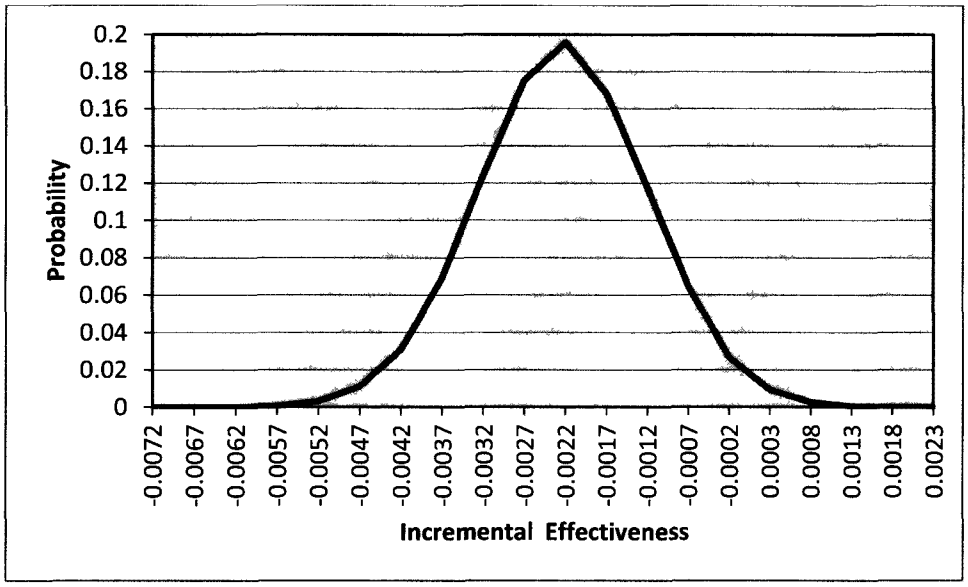


Figure 45. MCS incremental effectiveness probability of strategy 4 vs. strategy 3. Strategy 3 = a CDR, a DD, a CUS, and a CT; Strategy 4 = a CDR, a DD, a VQ, and a CUS. CDR = clinical decision rule; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS = compression ultrasonography; VQ = ventilation–perfusion lung scan.

An MCS generated incremental effectiveness values when PE strategies 5 and 3 were analyzed for effectiveness. Effectiveness, which is measured as additional lives saved (ALS), ranged from -0.00031 to 0.005045. Probability increased as incremental effectiveness increased, with the highest attained probability of 0.18501 and effectiveness value of 0.0026, after which probability decreased. The probabilities of attaining incremental effectiveness values of -.00031, .0005, .0014, .0023, .0035, .0041, .0044, .0047, and .0053 were .00001, .00139, .04456, .1819, .05099, .00717, .00162, .00052, and .00002, respectively (see Figure 46).

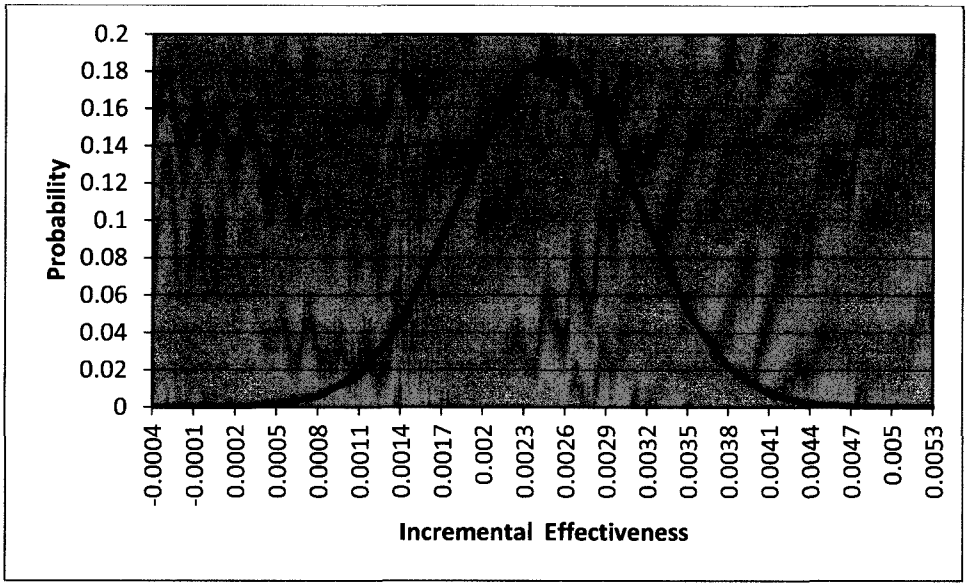


Figure 46. MCS incremental effectiveness probability of strategy 5 vs. strategy 3. Strategy 3 = a CDR, a DD, a CUS, and a CT; Strategy 5 = a CDR, a DD, a CT, a CUS, and a PA. CDR = clinical decision rule; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS = compression ultrasonography; PA = invasive pulmonary angiography.

Monte Carlo simulation of D-dimer test, computed tomography pulmonary angiography, compression ultrasonography, ventilation-perfusion lung scan, invasive pulmonary angiography, and treatment costs.

As graphed in Figure 47, MCS uncovered DD cost values ranging from $25.60 to $33. Probability increased as DD cost increased, with the highest attained probability of .417 at a cost of $28, after which probability decreased. Probabilities for the costs (in dollars) of 26, 30, 32, and 33 were .062, .333, .166, and .021, respectively.

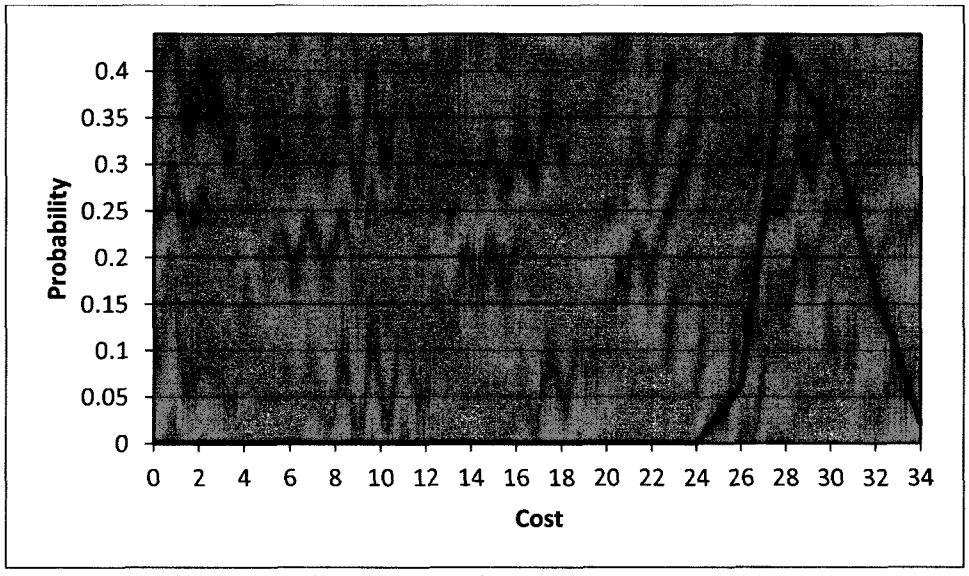


Figure 47. Probability distribution of D-dimer test (DD) cost.

As graphed in Figure 48, the MCS identified CT cost values ranging from $276 to $2,374. Probability increased as CT cost increased, with the highest attained probability of .093 at a cost of $800, after which probability decreased. Probabilities for the costs (in dollars) of 276, 400, 600, 1,000, 1,400, 1,800, 2,000, 2,200, and 2,374 were .001, .017, .062, .081, .057, .046, .024, .014 and .002, respectively.

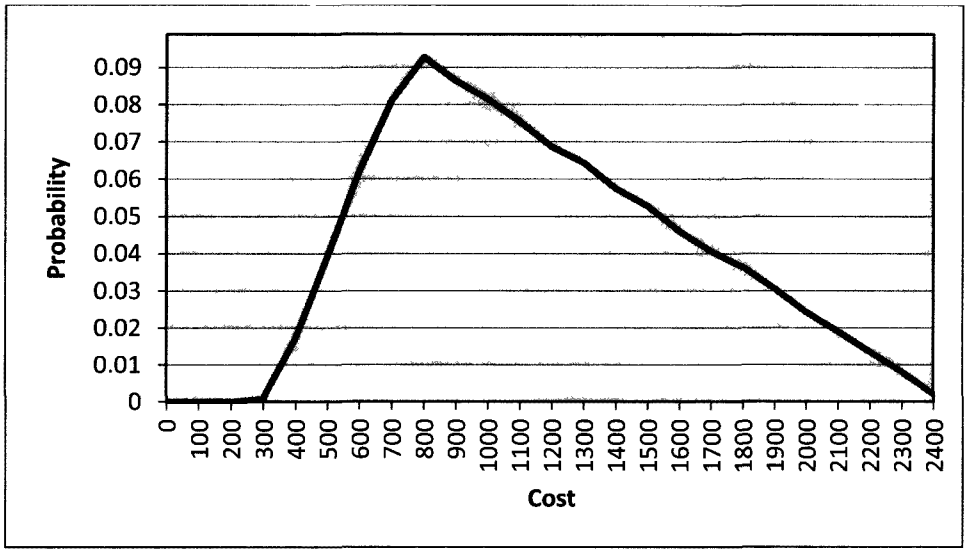


Figure 48. Probability distribution of computed tomography pulmonary angiography (CT) cost.

MCS revealed CUS cost values ranging from $137 to $431. Probability increased as CUS cost increased, with the highest attained probability of .128 at a cost of $320, after which probability decreased. Probabilities for the costs (in dollars) of 137, 180, 220, 260, 300, 340, 360, 400 and 431 were .001, .027, .058, .089, .124, .109, .066, .045, and .004, respectively (see Figure 49).

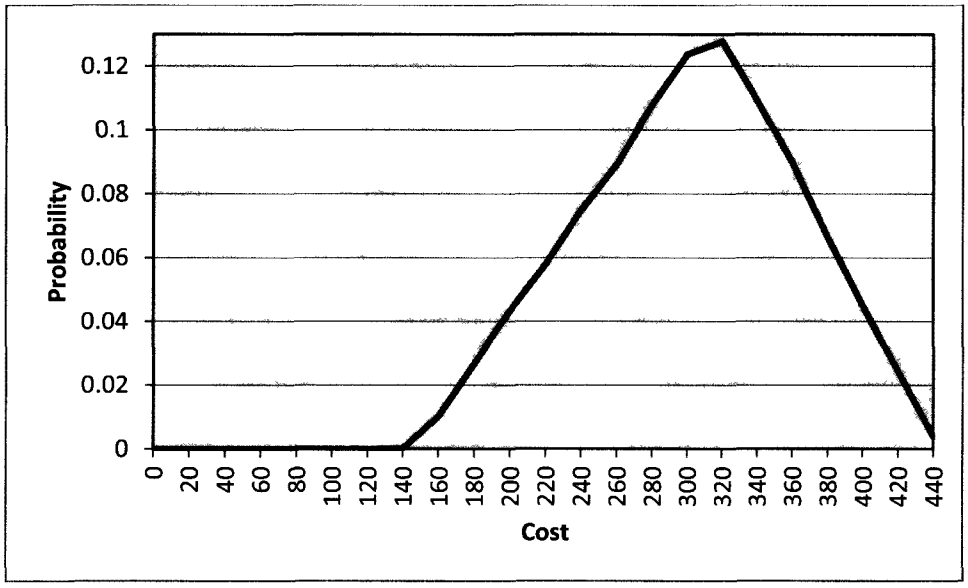


Figure 49. Probability distribution of compression ultrasonography (CUS) cost.

MCS uncovered VQ cost values ranging from $612 to $1,434. Probability increased as VQ cost increased, with the highest attained probability of .160 at a cost of $920, after which probability decreased. Probabilities for the costs (in dollars) of 612, 700, 770, 840, 1,050, 1,190, 1,330, 1,400 and 1,434 were .001, .025, .059, .094, .152, .102, .049, .026, and .003, respectively (see Figure 50).

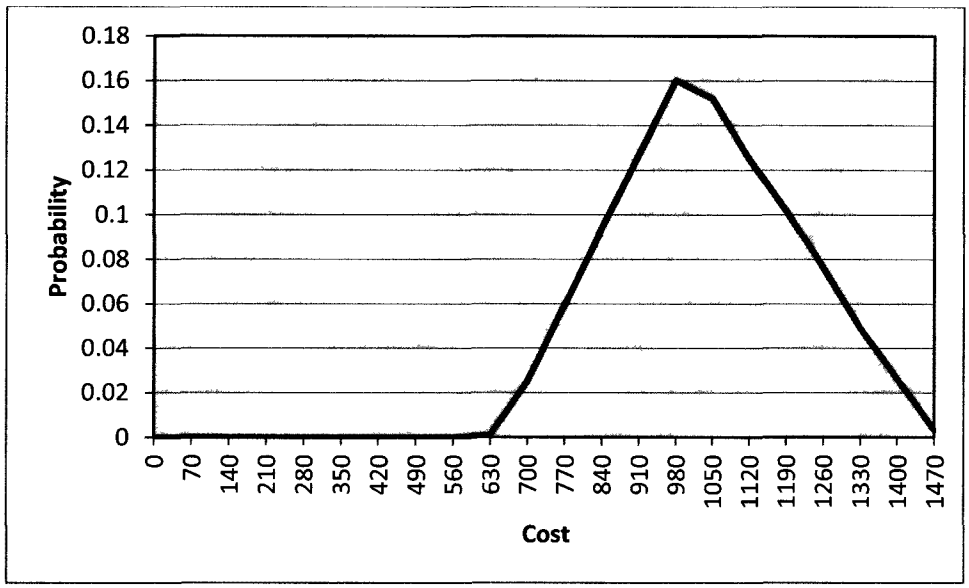


Figure 50. Probability distribution of ventilation-perfusion lung scan (VQ) cost.

MCS revealed PA cost values ranging from $1,072 to $8,370. Probability increased as PA cost increased, with the highest attained probability of .108 at a cost of $2,000, after which probability decreased. Probabilities for the costs (in dollars) of 1,200, 1,600, 2,400, 3,200, 4,000, 5,200, 6,000, 7,200 and 8,370 were .004, .071, .099, .086, .072, .055, .041, .023, and .003, respectively (see Figure 51).

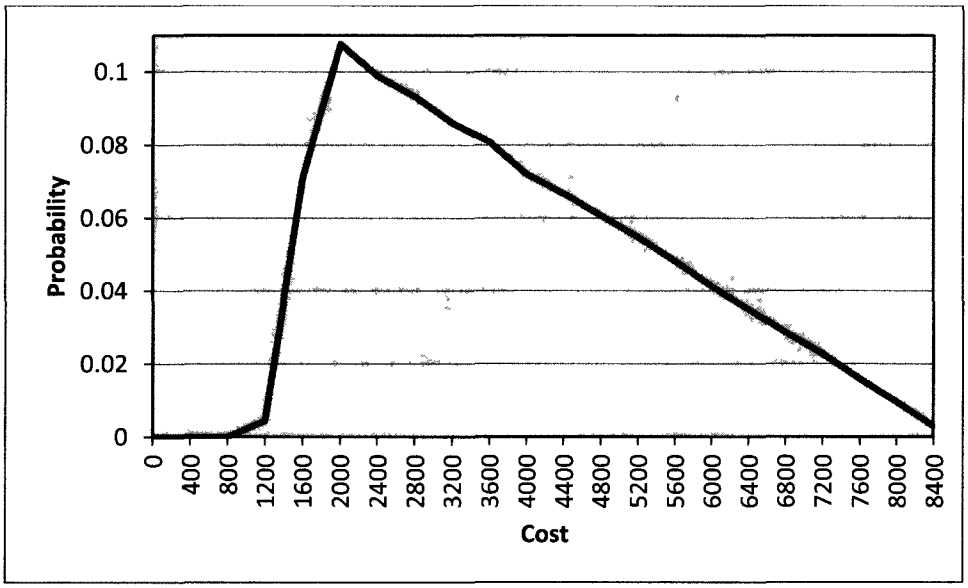


Figure 51. Probability distribution of invasive pulmonary angiography (PA) cost.

A Monte Carlo simulation unveiled treatment cost (Tr) values ranging from $1,450 to $1,639. Probability increased as treatment cost increased, with the highest attained probability of .638 at a cost of $1,600, after which probability decreased. Probabilities for the treatment costs (in dollars) of 1,520 and 1,639 were .274 and .088, respectively (see Figure 52).

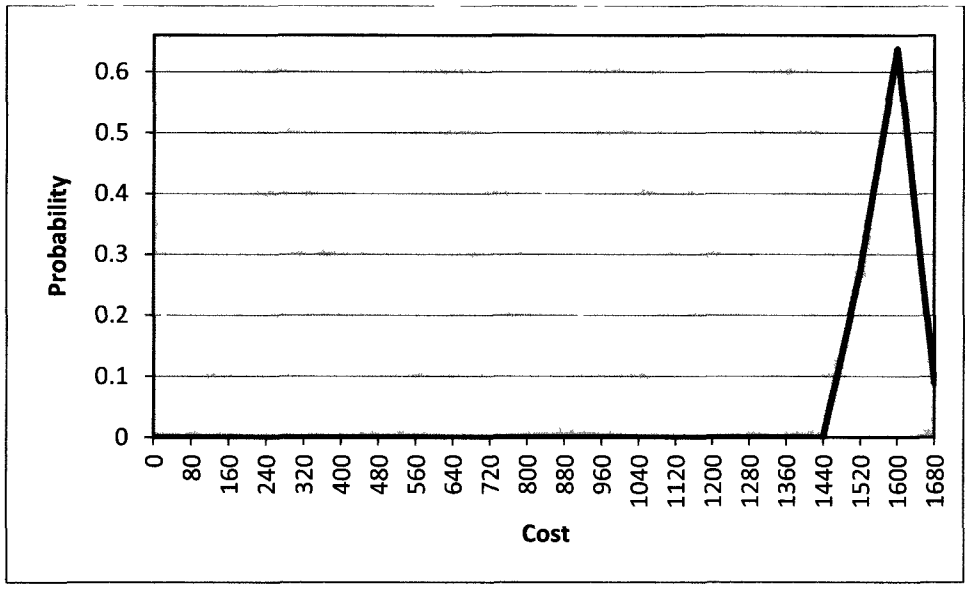
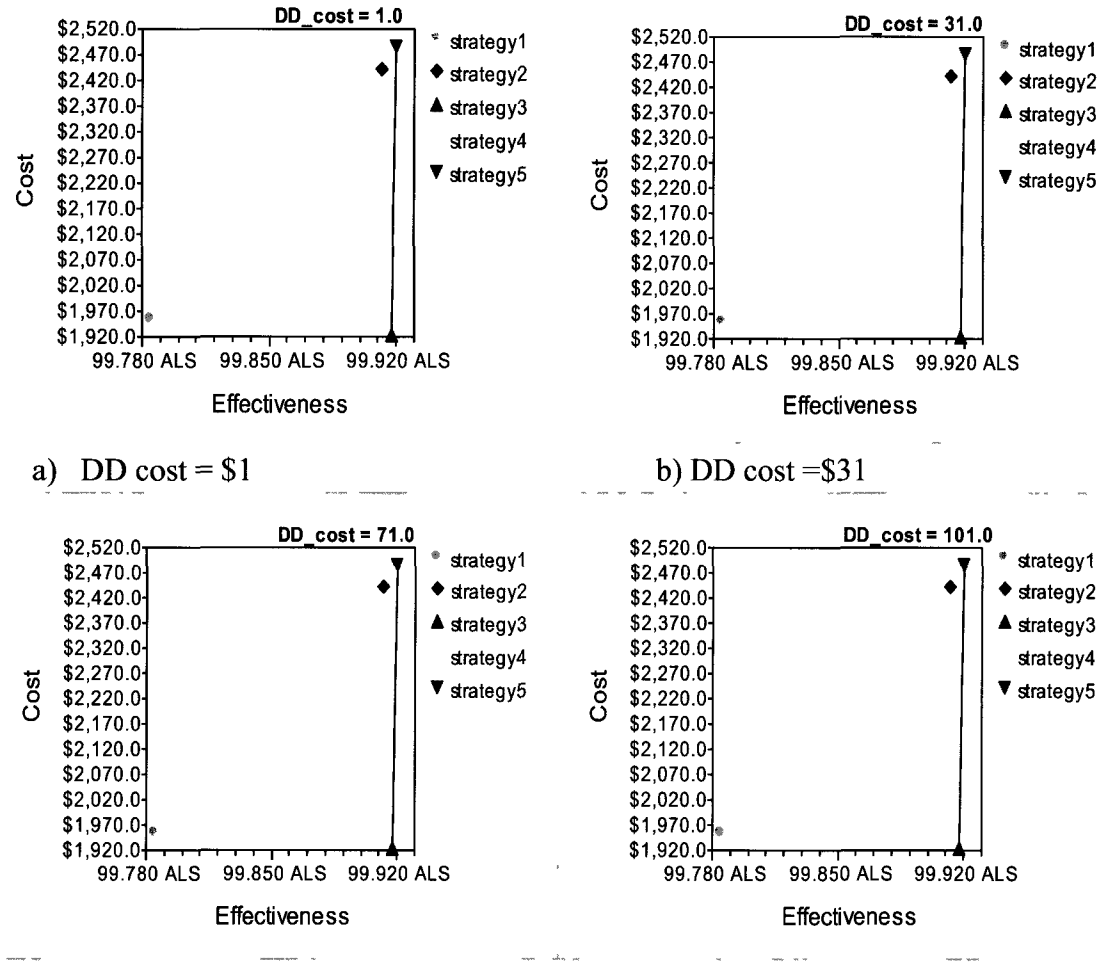


Figure 52. Probability distribution of treatment (Tr) cost.

One-Way Sensitivity Analysis

The DD cost in the one-way sensitivity analysis varied from $1 to $101, with all other factors (parameters) held constant. The analysis revealed that strategies 3 and 5 were cost-effective at each amount level (i.e., $1, $31, $71, and $101). Strategy 3 was the most cost-effective of all strategies and dominated strategies 1, 2, and 4 (see Figure 53).



a) DD cost = $1

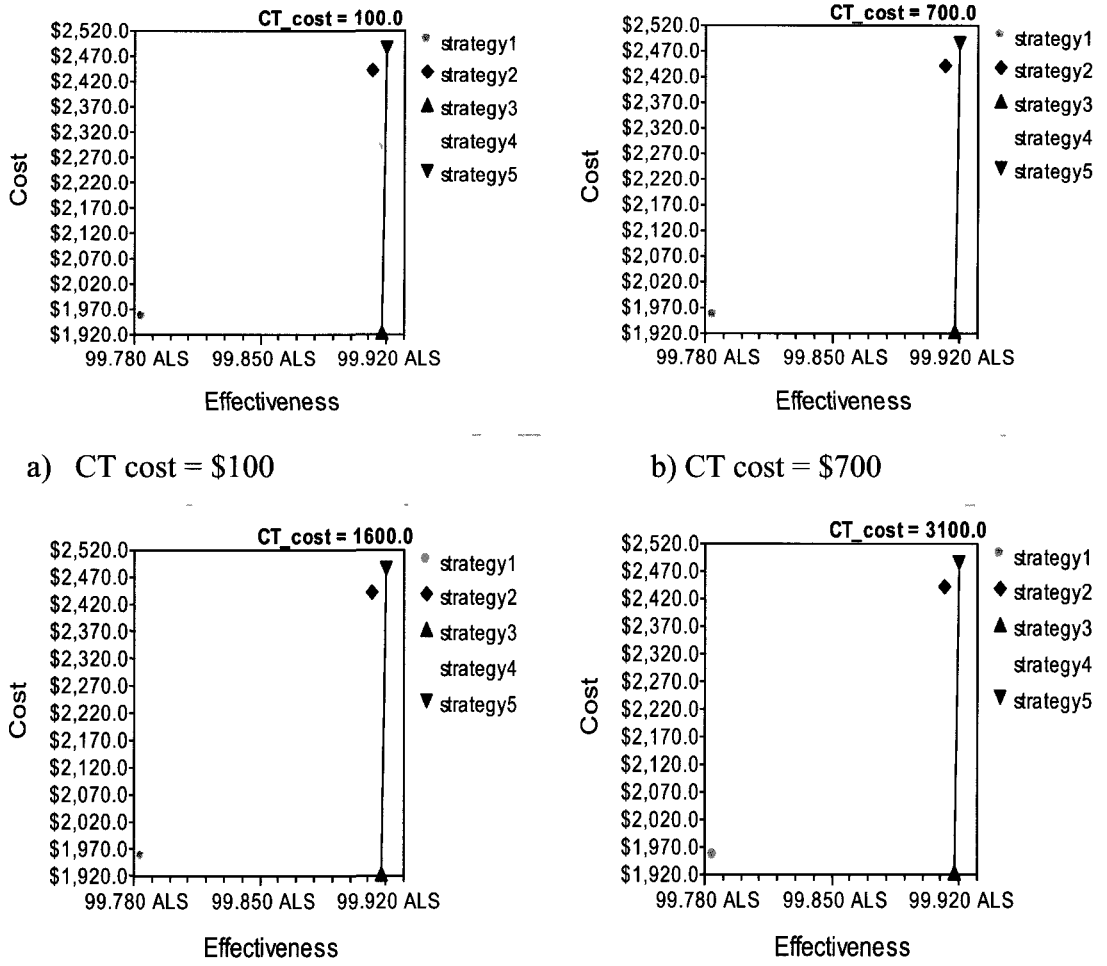
b) DD cost =$31

c) DD cost= $71

d) DD cost = $101

Figure 53. One-way sensitivity analysis on D-dimer test cost varying from $1 to $101. Strategy 1 = a CDR, a DD and a CT; Strategy 2 = a CDR, a DD, a CT, and a CUS; Strategy 3 = a CDR, a DD, a CUS, and a CT; Strategy 4 = a CDR, a DD, a VQ, and a CUS; Strategy 5 = a CDR, a DD, a CT, a CUS, and a PA. CDR = clinical decision rule; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS = compression ultrasonography; VQ = ventilation-perfusion lung scan; PA = invasive pulmonary angiography; ALS = additional lives saved.

Figure 54 reveals that the CT cost in the one-way sensitivity analysis varied from $100 to $3,100, with all other factors held constant. This analysis revealed that strategies 3 and 5 were cost-effective at each amount level (i.e., $100, $700, $1,600, and $3,100). Strategy 3 was the most cost-effective strategy and dominated strategies 1, 2, and 4.



a) CT cost = $100

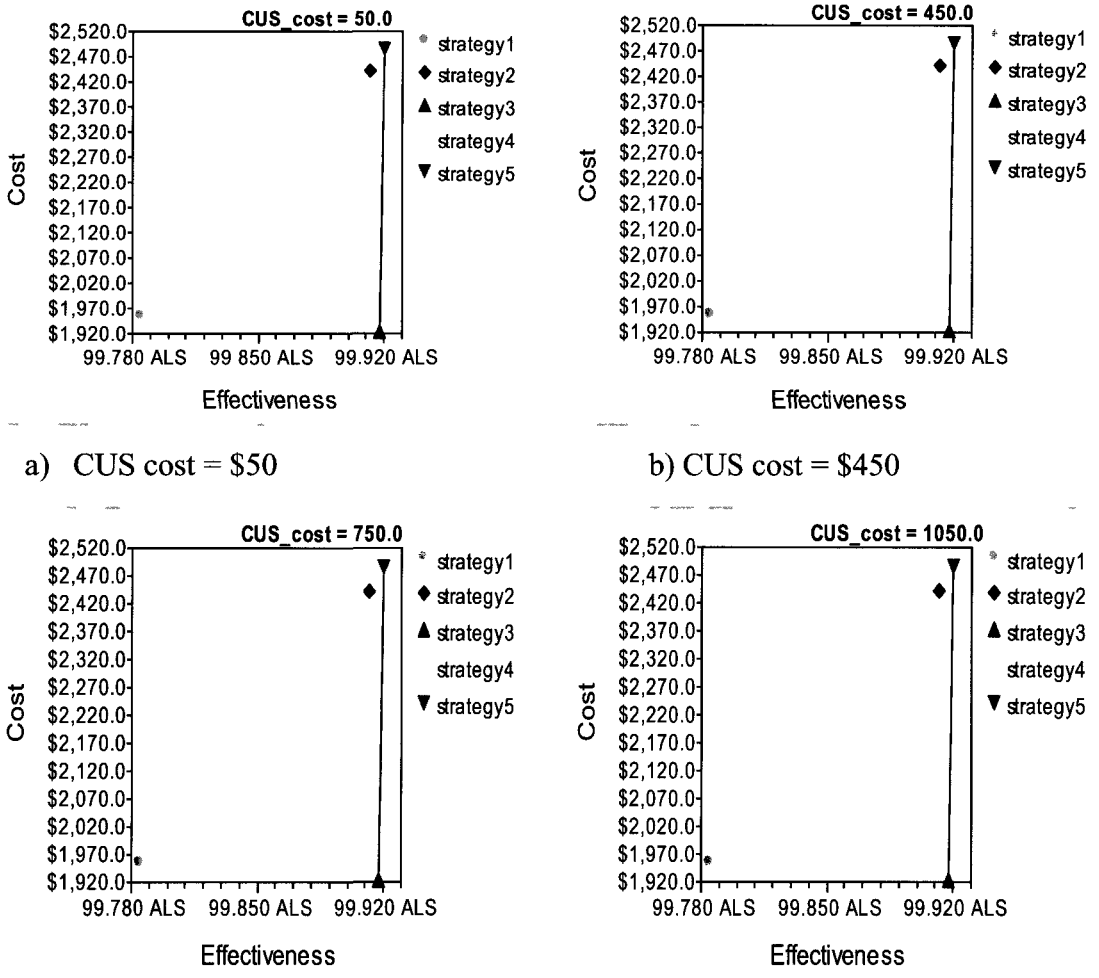
b) CT cost = $700

c) CT cost = $1,600

d) CT cost = $3,100

Figure 54. One-way sensitivity analysis on CT cost varying from $100 to $3,100. Strategy 1 = a CDR, a DD and a CT; Strategy 2 = a CDR, a DD, a CT, and a CUS; Strategy 3 = a CDR, a DD, a CUS, and a CT; Strategy 4 = a CDR, a DD, a VQ, and a CUS; Strategy 5 = a CDR, a DD, a CT, a CUS, and a PA. CDR = clinical decision rule; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS = compression ultrasonography; VQ = ventilation-perfusion lung scan; PA = invasive pulmonary angiography; ALS = additional lives saved.

Figure 55 indicates that the CUS cost in a one-way sensitivity analysis varied from $50 to $1,050, with all other factors held constant. The analysis revealed that strategies 3 and 5 were cost-effective at each amount level (i.e., $50, $450, $750, and $1,050). Strategy 3 was the most cost-effective strategy and dominated strategies 1, 2, and 4.



a) CUS cost = $50

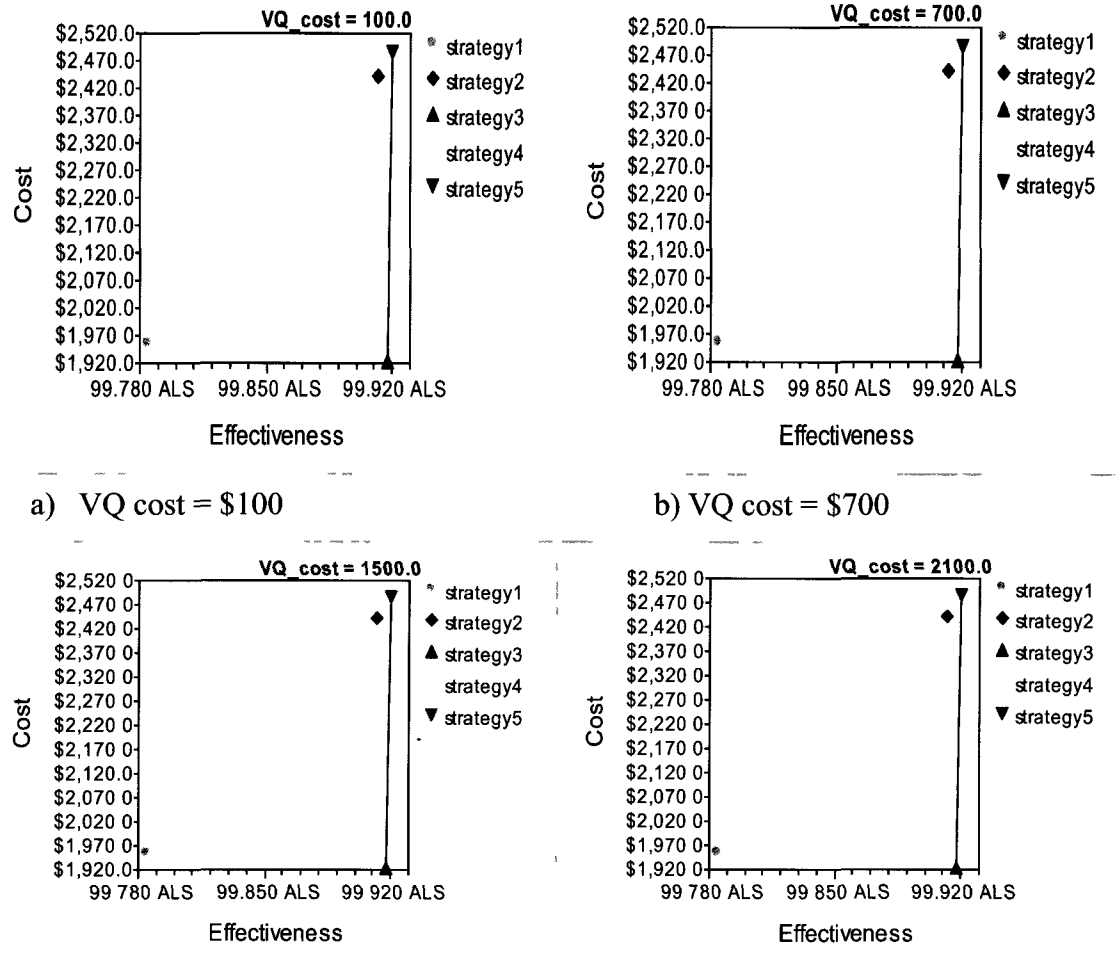
b) CUS cost = $450

c) CUS cost= $750

d) CUS cost = $1,050

Figure 55. One-way sensitivity analysis on CUS cost varying from $50 to $1,050. Strategy 1 = a CDR, a DD and a CT; Strategy 2 = a CDR, a DD, a CT, and a CUS; Strategy 3 = a CDR, a DD, a CUS, and a CT; Strategy 4 = a CDR, a DD, a VQ, and a CUS; Strategy 5 = a CDR, a DD, a CT, a CUS, and a PA. CDR = clinical decision rule; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS = compression ultrasonography; VQ = ventilation-perfusion lung scan; PA = invasive pulmonary angiography; ALS = additional lives saved.

A one-way sensitivity analysis revealed that the costs of VQ testing varied from $100 to $2,100 with all other factors held constant. Strategies 3 and 5 were identified as cost-effective at each amount level (i.e., $100, $700, $1,500, and $2,100). Strategy 3 remained the most cost-effective and dominated strategies 1, 2, and 4 (see Figure 56).



a) VQ cost = $100

b) VQ cost = $700

c) VQ cost = $1,500

d) VQ cost = $2,100

Figure 56. One-way sensitivity analysis on VQ cost varying from $100 to $2,100. Strategy 1 = a CDR, a DD and a CT; Strategy 2 = a CDR, a DD, a CT, and a CUS; Strategy 3 = a CDR, a DD, a CUS, and a CT; Strategy 4 = a CDR, a DD, a VQ, and a CUS; Strategy 5 = a CDR, a DD, a CT, a CUS, and a PA. CDR = clinical decision rule; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS = compression ultrasonography; VQ = ventilation-perfusion lung scan; PA = invasive pulmonary angiography; ALS = additional lives saved.

Results from the one-way sensitivity analysis of the cost of PA testing indicated cost variability from $100 to $9,100, with all other factors held constant. The analysis revealed that strategies 3 and 5 were cost-effective at each amount level (i.e., $100,

$1,900, $7,300, and $9,100). Strategy 3 was the most cost-effective strategy and dominated strategies 1, 2, and 4 (see Figure 57).

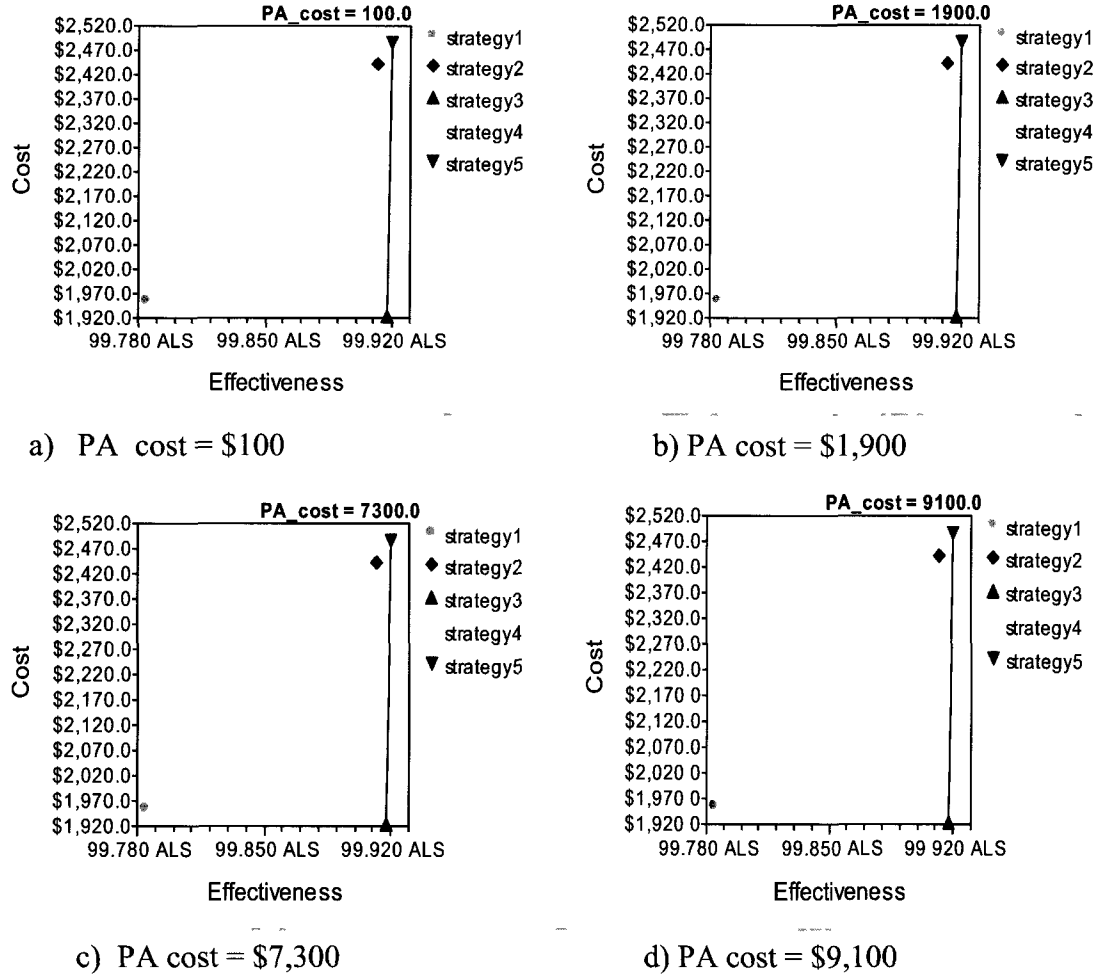
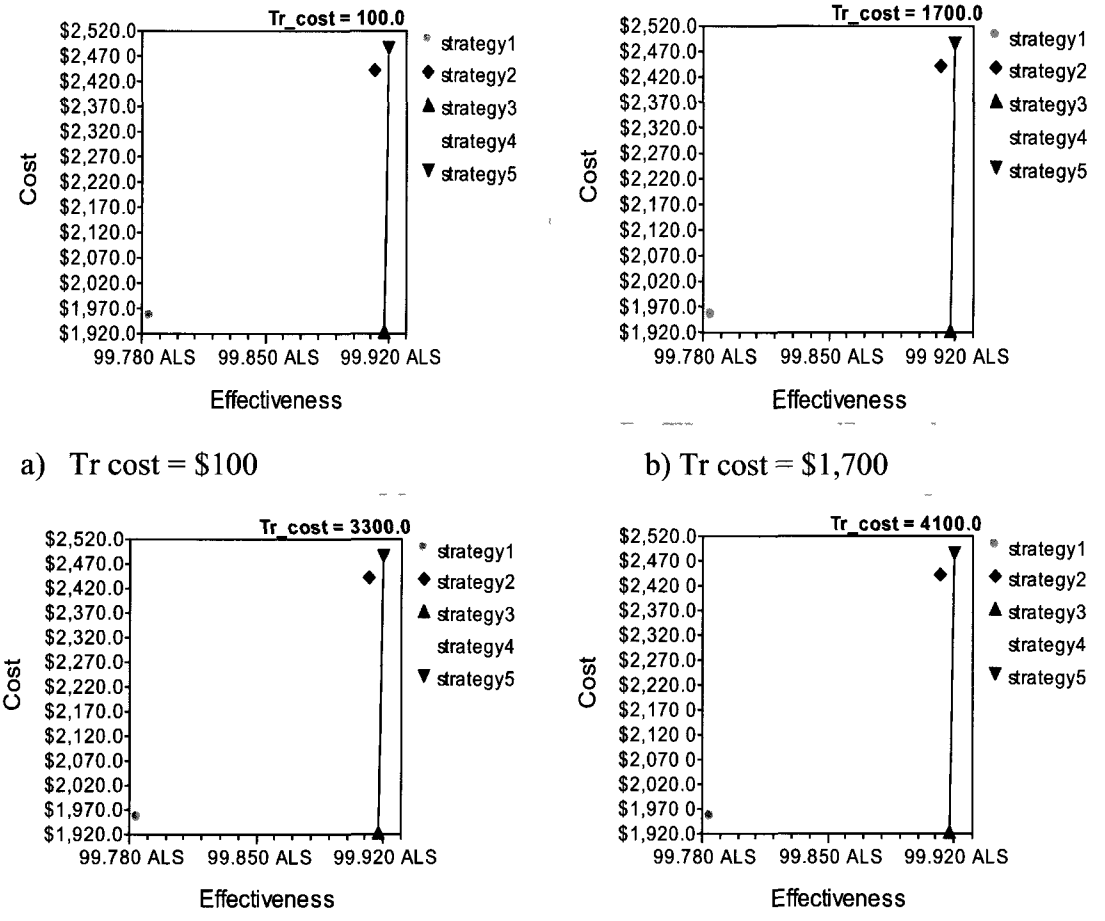


Figure 57. One-way sensitivity analysis on PA cost varying from $100 to $9,100. Strategy 1 = a CDR, a DD and a CT; Strategy 2 = a CDR, a DD, a CT, and a CUS; Strategy 3 = a CDR, a DD, a CUS, and a CT; Strategy 4 = a CDR, a DD, a VQ, and a CUS; Strategy 5 = a CDR, a DD, a CT, a CUS, and a PA. CDR = clinical decision rule; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS = compression ultrasonography; VQ = ventilation-perfusion lung scan; PA = invasive pulmonary angiography; ALS = additional lives saved.

The examination of PE treatment costs using a one-way sensitivity analysis showed that the cost varied from $100 to $4,100, with all other factors held constant. The

analysis revealed that strategies 3 and 5 were cost-effective at each amount level (i.e., $100, $1,700, $3,300, and $4,100). Strategy 3 was the most cost-effective strategy and dominated strategies 1, 2, and 4 (see Figure 58).



a) Tr cost = $100

b) Tr cost = $1,700

c) Tr cost = $3,300

d) Tr cost = $4,100

Figure 58. One-way sensitivity analysis on treatment cost varying from $100 to $4,100. Strategy 1 = a CDR, a DD and a CT; Strategy 2 = a CDR, a DD, a CT, and a CUS; Strategy 3 = a CDR, a DD, a CUS, and a CT; Strategy 4 = a CDR, a DD, a VQ, and a CUS; Strategy 5 = a CDR, a DD, a CT, a CUS, and a PA. CDR = clinical decision rule; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS = compression ultrasonography; VQ = ventilation-perfusion lung scan; PA = invasive pulmonary angiography; ALS = additional lives saved.

Two-Way Sensitivity Analysis

A two-way sensitivity analysis was employed to examine the impact of CEA results on simultaneous changes in the costs of two variables. This analysis revealed that strategy 3 was the dominant strategy for any pair of costs, indicating that it was the most cost-effective strategy. The results were robust for all imaging test changes. Specifically, the CUS cost varied from $50 to $1,050, the CT cost varied from $100 to $3,100, the VQ cost varied from $100 to $2,100, the PA cost varied from $100 to $9,100, and the treatment (Tr) cost varied from $100 to $4,100. The two-way analyses of the CUS and the CT cost, the CUS and the VQ cost, the CUS and the PA cost, and the CUS and the treatment cost are presented in Figure 59.

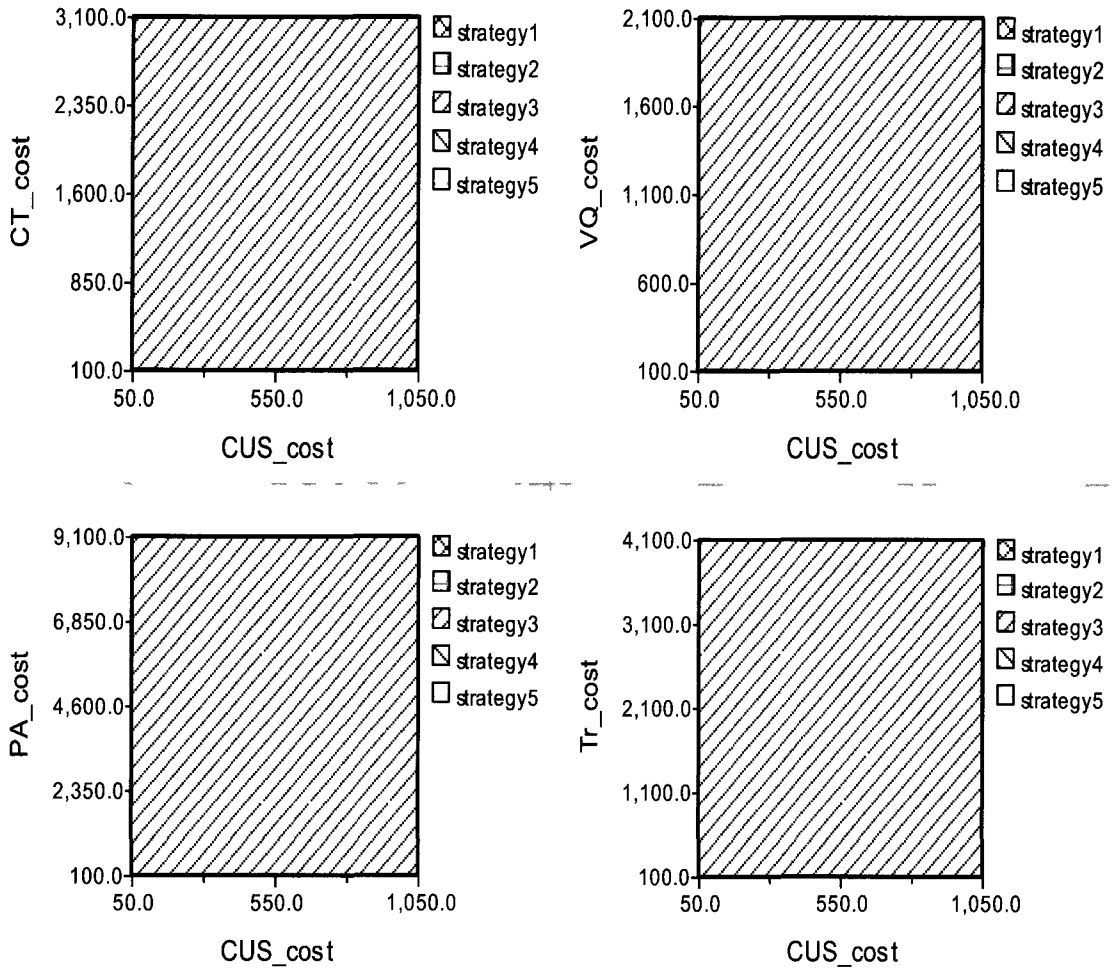


Figure 59. Two-way sensitivity analysis. Strategy 1 = a CDR, a DD and a CT; Strategy 2 = a CDR, a DD, a CT, and a CUS; Strategy 3 = a CDR, a DD, a CUS, and a CT; Strategy 4 = a CDR, a DD, a VQ, and a CUS; Strategy 5 = a CDR, a DD, a CT, a CUS, and a PA. CDR = clinical decision rule; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS = compression ultrasonography; VQ = ventilation-perfusion lung scan; PA = invasive pulmonary angiography; Tr = treatment.

Three-Way Sensitivity Analysis

A three-way sensitivity analysis examined the impact of CEA results on simultaneous changes in the costs of three variables. This analysis revealed that strategy 3 was the dominant strategy for any group of costs, indicating that it was the most cost-effective strategy. The results were robust for all imaging test changes. Particularly, the DD cost varied from $1 to $100, CUS cost varied from $50 to $1,050, the CT cost varied

from $100 to $3,100, the VQ cost varied from $100 to $2,100, the PA cost varied from $100 to $9,100, and the treatment (Tr) cost varied from $100 to $4,100. The three-way analyses of the CUS, the CT, and the DD costs are presented in Figure 60.

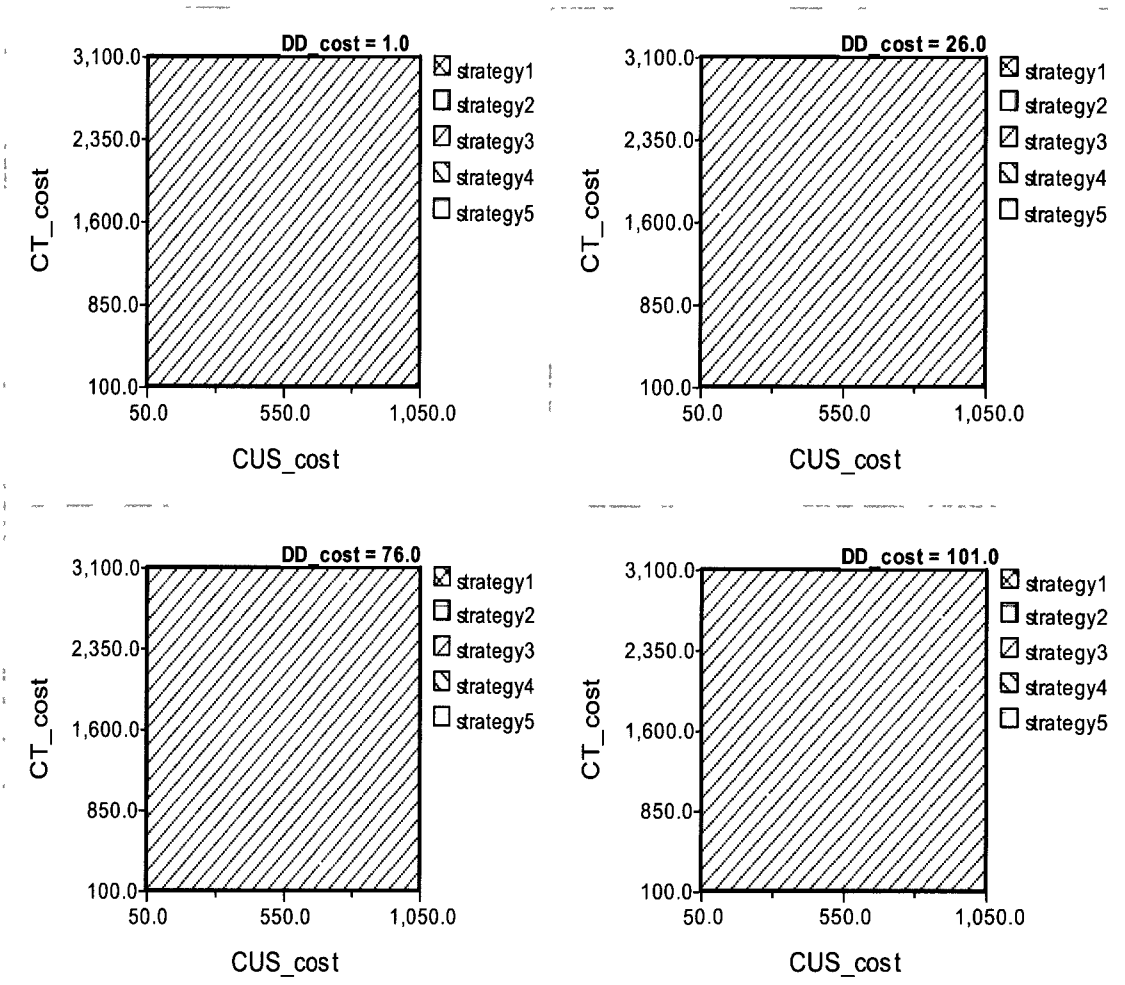


Figure 60. Three-way sensitivity analysis. Strategy 1 = a CDR, a DD and a CT; Strategy 2 = a CDR, a DD, a CT, and a CUS; Strategy 3 = a CDR, a DD, a CUS, and a CT; Strategy 4 = a CDR, a DD, a VQ, and a CUS; Strategy 5 = a CDR, a DD, a CT, a CUS, and a PA. CDR = clinical decision rule; DD = D-dimer test; CT = computed tomography pulmonary angiography; CUS = compression ultrasonography; VQ = ventilation-perfusion lung scan; PA = invasive pulmonary angiography.

CHAPTER 5

SUMMARY

This chapter presents the summary of the findings regarding parameter estimates, cost-effectiveness analyses, sensitivity analyses, limitations, and implications for practice and research. Differences between the research findings and those retrieved from the literature are addressed. Findings from the Monte Carlo simulation (MCS) probabilistic and one-way, two-way and three-way deterministic sensitivity analyses are compared.

Discussion

Parameter Estimates.

This research suggests that there is a linear increase in the adjusted-for-inflation direct costs. This study has demonstrated that trend line equations strongly support a linear increase in the adjusted-for-inflation direct costs, with high r^2 values indicating that more than 98% of the variation in the models is explained by these equations (see Tables 10 through 15).

Applying triangular distributions in a CEA to estimate expected direct cost values of PE diagnostic tests addresses variability in data retrieved from the literature, resolves uncertainty, and eliminates error in the assigned baseline values. This is a possible explanation for the differences between the expected cost values applied in the study and those identified in the literature. Consequently, by applying triangular distributions to estimate diagnostic test costs, the differences reported in the literature were combined (see Table 16 and Figures 9 through 20). All test and treatment costs were adjusted based

upon the estimations: DD ($28); CT ($1,121); CUS ($292); VQ lung scan ($1,003); PA ($3,676); and PE treatment cost for one year ($1,545).

The findings of this dissertation suggest that applying effectiveness based upon strategy failure rates to detect PE is an accurate way to address effectiveness payoff values in a CEA model. The use of γ distributions in a CEA assists with estimating expected strategy failure rates of the investigated PE diagnostic tests, addresses variability in data retrieved from the literature, resolves uncertainty, and eliminates error in the assigned baseline values. This may explain why the expected strategy failure rates applied in this study differ from those identified in the literature. Subsequently, by applying γ distributions to estimate PE diagnostic strategy failure rates, the differences reported in the literature were merged (see Table 19): strategy 1 (.576667); strategy 2 (1.099999); strategy 3 (.546667); strategy 4 (1.004999); and strategy 5 (.72500).

The use of γ distributions facilitates the estimating of sensitivity and specificity values of PE diagnostic D-dimer and imaging tests data obtained from the literature (see Tables 22 through 24). The application of γ distributions in a CEA to estimate expected sensitivity and specificity values of the investigated PE diagnostic tests addresses variability in the data retrieved from the literature, resolves uncertainty, and eliminates error in the assigned baseline values. It might explain why the expected sensitivity and specificity values applied in this study differ from those identified in the literature. By applying γ distributions to estimate PE diagnostic test sensitivity, the differences reported in the literature for sensitivity were combined: DD (95.174%); CT (88.112%); CUS (89.95%); VQ lung scan (82.775%); and PA (97.25%). Consequently, by applying γ distributions to estimate PE diagnostic test specificity, the differences reported in the

literature were combined: DD (47.775%); CT (94.569%); CUS (94.900%); VQ lung scan (90.5%); PA (97.0%).

The findings of this thesis further suggest that using a series of Bayes's theorem applications to estimate expected event probability values of the PE diagnostic tests based upon test sensitivities and specificities, addresses the accuracy of a given test. Consequently, in strategy 1 the accuracy of the CT is dependent upon the preceding DD results. In strategy 2, the accuracy of the CT is dependent upon the preceding DD results and the accuracy of the CUS is dependent upon the results of the preceding CT. In strategy 3, the accuracy of the CUS is dependent upon results from the preceding DD and the accuracy of the CT is dependent upon the preceding CUS. In strategy 4, the accuracy of the VQ lung scan is dependent upon the results from the preceding D-dimer test and the accuracy of the CUS is dependent upon a preceding VQ lung scan. In strategy 5, the accuracy of the CT is dependent upon the results from the preceding D-dimer test, the accuracy of the CUS is dependent upon the preceding CT, and the accuracy of the PA is dependent upon the preceding CUS (see Figure 21).

Cost-Effectiveness Analysis.

The cost-effectiveness analysis results demonstrated that strategy 3, comprising CDR, a DD, a CUS, and a CT, was the most cost-effective strategy and dominated strategies 1, 2 and 4. Additionally, strategy 5, comprising a CDR, a DD, a CT, a CUS, and a PA was a cost-effective strategy.

There is no assumption in this analysis about the different types of imaging tests. Imaging tests were clearly used in the model based upon the corresponding cost and effectiveness values as they were estimated by the statistical methodology of the analysis.

The use of a CUS after a high clinical probability or a positive D-dimer test is an appropriate, efficient, and safe approach suggested by several studies (Elias et al., 2005; Hull et al., 2001; Perrier et al., 2004; Righini et al., 2008; Van Erkel et al., 1999). The use of a CT after a high clinical probability or a positive D-dimer test and a negative CUS is considered an appropriate, efficient, and safe approach proposed by several studies (Elias et al., 2005; Perrier et al., 2004; Righini et al., 2008).

Sensitivity Analysis.

The results of the MCS probabilistic sensitivity analysis were robust for a number of distributions regarding PE diagnostic test costs, effectiveness, sensitivities, specificities, and event probabilities. Consequently, the sensitivity analysis results demonstrated that with a willingness-to-pay from $.01 to $3,000 strategy 3 demonstrated the highest probability of being cost-effective in comparison to the other strategies examined (see Table 32 and Figure 33).

The results of this investigation were robust over an extensive range of one-way, two-way, and three-way deterministic sensitivity analyses regarding PE diagnostic test costs (see Figures 53 through 60). The one-way sensitivity analysis revealed that strategy 3 remained the most cost-effective strategy in comparison to strategies 1, 2, 4, and 5 when applying the diagnostic test and treatment costs in various combinations. Specifically, the variation of D-dimer test costs from $1 to $101 revealed that both strategy 3 and strategy 5 remained cost-effective. The variation of CT costs from $100 to $3,100 revealed that both strategy 3 and strategy 5 remained cost-effective. The variation of CUS costs from $50 to $1,050 revealed that both strategy 3 and strategy 5 remained cost-effective. The variation of VQ lung scan costs from $100 to $2,100 revealed that

both strategy 3 and strategy 5 remained cost-effective. The variation of PA costs from $100 to $9,100 revealed that both strategy 3 and strategy 5 remained cost-effective. The variation of PE treatment cost from $100 to $4,100 revealed that both strategy 3 and strategy 5 remained cost-effective. In all cases for each variation, strategy 3 dominated strategies 1, 2, and 4.

Implications for Practice and Research

This research contributed to theory, methodology, and medical decision-making by exploring the boundaries of a complex medical diagnostic system, addressing uncertainty, and decision theory; providing a method specifically designed to assist medical decision-making under uncertainty; and assessing PE cost-effective strategies. The ability to determine the cost-effectiveness of diagnostic strategies may prove to be a valuable health policy planning tool at the national, state, or local level as well as for providers of health insurance programs. It also may prove vital for saving resources within a limited health budget, especially for countries facing deficit problems and/or a financial crisis such as Greece and Portugal (see IMF, 2011; OECD, 2010), or for smaller countries experiencing problems related to their occupation by foreign troops; for example, Cyprus (see Eleftheriou, 2009; IMF, 2011).

This thesis advocates for a clinical decision rule and a D-dimer test as a component of any PE diagnostic strategy. Therefore, an extensive use of D-dimer testing is recommended by this analysis. The increase in D-dimer test frequency will result in a substantial cost reduction of the overall PE diagnostic testing cost due to the decreased use of imaging tests. This shift in imaging test usage is valuable to low and intermediate clinical decision rule categories. The findings of this research also suggest that applying

triangular and γ distributions in a CEA facilitates the assessment of parameter estimates, addresses variability in data retrieved from the literature, resolves uncertainty, and eliminates error in the assigned baseline values. Further research is required to confirm these findings in a prospective study that establishes assumptions about the types of D-dimer and imaging tests performed. Finally, further research should be conducted to evaluate whether the methods implemented in this study are applicable for other diseases, such as for lung and cardiovascular diseases.

Conclusion

In conclusion, this CEA research suggests that, among the five PE diagnostic strategies investigated, the most cost-effective strategy appears to be strategy 3, comprising a CDR, a DD, a CUS, and a CT. An initial diagnosis should begin with a CDR and a DD since a negative DD rules out clinically suspected PE. If a positive DD is determined, then the diagnosis of PE should be investigated by performing a CUS. In patients with a positive CUS, a treatment should be applied; patients with a negative or nondiagnostic CUS require further investigation employing a CT. Alternatives to this approach such as strategy 5, which is composed of a CDR, a DD, a CT, a CUS, and a PA, appears to be a cost-effective, but it is a more expensive strategy than strategy 3. This strategy includes PA, which is an invasive test. Strategy 1, which consists of a CDR, a DD, and a CT, is a highly effective non-invasive technique but appears to be more expensive than strategy 3. Future work is needed to validate these findings in a prospective clinical trial before the delivery of a clinical recommendation.

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