CADTH

CADTH OPTIMAL USE REPORT

Optimal Strategies for the Diagnosis of Acute Pulmonary Embolism: A Health Technology Assessment

January 2018
Volume 6, Issue 3b
PROSPERO Registration Number: 42016046980

CADTH

Clinical Authors: Alison Sinclair, Kwakye Peprah, Teo Quay, Matthew McInnis, Eddy Lang, Melissa Severn, Sohail Mulla, Laura Weeks
Economic Author: Bernice Tsoi
Patient Perspectives and Experiences Authors: Elijah Herrington, Myuri Manogaran
Implementation Author: Sarah Garland
Ethics Author: Angel Petropaganos
Environmental Authors: Kwakye Peprah, Julie Polisena

Cite As: Optimal Strategies for the Diagnosis of Acute Pulmonary Embolism: A Health Technology Assessment. Ottawa: CADTH; 2018 Jan. (CADTH optimal use report; vol.6, no.3b).

ISSN: 1927-0127 (online)

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

CADTH

External Reviewers

This document was externally reviewed by content experts. The following individuals granted permission to be cited.

Dr. Michel Leblanc, MD, RCPSC ABNM
Chief of Staff
Nuclear Medicine, CIUSS-MCQ
University of Sherbrooke, Quebec

Dr. Nandini Dendukuri, PhD
Associate Professor
Department of Epidemiology, Biostatistics and Occupational Health Faculty of Medicine
McGill University, Quebec

Thomas Foreman, DHCE, MA
Ethicist
Health Ethics Alliance, Centre for Addiction and Mental Health
Sunnybrook Health Sciences Centre
Toronto, Ontario

Dr. Martin H. Reed, MD, FRCPSC, FACR
Radiologist
Department of Diagnostic Imaging
Children's Hospital
Winnipeg, Manitoba

Authorship

Clinical Review

Dr. Alison Sinclair led the clinical project protocol development and selected studies. She extracted, tabulated, and analyzed data; wrote the clinical section of the report; and revised the report based on reviewers' comments.

Kwakye Peprah contributed to article screening and selection, data extraction, and tabulation of data for the clinical review, and contributed to the writing of the clinical section of the report.

Teo Quay also contributed to article screening and selection, data extraction, and tabulation of data for the clinical review, and contributed to the writing of the clinical section of the report.

Dr. Matthew McInnis participated in the conceptualization of clinical approaches to imaging for pulmonary embolism and in the preparation and review of the draft reports.

Dr. Eddy Lang participated in the conceptualization of clinical approaches to imaging for pulmonary embolism and in the preparation and review of the draft reports.

Melissa Severn designed and executed the literature search strategies, wrote the literature search methods section and appendix, and managed report referencing.

Dr. Sohail Mulla contributed to the preparation of the clinical section in the protocol and provided methodological support throughout the project.

Dr. Laura Weeks contributed to the preparation of the clinical section in the protocol and provided methodological support throughout the project.

Economic Review

Dr. Bernice Tsoi led the economic protocol development, conducted the review of the economic literature, conducted the economic evaluation, wrote the economic section of the report, and revised the report based on reviewers' comments.

Patient Perspectives and Experience Review

Elijah Herrington contributed to the drafting and reviewing of the protocol sections for the patient perspectives and experience review; performed article selection, coding, and analysis; and reviewed and contributed to the drafting of the report.

Dr. Myuri Manogaran contributed to the drafting and reviewing of the protocol sections for the patient perspectives and experience review; performed article selection, coding, and analysis; and reviewed and contributed to the drafting of the report.

Implementation Review

Sarah Garland led the conception of the methodology for the implementation review and prepared the protocol sections for the implementation review, performed the analysis, and contributed to the drafting of the report.

Ethics Review

Dr. Angel Petropaganos conducted and wrote the ethics analysis of this report, participated in discussion and interpretation of the results.

Environmental Review

Kwakye Peprah contributed to article screening and selection, and to the writing of the environmental section of the report.

Dr. Julie Polisena contributed to article screening and selection, and to the writing of the environmental section of the report.

Acknowledgements

The authors would like to acknowledge the Health Technology Assessment Unit at the University of Calgary for reviewing the clinical data and draft health technology assessment report; Dr. Reem Mustafa, Dr. Payal Patel, Itziar Etxeandia Ikobaltzeta, and Dr. Parth Patel for reviewing and validating the clinical data; Andra Morrison for her contribution to the scoping of the clinical report; Tamara Radar for providing methodological support to the patient preferences and experiences review; Ken Bond for his contribution to the ethics review; and Kim Ghosh for her assistance in project management support.

Conflicts of Interest

There were no declarations of conflict of interest.

CADTH

Table of Contents

Tables

Figures

Abbreviations

3-D	three-dimensional
AUC	area under the curve
CI	confidence interval
CrI	credible interval
COPD	chronic obstructive pulmonary disease
CPR	clinical prediction rule
CT	computed tomography
CTEPH	chronic thromboembolic pulmonary hypertension
CTPA	computed tomography pulmonary angiography
CTV	computed tomography venography
DTA	diagnostic test accuracy
DVT	deep vein thrombosis
EANM	European Association of Nuclear Medicine
ECG	electrocardiography
ED	emergency department
HSROC	hierarchical summary receiver operating characteristic
HTA	health technology assessment
ICUR	incremental cost-utility ratio
LMWH	low-molecular-weight heparin
MAA	macroaggregated albumin
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
MRV	magnetic resonance venography
PA	pulmonary angiography
PE	pulmonary embolism
PERC	pulmonary embolism rule-out criteria
PTP	pretest probability
QALY	quality-adjusted life-year
QUADAS-II	Quality Assessment of Diagnostic Accuracy Studies, version 2
RCT	randomized controlled trial
ROBINS	Risk of Bias Assessment Tool for Nonrandomized Studies
ROBIS	Risk of Bias in Systematic Reviews
ROC	receiver operating characteristic
SD	standard deviation
SDC	structured data collection
SPECT	single-photon emission computed tomography
SROC	summary receiver operating characteristic
VKA	vitamin K antagonist
V/Q	ventilation/perfusion
V/Q SPECT	V/Q single-photon emission computed tomography
VTE	venous thromboembolism
US	ultrasound

Protocol Amendments

Section	Amendment	Page
Clinical	A decision was made to expand the search time frame for eligible studies based on feedback from clinical expert reviewers and CADTH's Health Technology Expert Review Panel, and on scoping of existing systematic reviews on the topic. Due to the perceived risk of exclusion of relevant literature with our original approach, a supplemental search was developed to retrieve systematic reviews published between January 1, 2011, and November 23, 2016. With the exception of the study design and date restrictions, the selection criteria for these systematic reviews was consistent with the original health technology assessment (HTA) protocol for research questions 2 and 3. Subsequently, primary studies included in the retrieved systematic reviews were screened based on the original inclusion criteria in the HTA protocol for research questions 2 and 3 to determine eligibility for inclusion, with the only deviation being no restriction on date of publication. Selected studies were incorporated into the analysis and reported alongside all previously identified literature. No supplemental search for primary studies was conducted.	p.19
Clinical	The protocol indicated that studies retrieved in alerts up to stakeholder review (September 2017) would be incorporated into the analysis and subsequent alerts would be included in the discussion. Due to the complexity of the analysis, studies identified in the alerts that met the selection criteria of the review were incorporated into the analysis up until February 1, 2017. Studies identified in the alerts that met the selection criteria of the review were incorporated into a summary section up until July 1, 2017, due to the large volume of literature and complex analyses.	p.20
Clinical	French-language studies were excluded due to lack of resources for translation, and this affected five studies.	p. 23
Clinical	In addition to the ROBIS tool, the systematic reviews in the clinical reviews were assessed using the following four items from AMSTAR: • Was the status of publication (i.e., grey literature) used as an inclusion criterion? • Was a list of included studies provided? • Was a list of excluded studies provided? • Was the conflict of interest included?	p. 24
Clinical	The protocol originally included PET-CT as a possible modality for the diagnosis of pulmonary embolism. During review of the report, the reviewers indicated that PET modalities were not used in clinical practice for this indication. Although the literature search included studies on PET-CT, they were removed from the scope.	p.29 (Table 1)

AMSTAR = Assessment of Multiple Systematic Reviews; HTA = health technology assessment; PET-CT = positron emission tomography–computed tomography; ROBIS = Risk of Bias in Systematic Reviews.

Executive Summary

Issue

The optimal diagnostic strategy for suspected pulmonary embolism (PE) among experts remains controversial, and it can differ based on factors related to the health care setting (i.e., urban, rural, or remote) that may affect access to imaging. The optimal diagnostic strategy would, in theory, have high diagnostic accuracy and clinical utility, at an acceptable cost, and would also be acceptable to patients and balance ethical considerations. However, issues of access may also influence what is considered optimal for different populations. Patient safety concerns associated with exposure to radiation and contrast media that accompanies several imaging studies also disproportionately affect specific patient groups, including pregnant women.

Objectives

The objective of this health technology assessment (HTA) is to assess the optimal diagnostic strategy for acute PE in urban, rural, and remote settings through an assessment of the diagnostic test accuracy, clinical utility, safety, cost-effectiveness, patients' perspectives and experience, implementation issues, and the environmental impact of strategies for the diagnosis of adults with suspected PE.

Clinical Evidence

Methods: An overview of systematic reviews on risk stratification strategies was performed for the research question, and a de novo systematic review and meta-analyses were conducted on diagnostic pathways and diagnostic imaging studies. The published literature was identified by searching the following databases: MEDLINE (1946–) with in-process records and daily updates, via Ovid; Embase (1974–) via Ovid; the Cochrane Database of Systematic Reviews; the Database of Abstracts of Reviews of Effects (DARE); Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCO; and PubMed. Two reviewers independently, and in duplicate, screened all titles and abstracts of citations identified by the search as well as the full-text articles.

Results: Six systematic reviews on risk stratification strategies and a total of 110 eligible studies that described the diagnostic test accuracy, comparative clinical utility, and/or safety of diagnostic pathways, including imaging studies and imaging studies alone, for the diagnosis of PE in adult patients were included. The results of the overview of systematic reviews indicated that the Wells rule for predicting PE probability, regardless of cut-off (< 2 or ≤ 4), showed greater specificity than either the Geneva score or the revised Geneva score. There were not enough data or consistency in trends to allow a conclusive statement about which clinical prediction rule (CPR) had the best sensitivity. Strategies combining CPRs and D-dimer testing were effective and safe to rule out PE in patients presenting with suspected PE symptoms.

No information on diagnostic test accuracy was available for pathway studies. Sufficient information was available for individual diagnostic test accuracy meta-analysis for computed tomography (CT), magnetic resonance imaging (MRI), ultrasound (US), ventilation/perfusion (V/Q), and V/Q single-photon emission computed tomography (V/Q SPECT). The meta-analysis included an adjustment for the use of variable and imperfect reference standards in

the pooled studies. With the exception of V/Q (sensitivity 0.864), all imaging modalities had pooled sensitivity greater than 0.950, and, with the exception of V/Q SPECT (specificity 0.914), all imaging modalities had pooled specificity greater than 0.940, with CT having both the highest estimates of sensitivity and specificity, and the least statistical heterogeneity. CT and V/Q SPECT both offer similar high estimates for sensitivity, and therefore the lowest number of missed diagnoses when used for rule-out testing. There was greater uncertainty in the estimates for US, V/Q, and V/Q SPECT. The results for thoracic US, in particular, varied widely according to the choice of the statistical model. We were unable to explain the heterogeneity with the available patient and study covariate data, although for V/Q and V/Q SPECT, the differing interpretation criteria and handling of indeterminate (nondiagnostic) values may have contributed. CT, V/Q, and V/Q SPECT have all been used as part of routine clinical practice, while US has limited use, and MRI is still being investigated.

Safety data tended to be sparsely reported, and renal and allergic adverse events or procedural complications were few and generally not serious for all modalities. Few studies reported radiation doses, although most studies that used CT identified concerns about radiation exposure in the discussion. Most of the studies excluded patients with absolute or even relative contraindications for imaging, potentially lowering the risk of adverse events. Conversely, many drew from an in-patient population, potentially raising the risk. It is therefore difficult to anticipate how much risk the risk of adverse events in the study population might differ from the general clinical population.

At least one study reported proportion with test failure for CT, MRI, Q SPECT, V/Q, and V/Q SPECT, found that test failure was low for all modalities; all but MRI (proportion with test failure 0.034) were below the accepted failure rate of 3% over three months. Moreover, proportions with test failure from diagnostic pathways (consisting of combinations of CPR, D-dimer, CT, and V/Q) were below 3% for eight of 10 pathways. There were no studies of diagnostic test accuracy in pregnant patients, and comparative utility data only for V/Q and CT. Proportions with test failure for both CT and V/Q modalities in pregnant patients were well below the acceptable threshold of 3% venous thromboembolism (VTE) risk over three months; however, there were more cases of VTE in patients negative for PE based on CT results.

Economic Evidence

Methods: A decision-analytic hybrid model was constructed to examine the clinical outcomes and costs associated with the diagnostic management of patients suspected of acute PE. It entailed an upfront decision tree that captured the short-term screening outcomes and a downstream Markov model to capture the long-term outcomes following a correct or incorrect diagnosis. The clinical pathway and decision-analytic model were developed by reviewing existing clinical and economic literature, and the conceptualization of the model and its structure was subsequently validated by clinical experts from different medical specialties involved at different stages of the diagnostic process and clinical management of PE (e.g., radiology, emergency medicine). The primary outcome was cost per quality-adjusted life-years (QALYs) gained, in 2017 Canadian dollars. As the clinical and cost consequences of a diagnosis of PE can persist indefinitely, a lifetime time horizon was adopted.

Results: The results of the economic analysis suggest that diagnosing patients with PE was generally cost-effective if willingness to pay was greater than $1,481 per QALY. A trade-off emerged between false-positives and false-negatives, as diagnostic strategies with higher

incremental cost-utility ratios (ICURs) had fewer false-negatives but were associated with more false-positive findings. A diagnostic strategy involving CT was most likely to be cost-effective as long as there are no contraindications, as CT was found to have the highest diagnostic test accuracy and the lowest proportion of nondiagnostic findings and was associated with the lowest costs to perform among diagnostic imaging modalities. The use of CPRs to determine clinical pretest probability of PE and the application of rule-out test for patients with low-to-moderate risk of PE may be cost-effective, while reducing the proportion of patients requiring CT and lowering radiation exposure (Table 1). The economic model was robust to most sensitivity analyses, including scenarios that explored alternative parameter inputs for diagnostic test accuracy. Parameters with the greatest impact on the results included the analyzed time horizon (i.e., three months), the prevalence of PE, and the management of patients with moderate pretest probability of PE based on the Wells criteria. In terms of specific patient populations, separate analyses were conducted on patients for whom CT was contraindicated or on patients who were pregnant. In a setting in which only nuclear medicine imaging modalities exist, diagnostic strategies involving V/Q SPECT, with leg US to resolve nondiagnostic findings, could be cost-effective depending on one's willingness-to-pay threshold. In pregnant patients, offering leg US earlier in the diagnostic pathway as an ancillary test before diagnostic imaging would be cost-effective if the willingness-to-pay threshold was greater than $7,882 per QALY.

Table 1: Economic Analysis Reference-Case Results

Strategy				Diagnostic test accuracy				Costs ($)	QALYs	Number of Patients Undergoing CT	Expected Effective Dose of Radiation (mSv)	ICUR ($/QALY)
Risk Stratification		Dx Imaging	Test for Non-Dx Findings	TP	FP	TN	FN					
No imaging				0	0	0.848	0.152	2,997	21.690	0	0	Reference
Revised Geneva	PERC > D-dimer	CT	CT	0.133	0.039	0.809	0.018	3,937	22.417	0.56	3.04	1,292
Wells: 3-tier	PERC > D-dimer	CT	CT	0.134	0.040	0.808	0.018	3,945	22.420	0.57	3.07	3,212
Wells: 2-tier	PERC > D-dimer	CT	CT	0.138	0.047	0.801	0.014	4,073	22.439	0.66	3.54	6,561
Wells: 2-tier	D-dimer	CT	CT	0.139	0.054	0.794	0.013	4,183	22.449	0.73	3.93	11,435
None		CT	CT	0.141	0.079	0.769	0.011	4,571	22.458	1	5.39	42,513

CT = computed tomography; Dx = diagnostic; FN = false-negative; FP = false-positive; ICUR = incremental cost-utility ratio; PERC = pulmonary embolism rule-out criteria; QALY = quality-adjusted life-year; TN = true negative; TP = true positive.

Patients' Perspectives and Experiences

Methods: A rapid review of the published qualitative literature was conducted to gain an understanding of patients', family members', and nonclinical caregivers' perspectives and experiences of the process of undergoing diagnosis for acute PE. Patient experiences information was identified by searching the following bibliographic databases: MEDLINE (1946–), with in-process records and daily updates, via Ovid; Embase (1974–) via Ovid; PsycINFO (1967–) via Ovid; CINAHL (1981–) via EBSCO; PubMed; and Scopus. To be eligible, studies must have explored or assessed the perspectives of patients and caregivers

directly and not indirectly, for example, through another person. A descriptive analysis was performed to characterize the included studies in terms of important study and patient characteristics (e.g., sample size, inclusion criteria), and a thematic analysis was conducted by a single reviewer.

Results: A total of 1,891 citations were identified in the literature search, and seven studies were included. Several studies on the individual experiences spoke to the ways in which the power of these diagnostic technologies to map out both current and prospective health concerns helped to mitigate various levels of discomfort felt throughout the respective examinations. Nonetheless, however powerful this prognostic potential “to know” may be, many participants still framed their experience in terms of their concerns with self-control, isolation, and lack of preparation. In addition, self-control could be placed under threat at any point throughout the imaging process. Moreover, physical reminders of the presence of loved ones or more verbal or visual reminders of a radiographer’s presence could serve as anchors throughout the imaging process and help alleviate related concerns. Similarly, although potentially irrelevant to the emergency room diagnostic process for PE, clear lines of communication between individual and clinicians before examination could help to alleviate these concerns.

Implementation Issues

Methods: A survey was developed to provide information and context on this topic, and conducted as part of a CADTH Environmental Scan. The objectives of the Environmental Scan were to identify current practice related to diagnostic strategies for PE in Canada; identify which tests, scans, and tools are available across Canadian jurisdictions and settings (i.e., urban, rural, and remote health care centres) to diagnose PE; and identify challenges and enablers to the diagnosis of PE, including relevant implementation issues in Canada. A targeted literature search was conducted to identify information on issues relevant to implementation of diagnostic strategies for PE in Canada. The peer-reviewed search strategy was developed. To supplement the findings of the survey and the literature search, an interview with a clinical expert in the field of emergency medicine was conducted. This interview centred on the expert views of the approach to diagnosing PE, including challenges to diagnosis and the Canadian context.

Results: Twelve survey responses (from clinicians, directors of diagnostic imaging, a medical director, and a department head) were received from five jurisdictions, and nine English-language primary studies were included in the summary of the literature. The results indicate that provider knowledge and choice, as well as patient factors, may influence the initial assessment and subsequent investigation of suspected PE, and policies and protocols can be used to support the diagnostic strategies for PE. Further resources, including staffing and access to tests, scans, and imaging, are differentially located across the country. As evidenced in the literature, and from the survey and interview, access to tools and tests used to diagnose PE varies across Canada and differs depending on whether a site is located in an urban centre, rural area, or remote setting.

Environmental Impact

Methods: A literature search was performed by an information specialist, using a peer-reviewed search strategy. Environmental impact information was identified through targeted literature searches of the following bibliographic databases: MEDLINE (1946–), with in-process records and daily updates, via Ovid; Embase (1974–) via Ovid; CINAHL (1981–) via EBSCO; Scopus; and PubMed. No methodological filters were applied to limit retrieval by study design. Retrieval was limited to documents published since January 1, 2007, and results were limited to English- and French-language publications. Two reviewers screened the titles and abstracts of all citations retrieved from the literature search for relevant studies and reports. Full-text articles were retrieved and assessed for inclusion by the two reviewers if either of them considered a citation potentially relevant to the research question.

Results: The literature search did not find any studies or reports that evaluated the environmental impact of imaging modalities for PE.

Ethical Issues

Methods: A review of the empirical and normative bioethics literature was conducted to identify two types of literature relevant to the identification and analysis of the potential ethical issues with diagnosing acute PE. Published literature was identified by searching the following databases: MEDLINE (1946–), Embase (1974–), and PsycINFO (1967–) via Ovid; Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCO; and PubMed. The main search concepts were PE or VTE and Wells or Geneva CPRs, PE rule-out criteria (PERC), D-dimer testing, CT technologies, MRI technologies, V/Q-based technologies, positron emission tomography–CT (PET-CT), and thoracic US (plus echocardiography). Retrieval was limited to documents published since January 1, 2006, and the search was limited to English- or French-language literature. The selection of relevant literature occurred in two stages. In the first stage, the title and abstracts of citations were independently screened for relevance by one reviewer. Articles were categorized as “potentially relevant” or “not relevant” based on whether ethical issues were explicitly mentioned. In the second stage, full-text reports that pertained to strategies for the diagnosis of acute PE and suggested implicit ethical issues were identified by two reviewers.

Results: The database search results yielded 590 records, and an additional 14 articles were found from a Google search for ethical issues related to radiology and deep vein thrombosis, more generally, were identified. A total of 42 articles were included in this study. Of these 42 articles, two explicitly acknowledged “ethics” related to the diagnosis of PE. The findings suggest that there is variation on the clinically and ethically appropriate diagnostic pathway for individual patients, given their unique histories, location, and medical needs. The ethical considerations related to the diagnosis of PE will vary to some degree for clinicians across different specialties. There are likely to be similar ethical considerations for different health care organizations, but the ways to address these ethical challenges may vary across organizations. At a systems level, there appears to be greater ethical difference between the various diagnostic pathways and imaging modalities for the diagnosis of PE. According to the economic models and clinical review, the use of CT seems to be the most likely candidate for the ethical provision of PE diagnosis.

Conclusions

The findings in the overview of reviews indicate that, while similar, the CPRs differ in their ability to identify a low-risk group of patients. Therefore, the economic analysis found that their cost-effectiveness varies, depending on the trade-off between sensitivity and specificity. For PERC, there is a risk of misdiagnosis, with more false-negative findings. With increasing willingness to pay, PERC ceases to be a cost-effective strategy. With respect to imaging modalities, CT had the highest diagnostic test accuracy and was the most cost-effective; however, CT also involved higher radiation exposure than all the other imaging modalities and is not appropriate for all patients (for example, patients who are pregnant, who have severe kidney disease, or who have an allergy to contrast media). For these patients, V/Q SPECT may be an appropriate alternative imaging modality within the diagnostic pathway, as seen from the clinical and economic evidence.

Patient factors and provider knowledge and choice can influence the initial assessment and subsequent investigation of suspected PE. As well, the variability of access to PE diagnostic tools and tests used across Canada and in urban, rural, and remote settings may influence PE diagnosis. More specifically, resources, including staffing and access to tests, scans, and imaging, are differentially located across the country. Policies and protocols can be established to support diagnostics strategies for PE. Additional support for PE diagnosis can come from clinical guidelines and other tools, such as computer prompts. The ethical issues associated with patients, clinicians, health care organizations, the health care system, and society are grounded in several principles, including beneficence, nonmaleficence, autonomy, and justice. The use of CT seems to be the most likely candidate for the ethical provision of PE diagnosis, as the results indicated that it is the most cost-effective modality.

Rationale and Policy Issues

Overview

Acute pulmonary embolism (PE) is the third most common acute cardiovascular disease, after myocardial infarction and stroke.[1] It is part of the continuum of venous thromboembolism (VTE), which also includes deep vein thrombosis (DVT).[2] Most PEs originate from thrombi in the leg or pelvic veins, which can dislodge and travel through the venous system, eventually obstructing blood vessels of the lung.[3] Evidence of lower-limb DVT is found in about 70% of patients who have sustained a PE,[1] but PE can also present in isolation.[4,5] An accurate estimate of PE incidence is difficult to obtain, because a significant proportion of PE is detected on autopsy,[6] and not all of these emboli are clinically relevant. It has been estimated that, in 80% of patients identified with PE at autopsy, the PE was unsuspected or undiagnosed before death.[7] Assuming the incidence rate in Canada is similar to that in the US, PE likely afflicts between 0.1% and 1% of the population.[7]

Mechanism and Outcomes

Blockages of the pulmonary artery and its branches can lead to obstruction of blood flow. Resulting pressure in the lungs may increase backflow of blood to the heart, leading to increased right heart pressure and causing right ventricular strain, which can, in turn, lead to cardiovascular compromise and low oxygen levels.[8] Other complications include pulmonary hemorrhage and loss of oxygen supply. PE is a major cause of emergency hospitalization, and clinical expression can range from asymptomatic disease to sudden death. Acute PE can lead to chronic thromboembolic pulmonary hypertension and right ventricular failure if it is not promptly diagnosed and treated.[4] Patients with delayed diagnosis tend to have worse outcomes.[9] Case fatality is high and can vary, depending on whether the condition is recognized and treated. Approximately 2% to 10% of patients treated for PE die from causes attributable to the condition.[10,11] Untreated PE can be fatal in up to 30% of patients. If administered promptly, anticoagulation therapy is highly effective at preventing extension of thrombus and can prevent mortality and morbidity associated with PE.[12]

Diagnosis

Diagnosis of PE typically requires a multi-component approach, involving initial clinical assessment of risk (i.e., risk stratification involving clinical prediction rules and ancillary tests, e.g., D-dimer, chest X-ray) followed by confirmation with diagnostic imaging. An overview of the challenges related to diagnosis and diagnostic strategies evaluated within this review is provided in the following sections.

Symptoms and Risk Factors

There are many challenges associated with diagnosing PE, among them the nonspecific nature of common PE symptoms, the most common of which include dyspnea and chest pain.[13,14] A number of conditions, including rib or vertebral body fracture, acute myocardial infarction, pulmonary edema, pneumonia, cancer, or interstitial lung disease, can have symptoms similar to those of PE. On the other hand, approximately 30% of patients with PE may be asymptomatic.[15] Non-specific symptoms can lead to over-testing, as PE may be considered in the differential diagnoses of a range of symptoms.

PE rarely occurs in the absence of risk factors, and the likelihood of PE increases when multiple risk factors are present. Factors associated with the development of PE can be inherited or acquired. Some common risk factors include, but are not limited to, malignancy, immobilization, surgery, extremity paresis, hormone replacement therapy or oral contraception, and factor V Leiden and other inherited or acquired thrombophilia conditions.[16] Patients who have DVT or who are taking medications that alter coagulation of the blood are also at risk of developing PE.[5,17] In addition, pregnant women are four to five times more likely to develop VTE, which is one of the leading causes of maternal death during childbirth.[18] This is, in part, due to physiological changes in coagulopathy and to mechanical factors such as vein compression in pregnancy. Many symptoms of PE may overlap with regular pregnancy symptoms, such as shortness of breath and edema in the lower limbs.

Risk Stratification

The likelihood of PE can be estimated using various risk-stratification approaches. A patient may initially undergo assessment with a clinical prediction rule (CPR) or clinical gestalt. Patients with a high probability of PE may proceed directly to imaging, while patients with low probability may undergo further testing such as pulmonary embolism rule-out criteria (PERC) or D-dimer testing to further assess the need for diagnostic imaging. This may be supplemented by additional biochemical or imaging studies to rule out differential diagnoses or strengthen estimates of PE risk. Determining PE risk during initial assessment may reduce the overall need for imaging, save diagnostic time and costs, and reduce complications, including downstream risks of radiation exposure.[19]

Clinical Prediction Rules

Evidence supports the practice of determining the clinical pretest probability of PE before proceeding with diagnostic testing.[20] The American College of Physicians has provided best-practice advice on the evaluation of patients with suspected acute PE, noting that the first step when evaluating a patient is to establish his or her pretest probability of PE.[21] Clinicians use clinical gestalt in decision-making around pulmonary embolism, although this process is less objective and tends to vary with experience.[22] CPRs (also called clinical decision rules) aim to determine risk profile and the necessity of undergoing diagnostic testing using a standardized approach. The American College of Physicians recommends using either the Wells or Geneva CPRs.[21]

The Wells rule was designed in 2000 based on an analysis of 40 clinical variables associated with PE. The analysis arrived at an approach that factors seven items, based on both objective criteria from patient history or physical examination and physician judgment, into a total score.[23] Typically, patients with scores lower than 4 are deemed to be at low risk for PE, although there is variation in the cut-offs applied. The Geneva score differs from the Wells rule in that additional diagnostic testing (electrocardiography and/or chest radiography, and arterial blood gas test) may contribute to the score, in addition to consideration of risk factors and clinical presentation.[23] A revised Geneva score has been developed that can be determined independently of the additional diagnostic tests.[24]

There is controversy regarding which rules are the most accurate for stratifying risk for acute PE,[24] but the Wells rule and Geneva score have received the most extensive validation in the widest range of settings.[24,25] The most appropriate tool may depend on the setting (i.e., low prevalence versus high prevalence [referred population]).[24,26] Adherence to protocols

incorporating the Wells rule and D-dimer testing has been demonstrated to result in a 20% to 30% reduction in the number of computed tomography (CT) examinations performed.[27]

D-dimer

D-dimer is one of several laboratory-based or imaging studies used to increase confidence in the decision to forego testing or to rule out PE. This test measures protein fragments produced when blood clots break down or in response to the use of fibrinolytic medication. Circulating levels are often elevated in patients with VTE. Patients judged to have a high probability of PE do not usually undergo D-dimer testing and proceed straight to imaging. A negative D-dimer test in a patient with a low probability of PE can support the decision to forego further investigation of PE. Conversely, a positive D-dimer test indicates that further imaging is necessary. Various quantitative (e.g., enzyme-linked immunosorbent assay [ELISA]), semi-quantitative (e.g., immunofiltration latex agglutination), and qualitative (e.g., immunochromatography) D-dimer assays are available, and these range in sensitivity.[28] Cut-offs for normal concentrations vary by assay and are based on factors such as age, clinical conditions (e.g., cancer), recent surgery, and pregnancy. D-dimer is available as a conventional laboratory-based test and as a point-of-care test. Point-of-care tests can be performed during patient examinations and are available within 10 to 15 minutes,[29] thus overcoming limitations of limited access to central laboratories and delays in receiving test results; however, laboratory-based tests may have higher sensitivity.[30]

Pulmonary Embolism Rule-Out Criteria

PERC is an additional tool that can be applied in patients with low pretest probability, following initial clinical assessment, to help assess whether D-dimer testing is necessary.[31] It is based on parameters that are available at initial emergency department assessment and uses an eight-factor decision rule. The clinician must answer “no” to all questions for a negative result, which can rule out PE and defers the need for further testing.

Ancillary Tests

In addition to D-dimer and PERC, other tests include, but are not limited to, lower-limb compression ultrasound (US), echocardiography (transthoracic or transesophageal), chest X-ray, capnography, and electrocardiography (ECG). Some modalities are used to rule out PE (by determining alternative diagnoses) or for prognostic assessment of confirmed PE.[32] Lower-limb compression US has low sensitivity, but adequate specificity; therefore, it can be used to rule in, but not rule out, PE.[33] US may be used in conjunction with other imaging modalities and in patients with contraindications to other tests.[34]

Limitations of Risk-Stratification Tools

Given that symptoms of PE are not specific, clinical features alone cannot confidently diagnose PE, and risk-stratification tools are rarely used in isolation.[13] The positive predictive value of risk-stratification strategies, particularly CPRs, may be influenced to some extent by the prevalence of disease in the population, as well as cut-off values used.[26] In addition, the use of risk-stratification strategies may not be appropriate in pregnancy. D-dimer levels increase during the course of pregnancy, and there is insufficient evidence for its use as a rule-out tool, though trimester-specific cut-offs have been proposed.[35] Although the utility of CPRs and D-dimer testing for ruling out unnecessary testing has been demonstrated, implementation of such a strategy may be challenging due to lack of awareness about safety, as well as concern about risks of omitting diagnostic imaging studies due to the high mortality rate associated with acute PE.[19,36,37] Nevertheless, these

scores may improve the efficiency of PE assessment and diagnostic yield of imaging studies,[25] and decrease the volume of unnecessary imaging studies. Their use is in line with initiatives by Choosing Wisely and society partners, which recommend that clinicians avoid CT angiography in patients who are stratified at low risk of PE and have either a negative PERC score or D-dimer measurement.[38] Choosing Wisely Canada recommends that CT and ventilation/perfusion (V/Q) studies not be ordered until risk stratification with a decision rule has been applied and D-dimer biomarker results have been obtained (when indicated).[39]

Diagnostic Imaging

Patients who are deemed at high risk of PE following risk stratification, or based on unstable presentation, usually undergo diagnostic testing for confirmation of disease positivity. Conventional pulmonary angiography (PA) has been previously regarded as the gold standard, but, due to its invasive nature, it has been overtaken by alternative modalities.[40,41] Other, less-invasive, methods of diagnosing PE include computed tomography pulmonary angiography (CTPA), magnetic resonance angiography (MRA), V/Q modalities including V/Q scanning planar scintigraphy, V/Q single-photon emission computed tomography (SPECT), or V/Q SPECT-CT, and thoracic US**.**

- CT uses X-rays, radiation detectors, and computerized analysis to assemble cross-sectional images of the body.[42] It allows for rapid imaging and diagnosis, as well as visualizing fine details of physical body structures, but is accompanied by exposure to radiation. CT is used to visualize clot formation in the lung.[43-45]
- MRI uses electromagnetic and radiofrequency fields as well as computerized analysis to assemble cross-sectional images of the body. It does not use ionizing radiation; thus, it is preferred for patients with contraindications to CT, such as allergy to contrast agents, or for children and pregnant women, who have a higher risk from radiation exposure. MRI enables visualization of soft-tissue details, including segmental and subsegmental vessels, but the time to conduct an examination, the requirement for the patient to be motionless within a small space, and inability to conduct examinations in patients with pacemakers and other metallic implants are limitations. MRI is used to visualize clot formation in the lung.[46-49]
- Several modalities are used to measure the V/Q ratio, which indicates the presence of a blood clot based on mismatch between air and blood flow in the lung. In all cases, radiopharmaceuticals are injected intravenously and inhaled and detected by scintigraphy (two-dimensional), SPECT, or SPECT-CT (both three-dimensional).[50]
  - V/Q scintigraphy uses gamma photons to generate two-dimensional or planar images.
  - V/Q SPECT uses nuclear medicine cameras to detect gamma rays from the radiopharmaceuticals and generate cross-sectional images. Duration of the examination tends to vary but is generally longer than CT. There is exposure to ionizing radiation, and scan quality may have a lower resolution. These scans also require a supply of radiopharmaceuticals.
  - V/Q SPECT-CT combines SPECT and CT imaging to generate both anatomic and functional information and to improve resolution of the scan. One drawback is the exposure to ionizing radiation involved with both scans.
- Thoracic US uses ultrasonic waves emitted and received by a transducer in combination with computerized analysis to generate images of chest structures. It is widely available at low cost and is not associated with exposure to ionizing radiation, but quality of the output is highly operator-dependent and tends to have a lower resolution than the other modalities mentioned.[51] In practice, it is more likely to be used for unstable patients who may not readily be transferred to diagnostic imaging.

As highlighted, each of these imaging modalities has strengths and limitations, and the appropriate modality may depend on the availability of the technology, the expertise of health care providers, adherence to acquisition protocols, and presence of specific patient risk factors (e.g., allergy to contrast agent) and clinical conditions (e.g., pregnancy).[1] Not all modalities are widely available or in routine clinical use in Canada and other developed countries. This may be due to lack of availability or expertise, or practical considerations such as increased time required and complexity of performing the examination.[52] For instance, MRI appears to be used far less than CT for PE diagnosis.[53] In one study, conducted over a two-year period, MRA examinations accounted for less than 6% of imaging studies conducted for the investigation of PE.[54]

V/Q scintigraphy was the first validated noninvasive procedure for the diagnosis of PE,[55] but CT overtook it as the most frequently used imaging modality to diagnose PE in 2001.[56] Although CT is widely considered a more definitive test, a large multi-centre study reported that both CT and V/Q imaging, used in conjunction with clinical probability assessment, D-dimer, and lower-limb US testing, resulted in similar low rates of VTE events during three-month follow-up.[57] CT is associated with exposure to ionizing radiation and iodinated contrast agents. Although the risk of malignancy associated with imaging is thought to be very low, and any increase attributable to imaging is difficult to detect, the risk is cumulative. Therefore, medical practice aims to keep radiation doses as low as reasonably achievable and to avoid overuse.[58] Other modalities, including nuclear medicine studies, also involve radiation burden, but it is significantly higher with CT, resulting in the suggestion that alternative imaging studies may be preferred in younger patients and pregnant women. It has been noted that the radiation burden may be lower with V/Q SPECT than V/Q scintigraphy.[59]

A surge in CT use and improvements in technology have led to an observed escalation in the diagnosis of PE (including subsegmental PEs of unclear clinical importance).[56,57] Major technical advances in CT technology have led to the use of CTPA combined with indirect CT venography, ECG-gated CTPA, and dual-source/dual-energy CTPA.[60] However, in patients with known allergy to contrast media, with severe renal failure, and who are pregnant, alternative imaging modalities are often considered, especially in the emergency setting.[34] A recent systematic review on medical overuse noted that CTPA and CT in patients with respiratory symptoms (i.e., not specific to PE) were among the procedures commonly noted in influential articles on the topic.[61]

Policy Issues

Of the total population of patients who are evaluated for suspected PE, few are confirmed to have the condition, indicating a low diagnostic yield of current evaluation methods.[26,62] Studies report a range of values for the diagnostic yield of CTPA, ranging from less than 5% to 30%, depending on the clinical characteristics of the patient pool and use of risk-stratification strategies.[63-66] False-positive test results, which, depending on pretest probability,[67] can occur in approximately 10% to 42% of patients[68] who undergo CT scanning, can lead to unnecessary anticoagulation therapy. This carries a substantial risk of adverse effects, including hemorrhage (occasionally fatal), drug interactions, inconvenience associated with repeated blood tests (possibly requiring time off work), implications for future dental and medical procedures, and costs (both to the patient and society).[69] False-negative CT results can also occur, which can lead to lack of necessary treatment and to complications and death.[70,71]

The uncertain benefit of increased testing and the significant expense of PE could suggest that current CT utilization patterns for the diagnosis of PE are not cost-effective.[21] This is reflected in the increased diagnosis of small or clinically insignificant PEs, which, if treated, may increase costs and possible harms (e.g., risk of bleeding) and may not reduce morbidity or mortality.[72] This is supported by statistics suggesting that diagnosed cases of PE have significantly increased in the US, but there has not been a corresponding drop in PE-related morbidity or mortality.[73-75] In light of these concerns, it is important to assess whether there are other cost-effective and safe alternatives.

The optimal diagnostic strategy for suspected PE among experts remains controversial,[76,77] and it can differ based on factors related to the health care setting (i.e., urban, rural, or remote) that may affect access to imaging. The optimal diagnostic strategy would, in theory, be one that has high diagnostic accuracy and clinical utility, at an acceptable cost; is acceptable to patients; is possible to implement; and balances ethical and environmental considerations. However, issues of access may also influence what is considered optimal for different populations. For instance, provision of timely diagnosis may be more challenging in rural and remote facilities due to lack of access to certain testing and imaging modalities and specialist expertise, as well as to geographical barriers to care. Inability to access optimal diagnostic testing in a timely manner could increase the risk for missed diagnoses as well as unnecessary anticoagulation due to either false-positives or long wait times to receive assessment.[7] Patient safety concerns associated with exposure to radiation and contrast media that accompanies several imaging studies also disproportionately affect specific patient groups, including pregnant women, and young women, for whom the risk of breast cancer associated with radiation is higher.[7]

Summary and Project Goals

Patients with suspected PE should be assessed using appropriate diagnostic tests in a timely manner.[3,78] Timing of access to diagnostic test results may have a significant impact on the management of the condition and the effective use of health care resources.[7] The heterogeneous clinical presentation of PE and lack of specific symptoms can lead to myriad problems. These include the wide application of testing, which can be very costly and may result in over-diagnosis, false-positives, and unnecessary treatment. Although guidelines for PE diagnosis recommend the use of imaging tests,[14] the optimal diagnostic strategy for suspected PE remains uncertain,[76,77] and it may vary depending on the health care setting due to access to the technology. Thus, the goal of this HTA is to conduct an assessment of the evidence to inform formulation of recommendations regarding the optimal diagnostic strategy, including risk stratification, for acute PE in the current context of care, considering benefits, harms, and costs, as well as patients' perspectives and experiences, implementation issues, and environmental impacts.

Policy Question

What is the optimal diagnostic strategy for acute PE in urban, rural, and remote settings? (For the purposes of this report, urban, rural, and remote settings will be discussed in the context of availability of testing modalities, geographical barriers and other accessibility concerns, and types of institutions [i.e., primary care to tertiary care].)

Objectives

The objective of this HTA is to address the policy question through an assessment of the diagnostic test accuracy, clinical utility, safety, cost-effectiveness, patients' experiences and perspectives, implementation issues, and environmental impacts of strategies for the diagnosis of adults with suspected PE.

Research Questions

The HTA will address the following research questions. Details on the specific interventions and outcomes are given in Table 2.

Clinical

"Diagnostic pathway" is defined in this report as a specific and deliberate sequence of assessments constituting strategies for initial risk stratification and ultimate determination of disease positivity. This is distinct from the use of the term "diagnostic imaging studies," which applies only to CT, magnetic resonance imaging (MRI), V/Q, and thoracic US-based studies used to diagnose PE. To acknowledge the order of assessment in the diagnostic pathway for PE, the clinical research questions are in order of intervention, starting with risk-stratification strategies and followed by complete diagnostic pathways and diagnostic imaging studies. This does not reflect the priority of the research questions.

Risk-Stratification Strategies

1. What are the A) diagnostic test accuracy, B) comparative clinical utility, and C) safety of Wells or Geneva CPRs for the risk stratification of adult patients presenting with PE symptoms in urban, rural, and remote settings:
    a) with or without the use of PERC
    b) with or without the use of D-dimer testing
    c) with or without the use of other biochemical or imaging risk-stratification strategies?

Diagnostic Pathways and Diagnostic Imaging Studies

2. What are the A) diagnostic test accuracy, B) comparative clinical utility, and C) safety of diagnostic pathways including imaging studies for the diagnosis of PE in adult patients in urban, rural, and remote settings?

3. What are the A) diagnostic test accuracy, B) comparative clinical utility, and C) safety of imaging studies for the diagnosis of PE in adult patients in urban, rural, and remote settings?

Cost-Effectiveness

4. What is the cost-effectiveness of diagnostic pathways, including imaging studies, to test adult patients suspected of PE?

Patients' Perspectives and Experiences

5. What are the experiences with the diagnostic process from the perspective of those who have undergone testing for acute PE, in any setting, including the emergency department, from the perspective of patients, their family members, and their nonclinical caregivers?

6. What are the experiences with diagnostic imaging for any reason and in any setting, including the emergency department, from the perspective of patients, their family members, and their nonclinical caregivers?

Implementation Issues

7. What are the issues associated with implementing the optimal use of diagnostic strategies, including imaging, for acute PE in adults in urban, rural, and remote settings?

Environmental Impact

8. What are the environmental impacts associated with the use of diagnostic pathways, including imaging studies, for the diagnosis of PE in adults in urban, rural, and remote settings?

Ethics

9. What are the key ethical considerations identified in the literature on strategies for diagnosing acute PE?

Question 1 was addressed by an overview of systematic reviews, and questions 2 and 3 by a systematic review of primary studies. Question 4 was addressed through a primary economic evaluation. The questions related to patients' experiences and perspectives (5 and 6) were addressed through a rapid review of the relevant qualitative literature. Implementation issues (question 7), and environmental factors (question 8) associated with imaging for PE diagnosis were addressed through literature searches and narrative summaries. Question 9 on ethics was completed through an ethics analysis, based primarily on the bioethics literature.

Methods

Clinical Review

Search Strategy

The literature search was performed by an information specialist, using a search strategy peer-reviewed according to the PRESS checklist — an evidence-based checklist for the peer review of electronic search strategies.[79]

For the clinical search for risk-stratification studies, published literature was identified by searching the following databases: MEDLINE (1946–) with in-process records and daily updates, via Ovid; Embase (1974–) via Ovid; the Cochrane Database of Systematic Reviews; the Database of Abstracts of Reviews of Effects (DARE); Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCO; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were PE/VTE and Wells or Geneva CPRs, PERC, and D-dimer testing.

Methodological filters were applied to limit retrieval to HTAs, systematic reviews, meta-analyses, network meta-analyses, and overviews of reviews. Retrieval was limited to documents published since January 1, 2011. The search was also limited to English- or French-language publications. Conference abstracts were excluded from the search results. The detailed strategy can be found in Appendix 1.

For the clinical search for diagnostic imaging studies, published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates, via Ovid; Embase (1974–) via Ovid; the Cochrane Central Register of Controlled Trials via Ovid; CINAHL via EBSCO; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH, and keywords. The main search concepts were PE/VTE and CT technologies, MRI technologies, V/Q-based technologies, PET-CT, and thoracic US (plus echocardiography).

Methodological filters were applied to limit retrieval to randomized controlled trials (RCTs) and nonrandomized studies. Retrieval was initially limited to documents published since January 1, 2006. This was later expanded to consider eligible articles with no date restriction imposed. These additional articles were retrieved through a supplemental search process involving a review of primary studies identified by reviewing existing systematic reviews on the topic. Details of this supplemental search and selection process are provided in Appendix 2. The search was also limited to English- or French-language publications. Conference abstracts were excluded from the search results. The detailed strategy can be found in Appendix 1.

The searches were completed on September 13, 2016. Regular alerts were established to update the searches until the publication of the final report. Regular search updates were performed on databases that do not provide alert services. Due to the complexity of the analysis studies identified in the alerts and that met the selection criteria of the review were incorporated into the analysis up until February 1, 2017. Studies identified in the alerts and that met the selection criteria of the review were incorporated into a summary section up until July 1, 2017.

Grey literature (literature that is not commercially published) was identified by searching the *Grey Matters* checklist (https://www.cadth.ca/grey-matters), which includes the websites of HTA agencies, clinical guideline repositories, systematic review repositories, economics-related resources, patient-related groups, and professional associations. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry.

Table 2: Search and Selection Criteria for Clinical Research Questions

Population	
Q1 to 3: Adult patients ≥ 18 years undergoing testing for acute PE[a] **Subgroups of interest:** • Pregnant women • Patients presenting for assessment at centres with access to imaging versus without access to imaging • Emergency room patients versus in-patients (secondary or tertiary care) • Patients who present with symptoms in the primary care setting • Geographical subgroups (urban, rural, and remote) • Patients with high versus low pretest probability	
Interventions	**Comparators (or Reference Standards)**
Q1: Risk Stratification[b]	
Wells or Geneva clinical decision rules ± PERC criteria ± D-dimer ± additional biochemical or imaging-based risk stratification strategies[c]	Q1A: • Composite reference standard (must include advanced diagnostic imaging tests [e.g., multidetector CT]) Q1 A, B, and C: • Any alternative clinical decision rule or modified or tailored tool (e.g., Wells, Geneva, or other) ± PERC criteria ± D-dimer ± additional biochemical or imaging-based risk-stratification strategies[c] • No clinical rule (gestalt)
Q2 and 3: Diagnostic Imaging	
Q2: Any of the interventions, including at least 1 of any clinical decision rule, and/or biochemical or imaging-based risk-stratification strategy)[c] **Q3:** Any of the following imaging studies • CT technologies[d] • MRI technologies • V/Q-based technologies[e] • Thoracic US (+ echocardiography)	Q2 and 3A: • Composite reference standard (must include advanced diagnostic imaging tests [e.g., multidetector CT]) Q2 and 3 A, B, and C: • Any alternative diagnostic imaging exam (± clinical decision rule ± biochemical or imaging-based risk-stratification strategies)
Outcomes[f]	
Q1 to 3: A) Diagnostic test accuracy (i.e., sensitivity, specificity, PPV, NPV, PLR, NLR, DOR, AUROC, Youden's Index) B) **Primary:** • Clinical utility (failure rate[g] [i.e., morbidity and mortality due to misdiagnosis at 30 days' follow-up])[h] **Secondary:** • Clinical utility (e.g., efficiency,[i] yield,[j] identification of patients with different diagnoses, change in referring physician's diagnostic thinking, change in patient management, change in patient outcomes) C) Harms (safety outcomes of imaging procedures [e.g., radiation exposure, CT-attributed malignancy, contrast nephropathy, patient discomfort, allergic reactions])	

Study Design
Q1: SRs with or without an MA, HTAs **Q2 and 3:** A) Diagnostic test accuracy outcomes: RCTs and nonrandomized studies (i.e., controlled clinical trials, cohort studies, and cross-sectional studies) B) Clinical utility outcomes: RCTs and nonrandomized controlled studies (i.e., controlled clinical trials, cohort studies, controlled before-and-after studies, and case-control studies) C) Safety outcomes: in addition to these study designs, nonrandomized studies without a control group (excluding nonsequential case series and case reports) will also be included
Time Frame
Q1: SRs published between January 2011 and July 1, 2017 **Q2 and 3:** Studies published between January 2006 and July 1, 2017

± = with or without; AUROC = area under the receiver operating curve; CT = computed tomography; DOR = diagnostic odds ratio; HTA = health technology assessment; MA = meta-analysis; MRI = magnetic resonance imaging; NLR = negative likelihood ratio; NPV = negative predictive value; PE = pulmonary embolism; PERC = pulmonary embolism rule-out criteria; PLR = positive likelihood ratio; PPV = positive predictive value; RCT = randomized controlled trial; SR = systematic review; US = ultrasound; V/Q = ventilation/perfusion .

[a] Excluding pediatric patients, patients with recurrent VTE, and patients with suspected DVT.

[b] For the purposes of this HTA, the term "risk stratification" refers to the determination of the likelihood of PE, rather than the likelihood of adverse events or mortality resulting from PE.

[c] Leg compression US, capnography, ECG, echocardiography, chest radiograph.

[d] Excluding single-detector, including computed tomographic angiography and venography and triple-rule-out CT.

[e] Including planar V/Q scan, V/Q SPECT, and V/Q SPECT-CT.

[f] No restriction on length of follow-up.

[g] The failure rate of a risk-stratification strategy is the proportion of suspected PE patients confirmed to have VTE or sudden unexplained death during the follow-up period although they were initially classified as having a low risk of PE by the strategy and excluded from imaging or anticoagulation as a result (false-negatives/true-negatives + false-negatives).

[h] This includes the risk of bleeding in patients with false-positive results who receive anticoagulation treatment.

[i] The efficiency of a risk-stratification strategy is the proportion of suspected PE patients classified by the strategy to have a low predicted probability of PE (sum of true and false-negatives/total cohort).

[j] The yield of an imaging modality referred to the proportion of studies with positive results for PE among all studies.

Eligibility Criteria

Risk Stratification

Systematic reviews were considered for inclusion if they examined the clinical probability of PE in adult patients using the Wells rule or the Geneva score. These CPRs can be applied using either the three-level or the two-level (dichotomized) scoring approach based on pre-specified cut-off score values. In the three-level approach, clinicians assess the presenting symptoms and score the probability of PE as "low," "moderate," or "high." The dichotomized approach assesses probability of PE as "unlikely" or "likely." Eligible systematic reviews were those that evaluated the Wells rule or the Geneva score and reported findings specific to the individual CPRs. Therefore, systematic reviews that examined CPRs in general, without specifying Wells rule or Geneva score, or systematic reviews that reported general findings without specific assignment to the Wells rule or the Geneva score, were excluded. Systematic reviews that focused on PERC or D-dimer testing alone or without specifying the accompanying CPR were also excluded. Since some of these exclusion criteria would have removed studies that would provide relevant inputs to support the parameterization of the economic model (See Economic Review), the systematic reviews that did not meet the inclusion criteria but were relevant to the economic model are summarized in Appendix 24. Studies in a pediatric population were excluded.

To be included for research question 1, systematic reviews must have included a detailed description of comprehensive selection criteria and search methods (i.e., as described in Assessment of Multiple Systematic Reviews [AMSTAR] checklist item 3). Also, the literature

search for the systematic review must have covered at least two electronic sources, adequately reported years searched and databases used, keywords or MeSH terms, and where feasible, provided the search strategy. The included primary studies of the systematic reviews must have been assessed for quality or risk of bias, and their findings synthesized quantitatively or qualitatively.

Systematic reviews were excluded if they did not meet the selection criteria outlined in Table 2 or if they were duplicate publications or published before 2011. Multiple publications of the same systematic review were excluded unless they provided new outcomes of interest.

Diagnostic Pathways and Diagnostic Imaging Studies

Previous systematic reviews and meta-analyses used models that assumed a perfect reference standard across all studies put forward for pooling, regardless of the reference standards used.[70,80-82] Based on the studies included by the authors of those reviews, we expected that we would also observe variation in reference standards across studies, particularly the use of composites of multiple tests. We also expected that, as instrumentation developed, newer and possibly more sensitive methods would be compared with established methods, and would, because of the misclassification, appear to be less accurate.

Therefore, we decided to address research questions 2 and 3 through a *de novo* systematic review of primary studies, with the selection criteria outlined in Table 2. Studies were excluded if they were case reports or case series, or if they were duplicate publications. Also, if there were multiple publications of the same study, the earliest reports were excluded unless they provided additional information on the outcomes of interest. There was no restriction regarding the time between symptom presentation and assessment, or length of follow-up. Studies were excluded if they were not published in English. The exclusion of French-language studies due to lack of resources for translation was a change from the original protocol and affected five studies (Appendix 10). Further, conference abstracts, published thesis documents, and studies that were not peer-reviewed were not included.

Screening and Selecting Studies for Inclusion

Risk Stratification (Question 1)

Two reviewers independently, and in duplicate, screened all titles and abstracts of citations identified by the search. At least one reviewer had to deem a citation to be potentially eligible to proceed to full review. The full-text articles were then assessed for inclusion by the two review authors, who independently selected studies using the pre-specified criteria, resolving any disagreements through discussion until consensus was reached. The study selection process is outlined in Appendix 8.

Diagnostic Test Meta-Analysis, Clinical Utilities, and Safety (Questions 2 and 3)

Teams of two reviewers independently screened titles and abstracts of all citations retrieved from the literature search, reference lists of identified eligible studies, and any articles identified by content experts, based on the screening checklist in Appendix 3. At least one reviewer had to deem a citation to be potentially eligible to proceed to full review. Two reviewers then independently reviewed the full-text articles based on the pre-determined selection criteria outlined in Table 1 and in Appendix 3. The two reviewers then compared their included and excluded studies based on full-text review and resolved any disagreements through discussion until consensus was reached, involving a third reviewer

when necessary. Details of the selection process for the supplementary search for primary studies are presented in Appendix 2.

The overall study selection process for all three questions is presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart[5] (Appendix 8). A list of excluded studies, with reasons for exclusion after full-text review, is provided in Appendix 10.

Data Extraction

Standardized data extraction forms (Appendix 4 and 5) were designed a priori in order to document and tabulate all relevant information from included studies. Three pairs of reviewers piloted pairs of included studies selected randomly. Items on the forms were added or removed as needed until consensus between reviewers was reached. The final data extraction items for question 1 included inclusion/exclusion criteria of the included systematic reviews, number and type of studies included, number of patients and patient characteristics, outcomes, quality appraisal, and method of pooling, whether statistical or narrative. Final data extraction questions for question 2 included study and patient characteristics, technical characteristics of index and reference tests, and diagnostic test accuracy data. Final data extraction items for question 3 included study and patient characteristics, technical characteristics of index and reference tests, and utility and safety data from the included studies. Use of terminology for sex/gender followed that reported in the papers.

Data extraction was conducted by one team of paired reviewers for research question 1 and three teams of paired reviewers for research questions 2 and 3. Data from each individual included study was either extracted by two reviewers working independently, or extracted by one reviewer and independently checked for accuracy by a second reviewer, depending upon the team. Disagreements were resolved through discussion, involving a third reviewer, if necessary. Authors of the studies included in this HTA were contacted to provide missing information or clarify any issues that arose.

All available data on diagnostic test accuracy were extracted. This included studies in which:

- results were reported for multiple readers, multiple sets of imaging conditions, and multiple interpretation criteria;
- a composite reference standard was used as the main comparison, but individual comparisons between the index test and one or more components of the reference standard were reported.

Methodological Assessments

Risk Stratification

For question 1, the Risk of Bias in Systematic Reviews (ROBIS) tool,[83] designed to assess the risk of bias in systematic reviews of RCTs and nonrandomized studies, was used.

Two reviewers piloted the quality assessment tool on pairs of randomly chosen studies and, once consistency in assessments was reached, independently assessed the methodological quality of half of the remaining studies. Once the assessments were completed, each reviewer checked the assessments conducted by the other reviewer. Disagreements were resolved through discussion, involving a third reviewer, if necessary. In addition to the

ROBIS tool,[83] the systematic reviews were assessed using the following four items from AMSTAR:

- Was the status of publication (i.e., grey literature) used as an inclusion criterion?
- Was a list of included studies provided?
- Was a list of excluded studies provided?
- Was the conflict of interest included?

Diagnostic Pathways and Diagnostic Imaging Studies

For research questions 2 and 3, individual studies reporting diagnostic test accuracy were assessed using the Quality Assessment of Diagnostic Accuracy Studies tool, version 2 (QUADAS-II).[84] RCTs addressing clinical utility or safety outcomes were assessed using the Cochrane Risk of Bias Tool.[85] Clinical nonrandomized controlled studies were assessed using the Risk of Bias Assessment Tool for Nonrandomized Studies (ROBINS-I).[86] Nonrandomized studies without a control group, which were eligible if they reported safety end points only, were addressed using the checklist developed by Moga et al.[87] Quality appraisal was carried out by one reviewer with confirmation by a second reviewer.

Domain scores for ROBINS-I were determined by the individual reviewers, so that a study could be considered at serious risk of bias in one domain, but not overall. For the purposes of summarizing the results, QUADAS-II domains were assessed according to the results of the signalling questions, where the lowest assessment given to an individual question was applied to the full domain. The Moga checklist did not describe a summary method, so we grouped the questions into domains and used the lowest individual assessment to determine overall domain results.

The results of the methodological assessments were not used to exclude primary studies from the review; however, any comparison between an index test and a reference test that explicitly included that index test was excluded from meta-analysis or narrative pooling, as this would introduce correlation between the index test and reference standard. A list of questions from the Cochrane, ROBINS-I, Moga, and QUADAS-II tools can be found in Appendix 11.

Summary of Evidence

Description of Study Characteristics and Findings

Risk Stratification

Data captured about the study characteristics covered the total number and designs of systematic reviews, years of publication, and countries of development, as well as the patients (population), the interventions evaluated, the comparator and/or reference standard, and the reported outcomes for the primary studies included in each systematic review. A table of all the primary studies of the included systematic reviews was prepared, showing which had overlapped among the systematic reviews. The relevant diagnostic accuracy and utility outcomes of the risk stratification strategies evaluated by the systematic reviews were recorded and reported. A summary of the characteristics of the included systematic reviews and the findings are provided in tables and described narratively.

Diagnostic Pathways and Diagnostic Imaging Studies

A summary of primary study characteristics — including the total number of studies by population, interventions, comparators, outcomes, study design (PICOS elements), and countries and years of publication — are provided in the form of tables and a narrative summary.

Description of Methodological Assessments

A narrative summary of the results of quality assessment for each included study is provided. The answers to the questions in the respective assessment tools are presented in the text and appendices as figures and tables.

Data Synthesis Methods

Risk Stratification

A narrative synthesis of the results of included systematic reviews was conducted for research question 1. The findings were grouped by outcome, with diagnostic test accuracy, clinical utility, and safety outcomes grouped separately. No re-synthesis of the findings from primary studies was conducted. Results were represented as reported in the systematic reviews, including a summary estimate and confidence interval (CI), measure of heterogeneity, and number of studies and participants contributing to each estimate, as available. Tables were developed to present results by outcome, and accompany the narrative summary, to ensure consistency of presented information across all included systematic reviews and to facilitate comparisons by the reader. Results were summarized by outcome for the overall study population and for each subgroup listed in Table 2, if available.

Statistical Analysis

Data Synthesis Methods

The results of studies included for questions addressed by a systematic review of primary studies (questions 2 and 3) were pooled using meta-analysis, if appropriate.

The decision whether to pool all studies or subsets of studies was made after review and exploration of heterogeneity. Clinical and methodological heterogeneity was assessed in consultation with clinical experts. This assessment considered patient and study design factors that might be expected to affect test performance. This included assessment of heterogeneity of composite reference standards used in the primary studies. If pooling was not appropriate, due to significant clinical heterogeneity, or methodological or statistical heterogeneity that could not be addressed analytically, the findings were synthesized narratively.

For each outcome of interest, analyses were conducted for the overall study population and for each subgroup listed in Table 1, as the data permitted.

Meta-Analysis of Diagnostic Test Accuracy Studies

Previous meta-analyses used models that assumed a perfect reference standard across all studies put forward for pooling, regardless of the reference standards used.[70,80-82] Based on the studies included by the authors of those systematic reviews, we expected that we would also observe variation in reference standards across studies, particularly the use of composites of multiple tests. We therefore used a Bayesian extension of the hierarchical summary receiver operating characteristic (HSROC) model developed by Rutter and

Gatsonis.[88] This extension accommodates imperfect and composite reference standards[89,90] and allows estimation of the HSROC curve and pooled sensitivity and specificity for the index test compared with a latent true disease state. It also provides predicted sensitivity, specificity, and credible intervals for a potential new study, drawn from the estimates and estimated variability, which can be used to assess heterogeneity. We assumed conditional independence of the index and reference, acknowledging evidence that suggests the results may be affected if test results correlated within positive and negative strata.[91,92] Given the expected high sensitivity and specificity of both index and reference, the magnitude of the effect of conditional dependence was expected to be small.[93]

We report pooled and predicted sensitivity, specificity, and credible intervals. As an illustration of the clinical implications, we calculate the number of false-positives and false-negatives for a cohort of 1,000 patients presenting with symptoms of PE, 150 of whom had PE (following literature estimates for the proportion of patients who receive imaging who have PE).[94] The number of false-positives was equal to (1 – sensitivity) × 150, and the number of false-negatives was equal to (1 – specificity) × 850. The upper and lower bounds of the credible intervals are used in similar calculations to estimate high and low estimates.

We also chose to pool studies using alternative statistical models (e.g., bivariate/Reistma, HSROC assuming a perfect reference standard) for comparison with published results; the results of these appear in Appendix 22.

Between-study heterogeneity within groups of studies was assessed using graphical presentations, including forest plots and plots of sensitivity and specificity in ROC-space, and calculation of between-study variance tau-squared, the credible intervals of the summary estimates of sensitivity and specificity, and the point estimates and credible intervals of a new (predicted) study. Where the confidence or credible intervals of the pooled estimate reflects sampling variability, the confidence or credible intervals of the predicted estimate also reflects heterogeneity.[89,95,96] A marked difference between the credible intervals of the pooled estimate and of the predicted new study indicates substantial heterogeneity, although there were at the time of writing no standard statistical measures of heterogeneity in diagnostic test accuracy (DTA) studies.[95] In addition, model convergence was assessed by visual review of the traces and posterior densities of estimated parameters.

Reasons for observed heterogeneity were to be explored by subgroup or multivariate regression analyses, given the availability of covariate data. Discussions with experts identified clinically relevant covariates for potential investigation in addition to the subgroups originally identified in Table 2. The combined list is:

- high versus low risk of PE
- pregnant women
- cancer patients
- hemodynamically unstable versus stable
- oral contraception or hormone replacement therapy users
- obese patients
- renal insufficiency
- existing pulmonary disease (chronic obstructive pulmonary disease)
- elderly patients

- access to imaging versus no access
- in-patient versus emergency department versus primary care
- urban versus rural versus remote
- trauma (provoked versus unprovoked PE).

For most covariates, detailed investigation proved not to be feasible, due to the limited availability of covariate data.

Summaries of study characteristics, graphical explorations of heterogeneity, and display of results were conducted using the statistical software R.[97] DTA meta-analyses were conducted in WinBUGS[98] using programs supplied by Dr. Nandini Dendukuri (http://www.nandinidendukuri.com/software). The bivariate model was run using R with package *mada*.[99] Details of all models are in the Statistical Appendix (Appendix 22).

Meta-Analysis of Primary Clinical Utility and Safety Studies

The results of studies included for questions addressed by a systematic review of primary studies of utility outcomes were pooled using meta-analysis, as described in the following sections. Where pooling was not appropriate, due to an insufficient number of studies, or substantial clinical, methodological, or statistical heterogeneity that could not be addressed analytically, the findings were synthesized narratively.

Although the initial statistical analysis plan, as described in the protocol,[100] was to synthesize pooled risk ratios and odds ratios for comparative data for utility end points, comparative data were sparsely reported, and, in most studies, only index test data were available. The available data were exclusively dichotomous, with counts of patients experiencing an outcome or an event, from which a proportion could be calculated. Where the number and heterogeneity of studies allowed, a pooled proportion was then calculated.

Where comparative data were available, the majority of studies had no or few patients with the outcome in either the index or the reference groups (as for failure rate), producing very wide uncertainty in the calculated risk ratios. A pooled risk difference and its 95% CI were therefore calculated, by preference. Where comparative data were not available, utility data were synthesized as single proportions, e.g., the proportion of patients with failure at three months, to provide single-arm estimates and input to the economic model.

Between-study statistical heterogeneity within groups of studies being considered for pooling was assessed using graphical presentations (including forest plots and plots of outcomes against covariates), and calculations of the I^2 and Cochran's Q test statistic. An $I^2 \geq 75\%$ was interpreted to indicate considerable heterogeneity across studies, as suggested by the *Cochrane Handbook for Systematic Reviews of Interventions*.[101] Cochran's Q test statistic was based on a level of statistical significance of $P = 0.1$.

For most end points, sparse data limited the planned exploration of heterogeneity by subgroup (as pre-specified in the protocol or identified prior to the analysis) or multivariate regression analyses. The covariates of potential interest were those listed for the diagnostic test accuracy section.

Where pooling was indicated, summary measures and CIs for the reported outcomes were reported. Random-effects models were used. Where both randomized and nonrandomized studies reported on the same outcome, RCTs were considered separately from

nonrandomized studies. The small number of RCTs meant that this comparison was narrative. Meta-analyses were carried out using R with package *metafor*.[102]

Where pooling was not indicated, a narrative synthesis was conducted, with tables to present outcome data alongside study and patient characteristics that appeared to influence outcome results. Our intent was to summarize the range of results, draw attention to similarities and differences by study and patient characteristics, comment on the direction and size of any observed effects across studies, and assess the likelihood of clinical benefit or harm.

Given the sparse and heterogeneous nature of our datasets, publication bias was not assessed.

Network Meta-Analysis

An exploratory network meta-analysis was considered but not done, due to the heterogeneity of the data. The scope of this analysis was presented in the protocol.[100]

Results

Question 1: Risk Stratification

Quantity of Research

A total of 310 citations identified by the literature search were screened independently by two review authors. The citations consisted of 298 abstracts from the original database search and 12 from search alerts. Following the initial phase of the screening, 261 were excluded for not meeting the inclusion criteria for this overview. The full text of 49 potentially relevant articles were retrieved and screened further for eligibility. One potentially relevant article was added from the grey literature search. Of the 50 full-text publications, six unique systematic reviews[24-26,103-105] were selected for inclusion, while 44 were excluded for various reasons. The study selection process is outlined in Appendix 8. The degree of overlap between the included systematic reviews, with respect to primary studies, was judged by building a matrix of primary studies included in the systematic reviews (Appendix 9). A list of excluded studies, with reasons for exclusion, has been provided in Appendix 10.

Description of Included Systematic Reviews

The six included systematic reviews[24-26,103-105] had a total of 82 unique primary studies, of which 13 were included in multiple systematic reviews (Appendix 9). One of these overlapping studies was included in three systematic reviews,[24,26,105] while each of the remaining 12 was included in two different systematic reviews. The reviews by Siccama et al., 2011,[103] and Wang et al., 2016,[25] had no overlap of primary studies, with each including studies that were unique to them (Appendix 9). Four of the systematic reviews[24-26,104] reported that they included prospective and retrospective cohorts studies, while two systematic reviews[103,105] did not report the designs of their included primary studies (Appendix 12). One of the eight primary studies in the systematic reviews by Wang et al.[25] was an RCT.

The characteristics of the included systematic reviews are summarized in Appendix 12. Five of the six systematic reviews reported that the primary studies they included were conducted in hospital settings and included emergency department (ED) patients, in-patients, or outpatients. The systematic review by Shen et al.[24] did not report information about the settings of its primary studies. Three systematic reviews[24,26,104] provided clear data about

patients' ages, while three did not.[25,103,105] For systematic reviews that stated ages, the mean age of included patients ranged from 45 to 76.1 years. A summary description of the characteristics of the individual systematic reviews follows.

Shen et al., 2016,[24] assessed the diagnostic test accuracy of the three-level Wells rule and the three-level Geneva score in a total of 3,613 patients with suspected PE in nine prospective and three retrospective cohort studies (Appendix 12). For each of the two CPRs, the probability of a patient being diagnosed with PE was classified as low, medium, and high. Patients assessed with the Wells rule were considered to have a low probability of PE if the score was less than 2.0, moderate if the score was between 2.0 and 6.0, and high if the score was higher than 6.0. The probability of a patient being diagnosed with PE was assessed by the revised Geneva score to be low if the score was 0 to 3 points, intermediate if the score was between 4 and10 points, and high if the score was 11 points or higher.

Lucassen et al., 2011,[26] assessed diagnostic accuracy and utility of the dichotomized Wells rule, the dichotomized Geneva score, and clinical judgment (gestalt) in a total of 55,268 patients with suspected PE in 52 prospective cohort studies (Appendix 12). For the Wells rule, data were reported for cut-off of 2 (Wells < 2) and for a cut-off of 4, (Wells ≤ 4). Data were reported for both the original Geneva and the revised Geneva scores. The cut-off score was 4 for both. Diagnostic accuracy outcomes were assessed for the CPRs alone, and utility outcomes were reported when the CPRs were combined with a D-dimer test to rule out PE, following which patients were excluded from imaging or anticoagulation therapy.

Siccama et al., 2011,[103] evaluated the diagnostic accuracy and safety of the Wells rule, the Geneva score, and the revised Geneva score in a total of 6,739 patients with suspected PE in nine primary studies (Appendix 12). The design of the included primary studies was not reported, and the cut-off scores of the CPRs were not specified.

Nine of the 31 primary studies in the systematic review by Sanders et al., 2015,[105] compared the diagnostic accuracy of clinical judgment (gestalt) with the dichotomized Wells rule (cut-off < 2 or ≤ 4), the Geneva score (cut-off ≤ 4), the revised Geneva score (cut-off < 4), and PERC. A total of 22,366 patients with suspected PE were studied (Appendix 12). The remaining primary studies (n = 22) of the systematic review[105] evaluated CPRs in medical conditions other than PE. Gestalt was applied either alone or in combination with what the authors called "structured data collection" (SDC). They provided no details about what was entailed in the SDC. The cut-off of the gestalt or gestalt plus SDC varied for the different comparisons and was variously reported as < 15% or < 20%, or, without a numerical value, as "low" or "alternate diagnosis not less likely."

Van Es et al.[104] assessed the efficiency and safety (failure rate) of the dichotomized Wells rule (cut-off ≤ 4) followed by D-dimer testing in the diagnostic management of 7,268 patients with suspected PE in six prospective studies (Appendix 12). Outcomes were reported separately for strategies based on the conventional D-dimer assay with a fixed cut-off of 500 mcg/L and for the age-adjusted D-dimer testing in which the cut-off changes according to the patients' age (age × 10 mcg/L). Imaging and anticoagulant therapy were withheld in patients who had a score on the Wells rule of 4 or less and a negative D-dimer test result, and they were followed prospectively for three months for symptoms of VTE. Patients underwent diagnostic imaging for PE if they had a score on the Wells rule of more than 4 or 4 or less with a positive D-dimer test. The age-adjusted D-dimer threshold was applied only in patients who were 50 years or older.

Wang et al., 2016,[25] assessed the utility of the Wells rule, Charlotte rule, and PERC in a total of 6,677 patients with suspected PE in a randomized trial and seven prospective or retrospective before-and-after nonrandomized studies (Appendix 12). A total of six studies applied the Wells rule. The dichotomized Wells rule was used in four studies in combination with a sensitive D-dimer assay, whereas the three-level Wells rule was used with D-dimer in two studies. The cut-offs were not specified for any of the modalities. By the research question for this overview of systematic reviews, the outcomes of the Charlotte rule or a stand-alone PERC are not of interest and have not been discussed.

Methodological Quality of Included Systematic Reviews

Five systematic reviews[24,26,103-105] included in this overview evaluated their primary studies for quality or risk of bias with the QUADAS-II instrument, while one systematic review[25] performed a similar assessment using the Cochrane Group Effective Practice and Organization of Care instrument.

All the systematic reviews were deemed to be at low risk of bias for study eligibility criteria according to the ROBIS tool (Appendix 15). Most concerns for high or very high potential for bias were related to items in domain 4 (synthesis and findings) and were due in large part to two systematic reviews.[24,103] The reasons for the poor scores of these systematic reviews[24,103] in the "synthesis and findings" domain of the ROBIS tool included inadequately reported predefined analyses, and failure to assess the sensitivity of findings as well as the heterogeneity and biases in their primary studies. For the domain "identification and selection of studies," one systematic review[104] was rated as having some risk of bias in the search strategy, for two reasons. First, there was no indication that methods additional to database searching were used to identify relevant studies, and, second, it was unclear whether the search included the appropriate range of sources of published and unpublished reports. In the same domain, two systematic reviews were lacking in information on search[103] and/or selection methods.[24,103] One systematic review did not provide enough information on study characteristics for interpretation.[103] In addition to the ROBIS tool, selected items from the AMSTAR checklist were applied to evaluate some aspects of reporting, including the declaration of sources of potential conflicts of interest. All the included systematic reviews listed their included primary studies, and all but one[103] provided statements of potential conflicts of interest. One systematic review[104] provided a list of excluded studies. Appendix 15 summarizes the results of the risk of bias assessment of the studies.

Outcomes of Included Systematic Reviews

Sensitivity and specificity were the outcome measures of interest for diagnostic accuracy, whereas yield, failure rate, and efficiency were the utility outcome measures for the diagnostic strategies. Four systematic reviews[25,26,104,105] reported utility outcomes, including two that also reported diagnostic accuracy outcomes.

Diagnostic Accuracy Findings

Four systematic reviews[24,26,103,106] reported diagnostic accuracy finding for CPRs that were not combined with D-dimer (Appendix 13).

Sensitivity and Specificity of Three-Level Wells Rule and Three-Level Geneva Score

A systematic review[24,26,103,106] of nine prospective cohort and three retrospective cohort studies (n = 3,613 patients) found that the sensitivity of the three-level Wells rule ranged from 63.8% to 79.3% compared with 55.3% to 73.6% for the three-level revised Geneva

score. The corresponding specificity values ranged 48.8% to 90.0% for three-level Wells rule compared with 51.2% to 89.0% for the revised Geneva score. A summary receiver operating characteristic (SROC) meta-analysis using a random-effects model showed that the diagnostic accuracy of the three-level Wells rule was higher than the three-level revised Geneva score. The Wells rule had an overall weighted area under the curve (AUC) of 0.778 (95% CI, 0.740 to 0.818) versus 0.693 (95% CI, 0.653 to 0.736) for the revised Geneva score (Appendix 13).

Sensitivity and Specificity of Dichotomized Wells Rule and Dichotomized Geneva Score

One meta-analysis[26] of 19 prospective cohort studies (n = 20,146) and one systematic review[105] of nine studies (n = 22,363) without meta-analysis reported outcomes for the dichotomized Wells rule and the dichotomized Geneva score. Overall, the sensitivity of Wells rule less than 2 ranged from 62% to 95%, and its specificity ranged from 19% to 75%. It should be noted that both the lower and upper ends of these ranges were reported in the systematic review,[105] which did not perform a meta-analysis because of the heterogeneity of its primary studies. Therefore, the wide interval between the limits could be due to the differences in the design and analysis applied by the primary studies of this systematic review.[105] The systematic review with meta-analysis[26] reported the sensitivity and specificity of Wells rule less than 2 as 84% and 58%, respectively (Appendix 13). The sensitivity of the revised Geneva score ranged from 89% to 91%, with specificity ranging from 33% to 37%. Further details are available in Appendix 13.

One systematic review[103] reported that, in one of its included studies (design of studies not reported) (n = 747), the Wells rule had a sensitivity of 100%, whereas its specificity decreased from 50% in patients younger than 65 years to 22% in patients older than 75 years (Appendix 12). The authors did not specify whether the index CPR was the three-level or the dichotomized Wells rule.

Utility Findings for the Wells Rule and the Geneva Score

Four systematic reviews[25,26,104,105] reported utility outcomes (yield, failure rate, and efficiency) for strategies involving CPRs and D-dimer testing (Appendix 14).

Yield of Computed Tomography Pulmonary Angiography

In a pooled analysis of four before-and-after cohort studies (n = 4,788), one SR[25] found that strategies that combined the Wells rule with D-dimer tests showed a CT yield of 12% compared with 9% for usual care in which clinical decision support was not applied. Thus, incorporating decision support into the diagnostic strategy resulted in a 3% increase in the CT yield (Appendix 14).

Failure Rate and Efficiency of Strategies Combining Clinical Prediction Rules and Quantitative D-dimer to Rule Out Pulmonary Embolism

One systematic review with meta-analysis[26] of four prospective cohort studies reported that the failure rate and efficiency of strategies combining quantitative D-dimer testing with a score on the Wells rule of 4 or less to rule out PE were 0.5% and 39%, respectively. The failure rate was 0% when the strategy combined quantitative D-dimer testing with the Geneva score, and 0.3% when combined with the simplified Geneva score (two studies each). The corresponding efficiency values were 21% and 23% (15 to 33) for the Geneva score and simplified Geneva score, respectively.

Failure Rate and Efficiency of Strategies Combining Clinical Prediction Rules and Qualitative D-dimer to Rule Out Pulmonary Embolism

One systematic review with meta-analysis[26] of four prospective cohort studies reported that the failure rate and efficiency of strategies combining quantitative D-dimer testing with a score on the Wells rule of less than 2 to rule out PE were 0.9% and 40%, respectively. When a score on the Wells rule of 4 or less was used in a similar strategy, the failure rate and efficiency were 1.7% and 42%, respectively (Appendix 14). There was no systematic review that presented results for a strategy combining qualitative D-dimer testing with the Geneva scores or revised Geneva score.

Failure Rate and Efficiency of Clinical Prediction Rules Without D-dimer to Rule Out Pulmonary Embolism

One systematic review[105] of seven studies (designs not specified) found that the failure rates and efficiency of using a score on the Wells rule of less than 2 to rule out PE ranged from 3.0% to 27.9% and from 17% to 73%, respectively. The wide interval between the limits may be due to the heterogeneity in the primary studies included the systematic review.[105] In the same systematic review,[105] the failure rates of a score on the Wells rule of 4 or less to rule out PE ranged from 5.5% to 8.7%, with corresponding efficiency range of 36% to 74% (two studies).

Failure Rate and Efficiency of Strategies Using Fixed Versus Age-Adjusted D-dimer to Rule Out Pulmonary Embolism

One systematic review[104] of six prospective cohort studies (n = 7,268) reported that, in combination strategies based on a score on the Wells rule of 4 or less, the overall failure rate was 0.65% with a fixed threshold D-dimer tests (cut-off 500 mcg/L) compared with 0.94% when the age-adjusted D-dimer tests were used (cut-off age × 10 mcg/L). The confidence intervals indicate that the failure rate did not reach the level of statistical significance in either case (Appendix 14). The overall efficiency increased from 28%, for the strategy applying the fixed threshold D-dimer test, to 33% for strategies which used the age-adjusted D-dimer tests (Appendix 14). The overall efficiency outcome indicated that the strategy using the age-adjusted D-dimer testing resulted in a 5% increase in suspected PE patients in whom imaging was safely withheld compared with fixed D-dimer testing.

Failure Rates in Subgroups

For the strategy with age-adjusted D-dimer testing, the failure rate increased from 0.59% in patients aged 50 years or younger to 2.1% in patients aged 75 years or older. Failure rate estimates were not calculated by age subgroups in the fixed D-dimer strategy. For patients with cancer, the failure rate decreased from 2.6% with fixed threshold D-dimer to 1.45% when the age-adjusted threshold was applied. However, in patients with chronic obstructive pulmonary disease (COPD) (n = 856), the failure rate increased from 0.74% to 1.2% using fixed threshold or age-adjusted D-dimer tests, respectively. The clinical significance of this was reported as unclear.

Efficiency in Subgroups

There was no difference in efficiency among patients aged 50 years or younger, regardless of whether the fixed threshold or the age-adjusted D-dimer test was used. However, in patients aged 75 years or older, the efficiency increased from 8.4% with the fixed threshold D-dimer to 20.3% when the age-adjusted D-dimer test was applied. In the subgroups of patients with cancer or COPD also, the use of the age-adjusted D-dimer tests resulted in increases in efficiency over the fixed threshold D-dimer tests. Thus, in the subgroups of

patients with suspected PE who are aged 75 years or older, as well as those with cancer or COPD, the authors reported that age-adjusted D-dimer testing can increase the proportion of patients in whom imaging can be withheld safely.

Summary of Findings

The following are the summary findings from the individual systematic reviews included in the overview without pooling.

Diagnostic Accuracy of the CPRs

- Wells rule less than 2 — The sensitivity ranged from 62% (95% CI, 54% to 70%)[105] to 95% (95% CI, 87% to 99%)[105] and the specificity ranged from 19% (95% CI, 15% to 24%)[105] to 75% (95% CI, 73% to 77%)[105]
- Wells rule 4 or less — The sensitivity ranged from 60% (95% CI, 49% to 69%)[26] to 83% (95% CI, 73% to 91%)[105] and the specificity ranged from 41% (95% CI, 35% to 46%)[105] to 80% (95% CI, 75% to 84%)[26]
- Geneva score — The sensitivity ranged from 72% (95% CI, 60% to 82%)[105] to 84% (95% CI, 81% to 87%)[26] and the specificity ranged from 50% (95% CI, 29% to 72%)[26] to 64% (95% CI, 57% to 71%)[105]
- Revised Geneva score — The sensitivity ranged from 89% (95% CI, 85% to 92%)[105] to 91% (95% CI, 73% to 98%)[26] and the specificity ranged from 33% (95% CI, 30% to 37%) to 37% (95% CI, 22% to 55%)[26]
- Revised Geneva score plus PERC — The sensitivity was 99% (95% CI, 97% to 99.6%)[105] and the specificity 9% (95% CI, 7% to 12%)[105]

In all comparisons within those systematic reviews that compared the Wells rule and the Geneva score, the Wells rule, regardless of cut-off (< 2 or ≤ 4), showed greater specificity than both the Geneva score and the revised Geneva score. In one systematic review[26] that had data on all four CPRs, the revised Geneva score showed the highest sensitivity, while a score on the Wells rule of 4 or less had the lowest sensitivity, and a score on the Wells rule of less than 2 and the Geneva score both showed similar, intermediate sensitivity.

Utility Outcomes of CPR-Based Diagnostic Strategies

- Strategies combining CPRs and D-dimer testing improved the ability to rule out PE in patients presenting with suspected PE symptoms. Applying a diagnostic strategy combining CPRs and the age-adjusted D-dimer testing resulted in greater efficiency among patients 51 years and older, with the highest gain observed in patients who were older than 75 years. The age-adjusted D-dimer tests have been reported to increase specificity significantly without a significant decrease in sensitivity.
- A diagnostic management strategy for suspected PE that incorporates CPRs increases the diagnostic yield of CTPA.

Question 2 and 3: Diagnostic Pathways and Diagnostic Imaging Studies

Quantity of Research

For research questions 2 and 3, a total of 5,455 citations were identified through the original database search (n = 4,985), supplemental search (n = 352), and search alerts (alert 1: n = 61, alert 2: n = 57). After removal of duplicates and addition of records identified through other sources (n = 4), 5,420 records remained. Of these 5,420 articles, 5,170 were excluded during screening of titles and abstracts, and 250 full-text articles were retrieved for review. An additional 99 studies were selected from the supplementary search. Of the 349 articles reviewed, 239 did not meet the inclusion criteria, leaving a total of 110 eligible studies that described the diagnostic test accuracy, comparative clinical utility, and/or safety of diagnostic pathways —including imaging studies and imaging studies alone — for the diagnosis of PE in adult patients. The study selection process is outlined in Appendix 8.

Of the 110 studies, none reported diagnostic test outcomes for pathways (question 2A) and 10 reported utility or safety outcomes for pathways (question 2B and 2C). Seventy reported diagnostic test outcomes for single imaging modalities, particularly CT, magnetic resonance imaging (MRI), US, perfusion (Q), Q SPECT, Q SPECT-CT, V/Q, V/Q SPECT, and V/Q SPECT-CT, and combinations of modalities, specifically CT with CT venography (CTV), MRI with MR venography (MRV), and MRI with V/Q (question 3A). Fifty-five studies reported utility or safety outcomes (some reported both DTA and utility or safety outcomes) and are described in the section on utility and safety (page 85), or, if they recruited pregnant or post-partum patients, are described in the section on PE imaging in pregnancy (page 101).

Question 2: Diagnostic Test Accuracy, Clinical Utility, and Safety for Pathway Studies

Diagnostic Test Accuracy

No studies reported diagnostic test accuracy results for pathway studies.

Clinical Utility and Safety

Ten studies reported clinical utility and safety results for pre-specified diagnostic pathways.[107-116]

The 10 studies included one RCT[116] and nine nonrandomized studies.[107-115] Three studies were multi-centre: one conducted in Switzerland and France;[114] one conducted in Switzerland, France, and Brussels;[116] and one in Italy.[115] Two of the single-centre studies were conducted in France;[107,111] and one each in Norway,[109] Italy,[112] the UK,[110] Switzerland,[113] and Spain.[108] Eight studies were conducted in secondary[107,111-114] and secondary/tertiary settings,[110,115,116] and the setting of two studies was unclear.[108,109] Seven studies had government funding,[107-109,112-114,116] one had private funding,[110] and two articles did not detail funding.[111,115] Reported follow-up was for three months in nine studies[107-111,113-116] and one year in the 10th study.[112]

The number of participants ranged from 114[113] to 1,819 patients.[116] Seven studies described pathways for diagnosis of PE in nonpregnant patients only (Table 31).[107-110,113,115,116] Three studies allowed the recruitment of pregnant patients,[111,112,114] but they represented between 0.5%[111] and 1.7%[114] of patients; therefore, the studies were summarized together. Three studies recruited in-patients,[107,111,113] three studies recruited ED patients,[108,111,114] one study recruited outpatients,[117] and one study recruited outpatients and in-patients.[115] Two studies did not report which patients were included.[110,112] Seven studies reported a formal

assessment of prior PE risk, six of which were mixed-risk,[107,108,112,114-116] and one high-risk.[109] Three studies did not report a formal assessment of risk.[110,111,113]

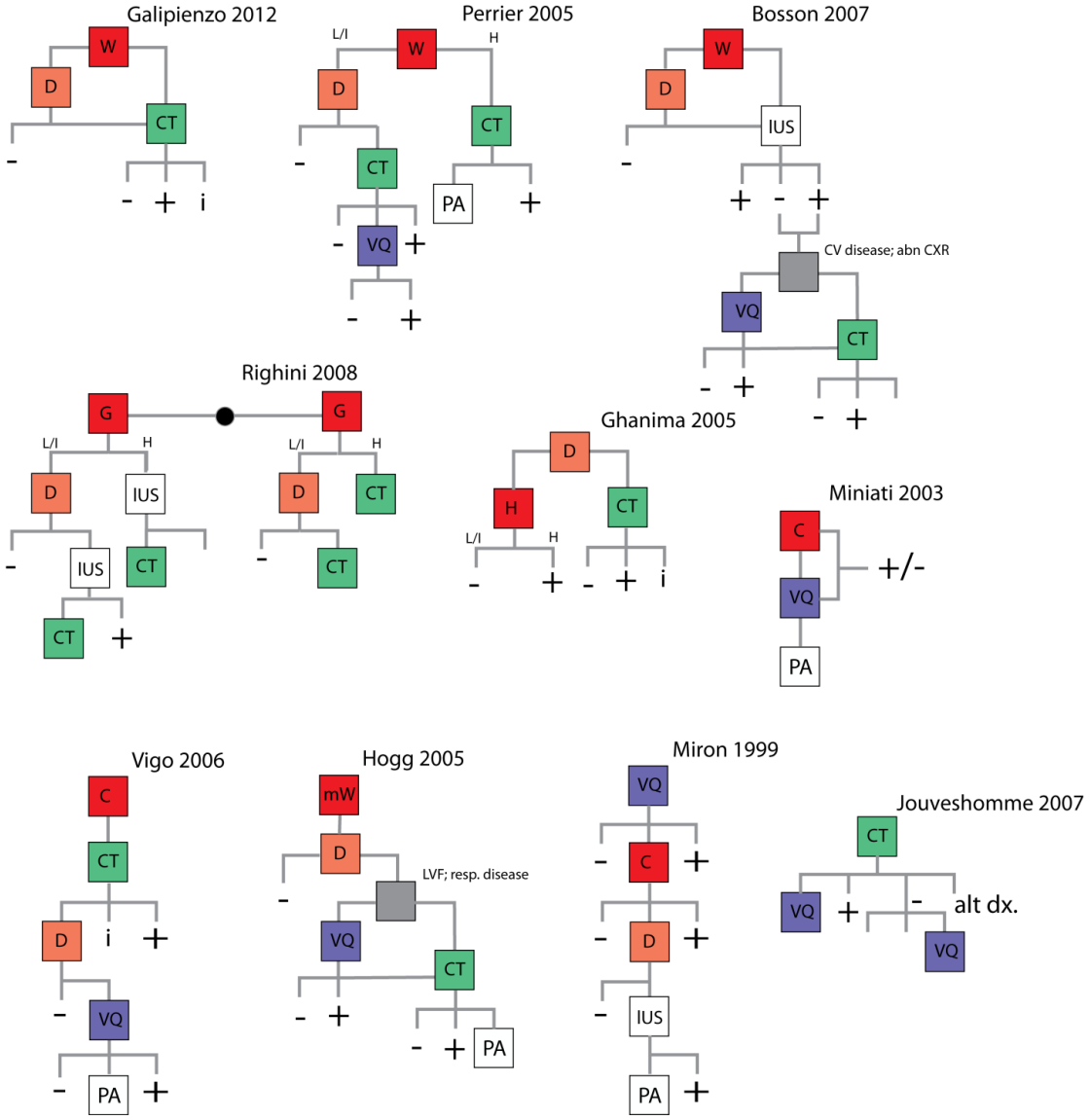
Pathway Characteristics

The schematics in Figure 1 summarize the elements of the pathways of specific importance to this review — clinical risk stratification (red), D-dimer measurement (orange), and diagnostic imaging (green) — to either diagnose or exclude PE. At each branch, the left represents negative/low-risk, and the right-hand branch represents positive/high risk.

Eight studies included clinical assessment[107-110,113-116] of probability of PE. Six studies used clinical probability to select the next test,[107,108,110,113,114,116] one used clinical probability in combination with probability by V/Q imaging,[112] and one did not report how the information was used.[115] All but two of the pathways[111,112] used D-dimer to select the next test, or to discontinue testing. In seven studies, the combination of a low clinical probability of PE with a negative D-dimer test result led to PE being excluded.[107-110,113,114,116]

Two studies included a single imaging modality, CT.[108,116] Four studies included two imaging modalities: all four studies used CT combined with V/Q,[107,111,114,115] one used CT combined with pulmonary angiography (PA),[109] and two used V/Q combined with PA.[112,113] One study included three modalities: CT, V/Q, and PA.[110] No pathway studies reported the other imaging modalities. In four studies, CT was the final imaging modality in the pathway,[107,108,114,116] and, in four, PA was the final imaging modality.[109,110,112,113] In the remaining studies, V/Q was the final imaging modality in one,[115] and digital subtraction angiography in one.[111]

Figure 1: Schematic of Pathway Studies



Red boxes = clinical risk, Alt dx = alternative diagnosis, C = clinical assessment, CT = computed tomography, D = D-dimer, G = Geneva score, H = high-risk, H (red box) = Hayes criteria, I = indeterminate, IUS = leg ultrasound, L = low-risk, L/I = low/intermediate risk, mW = modified Wells criteria, PA = pulmonary angiography, V/Q = ventilation/perfusion, W = Wells criteria.

Quality Appraisal

The single RCT[116] was assessed as being at low risk of bias in six of seven domains of the Cochrane Risk of Bias Tool and high risk of bias for performance bias due to knowledge of allocated interventions.

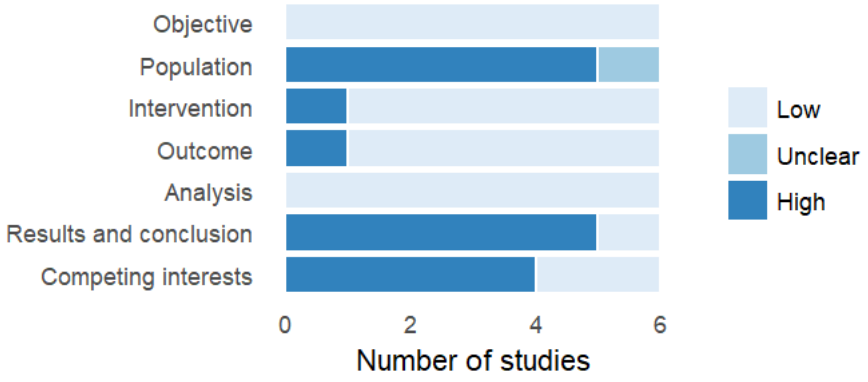
Three studies were appraised by ROBINS-I.[107,108,110] All three studies had a low risk of bias for patient selection, deviation from the protocol, and missing data. For risk of bias due to potential for confounding, application of the intervention, and determination of the outcome,

two studies had a low risk of bias, and one had a low/moderate risk. Overall, the studies were considered to be at low to low/moderate risk of bias.

Six studies were appraised by the Moga checklist (Figure 2).[109,111-115] Most studies were single-centre and therefore were assessed as having a high risk of bias in the summary domain for population, but the other population questions were deemed to have a low risk of bias, with the exception of the question "did participants enter the study at a similar point in the disease," which had a high risk of bias for one[114] and was unclear for two.[111,115] One study was considered to have a high risk of bias due to lack of clarity about anticoagulation use, which could affect the risk of recurrence,[111] and, in the same study, not all outcomes were reported. Studies were assessed as having a high overall risk of bias in results and conclusions due to lack of adverse event reporting; the other questions in that domain had a low risk of bias.

Detailed presentations of responses to individual signalling questions by study are shown in Appendix 17.

Figure 2: Risk of Bias for Single-Arm Pathway Studies



Outcomes

Failure Rate

Ten studies of diagnostic pathways reported the proportion of patients with test failure.[107-116] One study reported the results for more than one pathway, and the highest failure rate was selected for comparison.

For eight studies, the proportion of patients with failure for the intervention arm was between 0 to 0.017,[107-116] and the other two studies reported rates of 0.033 and 0.055, respectively (Table 3).

Table 3: Summary of Modalities, End Points, and Failure Rate Recorded for Pathways for Diagnosis of PE

Study	Sequence	End Points	Failure Rate (95% CI)
Galipienzo et al., 2012[108]	W, DD, CT	3-month VTE	0/57 0.00 (0.00 to 0.063)
Righini et al., 2008[116]	rG, DD, US, CT	3-month VTE, AE, treatment outcome	6/649 0.009 (0.003 to 0.020)
Bosson et al., 2007[107]	W, DD, leg US, V/Q, CT	3-month VTE	6/182 0.033 (0.012 to 0.070)
Jouveshomme et al., 2007[111]	CT, leg US, V/Q, DSA	3-month VTE or death	12/218 0.055 (0.029 to 0.094)
Vigo et al., 2006[115]	C, CT, DD, V/Q	3-month VTE	3/239 0.013 (0.003 to 0.036)
Hogg et al., 2006[110]	mW, DD, V/Q, CT, PA	Safety	3/408 0.007 (0.002 to 0.021)
Ghanima et al., 2005[109]	DD, CT, PA	3-month VTE, % diagnosed	2/221 0.009 (0.001 to 0.032)
Perrier et al., 2005[114] (did not exclude pregnant patients)	C, DD, CT	3-month VTE, AE, treatment outcome	5/292 0.017 (0.006 to 0.040)
Miniati et al., 2003[112]	C, V/Q, PA	% definitive diagnosis, recurrence in 1 year	1/230 0.004 (0.00 to 0.024)
Miron et al., 1999[113]	V/Q, C, DD, leg US, PA	% diagnosed	0/73 0.00 (0.00 to 0.049)

AE = adverse events; C = clinical assessment of risk; CI = confidence interval; CT = computed tomography; DD = D-dimer measurement; DSA = digital subtraction angiography; mW = modified Wells criteria; PA = pulmonary angiography; rG = revised Geneva scale; US = ultrasound; V/Q = ventilation/perfusion; VTE = venous thromboembolism; W = Wells rule.

Six studies reported VTE during three-month follow-up in patients who had PE excluded on the basis of low clinical probability and a negative D-dimer test and who did not receive anticoagulation.[107-109,114,116] The other studies did not incorporate that sequence[111,115,118] or did not report these patients separately.[110]

Alternative Diagnoses and Incidental Findings

One study of a diagnostic pathway reported that 94 of 284 patients (proportion 0.331) had one or more incidental findings, which were not specified.[111]

Safety

One pathway study reported adverse events associated with CT.[116] These are included in the CT section.

Question 3A: Diagnostic Test Accuracy of Single Imaging Modalities

Table 4 shows the matrix of counts for pairs of index tests and reference standards for DTA studies (in nonpregnant patients), following classification of index and reference tests. Studies may have included more than one pair of index test and reference standard, so the total number of pairs may be greater than the number of studies in the pool.

Results for individual modalities (and combinations of modalities) follow.

Table 4: Matrix of Counts for Pairs of Index Tests and Reference Standards Reported in Studies

	Reference Standard										
Index Test	**CC**	**CT**	**MRI**	**MSC**	**PA**	**SC**	**Sequential**	**V/Q**	**V/Q SPECT**	**V/Q SPECT-CT**	**Total**
CT	8	1	0	0	3	3	0	0	2	2	**19 (16)[a]**
CT-CTV	0	0	0	0	0	2	0	0	0	0	**2 (1)[a]**
MRI	2	8	0	0	4	1	1	0	0	0	**16 (15)[a]**
MRI-MRV	1	0	0	0	0	0	0	0	0	0	**1**
MRI-V/Q	1	0	0	0	0	0	0	0	0	0	**1**
US	1	6	1	1	0	1	0	1	0	0	**11**
Q	5	2	0	1	1	1	0	0	0	0	**10**
Q SPECT	2	0	0	0	0	0	0	0	0	0	**2**
Q SPECT-CT	3	0	0	0	0	0	0	0	1	0	**4**
V/Q	9	1	1	0	3	1	0	0	0	0	**15**
V/Q SPECT	6	5	0	0	0	1	0	4	0	0	**16**
V/Q SPECT-CT	0	1	0	0	0	0	0	0	3	0	**4**

CC = complex composite – reference standard including imaging in combination with D-dimer; CT = computed tomography; CT-CTV = computed tomography and CT venography; MRI = magnetic resonance imaging; MRI-MRV = magnetic resonance imaging and magnetic resonance venography; MRI-V/Q = magnetic resonance imaging combined with ventilation/perfusion imaging; PA = pulmonary angiography; Q = perfusion imaging; Q SPECT = perfusion-only SPECT; Q SPECT-CT = perfusion-only SPECT-CT; V/Q = ventilation/perfusion planar scintigraphy; V/Q SPECT = ventilation/perfusion SPECT; V/Q SPECT-CT = ventilation/perfusion SPECT-CT; SC = simple composite, only imaging modalities; Sequential = combination of imaging modalities used in sequence; SPECT = single photon-emission computed tomography; US = ultrasound.

[a] Figures in parentheses indicate the number of studies, where they differ from the number of contrasts.

Computed Tomography

Sixteen studies reported DTA outcomes for CT.[67,119-133]

Study and Patient Characteristics

Study information is summarized in Table 5, and detailed study characteristics are provided in Appendix 16.

Study Design

One study was an RCT,[119] and the rest were nonrandomized studies.[67,120-133] Recruitment for 10 studies was prospective,[67,119,121,123-126,128,132,133] five were retrospective,[122,127,129-131] and one was unclear.[120]

Country and Setting

Five studies were multi-centre, conducted in Denmark,[128] Sweden,[124] China,[131] and in Canada and the US.[67,133] The remaining studies were single-centre.[119-123,125-127,129,130,132] Of these, two were conducted in China,[119,121] two in France,[125,132] two in Germany,[120,122] two in the US,[123,134] and one in each of Belgium,[126] Japan,[129] and Switzerland.[130] Four studies were conducted in a secondary setting,[119,125,131,132] four in a secondary or tertiary setting,[67,127,128,133] one in a secondary centre ED setting,[126] one in a tertiary centre / ED setting,[130] and one in a secondary / tertiary ED setting.[123] Five studies did not specify the study setting.[120-122,124,129]

Funding

Five studies had government/institutional funding,[67,119,124,131,133] one declared no funding,[129] and one had private funding.[130]. Nine reports did not declare the funding source.[120-123,125-128,132]

Population

Studies recruited between 15[120] and 824 participants,[67,133] although not all patients were represented in the final diagnostic 2 × 2 table (Table 5). The most common reason for exclusion from the 2 × 2 table was a nondiagnostic reference test result, meaning that patients could not be classified as cases and noncases. Mean age ranged from 49.5 (standard deviation [SD] 15)[124] to 66.1 years (SD not given),[128] and the sex distribution (proportion female) was 0.46[120] to 0.73[128] Four studies recruited a mixture of in-patient and outpatients;[67,125,132,133] two selected outpatients;[119,130] one selected a mixture of outpatients, in-patients, and patients presenting at the ED;[123] and one each selected inpatients,[127] outpatients and patients presenting to the ED,[126] and patients presenting to the ED alone.[124] One did not specify patient status.[131] Eight studies reported a formally scored prior risk of PE, which was mixed, i.e., they recruited a mixture of low, moderate, and high prior risk of PE.[67,121,125,126,130-133]

Reference Standards

Reference standards were a complex composite reference standard including imaging in combination with D-dimer,[119-122,129-132] pulmonary angiography,[123-125] a simple composite comprising only imaging modalities,[67,126,133] V/Q SPECT,[127,128] and V/Q SPECT-CT.[120,128] Studies could report more than one comparison.

Technical Characteristics

The number of CT detectors ranged from two[125] to 64[119] and was not reported in six articles.[120,122,124,127,128,131] Two studies used dual-energy sources.[119,120]

Table 5: Summary of Study Information for Computed Tomography

Study	Reference (Composition of Composite)	Diagnostic N	Mean Age (Years)	Risk of PE	Number of Detectors
Lu et al., 2014[119]	CC (consensus reading, history, clinical data, supplementary imaging)	50	53.5	Not reported	64
Reinartz et al., 2004[122]	CC (V/Q, PA)	83	53.9	Mixed	Not reported
Thieme et al., 2012[120]	CC (clinical, V/Q SPECT-CT), V/Q SPECT-CT	15	64.0	Not reported	Not reported
Wang et al., 2009[121]	CC (consensus reading, all available)	75	51.0	Mixed	16
Okada et al., 2015[129]	CC (CT)	83	64.5	Not reported	64
Megyeri et al., 2014[130]	CC (CT, US, V/Q)	137	58.6	Mixed	16
He et al., 2012[131]	CC (CT, V/Q, PA, leg US)	544	53.3	Mixed	Not reported
Blanchere et al., 2000[132]	CC (CT, V/Q, PA, US)	179	61	Mixed	4
Nilsson et al., 2002[124]	PA	90	49.5	Not reported	Not reported
Qanadli et al., 2000[125]	PA	151	58.0	Mixed	2
Winer-Muram et al., 2004[123]	PA	93	54.8	Not reported	4
Coche et al., 2003[126]	SC (V/Q, DSA, CXR)	94	62.0	Mixed	4
Stein et al., 2006[67]	SC (CT, PA)	773	51.7	Mixed	4, 8,16
Stein et al., 2007[133]	SC (CT, PA)	773	51.7	Mixed	4, 8, 16
Mahdavi et al., 2013[127]	V/Q SPECT	60	60.0	Not reported	Not reported
Gutte et al., 2009[128]	V/Q SPECT, V/Q SPECT-CT	81	66.1	Not reported	Not reported

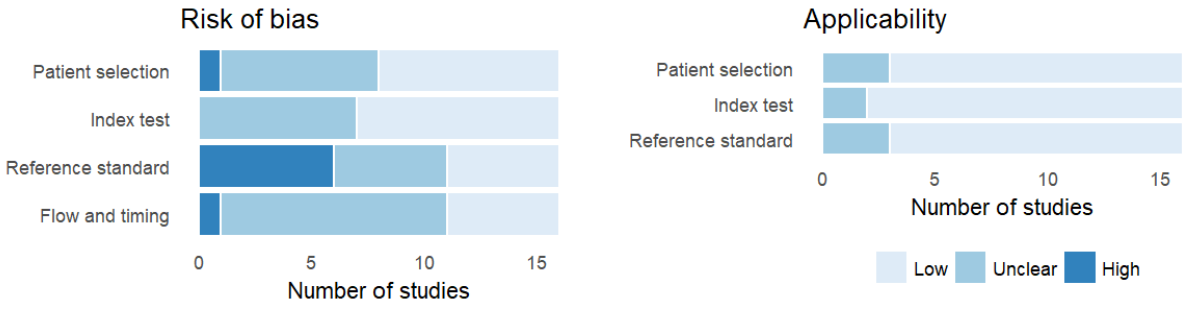
CC = complex composite reference standard including imaging in combination with D-dimer; CT = computed tomography; CXR = chest X-ray; DSA = digital subtraction angiography; PA = pulmonary angiography; V/Q = ventilation/perfusion planar scintigraphy; V/Q SPECT = ventilation/perfusion SPECT; V/Q SPECT-CT = ventilation/perfusion SPECT-CT; SC = simple composite, only imaging modalities; US = ultrasound.

Quality Appraisal

Figure 3 shows a summary of the risk of bias and applicability for all studies with CT as an index test. Reporting that was unclear or lacking in detail was responsible for the majority of "unclear" assessments, particularly for flow and timing, in which the sequence of testing was frequently unclear. One study was considered as having a high risk of bias for patient selection due to the inclusion of nonconsecutive patients.[126] The index test, as described, was generally appropriate to the question, and the reference test reflected standard practice for the diagnosis of PE (allowing for the known variability of reference standards). However, in diagnostic imaging studies, it is not uncommon for the final diagnosis to be made using all available information, including all available imaging. Studies that explicitly included the index test in the reference standard were rated as having a high risk of bias for the reference standard. Including the index test in the reference standard would result in a correlation

between the two tests that would enhance the observed performance of the index test. As a result, such studies have subsequently been excluded from pooling.[129-132] Studies were generally applicable to the question in patient selection, index test, and reference standard.

Figure 3: Risk of Bias and Applicability for All Studies With Computed Tomography as an Index Test



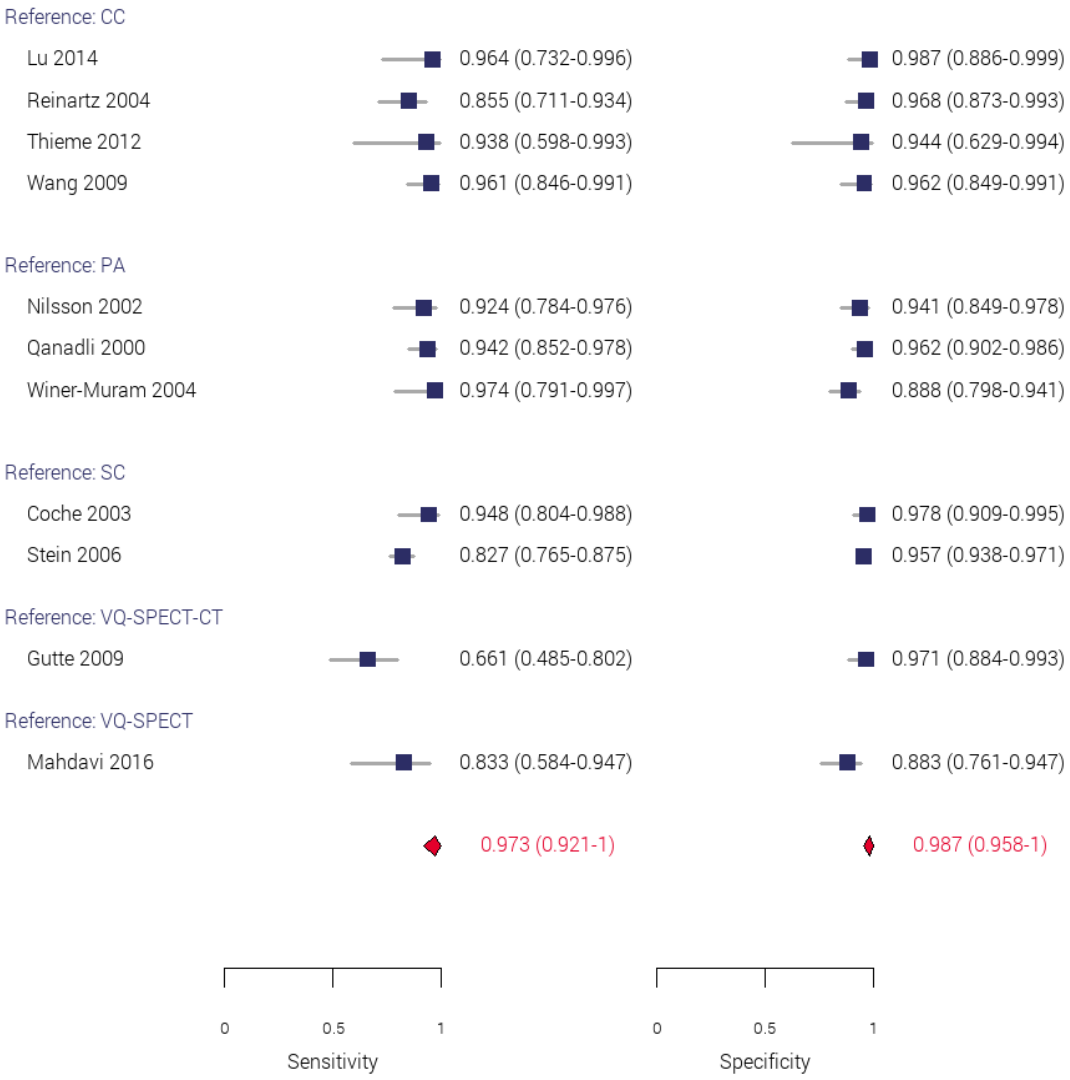
Detailed presentations of responses to individual signalling questions by study are shown in Appendix 17.

Summary of Diagnostic Test Results

Of the 16 studies, one was a post hoc analysis of an included study and was excluded from the overall pool but provided subgroup information.[133] Four studies featured one or more comparisons in which the index test was included in the reference assessment.[129-132] These comparisons were also excluded from the meta-analysis, leaving 11 studies.

The forest plot for the sensitivity and specificity for the 11 included studies is shown in Figure 4, grouped by reference standard, and ordered by the frequency with which the reference standard appears. The pooled value adjusted for imperfect reference standard appears in red.

Figure 4: Forest Plot for Studies With Computed Tomography as Index Test



CC = complex composite — reference standard including imaging in combination with D-dimer; PA = pulmonary angiography; V/Q SPECT = ventilation/perfusion SPECT; V/Q SPECT-CT = ventilation/perfusion SPECT-CT; SC = simple composite, only imaging modalities.

Note: Dark blue – individual study estimates without adjustment. Red – overall pool, including adjustment for imperfect and variable reference standard.

For patients in whom imaging was considered diagnostic, the overall pooled sensitivity with adjustment for imperfect reference standard is 0.973 (95% credible interval [CrI], 0.921 to 1.00) and the pooled specificity is 0.987 (95% CrI, 0.958 to 1.00). Therefore, of 1,000 patients, 150 of whom had PE,[94] an average of four patients (range 0 to 12) would receive a false-negative diagnosis and would be at risk of recurrent PE, and an average of 11 patients (range 0 to 36) would receive a false-positive diagnosis and would be at risk of complications (bleeding) from unnecessary treatment.

Heterogeneity

Both the forest plot (Figure 4) and receiver operating characteristic (ROC) scatterplots of sensitivity versus 1 – specificity (Appendix 22) indicated greater heterogeneity for sensitivity than specificity for CT across studies. The scatter appeared to cluster by reference standard. Despite the adjustment for the variability of the reference standard in our analysis, the prediction interval for a new study derived from the same statistical model (another indication of heterogeneity) was wider for sensitivity, 0.954 (95% CrI, 0.743 to 1.00), than for specificity, 0.969 (95% CrI, 0.807 to 1.00). The lower predicted mean values of sensitivity and specificity result from the wider credible intervals and the influence of outliers on the mean, while the pooled and predicted median values are similar.

There were insufficient data to investigate the effect of the predefined covariates on heterogeneity (see the section on Meta-Analysis of Diagnostic Test Accuracy Studies). Individual studies described the effect of prior PE risk and body weight as well as age and gender (see next section). For study setting, patient origins (in-patient, outpatient, ED), and PE risk, there was insufficient variation between studies for statistical adjustment (Appendix 22). All studies that assessed prior risk recruited a mixed population.

Individual Studies Describing the Effect of Covariates on Diagnostic Performance

Individual studies reported subgroup analyses for age,[133] gender,[133] prior PE risk,[67,131] and body weight.[130] With the exception of one study that reported a statistically significant difference of gender on specificity (0.93 in men, 0.97 in women; *P* = 0.015, in the presence of multiple statistical testing),[133] there were no studies that reported statistically significant effects of covariates on diagnostic performance. Detailed results appear in Appendix 21.

Computed Tomography and Computed Venous Tomography

One prospective, nonrandomized, multi-centre study compared the composite of CT and CTV with a simple composite reference standard.[67,133]

Study and Patient Characteristics

The study was conducted in the US and Canada, at a secondary / tertiary setting. The study recruited 773 in-patients and outpatients with an average age of 51.7 years. Prior risk of PE was formally appraised using the Wells criteria, and a mixed group of patients was included.

The reference standard was a simple composite using V/Q and PA.

Funding

Funding was from government sources.

Technical Characteristics

Patients underwent imaging by 4-, 8-, or 16-detector CT. The following criteria were used to diagnose PE: high-probability V/Q scan in the absence of a history of PE, abnormal findings on pulmonary digital subtraction angiography, abnormal findings in venous US, and nondiagnostic V/Q in the absence of a history of DVT at that site. Exclusion of PE required one of the following: normal V/Q scan or low- or very-low-probability V/Q scan combined with low clinical probability and normal venous US.

Detailed study characteristics are provided in Appendix 16.

Quality Appraisal

The study was considered as having a low risk of bias for the domains of “patient selection,” “index test,” and “reference standard,” and having an unclear risk of bias for flow and timing, on the basis of uncertainty about whether the interval between tests was appropriate (especially if anticoagulation was started on the basis of the results of the first imaging).

For applicability to the question, the study had a low risk of bias for all three domains: patient selection, index test, and reference standard.

The study was quality-appraised as part of the group of CT studies, with detailed quality appraisal results in Appendix 17.

Diagnostic Test Accuracy

For CT-CTV, the reported overall sensitivity was 0.90 (95% CI, 0.84 to 0.93), and the specificity was 0.95 (95% CI, 0.92 to 0.96).[67]

Effect of clinical prior risk of pulmonary embolism on diagnostic performance

This study also provided results stratified by Wells rule. There was no formal testing of the effect of predicted risk, but the CIs for sensitivity in the three strata overlapped, suggesting no significant effect of risk on sensitivity. Detailed results appear in Appendix 21.

Magnetic Resonance Imaging

Fifteen studies compared MRI with a reference standard.[135-149]

Study and Patient Characteristics

Table 6 shows study characteristics for the 15 MRI studies, including the composition of the reference standards.

Study Design

All studies were nonrandomized and prospective. All studies were single-centre, with the exception of one multi-centre study conducted in the US.[146]

Country and Setting

One single-centre study was conducted in Canada[149] and four studies in the US.[142,145,147,148] Two studies were conducted in China,[135,138] two in France,[139,140] and one study each in Germany,[141] Sweden,[137] the Netherlands,[143] Brazil,[136] and Australia.[144] Nine studies were conducted in secondary[135-137,139,141] or secondary and tertiary settings,[142,144,145,148] and three studies were conducted in secondary or tertiary ED settings.[140,146,149] One was unclear.[138]

Funding

Six studies reported government funding,[135,137-140,146] one study reported multiple funding sources,[144] one study did not receive funding,[136] one study reported private funding,[145] and six studies did not report their funding sources.[141-143,147-149]

Population

The number of patients recruited ranged from 14[148] to 818.[146] Three studies recruited in-patients;[135,137,141,145] two recruited in-patients or patients presenting at the ED;[140,149] one included a mix of in-patients and outpatients;[138] and one included a mix of in-patients, outpatients, and patients presenting to the ER.[146] Seven did not specify the patient

mix.[136,139,142-144,147,148] Four studies assessed prior probability of PE; in all cases, the studies recruited all risk levels.[137,140,141,146] The remaining studies did not report prior risk.

Reference Standards

Five reference standards were used: a complex composite reference standard including imaging in combination with D-dimer,[146,147] CT,[135-142] PA,[143-145,148] a simple composite comprising only imaging modalities,[148] and combination of imaging modalities used in sequence.[149] Some studies reported more than one reference standard.

Table 6: Summary of Study Information for Magnetic Resonance Imaging

Study	Reference	Diagnostic N	Mean Age (Years)	Risk of PE
Ohno et al., 2004[147]	CC (PA, V/Q, FU)	48	55.0	Not reported
Stein et al., 2010[146]	CC (CT, V/Q)	273	49.0	Mixed
Grist et al., 1993[142]	CT	14		Not reported
Kluge et al., 2006[141]	CT	62	60.9	Mixed
Li et al., 2017[135]	CT	29	55.0	Not reported
Nyren et al., 2016[137]	CT	33		Mixed
Pasin et al., 2017[136]	CT	91	63.0	Not reported
Revel et al., 2012[140]	CT	198	59.8	Mixed
Revel et al., 2013[139]	CT	198	60	Not reported
Zhang et al., 2013[138]	CT	27	38.2	Not reported
Gupta et al., 1999[144]	PA	36	59.0	Not reported
Meaney et al., 1997[145]	PA	30	52.0	Not reported
Oudkerk et al., 2002[143]	PA	118	53.0	Not reported
Erdman et al., 1994[148]	PA, SC (V/Q, clinical)	30		Not reported
Pleszewski et al., 2006[149]	Sequential	48	55.0	Not reported

CC = complex composite – reference standard including imaging in combination with D-dimer; CT = computed tomography; FU = follow-up; PA = pulmonary angiography; SC = simple composite, only imaging modalities; Sequential = combination of imaging modalities used in sequence; V/Q = ventilation/perfusion planar scintigraphy.

Technical characteristics

Table 7 shows a summary of technical information and examination sequences for the 14 MRI studies.

Table 7: Summary of Technical and Sequence Information for Magnetic Resonance Imaging Studies

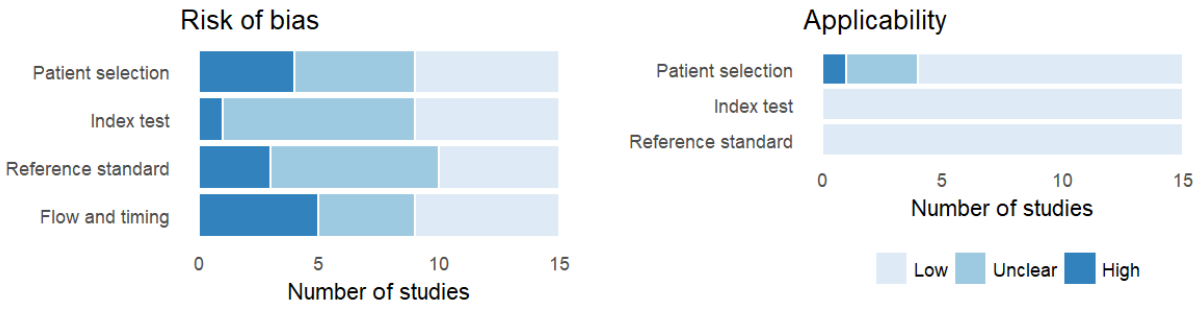
Author	Field	Slices	Contrast	Breath Hold	Non–Contrast-Enhanced	3-D MRA	Perfusion
Ohno et al., 2004[147]	1.5	5	Yes	Yes		x	
Stein et al., 2010[146]	1.5		Yes	Yes		x	
Grist et al., 1993[142]	1.5	5-10	No	Yes	X		
Kluge et al., 2006[141]	1.5	1.5-4	Yes	Yes	X	x	x
Li et al., 2017[135]	3	4	Yes	Yes		x	
Nyren et al., 2016[137]	1.5	4.5	No	No	X		
Pasin et al., 2017[136]	1.5	3-4	No	No	X		
Revel et al., 2012[140]	1.5	2.4-5	Yes	Yes	X	x	x
Revel et al., 2013[139]	1.5	2.4-5	Yes	Yes	X	x	x
Zhang et al., 2013[138]	3	1.3	Yes	Yes		x	
Gupta et al., 1999[144]	1.5	10	Yes	Yes		x	
Meaney et al., 1997[145]	1.5	3-4	Yes	Yes		x	
Oudkerk et al., 2002[143]	1.5	1.25	Yes	Yes		x	
Erdman et al., 1994 [148]	0.35	10	No	Unclear	x		
Pleszewski et al., 2006[149]	1.5	2-4	Yes	Yes		x	

3-D = three-dimensional; MRA = magnetic resonance angiography.

Quality Appraisal

Figure 5 shows a summary of the risk of bias and applicability for all studies with MRI as an index test. Reporting that was unclear or lacking in detail was responsible for the majority of "unclear" assessments. Issues in study selection were nonconsecutive recruitment and inclusion of a subset of healthy patients. One study had a high risk of bias due to lack of information about the index test.[140] Studies at high risk of bias due to the reference standard were identified as having possibly inappropriate reference standards, or applying different reference standards across the patient group.[137,140,149] Studies with a high risk of bias for flow and timing [135,137,140,146,149] did not apply the same reference standard across all patients, had not defined a specific protocol or pathway, or had an inappropriate interval between tests. Studies were generally applicable to the question for patient selection, index test, and reference standard, with the exception of one study that was at high risk of bias for applicability, as both setting and inclusion/exclusion criteria were not well described.[143]

Figure 5: Risk of Bias and Applicability for All Studies With Magnetic Resonance Imaging as an Index Test



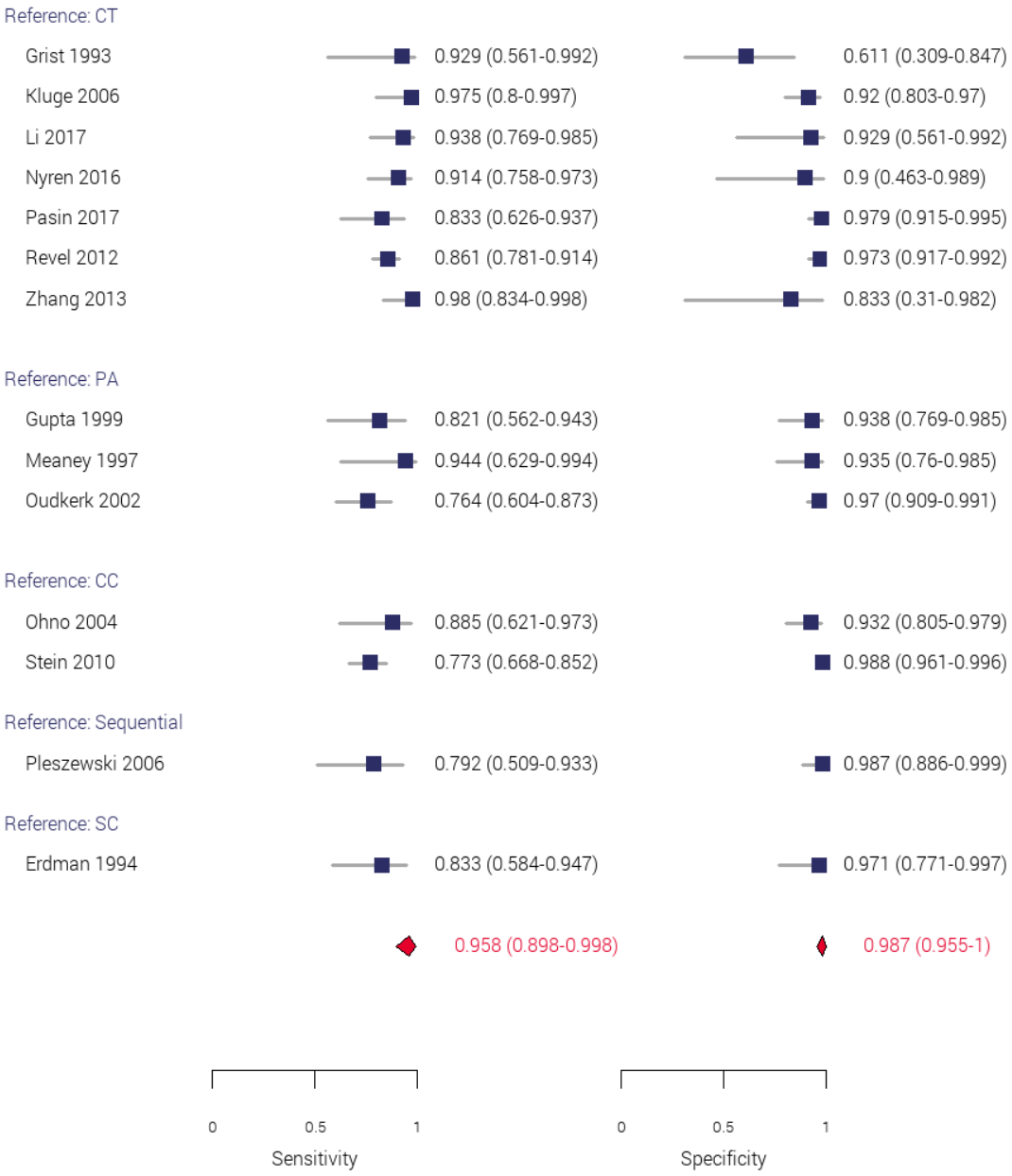
Detailed presentations of responses to individual signalling questions are given in Appendix 17.

Summary of Diagnostic Test Results

One study was excluded from the main pool because it had duplicate patients.[139] The study reported subgroups of interest, and is described in this report. Fourteen studies were included in the meta-analysis.

The forest plot for the sensitivity and specificity for all included studies is shown in Figure 6, grouped by reference standard, and ordered by the frequency with which the reference standard appears. The pooled value adjusted for imperfect reference standard appears in red.

Figure 6: Forest Plot for Studies With Magnetic Resonance Imaging as Index Test



CC = complex composite — reference standard including imaging in combination with D-dimer; CT = computed tomography; PA = pulmonary angiography; SC = simple composite, only imaging modalities; Sequential = combination of imaging modalities used in sequence.

Dark blue – individual study estimates without adjustment. Red – overall pool, including adjustment for imperfect and variable reference standard.

For patients in whom imaging was considered diagnostic, the pooled mean sensitivity with adjustment for imperfect reference standard is 0.959 (95%CrI, 0.898 to 0.998) and the pooled mean specificity is 0.987 (95%CrI, 0.955 to 1.00). Therefore, of 1,000 patients, 150 of whom had PE,[94] an average of six patients (range 0 to 15) would receive a false-negative diagnosis and would be at risk of recurrent PE, and an average of 11 patients (range 0 to 38) would receive a false-positive diagnosis and would be at risk of complications (bleeding) from unnecessary treatment.

Heterogeneity

Both the forest plot (Figure 6) and ROC scatterplots of sensitivity versus 1 – specificity (Appendix 22) indicated greater heterogeneity for sensitivity than specificity for CT across studies. There was a suggestion of clustering by reference standard. Despite the adjustment for the variability of the reference standard in our analysis, the prediction interval for a new study derived from the same statistical model (another indication of heterogeneity) was wider for both sensitivity and specificity than for the pooled estimates, with predicted mean sensitivity 0.930 (95%CrI, 0.652 to 1.00) and predicted mean specificity, 0.962 (95%CrI, 0.721 to 1.00). The lower predicted mean values of sensitivity and specificity result from the wider CrIs and the influence of outliers on the mean, while the pooled and predicted median values are similar.

We had insufficient data to investigate the effect of the predefined covariates on heterogeneity (see the section on Meta-Analysis of Diagnostic Test Accuracy Studies). For study setting, patient origins (in-patient, outpatient, ED), PE risk, and the post hoc variable of field strength, there was insufficient variation between studies for statistical adjustment (Appendix 22). All studies that assessed prior risk recruited a mixed population. One individual study provided a stratified analysis of prior PE risk (see next section).

Individual Studies Describing the Effect of Covariates on Diagnostic Performance

One nonrandomized study reported results stratified by prior risk according to the Geneva score, in a cohort of patients recruited to have high Geneva score or elevated D-dimer.[140] There was no consistent trend across risk strata. Detailed results appear in Appendix 21.

Effect of Magnetic Resonance Imaging Sequence on Diagnostic Performance

Two studies compared the results of more than one set of imaging conditions.[139,141] In Revel et al., 2013,[139] both sensitivity and specificity were highest for contrast-enhanced three-dimensional (3-D) angiography. In Kluge et al., 2006,[141] the highest sensitivity was obtained by magnetic resonance perfusion imaging, and the highest specificity by real-time MRI. Detailed results appear in Appendix 21.

Magnetic Resonance Imaging and Magnetic Resonance Venography (MRI-MRV)

One prospective, nonrandomized, multi-centre study reported the combination of MRI and MRV.[146]

Study and Patient Characteristics

The study was conducted in the US, in secondary settings.

A total of 818 patients were enrolled, from in-patients and outpatients, and ED, and 175 completed both imaging modalities. Prior risk of PE was formally assessed, and patients were recruited across all risk strata.

The study reference standard was a complex composite involving risk stratification and CT and V/Q imaging.[146]

Funding

The study was supported by government funding.

Technical Characteristics

The study used a 1.5 T magnet and contrast-enhanced 3-D angiographic sequences.

Detailed study information is available in Appendix 16.

Quality Appraisal

The study was considered as having a low risk of bias for the index test and reference standard, a high risk of bias for flow and timing (not all patients received the same reference standard, and there was an up to 72-hour interval between the tests, during which anticoagulation was started), and an unclear risk of bias for patient selection (recruitment depended on the availability of the trial nurse).

For applicability to the question, the study had a low risk of bias for all three domains: patient selection, index test, and reference standard.

The study was quality-appraised as part of the set of MRI studies, with detailed quality appraisal available in Appendix 17.

Diagnostic Test Results

For MRI-MRV, including only patients with scans considered technically adequate, the sensitivity was 0.92 (95% CI, 0.83 to 0.97), and the specificity was 0.96 (95% CI, 0.91 to 0.99). If scans considered technically inadequate (52% of patients) were included under the intent to diagnose assumption (inadequate cases were counted as false-negative, inadequate noncases as false-positive), the sensitivity was 0.63 (95% CI, 0.53 to 0.72) and the specificity was 0.38 (95% CI, 0.32 to 0.44).

Magnetic Resonance Imaging and Ventilation/Perfusion Planar Scintigraphy (MRI-V/Q)

One prospective, nonrandomized, single-centre study reported the diagnostic properties of combined contrast-enhanced MRI and V/Q,[147] compared with a complex composite including PA, V/Q imaging, and clinical follow-up.

Study and Patient Characteristics

The study was conducted in the US, but setting, patient group, and funding were not clearly reported.

The study recruited 48 in-patients and outpatients with an average age of 55 years. Detailed study information is available in Appendix 16.

Funding

Funding was not clearly reported.

Technical Characteristics

The study used a magnet of field strength 1.5 T, with contrast-enhanced 3-D MR angiography by 3-D spoiled gradient-echo (SPGR) MRI. V/Q scanning was carried out with 185 MBq 99mTc-macroaggregated albumin (MAA) (perfusion) and 81 mKr (ventilation).

Quality Appraisal

The study was considered to have a low risk of bias for the domain of patient selection, and an unclear risk of bias for index test, reference standard, and flow and timing, due to unclear reporting of the interval between index test and reference standard, and whether test and reference standard were interpreted without knowledge of each other.

For applicability to the question, the study had a low risk of bias for all three domains: patient selection, index test, and reference standard.

The study was quality-appraised as part of the group of MRI studies, and detailed quality appraisal results are available in Appendix 17.

Diagnostic Test Results

The combination of contrast-enhanced MRI and V/Q had a sensitivity of 0.92 and specificity of 0.94. For contrast-enhanced MRI alone, the sensitivity was 0.83 and the specificity, 0.94. For V/Q alone, the sensitivity was 0.67 and the specificity, 0.78 (confidence intervals were not reported).

Thoracic Ultrasound

Ten studies compared thoracic US with a reference standard.[117,150-158]

Study and Patient Characteristics

Study information is summarized in Table 8, and detailed study characteristics are provided in Appendix 16.

Study Design

All studies were of nonrandomized design. Nine were prospective[117,150-153,155-158] and one, retrospective.[154]

Country and Setting

Three were conducted in Austria,[117,157,158] three in Germany,[153,154,156] and one each in France,[155] Italy,[151] Turkey,[152] and Iran.[150] One, the largest, was indicated as multi-centre,[151] eight as single-centre,[117,150,152-157] and one was not specified.[158] Three were conducted in secondary or secondary / tertiary institutions,[152,155,158] and two were conducted in secondary centre EDs.[150,151] Five did not specify type of setting.[153,154,156-158]

Funding

Three studies reported receiving no funding,[150-152] and seven did not report the type of funding.[117,153-158]

Population

The number of patients ranged from 33[153] to 357.[151] The mean age ranged from 52.8 years[150] to 71.0 years.[151] Two studies involved outpatients and patients presenting to the ED,[150,159] and one, in-patients.[117] Seven did not specify the patient mix.[152-158] The prior risk

of PE was formally assessed in six studies, three of which recruited symptomatic patients with all levels of risk,[117,155,158] and two of which recruited symptomatic patients at moderate/high risk.[150-152] Four studies did not report prior risk.[153,154,156,157]

Reference Standards

Eleven comparisons were reported for six reference standards (a complex composite reference standard including imaging in combination with D-dimer,[155] CT,[150-154,156] MRI,[117] multiple simple composites in which reference standard was more than one combination of imaging modalities,[156] a simple composite comprising only imaging modalities,[157] and V/Q[158]).

Technical Characteristics

The most commonly used thoracic US probe frequencies were 3.5 MHz to 5 MHz.[117,151-153,155,157,158,160] Other probe frequencies were 3 MHz,[157] 4 MHz to 8 MHz,[151] 7 MHz or 7.5 MHz,[117,150,153,157,158] and 10 MHz.[117] PE was diagnosed through the observation of triangular or wedge-shaped (sometimes round) pleural-based or subpleural hypoechoic lesions or infarcts, a consistent definition across studies.

Table 8: Summary of Study Information for Thoracic Ultrasound

Study	Reference	N	Mean Age (Years)	Risk of PE	Probe
Mohn et al., 2003[155]	CC (V/Q, LUS, PA, FU)	74	66.0	Mixed	5 MHz linear
Abootalebi et al., 2016[150]	CT	77	52.8	Mixed	3.5 MHz, 5 MHz
Comert et al., 2013[152]	CT	50	54.1	Intermediate	3.5 MHz convex
Nazerian et al., 2014[151]	CT	357	71.0	Intermediate	4 MHz to 8 MHz linear, 3.5 MHz to 5 Hz convex
Pfeil et al., 2010[153]	CT	33	65.4	Not reported	3.5 MHz to 5 MHz convex, 7.5 MHz linear
Reissig et al., 2001[156]	CT, MSC	62	62.8	Not reported	Not reported
Reissig et al., 2004[154]	CT	62	62.2	Not reported	Not reported
Lechleitner et al., 2002[117]	MRI	52	69.0	Mixed	3.5 MHz, 5 MHz
Mathis et al., 1993[157]	SC (V/Q, PA)	54	63.0	Not reported	5 MHz (sometimes 3.5 MHz or 5 MHz)
Lechleitner et al., 1998[158]	V/Q	64	66.0	Mixed	3.5 MHz, 7.5 MHz, 10 MHz

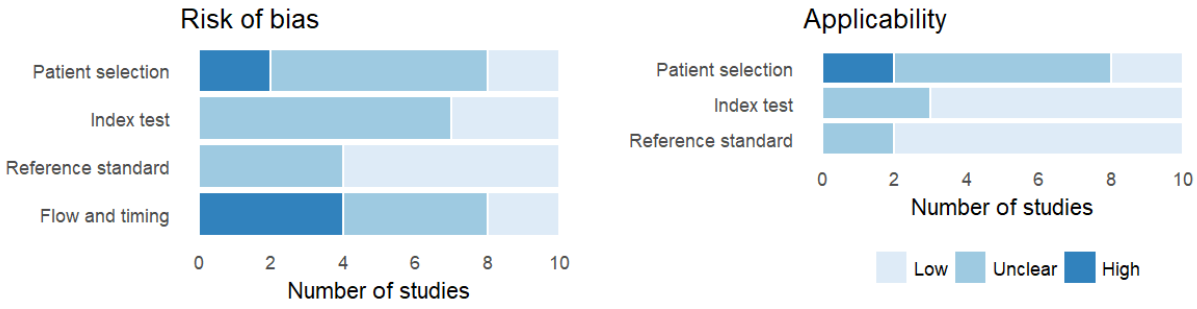
CC = complex composite — reference standard including imaging in combination with D-dimer; CT = computed tomography; DSA = digital subtraction angiography; FU = follow-up; LUS = leg ultrasound; MRI = magnetic resonance imaging; MSC = multiple simple composites in which reference standard was more than one combination of imaging modalities; PA = pulmonary angiography; SC = simple composite, only imaging modalities; V/Q = ventilation/perfusion planar scintigraphy.

Quality Appraisal

Figure 7 shows a summary of the risk of bias and applicability for all studies with US as an index test. The majority of ratings of unclear risk of bias were due to insufficient detail or unclear reporting. Studies with a high risk of bias for patient selection did not report exclusion criteria,[152,157] and for the two studies with a high risk for applicability, the patient selection was not clear.[154,156] In two of the four studies with a high risk of bias for flow and timing, not all patients were included in the analysis,[117,156] and in the other two, not all received the same reference standard.[155,158] Two studies had a high risk of bias for applicability to the question in patient selection, due to lack of clarity around patient selection

criteria;[154,156] the others had a low or unclear risk for patient selection, index test, or reference standard.

Figure 7: Risk of Bias and Applicability for All Studies With US as an Index Test

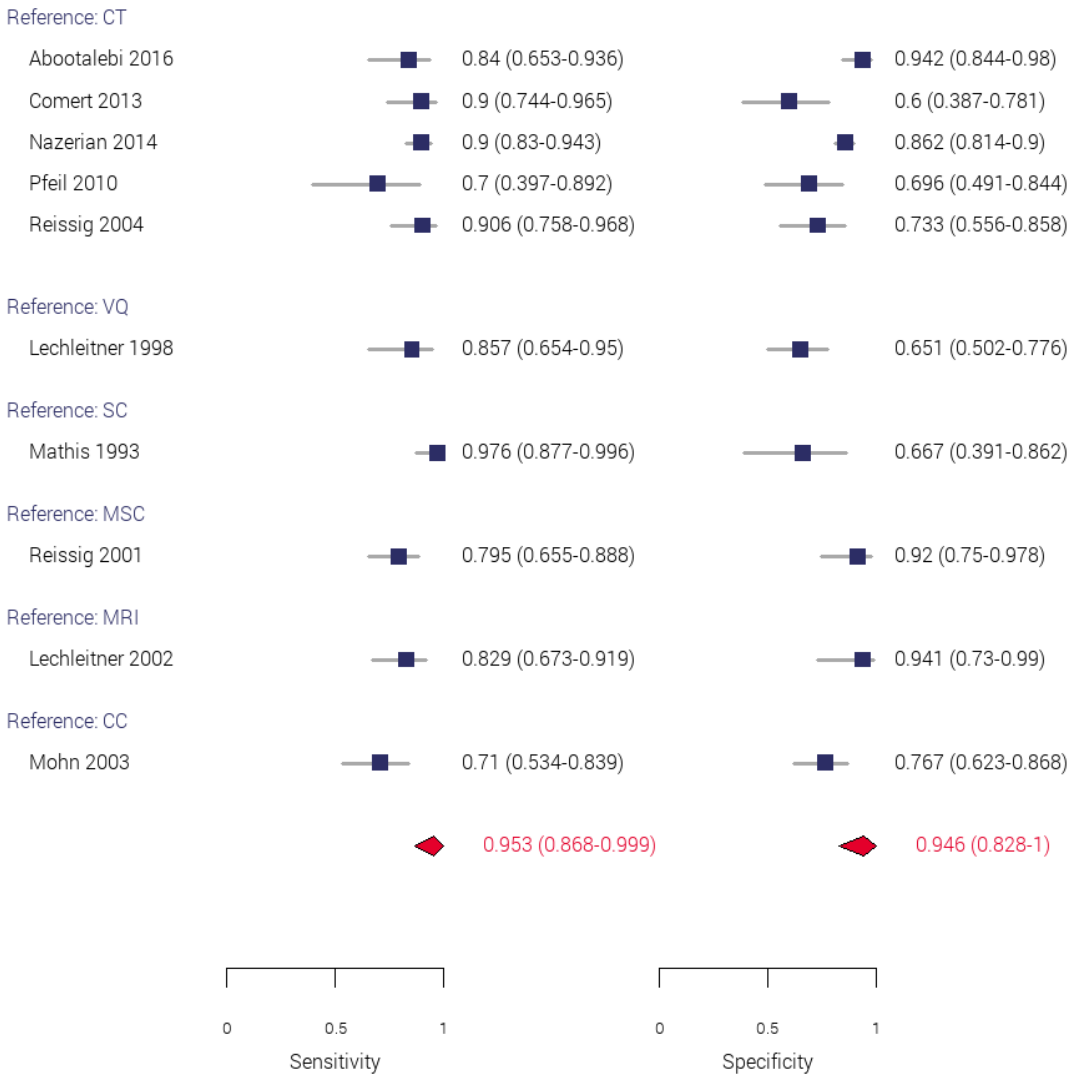


Detailed presentations of responses to individual signalling questions are given in Appendix 17.

Summary of Diagnostic Test Results

The forest plot for the sensitivity and specificity for the 10 included studies is shown in Figure 8, grouped by reference standard, and ordered by the frequency with which the reference standard appears. The pooled value adjusted for imperfect reference standard appears in red.

Figure 8: Forest Plot for Studies With Thoracic Ultrasound as Index Test



CC = complex composite reference standard including imaging in combination with D-dimer; CT = computed tomography; MRI = magnetic resonance imaging; MSC = multiple simple composites in which reference standard was more than one combination of imaging modalities; SC = simple composite, only imaging modalities; V/Q = ventilation/perfusion.

Dark blue – individual study estimates without adjustment. Red – overall pool, including adjustment for imperfect and variable reference standard.

For patients in whom imaging was diagnostic, the pooled sensitivity with adjustment for imperfect reference standard is 0.953 (95% CrI, 0.867 to 0.999) and the pooled specificity is 0.946 (95% CrI, 0.828 to 1.000). Therefore, of 1,000 patients, 150 of whom had PE,[94] an average of seven patients (range 0 to 20) would receive a false-negative diagnosis and would be at risk of recurrent PE, and an average of 46 patients (range 0 to 146) would

receive a false-positive diagnosis and would be at risk of complications (bleeding) from unnecessary treatment.

The meta-analysis showed a large increase in both sensitivity and specificity upon adjustment for imperfect reference standard (Appendix 22). For consistency with the analyses for other modalities, the model with adjustment for imperfect reference standard is reported, but it should be interpreted with caution, as the data are both sparse and heterogeneous.

Heterogeneity

Both the forest plot (Figure 8) and an ROC scatterplot of sensitivity versus 1 – specificity (Appendix 22) indicated heterogeneity for sensitivity and specificity. The predicted sensitivity for a new study derived from the same statistical model is 0.917 (95% CrI, 0.553 to 1.00) and the predicted specificity for a new study is 0.927 (95% CrI, 0.638 to 1.000). The lower predicted mean values of sensitivity and specificity result from the wider CrIs and the influence of outliers on the mean, while the pooled and predicted median values are similar.

We had insufficient data to investigate the effect of the predefined covariates on heterogeneity (see the section on Meta-Analysis of Diagnostic Test Accuracy Studies). For study setting, patient origins (in-patient, outpatient, ED), and PE risk, there was insufficient variation between studies for statistical adjustment (Appendix 22). Only one study reported risk of PE, and recruited a mixed-risk cohort.

No individual studies reported stratified results for any covariates of interest.

Perfusion Imaging (Q)

Eleven studies compared perfusion imaging with a reference standard.[121,131,161-169]

Study and Patient Characteristics

Study Design

All studies were nonrandomized. Six were prospective[121,162,166-169] and five, retrospective.[131,161,163-165]

Country and Setting

Four were multi-centre, conducted in Slovenia,[161] the US,[164] China,[131] and the Netherlands and Belgium.[167] The rest were single-centre studies, with two conducted in Italy,[165,168] two in Belgium,[162,169] and one each in the US,[163] Poland,[166] and China.[121] Six were in secondary or tertiary care centres,[161,163,165-167,169] two were in a secondary centre ED,[162,164] one was in a secondary centre,[131] and two did not specify setting.[121,168]

Funding

Four studies reported receiving government funding,[131,164,166,168] three did not receive funding,[162,163,167] and four studies did not report funding.[121,161,165,169]

Population

Studies recruited between 53[162] and 890 patients.[168] The number of patients contributing to the diagnostic 2 × 2 table is shown in Table 9. Three studies recruited in-patients;[161,165,166] one recruited in-patients and outpatients;[167] one in-patients, outpatients, and ED patients;[164] and one recruited from the ED.[162] Four did not report where patients were recruited

from.[121,163,168,169] Six studies reported the formally evaluated risk of PE, one as high[167] and five as mixed.[121,131,162,164,168] Five did not report risk.[161,163,165,166,169]

Reference Standards

The reference standards were a complex composite reference standard including imaging in combination with D-dimer,[121,131,161,163,166,169] CT,[165,167] multiple simple composite (patients received different modalities as part of the simple composite),[164] a simple composite comprising only imaging modalities,[162] and pulmonary angiography.[168]

Technical Characteristics

All studies used 99mTc-labelled macro-aggregated albumin injection for visualization, with doses ranging from 110 MBq[162] to 370 MBq.[121,131] Seven studies used the prospective investigative study of acute pulmonary embolism diagnosis (PISAPED) criteria for PE diagnosis,[131,161,162,164,165,167,168] two used a modified version of the prospective investigation of pulmonary embolism diagnosis (PIOPED)[121] or PIOPED II[164] criteria that allowed for the absence of ventilation results, and two used study-specific interpretations.[129,166] Under the PISAPED criteria, PE was considered to be present if there were single or multiple wedge-shaped perfusion defects, irrespective of abnormalities on the chest X-ray. PE was absent if there were either no perfusion defects of any kind, non–wedge-shaped defects, or defects smaller than or equal to chest radiograph abnormalities in size and shape. All other findings were considered nondiagnostic.

Study information is summarized in Table 9, and detailed study characteristics are provided in Appendix 16.

Table 9: Summary of Study Information for Perfusion Imaging

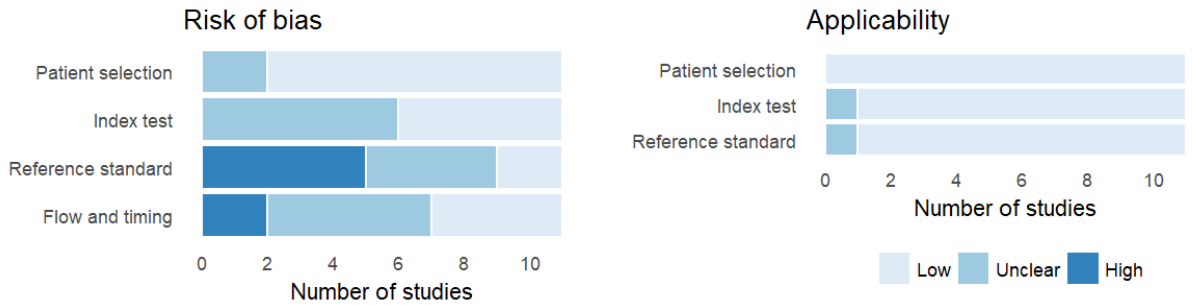
Study	Reference	N	Mean Age (Years)	Risk of PE	Dose (MBq) / Isotope	Index Interpretation
Mazurek et al., 2015 [166]	CC (CT)	84	68.3	Not reported	185/99mTc	Study-specific
Skarlovnik et al., 2014 [161]	CC (unclear)	77	71.5	Not reported	120 to 200/99mTc	PISAPED
Wang et al., 2009 [121]	CC (unclear)	75	51.0	Mixed	185 to 370/99mTc	Modified PIOPED
Lu et al., 2014[163]	CC (leg US, Q SPECT-CT, CT, V/Q)	106	63	Not reported	4 mCi/99mTc	Study-specific
He et al., 2012[131]	CC	544	53.3	Mixed	185 to 370/99mTc	PISAPED
Collart et al., 2002[169]	CC (CT, V/Q)	66	Not reported	Not reported	150 to 190 MBq of 99mTc	PIOPED
Rubini et al., 2007 [165]	CT	107	60.0	Not reported	185/99mTc	PISAPED
van Es et al., 2015 [167]	CT	74	38.0	High	148 to 155/99mTc	PISAPED
Sostman et al., 2008[164]	MSC (PA, CT)	910	51.7	Mixed	4 mCi/99mTc	PISAPED, modified PIOPED II
Miniati et al., 1996 [168]	PA	580	64.3	Mixed	180/99mTc	PISAPED
Tondeur et al., 2007 [162]	SC (CT, V/Q)	30	60.0	Mixed	110/99mTc	PISAPED

CC = complex composite — reference standard including imaging in combination with D-dimer; CT = computed tomography; MSC = multiple simple composite in which reference standard was more than one combination of imaging modalities; PA = pulmonary angiography; Q SPECT-CT = perfusion single-photon emission CT; SC = simple composite, only imaging modalities; V/Q = ventilation/perfusion planar scintigraphy; US = ultrasound.

Quality Appraisal

Figure 9 shows a summary of the risk of bias and applicability for all studies, with Q as an index test. The majority of ratings of unclear risk of bias were due to insufficient detail or unclear reporting. Studies that had a high risk of bias for the reference standard included the index test in the reference standard,[131,163,169] or the reference test was interpreted with knowledge of the index test results.[170] Two studies did not apply the same reference standard across all patients, one using clinical follow-up in patients who could not undergo definitive imaging.[164,168] Studies were at low or, in two cases,[167,171] unclear, measures of applicability to the question, for the index[167] and reference tests.[121]

Figure 9: Risk of Bias and Applicability for All Studies With Q as an Index Test



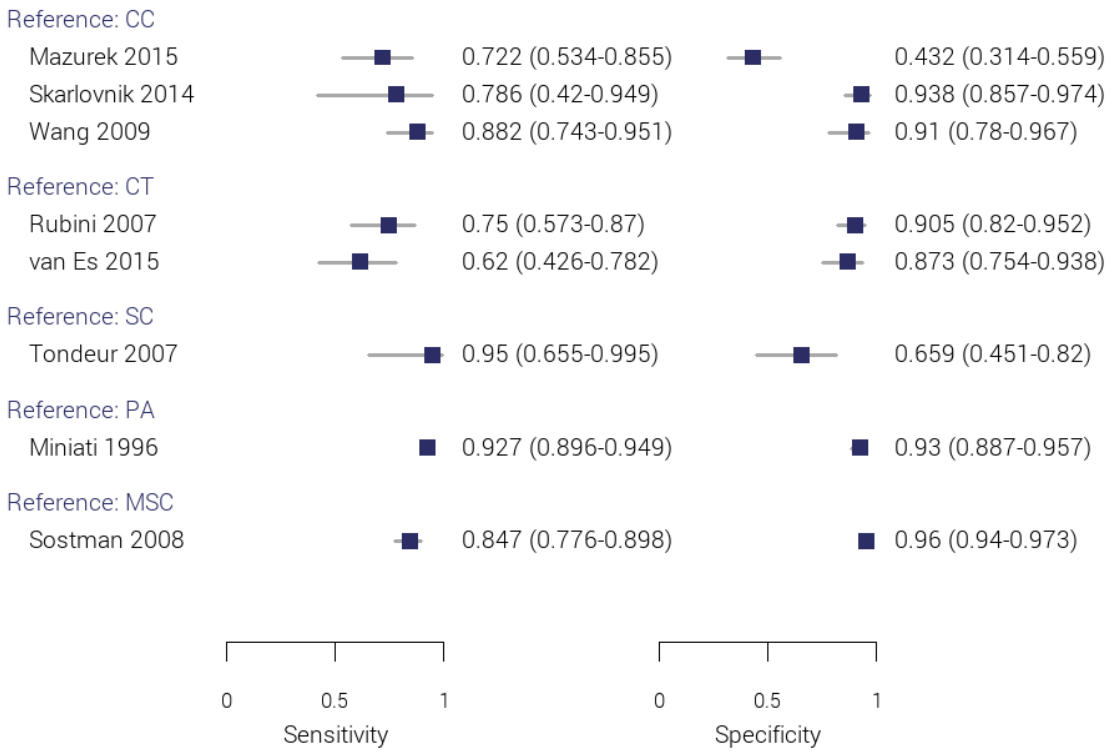
Detailed presentations of responses to individual signalling questions are given in Appendix 17.

Summary of Diagnostic Test Results

Three studies were excluded from possible pooling because the index test was included in the reference standard.[131,163,169] Eight remaining studies reported eight comparisons, with five reference standards: a complex composite reference standard including imaging in combination with D-dimer ,[121,161,172] CT,[165,167] multiple simple composites in which reference standard was more than one combination of imaging modalities,[164] PA,[168] and a simple composite comprising only imaging modalities.[162]

The forest plot for the sensitivity and specificity for the eight included studies is shown in Figure 10, grouped by reference standard, and ordered by the frequency with which the reference standard appears. Given the small number of studies, the heterogeneity evident in the forest plot, the very wide credible intervals resulting from analyses, and the appearance of the posterior density plots and convergence traces, pooling of studies was considered inappropriate and a meta-analysis was not reported.

Figure 10: Forest Plot for Studies With Perfusion as Index Test



CC = complex composite — reference standard including imaging in combination with D-dimer; CT = computed tomography; MSC = multiple simple composites — in which reference standard was more than one combination of imaging modalities; PA = pulmonary angiography; SC = simple composite, only imaging modalities.

Dark blue – individual study estimates without adjustment.

The reported sensitivity of perfusion for the diagnosis of PE ranged from 0.62 (95% CI, 0.426 to 0.782) against a reference standard of CT,[167] to 0.927 (95% CI, 0.896 to 0.949) against a reference standard of PA.[168] The reported specificity of perfusion for the diagnosis of PE ranged from 0.432 (95% CI, 0.314 to 0.559)[166] against a complex composite reference standard to 0.930 (95% CI, 0.889 to 0.956) against a reference standard of PA.[168]

Heterogeneity

Both the forest plot (Figure 10) and an ROC scatterplot of sensitivity versus 1 – specificity (Appendix 22) indicated heterogeneity for sensitivity and specificity.

We had insufficient data to investigate the effect of the predefined covariates on heterogeneity (see the section on Meta-Analysis of Diagnostic Test Accuracy Studies). Individual studies described the effect of prior PE risk as well as by age (see next section). For study setting, patient origins (in-patient, outpatient, ED), and PE risk, there was insufficient variation between studies for statistical adjustment (Appendix 22).

Individual Studies Describing the Effect of Covariates on Diagnostic Test Performance

One study[131] reported results stratified by risk, and one study stratified results by age and assessed the effect of lung disease.[164] A third study restricted recruitment to patients less than 51 years old.[167] Sensitivity appeared to increase with risk, while specificity was unaffected, although this was not statistically tested.[131] Age and lung disease appeared to affect sensitivity and specificity,[164] but lung disease influenced the proportion of nondiagnostic scans.[164] Detailed results appear in Appendix 21.

Perfusion–Single-Photon Emission Tomography (Q SPECT)

Three studies compared Q SPECT with a reference standard.[166,169,173]

Study and Patient Characteristics

All studies were single-centre, nonrandomized studies, conducted in Poland,[166] Belgium,[169] and Sweden.[173] Two were prospective[166,169] and one, retrospective.[173] All were conducted at a secondary or secondary/tertiary centre.

One study recruited 84 in-patients,[166] the second 152 patients (primarily outpatients),[173] and the third, 70 patients, whose source was not described.[169] The median age of patients in one study was 61 years, and the mean age in the second was 68.5 years. The third did not indicate age. None reported a formally assessed risk of PE.

One study used CT in its composite reference standard,[173] and the other used CT, thoracic US, and V/Q SPECT.[166]

Funding

One study received government funding,[166] one private funding,[173] and the third did not report funding.[169]

Technical Characteristics

All studies used 99mTc-labelled MAA, at doses of 120 MBq[173] to 185 MBq.[166] One study used the European Association of Nuclear Medicine (EANM) criteria, under which a positive scan showed single or multiple wedge-shaped perfusion defects,[173] and a negative scan showed no defects or perfusion defects other than wedge-shaped. The other defined a

positive scan as at least one segmental or two subsegmental defects without lung parenchymal abnormalities.[166] The third did not specify.[169]

Detailed study characteristics are provided in Appendix 16.

Quality Appraisal

Two studies had a low risk of bias for patient selection, and one had an unclear risk of bias. One study had a low risk of bias, and two had an unclear risk of bias, for index test. Two studies had a high risk of bias,[169,173] and one had an unclear risk of bias, for the reference standard,[166] as it was either apparent or suspected that the index test was not interpreted without knowledge of the reference standard. One study had a high risk of bias for study flow, as not all patients received the same reference standard;[173] one had a low risk of bias,[169] and one had an unclear risk of bias, due to uncertainty about the interval between tests.[166]

All studies had a low risk for the domains of applicability to the question, patient selection, index test, and reference standard.

Detailed presentations of responses to individual signalling questions are given in Appendix 17.

Diagnostic Test Accuracy Results

One study[169] incorporated the index test in the reference standard and was not eligible for pooling.

In one study, the sensitivity of Q SPECT was 0.898 (95% CI, 0.722% to 0.962)[173] and the specificity 0.946 (95% CI, 0.897 to 0.982).[173] In the other, the sensitivity of Q SPECT was 0.885 (95% CI, 0.698 to 0.976),[166] and the specificity 0.466 (95% CI, 0.333 to 0.601).[166]

There were no reports on subgroups of interest.

Perfusion–Single-Photon Emission Tomography–Computed Tomography (Q SPECT-CT)

Four nonrandomized studies compared Q SPECT-CT with a reference standard.[163,166,174,175]

Study and Patient Characteristics

All studies were nonrandomized and single-centre. Two were prospective[166,174] and two retrospective.[163,175] Two studies were conducted in the US,[163,175] and one each in France[174] and Poland.[166] Three were conducted at a secondary/tertiary centre,[163,166,174] and one did not specify.

Studies recruited between 49[175] and 393 patients.[174] One study recruited in-patients,[166] one recruited in-patients and outpatients,[174] and two did not specify.[163,175] None of the studies reported the prior risk of PE.

The reference standard in one study was V/Q SPECT,[174] and the other three used a complex composite.[163,166,175] One composite consisted of leg US, CT, Q, V/Q, Q SPECT-CT;[175] another consisted of leg US, CT, V/Q, Q SPECT-CT;[163] and the third was unclear.[166]

Funding

One study received government funding,[166] one received none,[163] and two did not report funding.[174,175]

Technical Characteristics

The studies used 99mTc-labelled MAA at doses ranging from 110 MBq[175] to 200 MBq.[174] A PE-positive scan required least one segmental (at least 50%),[163,175] or one segmental or two subsegmental perfusion defects without lung parenchymal defects.[166,174] Where specified, a PE-negative scan required a normal perfusion pattern, defects that did not align with the pulmonary vasculature, or defects due to abnormalities in the lung parenchyma.[166,175]

Quality Appraisal

For patient selection, two studies had a low risk of bias,[163,166] and two had an unclear risk.[174,175] For the index test, two studies had a low risk of bias,[174,175] and two had an unclear risk.[163,166] For the reference test, three studies had an high risk of bias,[163,174,175] due to the inclusion of the index in the reference test, and one had an unclear risk. For flow and timing, three studies had a low risk of bias,[163,174,175] and one had an unclear risk of bias.[166] In most cases, the assessment of unclear risk of bias was due to lack of clarity in the reporting.

For applicability to the question of patient selection, index test, and reference test, all studies had a low risk of bias.

Diagnostic Test Accuracy Results

Three studies included the index test in the reference standard.[163,174,175]

In the remaining study, against a composite reference standard, the sensitivity of Q SPECT-CT was 1.00 (95% CI, 0.868 to 1.00) and the specificity was 0.828 (95% CI, 0.706 to 0.914).[166]

There were no reports on clinical subgroups of interest.

Ventilation/Perfusion Scintigraphy (V/Q)

Fourteen studies compared V/Q imaging with other imaging modalities.[117,121,122,126,131,132,147,160,161,163,169,176-179]

Study and Patient Characteristics

Study information is summarized in Table 10, and detailed study characteristics are provided in Appendix 16.

Study Design

All studies were nonrandomized. Nine were prospective,[117,121,126,132,147,160,176-178] and five were retrospective.[122,131,161,163,179]

Country and Setting

Four were multi-centre: one conducted in the US;[177] one in Slovenia;[161] one in China;[131] and the third in Slovenia, Turkey, Czech Republic, Uruguay, and India.[160] The single-centre studies were conducted in Canada,[179] two in the US,[147,163] and one each in Belgium,[126] Scotland,[178] Austria,[117] France,[132] Germany,[122] Denmark,[176] and China.[121] The settings were secondary[117,131,132,178] or secondary/tertiary health care,[160,161,163,176] or secondary-setting ED,[126,177] with four studies not reporting setting.[121,122,147,179]

Funding

One study received government funding,[177] and two reported receiving no funding.[160,163] Seven studies did not report funding.[117,121,122,126,132,147,161,176,178,179]

Population

Studies recruited between 38[179] and 931 patients.[177] Two studies recruited in-patients;[117,161] one recruited outpatients and ED patients;[126] one in-patients and outpatients;[132,160] and one in-patients, outpatients, and ED patients.[177] The other eight did not report the mix of patients they recruited.[121,122,131,147,163,176,178,179] The mean age of patients ranged from 51.0 years[121] to 71.5 years.[161] The six studies that reported the results of formal assessment for risk of PE all recruited a mixture of risk levels.[117,121,126,131,132,160]

Reference Standards

The studies compared V/Q with five reference standards: a complex composite reference standard including imaging in combination with D-dimer,[121,122,131,132,147,161,163,176] CT,[160] MRI,[117] PA,[177-179] and a simple composite comprising only imaging modalities.[126]

Technical Characteristics

For perfusion imaging, all studies used 99mTc MAA, administered intravenously at doses ranging from 74 MBq[117] to 370 MBq.[121,131] For ventilation imaging, most studies used 99mTc as an isotope.[117,121,122,131,160,161,163,178,179] Three studies[126,147,176] used 81 mKr. Two studies[132,177] and one site in a multi-centre study used 133 Xe.[160] Interpretation criteria varied across the studies, with most using PIOPED or a revised or modified version of PIOPED or PIOPED II (Table 10).

Table 10: Summary of Study Information for Ventilation/Perfusion

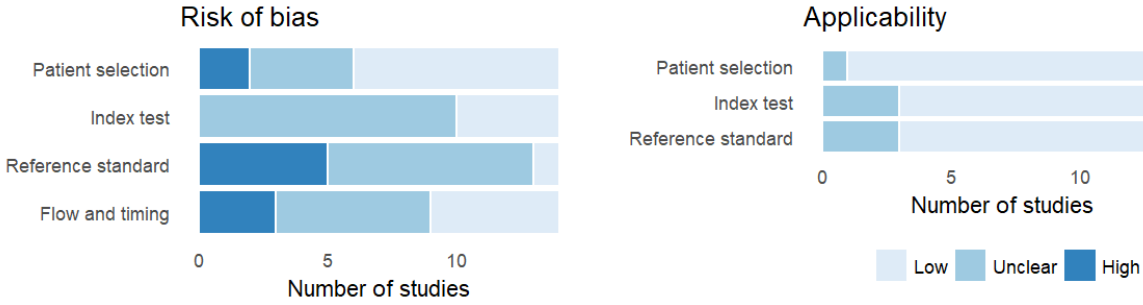
Study	Reference	Diagnostic N	Mean Age (Years)	Risk of PE	Index Interpretation
Ohno et al., 2004[147]	CC (V/Q, PA)	48	55.0	Not reported	Modified PIOPED
Reinartz et al., 2004[122]	CC (PA)	82	53.9	Not reported	PIOPED
Skarlovnik et al., 2014[161]	CC (CT)	82	71.5	Not reported	PIOPED II Revised
Wang et al., 2009[121]	CC (unclear)	75	51.0	Mixed	Modified PIOPED
Blanchere et al., 2000[132]	CC (PA, CT, V/Q, US)	179	61	Mixed	Study-specific
Gutte et al., 2010[176]	CC (V/Q), V/Q	36	74	Not reported	Study-specific
He et al., 2012[131]	CC (CT, V/Q, PA)	477	53.3	Mixed	PIOPED
Lu et al., 2014[163]	CC (CT, V/Q, Q SPECT-CT)	93	63.4	Not reported	Study-specific
Watanabe et al., 2015[160]	CT	127	59.0	Mixed	Modified PIOPED
Lechleitner et al., 2002[117]	MRI	37	69.0	Mixed	PIOPED
Gray et al., 1990[178]	PA	48	56.0	Not reported	Study-specific
PIOPED Investigators 1990[177]	PA	409	56.1	Not reported	PIOPED
Woods et al., 1989[179]	PA	22		Not reported	Modified Biello, PIOPED
Coche et al., 2003[126]	SC (V/Q, PA)	94	62.0	Mixed	PIOPED II

CC = complex composite — reference standard including imaging in combination with D-dimer; CT = computed tomography; PA = pulmonary angiography; PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis; Q SPECT-CT = perfusion single-photon emission CT; SC = simple composite, only imaging modalities; V/Q = ventilation/perfusion planar scintigraphy.

Quality appraisal

Figure 11 shows a summary of the risk of bias and applicability for all studies with V/Q as an index test. Reporting that was unclear or lacking in detail was responsible for the majority of "unclear" assessments. The studies with a high risk of bias for patient selection both recruited nonconsecutive patients.[126,179] One, due to resource constraints, recruited only during the daytime.[179] Five studies had a high risk of bias for the reference test, since they included the index test in the reference standard,[131,163] or otherwise did not establish the diagnosis independently.[121,132,176] For study flow and timing, studies were considered to have a high risk of bias when not all patients received the same reference test,[160] the allowed interval between the test and diagnostic confirmation was long enough for the patient's status to change,[126] or not all included patients were in the diagnostic calculation.[160,178] All studies had a low or, in a few cases, unclear risk of bias for applicability to the question, again due to a lack of detail in reporting.

Figure 11: Risk of Bias and Applicability for All Studies With Ventilation/Perfusion as an Index Test



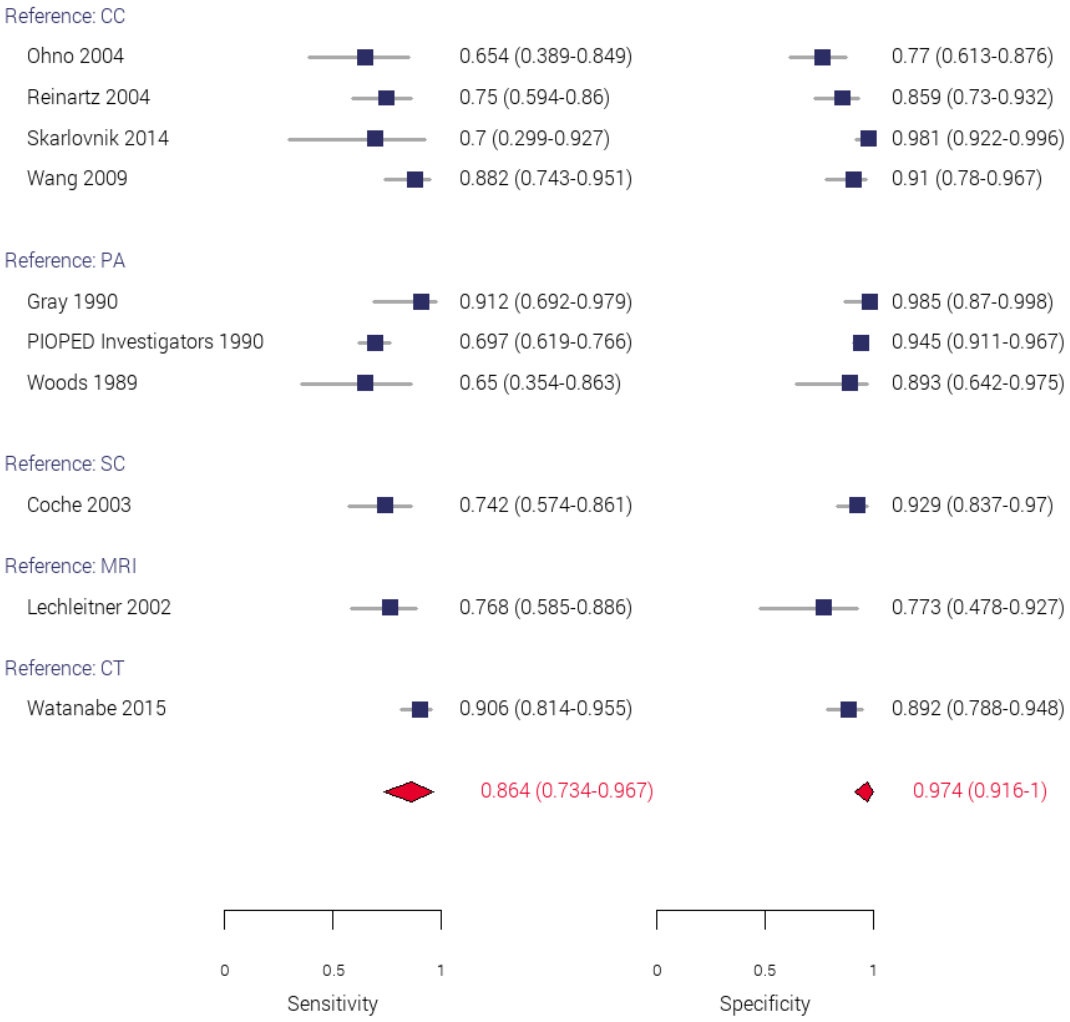
Detailed presentations of responses to individual signalling questions are given in Appendix 17.

Summary of Diagnostic Test Results

Two studies were excluded as post hoc analyses[180,181] and two comparisons were excluded because the index test was included in the reference standard,[131,163] leaving a total of 10 studies.

The forest plot for the sensitivity and specificity for all included studies is shown in Figure 12, grouped by reference standard and ordered by the frequency with which the reference standard appears. The pooled value adjusted for imperfect reference standard appears in red.

Figure 12: Forest Plot of Studies With Ventilation/Perfusion as Index Test



CC = complex composite — reference standard including imaging in combination with D-dimer; CT = computed tomography; MRI = magnetic resonance imaging; PA = pulmonary angiography; SC = simple composite, only imaging modalities.

Dark blue – individual study estimates without adjustment. Red – overall pool, including adjustment for imperfect and variable reference standard.

For patients in whom imaging was considered diagnostic, the pooled sensitivity with adjustment for imperfect reference standard is 0.864 (95% CrI, 0.734 to 0.967), and the pooled specificity is 0.974 (95% CrI, 0.916 to 1.00). Therefore, of 1,000 patients, 150 of whom had PE,[94] an average of 20 patients (range five to 40) would receive a false-negative diagnosis and would be at risk of recurrent PE, and an average of 22 patients (range one to 71) would receive a false-positive diagnosis and would be at risk of complications (bleeding) from unnecessary treatment.

Heterogeneity

Both the forest plot (Figure 12) and an ROC scatterplot of sensitivity versus 1 – specificity (Appendix 22) suggest heterogeneity in both sensitivity and specificity for V/Q, with greater variability in sensitivity. There is no obvious grouping by reference standard, although three reference standards are represented by only a single study. Comparison of the CrIs for the pooled and the predicted sensitivity and specificity suggests greater heterogeneity for sensitivity, and the heterogeneity for both measures is substantial. The predicted sensitivity for a new study derived from the same statistical model is 0.832 (95% CrI, 0.434 to 0.995) and the predicted specificity for a new study is 0.945 (95% CrI, 0.650 to 1.00). The lower predicted mean values of sensitivity and specificity result from the wider credible intervals and the influence of outliers on the mean, while the pooled and predicted median values are similar.

We had insufficient data to investigate the effect of the predefined covariates on heterogeneity (see the section on Meta-Analysis of Diagnostic Test Accuracy Studies). One study (not included in the pool) stratified the effect of prior PE risk (see next section). For study setting, patient origins (in-patient, outpatient, ED), and PE risk, there was insufficient variation among studies for statistical adjustment (Appendix 22). All studies that assessed prior risk recruited a mixed population.

Individual Studies Describing the Effect of Covariates on Diagnostic Performance

One study[131] reported results for V/Q imaging stratified by the Wells criteria. This study was not included in the overall pool, as the index test was explicitly included in the reference assessment. Diagnostic test performance did not appear to vary significantly with prior risk, although there was no formal test of statistical significance. Detailed results appear in Appendix 21.

Ventilation/Perfusion Scintigraphy–Single-Photon Emission Computed Tomography (V/Q SPECT)

Thirteen studies compared V/Q SPECT imaging with other imaging modalities.[122,128,161,169,176,182-189]

Study and Patient Characteristics

Study information is summarized in Table 11, and detailed study characteristics are provided in Appendix 16.

Study Design

All 13 studies were nonrandomized. Eight were prospective,[128,169,176,182,183,185,188,189] four were retrospective,[122,161,184,186] and one was unclear.[187]

Country and Setting

Three were multi-centre, one conducted in each of Slovenia,[161] Denmark,[128] and Australia.[183] Of the nine single-centre studies, two were conducted in each of Germany,[122,186] Sweden,[184,189] and Spain;[182,188] and one each in France,[187] Denmark,[176] Belgium,[169] and Australia.[185] Nine studies were conducted in a secondary/tertiary setting,[128,161,169,176,182-185,189] one in an ED setting,[188] and for three the setting was unspecified.[122,186,187]

Funding

Three received government funding,[184,187,189] and one received industry funding.[183] Nine studies did not report funding sources.[122,128,161,169,176,182,185,186,188]

Population

Studies recruited between 36[176] and 1,785 patients.[184] Three studies recruited in-patients;[161,182,183] one study recruited outpatients and patients presenting to the ED;[188] and one recruited both.[190] Seven studies did not clearly report the source of their patients.[122,128,169,176,184-187,189] The mean age of patients was 53.9[186] years to 79.6 years.[182] None of the studies reported a formal assessment of prior risk of PE.

Reference Standards

The studies reported 14 comparisons involving three reference standards: a complex composite reference standard including imaging in combination with D-dimer,[122,128,161,169,176,185] CT,[183,184,186-188] and V/Q.[176,182,189]

Technical Characteristics

For all studies, 99mTc MAA was used as a tracer for perfusion, in doses of 100 MBq[161,189] to 300 MBq.[187] Ten studies used 99mTc as the tracer for ventilation,[122,161,182-189] in the form of DTPA (diethylene-triamine-pentaacetate) or Technegas, while three studies used 81 mKr.[128,169,176] Ventilation dose was variably reported, with four studies reporting the total dose used in inhalation as 445 MBq[187] to 700 MBq,[182] four reporting the accumulated dose in the lungs as 20 MBq[161] to 50 MBq,[186] and the rest not reporting dose.[169,176,183,185,188] Interpretation criteria were heterogeneous (Table 11).

Table 11: Summary of Study Information for Ventilation/Perfusion Single-Photon Emission Computed TomographyStudies

Study	Reference	Diagnostic N	Mean Age (Years)	Risk of PE	Index Interpretation
Harris et al., 2007[185]	CC (V/Q, CT, CTV)	37	66.0	Not reported	Modified PIOPED
Reinartz et al., 2004[122]	CC (PA)	83	53.9	Not reported	PIOPED
Skarlovnik et al., 2014[161]	CC (CT)	49	71.5	Not reported	EANM
Gutte et al., 2009[128]	CC (CT, V/Q SPECT)	81	65	Not reported	Study-specific
Bajc et al., 2008[184]	CT	105	Not reported	Not reported	Study-specific
Ibanez-Bravo et al., 2016[188]	CT	48	Not reported	Not reported	EANM
Miles et al., 2009[183]	CT	79	71.9	Not reported	Study-specific
Reinartz et al., 2006[186]	CT	53	56.4	Not reported	Study-specific
Weinmann et al., 2008[187]	CT	94		Not reported	PIOPED II
Bajc et al., 2004[189]	V/Q	52		Not reported	Study-specific
Gutte et al., 2010[176]	V/Q	33	71.9	Not reported	Study-specific
Le Duc-Pennec et al., 2012[190]	V/Q	205	64.3	Not reported	Revised PIOPED
Quirce et al., 2014[182]	V/Q	39	79.6	Not reported	EANM

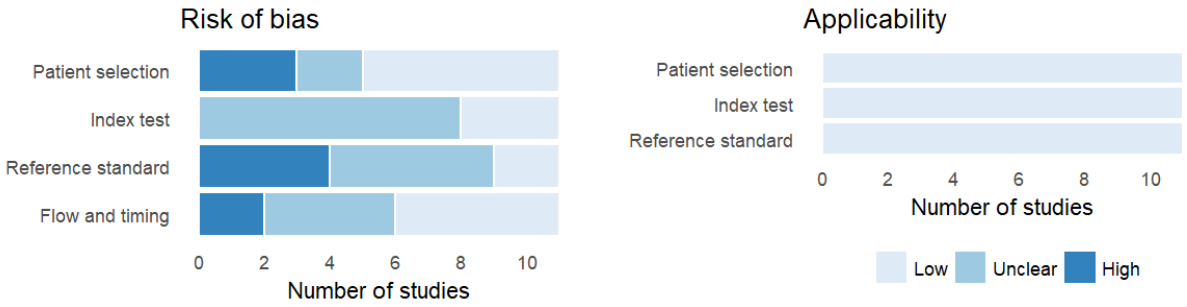
CC = complex composite — reference standard including imaging in combination with D-dimer; CT = computed tomography; EANM = European Association of Nuclear Medicine; PA = pulmonary angiography; PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis; SC = simple composite, only imaging modalities; V/Q = ventilation/perfusion planar scintigraphy.

Quality Appraisal

Figure 13 shows a summary of the risk of bias and applicability for all studies with V/Q SPECT as an index test. Reporting that was unclear or lacking in detail was responsible for the majority of “unclear” assessments. One study included patients only when the diagnostic imaging equipment was available,[189] potentially producing a nonrepresentative population, and two had a high risk of bias due to possibly inappropriate exclusions[183] or a high rate of exclusions.[187] Studies that had a high risk of bias due to the inclusion of the index in the reference test,[128,176] or had other concerns about the accuracy of their particular reference standard.[182,188,189] In two studies, the number of patients excluded from the analysis represented a high risk of bias.

All studies were considered to have a low risk of bias for applicability of patient selection, index test, and reference test.

Figure 13: Risk of Bias and Applicability for All Studies With Ventilation/Perfusion Single-Photon Emission Computed Tomography as an Index Test



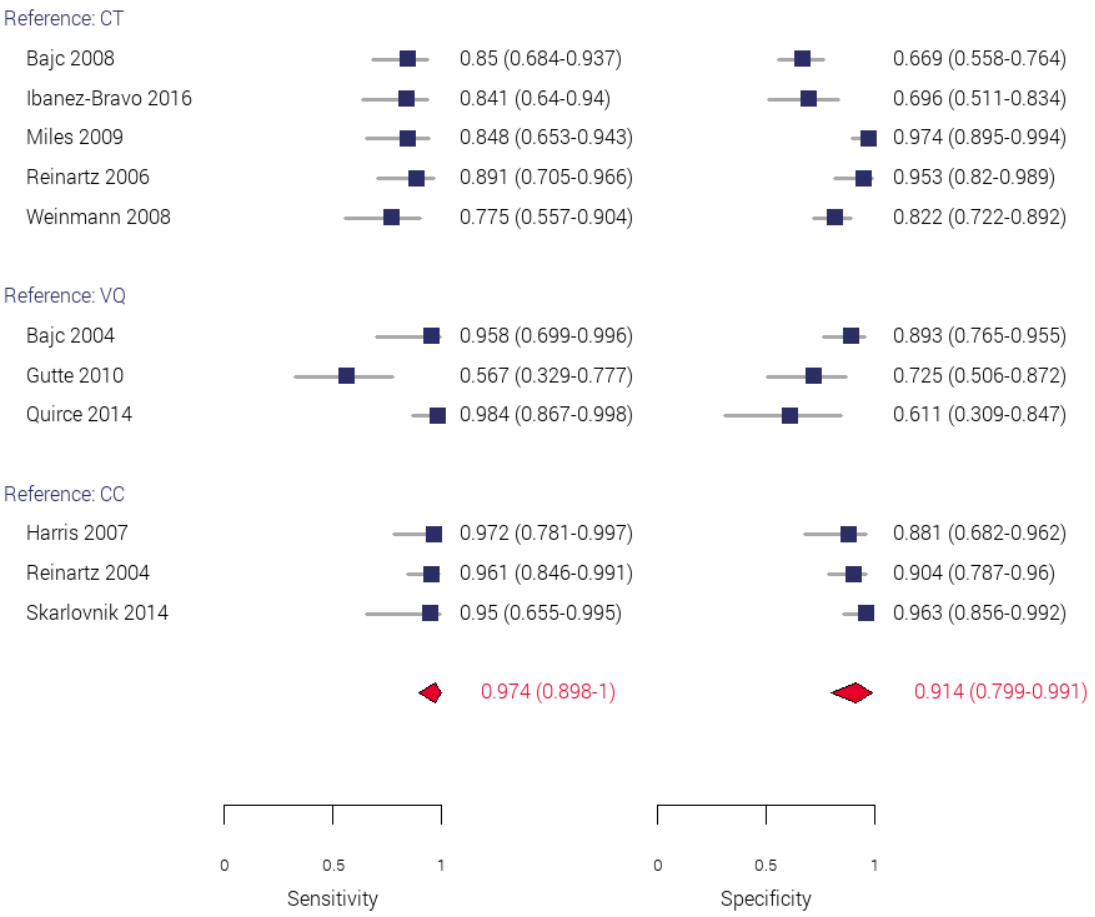
Detailed presentations of responses to individual signalling questions are given in Appendix 17.

Summary of Diagnostic Test Accuracy

Two index text–reference standard comparisons were excluded from the pool because the index was included in the reference.[128,176] For one study, data were available for a direct comparison of V/Q SPECT with V/Q, which was included.[128] An additional study was excluded from the analysis following reviewer feedback that the criteria used for the interpretation of the index test scans were no longer considered valid.[190]

The forest plot for the sensitivity and specificity for the 11 included studies is shown in Figure 14 grouped by reference standard and ordered by the frequency with which the reference standard appears. The pooled value adjusted for imperfect reference standard appears in red.

Figure 14: Forest Plot of Studies With Ventilation/Perfusion Single-Photon Emission Computed Tomography as Index Test



CC = complex composite — reference standard including imaging in combination with D-dimer; CT = computed tomography; SC = simple composite, only imaging modalities; V/Q = ventilation/perfusion planar scintigraphy.

Dark blue – individual study estimates without adjustment. Red – overall pool, including adjustment for imperfect and variable reference standard.

For patients in whom imaging was considered diagnostic, the pooled sensitivity, with adjustment for an imperfect reference standard, was 0.974 (95% CrI, 0.898 to 1.00) and the pooled specificity was 0.914 (95% CrI, 0.799 to 0.991). Therefore, of 1,000 patients, 150 of whom had PE,[94] an average of four patients (range 0 to 15) would receive a false-negative diagnosis and would be at risk of recurrent PE, and an average of 73 patients (range eight to 171) would receive a false-positive diagnosis and would be at risk of complications (bleeding) from unnecessary treatment.

Heterogeneity

Both the forest plot and an ROC scatterplot of sensitivity versus 1 – specificity (Appendix 22) indicated heterogeneity for sensitivity and specificity. There was a suggestion of clustering by reference standard. Despite the adjustment for the variability of the reference standard in our analysis, the prediction interval for a new study derived from the same statistical model

(another indication of heterogeneity) was very broad for both sensitivity, 0.924 (95% CrI, 0.477 to 1.00), and specificity, 0.860 (95% CrI, 0.358 to 1.00). The lower predicted mean values of sensitivity and specificity result from the wider credible intervals and the influence of outliers on the mean, while the pooled and predicted median values are similar.

We had insufficient data to investigate the effect of the predefined covariates on heterogeneity (see the section on Meta-Analysis of Diagnostic Test Accuracy Studies). For study setting, patient origins (in-patient, outpatient, ED), and PE risk, there was insufficient variation between studies for statistical adjustment (Appendix 22). Only one study reported risk of PE, and provided a stratified analysis (next section).

Effect of Risk of PE on Diagnostic Performance

One study[188] reported results for perfusion imaging stratified by the Wells criteria. Diagnostic test performance did not appear to vary significantly with prior risk, although there was no formal test of statistical significance. Detailed results appear in Appendix 21.

Ventilation/Perfusion Scintigraphy–Single-Photon Emission Computed Tomography–Computed Tomography (V/Q SPECT-CT)

Four studies compared V/Q SPECT-CT imaging with two reference standards.[128,174,191,192] Two were prospective,[128,174] and two were retrospective.[174,191]

Study and Patient Characteristics

Study information is summarized in Table 12, and detailed study characteristics are provided in Appendix 16.

All studies were nonrandomized. One was a multi-centre study conducted in Denmark,[128] and the others were single-centre studies conducted in Australia[191,192] and France.[174] All four were conducted in a secondary/tertiary setting.[128,174,191,192]

Studies recruited between 81[128] and 393[174] patients. Age ranged from a mean of 51.0[191] to a median of 71 years.[128] One study recruited in-patients or outpatients,[174] and the others did not report the patients recruited.[128,191,192] None reported the prior risk of PE.

The reference standards used were CT[192] and V/Q SPECT-CT.[128,174,191]

Funding

Three studies did not report funding[128,174,192] and one did not receive funding.[191]

Technical Characteristics

One of the four studies did not report imaging conditions.[191] The two others both used 99mTc TAA (thioacetamide) for perfusion imaging, at 150 MBq[128] and 200 MBq.[174,192] For ventilation imaging, two used 81 mKr,[128,174] and one 99mTc-Technegas (40 MBq accumulation).[192] All four studies used study-specific imaging criteria based on the identification of V/Q mismatches not corresponding to anatomic abnormalities.

Table 12: Summary of Study Information for Ventilation/Perfusion Single-Photon Emission Computed Tomography–Computed Tomography Studies

Study	Reference	Diagnostic N	Mean Age (Years)	Risk of PE	Index Interpretation
Bhatia et al., 2016[192]	CT	102	53.0	Not reported	Study-specific
Gutte et al., 2009[128]	V/Q SPECT	77	71.9	Not reported	Study-specific
Ling et al., 2012[191]	V/Q SPECT	106	51.0	Not reported	Study-specific
Le Roux et al., 2015[174]	V/Q SPECT	393	Median 71	Not reported	Study-specific

CT = computed tomography; V/Q SPECT = ventilation/perfusion single-photon emission tomography.

Quality Appraisal

For patient selection, three studies had a low risk of bias and one was unclear. For the index test, three studies had a low risk of bias and one was unclear. Ratings of unclear were predominantly due to lack of detail in reporting. For the reference test, two studies had a high risk of bias, one because the index test was included in the reference[174] and the other because all information was used for the final diagnosis;[128] and two had an unclear risk of bias. For flow and timing, two had a low risk of bias,[174,191] and two had an unclear risk of bias.[128,192]

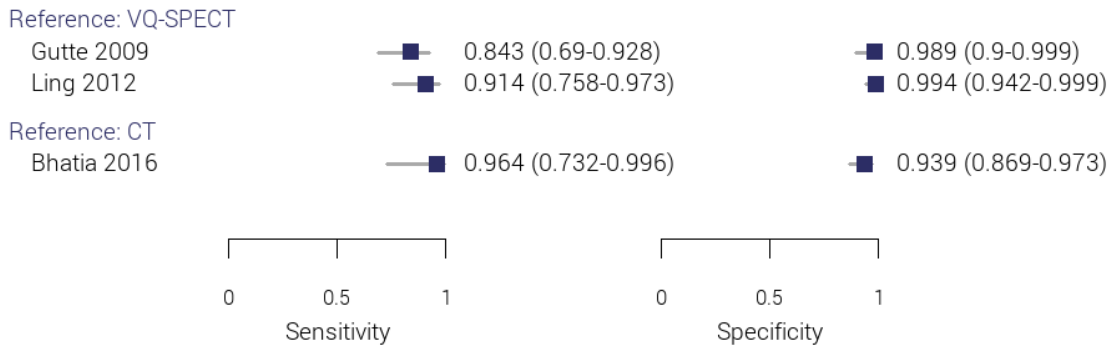
All studies were considered as having a low risk of bias for all domains of applicability to the question.

Detailed presentations of responses to individual signalling questions are given in Appendix 17.

Summary of Diagnostic Test Results

One comparison was excluded because the index was included in the reference.[174] The forest plot for the sensitivity and specificity for all included studies is shown in Figure 15, grouped by reference standard and ordered by the frequency with which the reference standard appears. Given the small number of studies, a meta-analysis was not performed.

Figure 15: Forest Plot of Studies With Ventilation/Perfusion Single-Photon Emission Computed Tomography–Computed Tomography as Index Test



CT = computed tomography; V/Q SPECT = ventilation/perfusion single-photon emission computed tomography.
Dark blue – individual study estimates without adjustment.

The reported sensitivity of V/Q SPECT-CT for the diagnosis of PE ranged from 0.843 (95% CI, 0.690 to 0.928), against a reference standard of V/Q SPECT,[128] to 0.964 (95% CI, 0.732 to 0.996), against a reference standard of CT.[192] The reported specificity of V/Q SPECT-CT for the diagnosis of PE ranged from 0.939 (95% CI, 0.869 to 0. 973) against a reference standard of CT,[192] to 0.994 (95% CI, 0.942 to 0.999), against a reference standard of V/Q SPECT.[191]

Individual Studies Describing the Effect of Covariates on Diagnostic Test Performance

One study included[192] found no significant difference in diagnostic test accuracy of V/Q SPECT-CT compared with CT for transplant or pre-existing lung disease.

Summary of Diagnostic Test Accuracy Results

Seventy studies reported results for diagnostic test accuracy for an eligible index imaging modality compared with an eligible reference modality in nonpregnant patients. (Imaging in pregnancy is discussed in a separate section.) One or more studies reported DTA findings for CT, MRI, US, Q, Q SPECT, Q SPECT-CT, V/Q, V/Q SPECT, V/Q SPECT-CT, and combinations of modalities CT and CTV (CT venography), MRI and MRV (MR venography), and MRI and V/Q.

Five individual modalities had sufficient data to allow for meta-analysis: CT, MRI, US, V/Q, and V/Q SPECT (Table 13). The remaining modalities had data that allowed only for narrative summary results (Table 14). The findings in the two tables cannot be directly compared, as the meta-analysis included an adjustment for variable or imperfect reference standard, and the narrative results are reported against the individual study reference standards, without adjustment.

Table 13: Summary of Meta-Analysis Diagnostic Test Accuracy Results

Modality (Number of Studies)	Estimate	Sensitivity (95% CrI)	Specificity (95% CrI)	Estimated for 1,000 Patients, 150 with PE[a]			
				TP	TN	FN	FP
CT (n = 11)	Pooled	0.973 (0.921 to 1.00)	0.987 (0.958 to 1.00)	146	839	4	11
	Predicted new	0.954 (0.743 to 1.00)	0.969 (0.807 to 1.00)				
MRI (n = 14)	Pooled	0.959 (0.898 to 0.998)	0.987 (0.955 to 1.00)	144	839	6	11
	Predicted new	0.930 (0.652 to 1.00)	0.962 (0.721 to 1.00)				
US (n = 10)	Pooled	0.953 (0.867 to 0.999)	0.946 (0.828 to 1.000)	143	804	7	46
	Predicted new	0.917 (0.553 to 1.00)	0.927 (0.638 to 1.000)				
V/Q (n = 10)	Pooled	0.864 (0.734 to 0.967)	0.974 (0.916 to 1.00)	130	828	20	22
	Predicted new	0.832 (0.434 to 0.995)	0.945 (0.650 to 1.00)				
V/Q SPECT (n = 11)	Pooled	0.974 (0.898 to 1.00)	0.914 (0.799 to 0.991)	146	777	4	73
	Predicted new	0.924 (0.477 to 1.00)	0.860 (0.358 to 1.00)				

CrI = credible interval; CT = computed tomography; MRI = magnetic resonance imaging; PE = pulmonary embolism; US = ultrasound; V/Q = ventilation/perfusion; V/Q SPECT = ventilation/perfusion single-photon emission computed tomography.

[a] Given 1,000 hypothetical patients, 150 of whom have PE, the estimated number of correctly diagnosed cases (TP), correctly diagnosed noncases (TN), missed PEs (FN), and incorrectly diagnosed noncases (FP).

Table 14: Summary of Narrative Diagnostic Test Accuracy Results

Modality (Number of Studies)	Sensitivity (95% CI)	Specificity (95% CI)
Q (n = 8)	0.62 (0.426 to 0.782) to 0.927 (0.896 to 0.949)	0.432 (0.314 to 0.559) to 0.930 (0.889 to 0.956)
Q SPECT (n = 2)	0.885 (0.698 to 0.976) to 0.898 (0.722 to 0.962)	0.466 (0.333 to 0.601) to 0.946 (0.897 to 0.982)
Q SPECT-CT (n = 1)	1.00 (0.868 to 1.00)	0.828 (0.706 to 0.914)
V/Q SPECT-CT (n = 3)	0.843 (0.690 to 0.928) to 0.964 (0.732 to 0.996)	0.939 (0.869 to 0. 973) to 0.994 (0.942 to 0.999)

CI = confidence interval; Q = perfusion planar scintigraphy; Q SPECT = perfusion single-photon emission computed tomography; Q SPECT-CT = perfusion single-photon emission computed tomography– computed tomography; V/Q SPECT = ventilation/perfusion single-photon emission computed tomography.

According to the meta-analysis, CT offered the highest sensitivity and specificity, with fewest misdiagnoses. The meta-analytic pool for CT was the least statistically heterogeneous, with the narrowest credible intervals for a predicted new study. CT and V/Q SPECT both offer similar high estimates for sensitivity, and therefore the lowest number of missed diagnoses when used for rule-out testing. The pools for US, V/Q, and V/Q SPECT were considerably more statistically heterogeneous than for CT or MRI, with lower bounds for prediction intervals for a new study in the region of 0.5. The results for US changed substantially when the adjustment for imperfect reference standard was applied, and thus that result is considered least reliable.

It should be noted that the diagnostic test performance reported is for patients with a definitive test result (positive or negative) and does not include those who had nondiagnostic

or indeterminate findings. Exclusion of nondiagnostic or indeterminate findings likely results in higher sensitivity and specificity than would be seen in practice. Studies did not consistently report the final diagnosis for indeterminate index tests to allow for analytic adjustment, nor were they consistent in their exclusions for all patients entering the study, and those for whom diagnostic results were reported. The proportion of patients with nondiagnostic studies for CT was 0.034 (pooled, 95% CI, 0.024 to 0.050), for MRI between 0 and 0.292, for V/Q from 0.071 to 0.574, and for V/Q SPECT from 0 to 0.222. One small study reported no nondiagnostic exams for US. The basis of the variability could not be established: aside from the differences in exclusions, studies used different interpretation criteria and varied in the strictness of their definition of inadequacy.

Other quality concerns included the exclusion of patients who did not receive both index test and reference standards, patients who possibly represented a more symptomatic or severe group, and the interval between index and reference tests. The latter would have most impact in studies in which the reference test was conducted first and anticoagulation started prior to conducting the index test, leading to possible false-negatives in the index test.

For CT, individual studies assessed the effect of prior risk of PE, age, gender, and body weight. Prior risk of PE affected accuracy, compared with a complex composite, but we did not have the available data to test adjustment of the meta-analysis model. Age and body weight did not appear to affect the performance of the test in individual stratified studies; in an individual study that stratified results, there was a suggestion that gender might affect specificity, but the study had conducted multiple testing without statistical adjustment.

For MRI, one study assessed the effect of prior PE on imaging performance; MRI appeared to be relatively insensitive to prior risk.

For perfusion imaging, pre-existing lung disease did not have a consistent effect on test performance.

Study settings in the retrieved articles were exclusively secondary and tertiary health care centres in urban settings; no studies were retrieved that were conducted in rural or remote settings. When studies recruited a mix of in-patients, outpatients, and ED patients, they did not report subgroups.

Other covariates and disease states of interest primarily appeared as reasons for exclusion, either as formal exclusion criteria, or because patients could not complete imaging: e.g., renal insufficiency and cardiogenic shock/hemodynamic instability.

There were no DTA results from studies that reported performance in pregnancy.

Question 3B and C: Utility and Safety in Nonpregnant Patients

Of the 110 studies described under study selection, 65 contributed utility and safety outcomes (some also reported DTA outcomes). These are discussed by modality.

Computed Tomography

Twenty-six studies reported utility and/or safety results for CT.[57,67,109,110,115,118,121,125,126,130-132,160,193-205]

Study and Patient Characteristics

Study Design

One study was an RCT,[57] and 25 were nonrandomized studies.[67,109,110,115,118,121,125,126,130-132,160,193-205]

Country and Setting

Seven studies were multi-centre: two in Canada and the US;[57,67] one in Slovenia, Turkey, Czech Republic, Uruguay, and India;[160] and one each in Canada,[205] the Netherlands,[197] Italy,[115] and China.[131] Nineteen studies were single-centre; five were conducted in France;[125,132,193,198,203] three in Spain;[118,199,201] three in the US;[194,195,200] and one each in Italy,[202] the UK,[110] Belgium,[126] Norway,[109] Switzerland,[130] Tunisia,[196] China,[121] and India.[204] Seventeen studies were conducted in secondary[118,125,126,131,132,193,196,201,202] or secondary or tertiary settings,[57,67,115,160,194,197,199,205] two in a tertiary setting,[130,204] and one in an ED.[109] In five studies, the setting was not specified.[121,195,198,200,203]

Funding

Seven studies received government funding,[57,67,109,118,131,197,199] one study received private funding,[130] one study received industry funding,[110] and two studies did not receive funding.[160,198] Fifteen studies did not report funding sources.[115,121,125,126,132,193-196,200-205]

Population

The total number of included participants ranged from 50[204] to 3,306.[197] The mean age ranged from 38.3[110] to 71,[115] and the proportion of women from 0.26[130] to 0.70.[126] One study recruited in-patients,[193] three recruited outpatients,[109,126,130] five recruited in-patients and outpatients,[67,115,125,132,160] two recruited in-patients and ED patients,[201,202] and one recruited in-patients, outpatients, and ED patients,[57] and two recruited ED patients alone.[118,197,199] Eleven studies did not identify which group were recruited.[110,121,131,194-196,198,200,203-205] In the studies that reported a formal assessment of risk, five studies selected high-risk patients,[109,193,199,200,204] one selected intermediate-risk patients,[57] and 13 selected a mixed population of patients.[67,115,118,121,125,126,130-132,160,201,202,205] Seven studies did not report the prior risk.[110,194-198,203]

Technical Characteristics

The number of CT detectors ranged from one[201] to 384.[198] Five studies did not report the number of detectors.

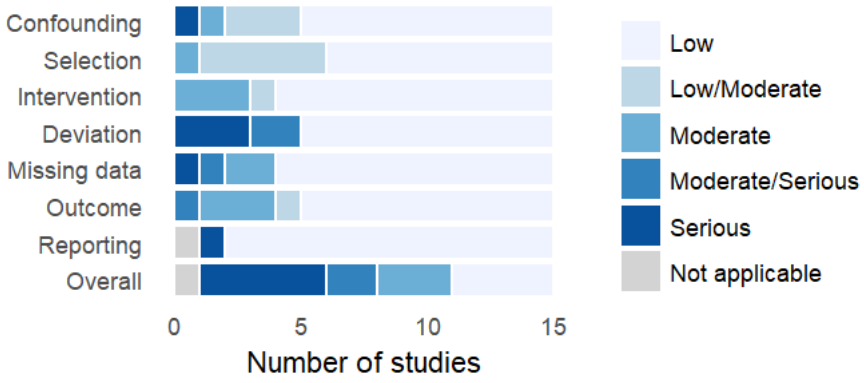
Quality Appraisal

The single RCT[57] was assessed as having a low risk of bias in six of seven domains of the Cochrane Risk of Bias Tool and unclear risk of performance bias due to knowledge of allocated interventions.

Fifteen studies were assessed as comparative studies by the ROBINS-I tool.[57,67,110,121,125,126,130-132,160,194-197,199,200] Summary results are shown in Figure 16. Sources of serious risk of bias were exclusions of patients who had both a negative CT and received anticoagulation therapy (confounding);[194] different reference standards applied across the study;[126,130] a high proportion of indeterminate results in the reference standard (V/Q or V/Q SPECT), which might be associated with PE severity; or exclusions due to missing data.[200] Several studies were considered to have a serious overall risk of bias.[121,126,160,194,200] Studies included in the comparison of failure rates[57,126,130,198,199,204] ranged from moderate to serious

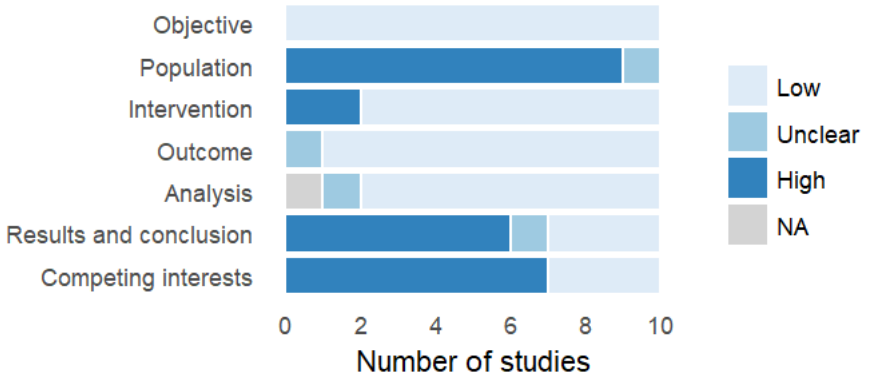
risk of bias, with serious risk of bias predominantly arising from inconsistent imaging across all patients. However, for many of the outcomes of interest, studies did not report comparative data and could only contribute to single-arm studies. The most relevant domains for these summaries were selection of appropriate patients, correct implementation of the intervention, and measurement of the outcome, which had a low-to-moderate risk of bias for all studies.

Figure 16: Risk of Bias for Comparative Studies of Computed Tomography as Index Test



Ten studies were assessed as single-arm studies by the Moga checklist.[109,115,118,193,198,201-205] Summary results are shown in Figure 17. The principal reason for studies having a high risk of bias in the population domain were uncertainty about whether patients entered the study with the same severity of disease,[118,193,201,202,205] and studies being conducted at a single-centre.[109,118,193,198,201-204] Two studies did not clearly describe interventions or co-interventions (especially anticoagulation, which would have influenced the risk of recurrent PE).[198,204] Studies assessed to have a high risk of bias for reporting results and conclusions[109,118,193,202,204,205] failed to report one or more of all outcomes, loss to follow-up, or uncertainty around estimates. The majority of studies did not report competing interests and funding.[115,118,193,201,202,204,205] Studies all included an objective, and presentation of outcome and analysis had a low risk of bias.

Figure 17: Risk of Bias for Single-Arm Studies of Computed Tomography



Detailed presentations of responses to individual signalling questions by study are shown in Appendix 17.

Outcomes

Failure Rates

Single-Arm Studies of Test Failure: Nineteen studies reported test failure (proportion of patients with negative imaging results who were diagnosed with VTE during follow-up) for CT as an index test.[57,109,110,115,118,126,130,132,193,194,196-204] None of them reported failure rate for the first 30 days alone. Fourteen reported test failure in the first three months after imaging, and five reported failure in the first six months after imaging. The majority of the studies reported failure in patients who did not receive anticoagulation therapy.

The proportion of diagnostic failures reported in individual studies ranged from 0[126,130,198,202] to 0.048.[204] For all studies at all durations of follow-up, the pooled proportion of failure was 0.008 (95% CI, 0.004 to 0.013; I^2 = 55.0%, Q = 38.5, df = 19, *P* = 0.003)**.** Removal of Pesavento et al., 2011, which was identified as a statistical outlier on model diagnostic, reduced the I^2 to 24%, but the pooled result was little changed, at 0.009 (95% CI, 0.006 to 0.014), and the study was not distinctive in its characteristics.

There were insufficient data to investigate the effect of the predefined covariates on heterogeneity (see Meta-Analysis of Diagnostic Test Accuracy Studies). For study setting, patient origins (in-patient, outpatient, ED), and PE risk, there was insufficient variation among studies for statistical adjustment (Appendix 22). A graphical summary of the proportion of failures by setting suggested that failure might be higher in the secondary category alone. However, given the small number of centres in each setting, this is liable to be a result of random variation.

Fourteen studies reported test failure in the first three months after imaging.[57,109,110,115,118,130,132,197-199,201-204] Individual study failure rates ranged from 0[126,130,198,202] to 0.048.[204] The pooled proportion of patients with test failure in the first 3 months was 0.007 (95% CI, 0.003 to 0.012; n = 14; I^2 = 58.4%; Q = 31.0, df = 14, *P* = 0.003).

Five studies reported failure in the first six months after imaging.[126,193,194,196,200] Individual proportions of patients with test failure ranged from 0[126] to 0.034.[196] The pooled failure rate in the first six months was 0.015 (95% CI, 0.006 to 0.027; n = 5; I^2 = 0, Q = 5.1, df = 4, *P* = 0.275).

Comparative Studies of Test Failure: Six studies,[57,126,130,198,199,204] including one RCT,[57] reported the proportion of patients with test failure compared with reference standards: a complex composite reference standard including imaging in combination with D-dimer,[130,199,204] CT (different imaging conditions),[198] a simple composite comprising only imaging modalities,[126] and V/Q.[57]

In the RCT, patients with suspected PE were randomized to undergo CT (CTPA) or V/Q, with a primary outcome of failure rate over three months.[57] Two of 516 patients with negative CT results developed VTE in three-month follow-up (0.4%), compared with six of 611 patients (1%) with a negative (normal) V/Q scan, a nonsignificant difference of –0.006 (95% CI, –0.016 to 0.030). One patient with a negative CT result experienced a PE within 30 days' follow-up (0.002). Two patients with negative V/Q results experienced a PE within 30 days (0.003), and one experienced a proximal DVT. One PE was fatal, at 49 days in a patient with negative V/Q result.

The pooled risk difference across the five nonrandomized studies was also nonsignificant, at 0.001 (95% CI, –0.009 to 0.010; I^2 0.0%; Q = 0.635, df = 4, *P* = 0.959).

Nondiagnostic Examinations

Fourteen studies reported on the number of examinations that were nondiagnostic.[67,109,121,125,126,131,132,160,195,197,200,202,203,205] For CT, nondiagnostic examinations were due to technical inadequacy, such as insufficient filling of pulmonary vessels with contrast. One study was omitted from the pooled analysis, as it selected for patients who had already undergone an indeterminate V/Q scan.[200] The proportion of studies that was nondiagnostic ranged from 0.011[126] to 0.097.[200] The pooled rate of nondiagnostic examinations was 0.034 (95% CI, 0.023 to 0.047, n = 14; I^2 = 85.4%; Q = 89.2, df = 13, *P* < 0.0001).

There were insufficient data to investigate the effect of the predefined covariates on heterogeneity (see Meta-Analysis of Diagnostic Test Accuracy Studies). For study setting, patient origins (in-patient, outpatient, ED), and the number of CT slices, there was insufficient variation among studies for statistical adjustment (Appendix 22). We could not investigate whether prior risk of PE explained heterogeneity due to insufficient data. Variability in description made it difficult to quantify nuances of patient selection or definition of nondiagnostic examinations, which appeared to range from pragmatic (sufficient to include or exclude) to strict (required visualization of all arteries). Handling of disagreement between readers also varied among studies.

Alternative Diagnoses and Incidental Findings

Five nonrandomized studies that used CT as an index test reported alternative diagnoses or incidental findings for a proportion of 0.194 to 0.300 of patients.[115,126,199,202,204] A sixth study reported a single alternative diagnosis.[125] Pneumonia and parenchymal lung disease were the most common alternative diagnoses (Appendix 19).

Safety

One study comparing CT with V/Q planar scintigraphy reported no “serious complications” associated with any of the imaging modalities (contrast CT, V/Q, and PA).[126]

Contrast Nephropathy and Acute Renal Failure: Four studies involving CT reported the need for renal replacement therapy or severe renal failure as an outcome.[116,202,206] An RCT investigating the effect of adding leg US to a pathway consisting of D-dimer and CT reported no acute renal failure or initiation of hemodialysis in either arm of the study, neither 509 patients undergoing D-dimer–leg US–CT nor 535 patients undergoing D-dimer–CT.[116] In one nonrandomized study, one instance of severe acute renal failure was reported (0.27%),[202] and, in two other studies, no acute renal failure or need for renal replacement therapy was reported in 1,224[206] and 189 patients,[207] respectively.

Four studies involving CT reported the incidence of patients with serum creatinine increased above baseline.[126,200,206,207,207] One study reported a single patient (1.4%) with a transient increase of serum creatinine to 2.2 mg/dL.[126] Two studies used the definition of an increase in serum creatinine of 0.5 mg/dL or greater and/or 25% or greater, met by 4%[206] and 13% of patients, respectively.[207] In the fourth study, 4.3% had an increase in serum creatinine of more than 1 mg/dL.[200]

Allergic Reaction: Three studies involving CT reported allergic reactions to contrast administration.[67,116,125] One intra-procedural anaphylactic reaction was recorded in a study of

185 patients.[125] In the same study, one patient had an allergic reaction to contrast used for PA. In a randomized comparison of pathways including CT (D-dimer–US–CT versus D-dimer–CT), 1 of 509 (0.2%) patients in the D-dimer–US–CT pathway and 2 of 535 (0.4%) patients in the D-dimer–CT pathway had a mild cutaneous skin reaction on contrast administration.[116] In a nonrandomized study involving 1,095 patients who underwent CT, 4 (< 1%) had a mild allergic reaction, described as itching, swollen eyelids, or vomiting.[67]

Extravasation of Contrast: One study involving CT reported extravasation of contrast.[116] An RCT investigating the effect of adding leg US to a pathway consisting of D-dimer and CT found that 1 of 509 (0.2%) patients and 2 of 535 (0.4%) patients had extravasation of contrast in the D-dimer–US–CT and D-dimer–CT arms, respectively.[116]

Radiation Exposure: Five studies reported CT radiation dose, three of which explored protocols to reduce radiation and/or contrast exposure,[119,163,198] and two of which reported radiation dose and estimated cancer incidence in a cohort.[205,208]

One study compared a standard protocol with a reduced-dose protocol, with adjustment in voltage, pitch, and contrast dose,[119,198] reporting statistically significant differences in volume CT dose index, dose-length product, and effective dose (1.7 ± 0.5 mSv versus 0.9 ± 0.2 mSv, $P < 0.001$), between the standard-dose and reduced-dose protocols.[119] One study explored the effect of reducing contrast dose on image quality and reported an effective dose of 2.9 mSv for both groups.[198] One study of nuclear medicine modalities (described in their respective sections) calculated 15 mSv for total radiation exposure for the study's standard CT protocol.[163]

One study reported a mean effective dose for CT angiography of 4.35 mSv for a cohort of 691 patients.[208] Based on the estimated doses to individual organs, baseline rates from the Surveillance, Epidemiology and End Results (SEER) data, and the BEIR VII data (National Research Council), they calculated a lifetime attributable risk of organ-specific cancer of up to 49.8 per 100,000 persons exposed for 20-year-old women (breast cancer) and 22.4 per 100,000 persons exposed for 20-year-old men. The absolute risk for all cancers was less than 0.01%, but the cumulative relative risk attributable to a single CT was up to 2.76%, for young women. A second study retrospectively evaluated 1,424 patients, assessing dose, lifetime attributable risk of cancer mortality, and risk–benefit ratio.[205] The estimated effective dose was 8.4 mSv for women and 9.7 mSv for men. With adjustment for dose, age, and sex, the lifetime attributable risk for cancer death in their cohort was 33 per 100,000 in women and 28 per 100,000 in men. Lifetime attributable risk was also higher in ambulatory patients.

Magnetic Resonance Imaging

Seven studies reported utility and/or safety results for MRI.[54,138-141,146,209]

Study and Patient Characteristics

Study Design

All studies were nonrandomized.

Country and Setting

One study was multi-centre, conducted in the US,[146] and six were single-centre. Of the six, two were conducted in Germany,[141,209] two in France,[139,140] and one each in the US[54] and China.[138] Six studies were conducted in secondary[54,139,141,146,209] or secondary/tertiary centres,[140] while the setting of one was unclear.[138]

Funding

Four studies received government funding,[138-140,146] one received no funding,[54] and two did not report funding.[141,209]

Population

The number of patients recruited ranged from 27[138] to 818.[146] The mean age ranged from 38.9 years (SD 14.4 years)[138] to 60.9 years (SD 15.7 years),[141] and the proportion of women from 0.22[54] to 0.59.[146] Two studies recruited only in-patients;[141,209] one recruited in-patients, outpatients, and ED patients;[146] and one recruited in-patients and ED patients.[140] Three did not report on the patients recruited.[54,138,139] Three studies reported the prior risk of PE, all of which recruited patients at mixed risk,[140,141,146] and four did not report the risk.[54,138,139,209]

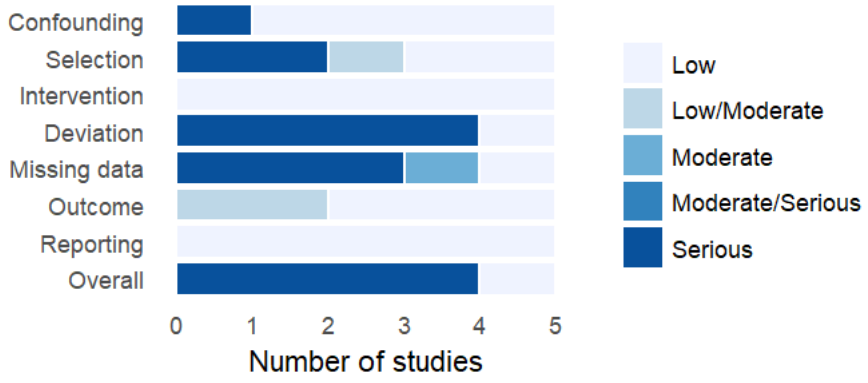
Technical Characteristics

Five studies used 1.5 Tesla units,[54,139-141,146] one study used a 3 Tesla unit,[138] and one did not report field strength.[209]

Quality Appraisal

Five studies were assessed as comparative studies by the ROBINS-I tool.[138-141,146] Summary findings are shown in Figure 18. Overall risk of bias was low for one study and serious for four.[138-140,146] Serious risk of bias was predominantly due to the exclusion of patients with nondiagnostic index test results, which contributed to selection bias; protocol deviations leading to patients not receiving planned imaging; and missing data, meaning that the patients for whom utilities are reported may not represent those recruited. As comparative data were not available for the outcomes of interest, the biases affecting comparisons were less relevant.

Figure 18: Risk of Bias for Comparative Studies of Magnetic Resonance Imaging as Index Test



Two studies were assessed as single-arm studies by the Moga checklist.[54,209] Both studies described an appropriate intervention and analysis. Both studies were single-centre, so were considered at high risk for selection bias, and did not report adverse events, length of follow-up, or competing interests. The primary outcome of one study was poorly defined, but the utilities outcomes were valid.

Detailed presentations of responses to individual signalling questions by study are shown in Appendix 17.

Outcomes

Proportion of Patients with Test Failure

One study[54] reported four VTEs and one PE in patients with an initial negative scan over the first year of follow-up (proportion 0.034, 95% CI, 0.011 to 0.077).

Nondiagnostic Studies

Six studies reported the number of MRI examinations that were nondiagnostic,[54,138-140,146,209] primarily due to technical inadequacy. Two studies reported the same group of patients examined by multiple sequences;[139,140] one reported an overall, consensus reading.[140] Proportions of nondiagnostic examinations across the five unique studies ranged from 0[138] to 0.292,[140] while the nondiagnostic rate for individual sequences was as high as 0.494.[139] The data set was too statistically heterogeneous to pool (I^2 = 97.5; Q = 212.1, df = 5, P < 0.0001).

As MRI is not routinely used for diagnosis of PE at present,[53] studies tended to be more exploratory in nature, testing variable imaging conditions. Nevertheless, the variability in the proportion of nondiagnostic examinations across studies does not have an obvious relationship to the MRI sequences. From review of patient flow, studies did not obviously differ in their approach to excluding patients. The definition for nondiagnostic examinations tended to be pragmatic, depending on whether a diagnosis could be made with confidence; it is possible that the variability reflected the differing experience and practice of radiologists.

Alternative Diagnoses and Incidental Findings

Two studies that used MRI as an index test reported alternative diagnoses or incidental findings for a proportion of 0.129[141] and 0.445[209] of patients. One study of US as an index test also reported findings for MRI. Details are shown in Appendix 19.

Safety

Adverse Event Outcomes: One study of MRI compared with CT and V/Q planar scintigraphy included a general statement on adverse event outcomes. In this study there were "no serious adverse events" related to MRI, venography, or other tests during a six-month follow-up that included 84% of patients.[67]

Extravasation of Contrast: In one study, 1 of 275 patients was unable to complete the MRI protocol due to extravasation of contrast.[140]

Thoracic Ultrasound

Two studies reported utility and/or safety results for US studies.[117,155]

Study and Patient Characteristics

Both studies were nonrandomized, single-centre studies at secondary settings, conducted in Austria[117] and France.[155] Neither reported funding.[117,155]

The number of patients recruited was 55 in one study[117] and 74 in the other.[155] The mean age in one study was 69 years[117] and in the other 66 years (SD 17).[155] One study recruited in-patients,[117] and the other did not report which patients were recruited.[155] Both recruited a mixed-risk group of patients.[117,155]

Technical Characteristics

One study used a 5 MHz transducer,[155] and the other used frequencies of 3.5 MHz, 7.5 MHz, and 10 MHz.[117]

Quality Appraisal

One study was assessed by ROBINS-I.[117] Most domains were assessed as having a low risk of bias, but there were significant deviations from the protocol involving patients not receiving the planned imaging, leading to an overall assessment of moderate risk of bias.

One study was assessed by the Moga checklist.[155] It was a single-centre study, did not provide a clear description of the intervention, and did not report follow-up or conflict of interest. Other domains had a low risk of bias.

Outcomes

Failure Rates

One study reported no failures in 43 patients.[155]

Nondiagnostic Examinations

One study using US as an index test reported three nondiagnostic (indeterminate) examinations, out of 55 patients imaged with US (proportion 0.018).[117]

Alternative Diagnoses and Incidental Findings

One study reported alternative diagnoses and incidental findings in 19 of 55 patients (proportion 0.345).[117] Details are in Appendix 19.

Perfusion-Only (Q)

Six studies reported utility and/or safety results for perfusion-only studies.[131,160,161,164,167,168]

Study and Patient Characteristics

Study Design

All studies were nonrandomized.

Country and Setting

Five studies were multi-centre, conducted in the US,[164] Netherlands and Belgium,[167] Slovenia, Turkey, Czech Republic, Uruguay and India,[160] Slovenia,[161] and China.[131] One single-centre study was conducted in Italy.[168] Five studies were conducted in secondary[131,164] and secondary/tertiary settings,[160,161,167] and one did not identify the setting.[168]

Funding

Three studies received government funding,[131,164,168] two reported receiving no funding,[160,167] and one study did not report funding.[161]

Population

Studies recruited between 76[167] and 910 patients.[164] The age ranged from a median of 40 years (29 to 45 years)[167] to a median of 72 years.[161] One study recruited in-patients,[161] two recruited in-patients and outpatients,[160,167] and one recruited in-patients, outpatients, and ED patients.[164] Two did not report the patients they recruited.[131,168] Four studies recruited a mixed-risk group of patients,[131,160,164,168] and one recruited patients at high prior risk of PE.[167] One study did not report prior risk.[161]

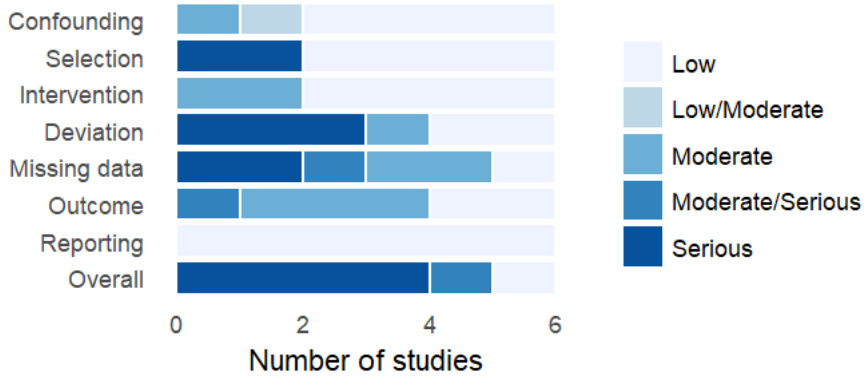
Technical Characteristics

All studies used 99mTc-labelled MAA injection for visualization, with doses ranging from 120 MBq[161] to 200 MBq.[161] Studies used the PISAPED,[131,164,167,168] PIOPED II,[131,164] and EANM guidelines[161] for interpretation.

Quality Appraisal

Six studies were assessed by ROBINS-I.[131,160,161,164,167,168] A summary of findings is shown in Figure 19. Studies were noted as having a high risk of bias as a result of protocol deviation[164,168] or missing data[161,164] due to a high proportion of indeterminate studies. One study excluded these patients with indeterminate findings,[164] and another referred only patients with an abnormal lung scan for further testing, resulting in selection bias and possibly biasing the interpreter of the lung scan.[168] Since comparative data were not available, biases that affect the comparison between groups are less relevant.

Figure 19: Risk of Bias for Comparative Studies of Perfusion as an Index Test



Detailed presentations of responses to individual signalling questions by study are shown in Appendix 17.

Outcomes

Nondiagnostic Examinations

Five studies reported the number of perfusion examinations that were nondiagnostic, primarily due to technically adequate but indeterminate examinations. Proportions of nondiagnostic examinations ranged from 0[131,160] to 0.214.[161] The data set was heterogeneous to pool (I^2 = 98.4; Q = 360.6, df = 4, *P* < 0.0001).

From available data, the source of heterogeneity could not be determined. For perfusion examinations, nondiagnostic examinations are predominantly technically adequate examinations with indeterminate results. The variability in the proportion of nondiagnostic examinations across studies did not appear to be related to the interpretation criteria, as defined by the papers. From review of the patient flow, studies did not obviously differ in their approach to excluding patients prior to screening, or the approach to reporting of their imaging, which might have been reflected in the proportion of nondiagnostic examinations.

Safety

One study reported an estimated radiation dose for perfusion scanning alone of 3 mSv.[163]

Perfusion–Single-Photon Emission Tomography (Q SPECT)

One nonrandomized study reported utility outcomes for Q SPECT.[173] No studies reported safety outcomes.

Study and Patient Characteristics

The study was a single-centre study conducted at a secondary setting in Sweden.[173] Funding was not reported.

The study recruited 152 patients, primarily outpatients.[173] Prior risk of PE was not reported.[173]

Technical Specifications

The study used 120 MBq 99m-Tq-MAA given intravenously for visualization and EANM criteria for interpretation.[173]

Quality Appraisal

One study was assessed by ROBINS-I.[117] Two domains (intervention and missing data) were assessed as having a low risk of bias, and four as having a low/moderate risk of bias (risk of confounding, risk of selection bias, deviation from the protocol, and overall reporting). Overall risk of bias was low/moderate. Only single-arm data were available for Q SPECT.

Outcomes

Proportion of Patients with Test Failure

One study[173] reported no failures in patients with negative scans over three months of follow-up.

Nondiagnostic Examinations

One study reported no nondiagnostic examinations for Q SPECT.[173] Nondiagnostic was defined as non–wedge-shaped perfusion deficits.

Perfusion–Single-Photon Emission Tomography–Computed Tomography (Q SPECT-CT)

No studies reported utility or safety outcomes for Q SPECT-CT.

Ventilation/Perfusion (V/Q)

Eleven studies reported utility and/or safety results for V/Q.[117,121,126,131,160,161,176-178,180,183]

Study and Patient Characteristics

Study Design

All studies were nonrandomized.

Country and Setting

Six were multi-centre studies: one conducted in Slovenia, Turkey, Czech Republic, Uruguay, and India;[160] two conducted in the US[177,180] and one each conducted in Slovenia,[161] Australia,[183] and China.[131] The five single-centre studies were conducted in Belgium,[126] Denmark,[176] Scotland,[178] Austria,[117] and China.[121] All studies were conducted in a secondary[117,126,131,177,178,180] or secondary/tertiary setting,[160,161,176,183] with the exception of one whose setting was not reported.[121]

Funding

Three studies received government funding,[131,177,180] one received industry funding,[183] one reported no funding,[160] and six did not report funding received.[117,121,126,161,176,178]

Population

The studies recruited between 36[176] and 951 patients.[180] Three studies recruited in-patients,[117,161,183] one recruited outpatients,[126] one recruited in-patients and outpatients,[160] and two recruited in-patients, outpatients, and ED patients.[177,180] Four studies did not report the patient origins.[121,131,176,178] Six studies recruited a mixed-risk group of patients,[117,121,126,131,160,180] and five did not report the prior PE risk.[161,176-178,183]

Technical Characteristics

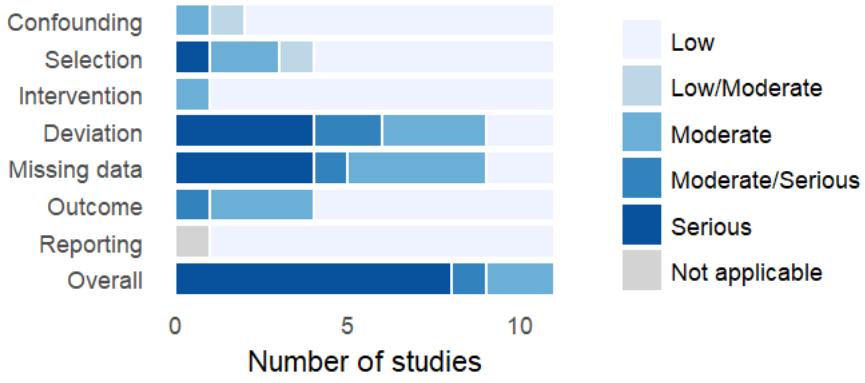
With the exception of one study that did not provide details,[160] all studies used 99mTc-labelled MAA injection for perfusion visualization, with doses ranging from 100 MBq[161] to

370 MBq.[131] For ventilation, six studies used 99mTc-labelled DTPA or Technegas,[121,126,131,160,161,183] two used 81 mKr,[126,176] and three used 113 Xe.[160,177,178] Interpretation criteria varied widely, with studies using PIOPED, PISAPED and modifications and revisions, and study-specific criteria.

Quality Appraisal

All studies were assessed by ROBINS-I.[117,121,126,131,160,161,176-178,180,183] The summary of findings is shown in Figure 20. Eight studies[121,126,160,161,176,177,180,183] were considered to have a serious risk of bias, primarily due to post hoc exclusions from the analysis or for a high proportion of nondiagnostic findings. Since comparative data were not available, biases that affect the comparison among groups (e.g., confounding or deviations involving the comparator) are less relevant.

Figure 20: Risk of Bias for Comparative Studies of Ventilation/Perfusion Planar Scintigraphy as Index Test



Detailed presentations of responses to individual signalling questions by study are shown in Appendix 17.

Outcomes

Proportion of Patients with Test Failure

Two studies[177,178] reported no failures in patients with negative scans, out of 21[177] and 28 patients,[154] respectively. Duration of follow-up was one year[177] and unknown.[178]

One study reported comparative proportions of failures,[178] with no failures in 28 patients who had a V/Q scan read as normal (proportion 0; 95% CI, 0 to 0.123), compared with no failures in 51 patients who had a PA scan interpreted as normal (proportion 0; 95% CI, 0 to 0.161).

Nondiagnostic Examinations

Ten studies reported the number of V/Q examinations that were nondiagnostic,[117,121,126,131,160,161,177,178,180,183] primarily due to technically adequate but indeterminate examinations. Two studies reported the results for multiple interpretation criteria, and the highest rate was selected for comparison. The proportion of nondiagnostic examinations ranged from 0.071[121] to 0.574,[160] and the data set was too heterogeneous to pool (I^2 = 97.1%; Q = 237.3, df = 9, P < 0.0001).

Ventilation/Perfusion Scintigraphy–Single-Photon Emission Computed Tomography (V/Q SPECT)

Eleven nonrandomized studies reported utility and/or safety results for V/Q SPECT.[127,161,176,182-185,188,189,210,211]

Study and Patient Characteristics

Two studies were multi-centre, conducted in Slovenia[161] and Australia.[183] One single-centre study was conducted in Canada,[211] one in the US,[127] two in Sweden,[184,189] two in Spain,[182,188] and one each in the UK.[210] Denmark,[176] Australia.[185] Nine studies were conducted in a secondary care setting,[127,161,176,182-185,188,189,210,211] and the setting for two was unclear.

Studies recruited between 36[176] and 1,785 participants.[184] Four studies involved in-patients,[127,161,182,183] one involved outpatients,[188] and six did not report the origins of patients.[176,184,185,189,210,211] None of the studies reported prior clinical risk of PE.

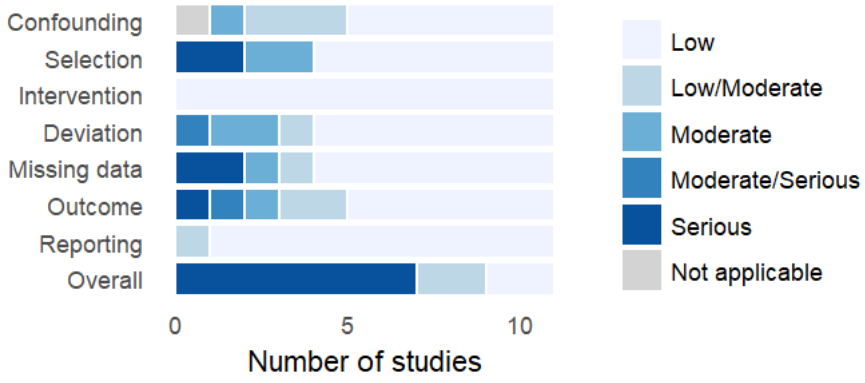
Technical Characteristics

With the exception of one study that did not provide details,[160] all studies used 99mTc-labelled MAA injection for perfusion visualization, with doses ranging from 100 MBq[161] to 185 MBq.[183] For ventilation, eight studies used 99mTc-labelled DTPA or Technegas,[127,161,182-184,188,189,211] two used 81 mKr,[176,210] and one did not report.[185] Interpretation criteria varied widely, with studies using PIOPED, PISAPED and modifications and revisions, and study-specific criteria.

Quality Appraisal

All studies were assessed by ROBINS-I. A summary of findings is shown in Figure 21. Seven studies were considered to have a serious risk of bias overall.[127,161,176,182,183,188,211] Two studies had a serious risk of selection bias,[127,182] in both cases because inclusion was contingent on receiving both tests, but testing was affected by either the results of the other test, or on clinical condition. Two studies had a serious risk of bias due to the handling of missing data due to indeterminate test results.[161,176] In two studies, treatment with anticoagulation was not primarily determined by imaging results, but by clinical suspicion or other tests.[188,211]

Figure 21: Risk of Bias for Comparative Studies of Ventilation/Perfusion Single-Photon Emission Computed Tomography as Index Test



Detailed presentations of responses to individual signalling questions by study are shown in Appendix 17.

Outcomes

Proportion of Patients with Test Failure

One study reported no failures in 405 patients with negative scans at three months' follow-up.[212]

Nondiagnostic Examinations

Ten studies reported the number of V/Q SPECT examinations that were nondiagnostic,[127,161,182-185,188,189,210,211] primarily due to technically adequate but indeterminate results. The proportion of nondiagnostic examinations ranged from 0[161,183] to 0.220,[185] and the data set was too statistically heterogeneous to pool (I^2 = 94.1%; Q = 97.4, df = 9, P < 0.0001).

Removing Harris et al., 2007,[185] which appeared to be a statistical outlier on model diagnostics, did not substantially improve heterogeneity (I^2 = 87%). None of the following covariates appeared to independently explain the observed heterogeneity, either through examination of stratified scatterplots or results of adjusted statistical models: age, sex as represented by proportion of women, centre, study setting, patient origins, and prior risk. From review of the patient flow, studies did not obviously differ in their approach to excluding patients prior to screening, or from reporting of their imaging, which might have been reflected in the proportion of nondiagnostic examinations.

Ventilation/Perfusion–Single-Photon Emission Computed Tomography–Computed Tomography (V/Q SPECT-CT)

One diagnostic test accuracy study of V/Q SPECT-CT also reported mean radiation doses for the equipment during the study period.[192]

Study and Patient Characteristics

The study was conducted at a single secondary/tertiary centre in Australia.[192]

A total of 102 patients were recruited. It was unclear where (in-patient, outpatient, or ED) patients were recruited, and the prior risk of PE was not reported.

Technical Characteristics

Perfusion was conducted with 200 MBq of 99m-Tc MAA.[192] Interpretation criteria were not described.

Funding

The funding source of the study was not specified.

Quality Appraisal

The diagnostic test accuracy quality appraisal is described under the section for V/Q SPECT-CT for question 2.

Outcomes

Safety

Radiation Exposure: The effective dose for V/Q SPECT-CT was 3.6 mSv (2.8 mSv for SPECT and 0.8 mSv for low-dose CT). The absorbed dose to female breast tissue was 3.27 mSv.

Summary of Utility and Safety Findings

The pooled proportion of patients with recurrent VTE following a negative CT scan at three and six months was, 0.008 (95% CI, 0.005 to 0.012) and 0.018 (95% CI, 0.008 to 0.031), respectively. There was no difference between CT and the available reference standards in a well-conducted RCT comparing CT and V/Q or in five nonrandomized studies, pooled risk difference 0.001 (95% CI, –0.009 to 0.010). For MRI, one study reported a failure rate over the first year of 0.034 (95% CI, 0.011 to 0.077). For the other modalities, either there were no failures in the one or two studies reporting (Q SPECT, Q SPECT-CT, V/Q, V/Q SPECT), or no studies reporting failure rates (US, Q, V/Q SPECT-CT).

All 10 studies reporting diagnostic pathways reported failure rates, which were generally very low.

The proportion of patients with nondiagnostic studies for CT was 0.034 (pooled, 95% CI, 0.023 to 0.047), for MRI from 0 to 0.292, for V/Q from 0.071 to 0.574, and for V/Q SPECT from 0 to 0.222. One small study reported a proportion of 0.053 nondiagnostic examinations for US, and the other modalities had no data. Technical inadequacy accounted for the nondiagnostic CT and MRI studies, and technically adequate but indeterminate studies (intermediate or low probability of PE) accounted for the nondiagnostic studies in the nuclear medicine modalities.

For CT and MRI, the proportion of patients for whom an alternative diagnosis could be established by imaging was high, up to 0.445. Alternative diagnoses were not reported in studies of US and nuclear medicine modalities.

Although studies for utility outcomes were selected on the basis of their comparative design (safety studies could be single-arm), the majority did not include data for both the index and the reference test, and, therefore, comparative data were limited. The impact of missing data on the index tests would vary according to the outcome and the reason patient data were missing. Exclusions prior to imaging would affect whether the patients who proceeded to imaging were representative of the population of interest and would likely be due to more severe illness. Nondiagnostic studies were an outcome themselves. Failure rate was measured in patients with negative test results, thereby requiring exclusion of negative studies, although severity of illness could affect both the ability to obtain a diagnostic scan and the risk of recurrence.

Safety data were sparsely reported. Adverse events were generally not serious, with no reported renal failure or requirement for dialysis and few allergic reactions (although there was one report of an anaphylactic reaction). Few studies reported radiation exposure, although most cited reports that radiation dose was highest with CT, and lower for nuclear medicine modalities.

Question 3B and C: Clinical Utility and Safety in Pregnant Patients

Thirteen studies[111,112,114,162,213-221] included populations or subgroups of pregnant or postpartum women. Four studies did not report outcomes in the pregnancy subgroup, and so are included in the preceding summary for nonpregnant patients.[111,112,114,162]

Summary of Study Characteristics

Study characteristics for the nine studies[213-221] reporting on pregnant populations are presented in Appendix 20.

Study Design

All studies were nonrandomized, three were prospective cohorts,[216,217,220] and six were retrospective. The six retrospective studies were cohort studies[213-215,221] and case–control studies.[218,219] Six studies were comparative,[213-215,217,219,220] and three were noncomparative studies with safety data.[216,218,221]

Country of Origin

The studies were conducted in Canada,[216] Ireland,[215,218] Sweden,[217] the US,[213,214,221] and the UK.[219,220] There were a mix of multi-centre[213,216] and single-centre studies. [214,215,217-221] All studies were conducted in secondary or tertiary care community or academic hospitals.[213-221]

Patient Population

All study participants were pregnant women with a suspected acute PE. Information on patient status (e.g., in-patient, outpatient and ED), and geographical setting (urban, rural, or remote) was limited. One study[202] reported including both in-patients and outpatients. Sample sizes ranged from 50 to 343 participants. All studies included women at different stages of pregnancy. None of the studies reported on pre-specified PE risk level (as determined by clinical judgment or prediction rules) prior to undergoing imaging.

Index Tests and Reference Standards

Two studies compared Q SPECT, V SPECT, or V/Q SPECT with CT.[217,219] Three noncomparative studies reporting on safety outcomes were included: two investigating the use of CT[218,221] and one[216] assessing V/Q planar scintigraphy. Two studies compared CT with Q planar scintigraphy,[213,220] and two studies compared CT with V/Q scintigraphy.[214,215]

Outcomes and Funding

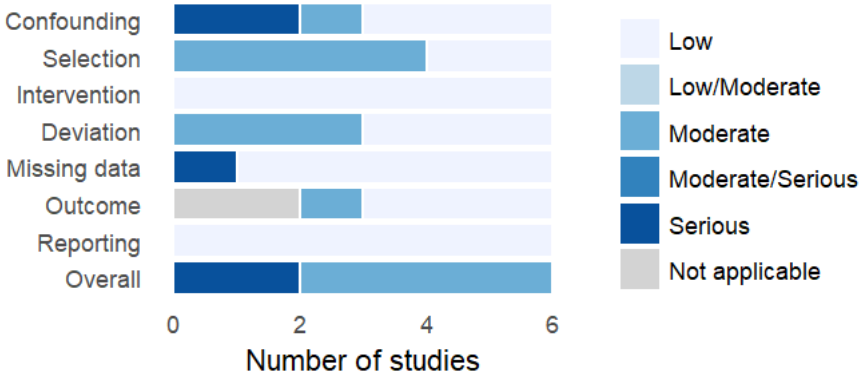
Studies included data on clinical utility and safety. No studies reported on diagnostic test accuracy compared with an appropriate reference standard. Funding was provided through government or academic grants;[216,217,219] otherwise, the source was not disclosed.[213-215,218,220,221]

Quality Appraisal

Six nonrandomized studies contained comparative data and were assessed using the ROBINS-I tool.[213-215,217,219,220] A summary of findings is shown in Figure 22. Two studies were considered to have an overall high risk of bias according to the reviewer's assessment,[213,215] and the rest a moderate risk of bias. All studies compared two groups who received different imaging, and the studies with a high risk of bias were those that did so without adjustment and were at risk of baseline confounding.[213,215] Another study had a

high risk of bias in the domain of missing data due to a substantial number of nondiagnostic studies.[219]

Figure 22: Risk of Bias for Comparative Studies in Pregnancy



Also, it should be noted that a systematic review by van Mens et al. published in early 2017[222] reported that it could not include a study by Cahill et al. 2009[214] due to discrepancies between the original study results and additional data provided on the pregnant patient subgroup that could not be resolved by the authors. We included the results from the published studies.

Three noncomparative studies were assessed using the Moga checklist.[216,218,221] Two were single-centre, so considered to have a high risk of bias for population.[218,221] Two studies had a high risk of bias for the intervention, as co-interventions could have affected the relationship between diagnostic imaging and pregnancy outcomes.[216,223] One study had a high risk of bias for outcome measurement due to using hospital-available data.[216]

Detailed presentations of responses to individual signalling questions by study are shown in Appendix 17.

Summary of Diagnostic Test Results

Diagnostic test accuracy findings were not reported by any of the studies of pregnant patients.

Summary of Utility Results

Failure Rate

Failure rates (i.e., morbidity and mortality due to misdiagnosis at 30 days' follow-up), presented by modality for comparison, are reported in Table 15. Overall, rates of VTE or isolated PE in patients with negative or indeterminate test findings were low.

Several studies reported the failure rate only for the primary imaging study. In patients screened with V/Q SPECT in one study, none of the 116 patients in whom PE was ruled out were subsequently diagnosed with PE.[217] In one noncomparative study, patients with nondiagnostic or normal V/Q scans who did not receive anticoagulation did not have any VTEs during follow-up.[216] In one study, patients with indeterminate V/Q scans did not have any VTEs upon CT or during follow-up.[220] In two other noncomparative studies, patients negative for PE with CT did not have any VTEs during follow-up.[218,221]

For the studies reporting comparative failure rates, in patients with negative or indeterminate tests, a final diagnosis of PE was made in one patient in the CT group in each of two studies,[213,215] and no patients in the V/Q [215] or Q scanning[213] groups.

Table 15: Failure Rate by Modality

Study	CT, n/N (%)	V/Q, n/N (%)	*P* value
Browne et al., 2014[218]	0/70 (0)	–	–
Bajc et al., 2015[217]	–	0/116 (0)[a]	–
Bourjeily et al., 2012[221]	0/318 (0)	–	–
Shahir et al., 2010[213]	1/94 (1)	0/94 (0)	NR
Ridge et al., 2009[215]	1/8	0/0	NR
Scarsbrook et al., 2007[220]	–	0/7	–
Chan et al., 2002[216]	–	0/0	–

CT = computed tomography; NR = not reported.

[a] V/Q SPECT.

Indeterminate or Nondiagnostic Tests

Rates of indeterminate tests by modality are presented in Table 16. The trend was toward a greater number of indeterminate or nondiagnostic tests in the CT group when the comparison was made with V/Q modalities; however, the rates were generally low.

Two studies[217,219] reported numerically higher rates of indeterminate tests for patients who received CT versus V/Q SPECT but did not report on statistical significance.

One study[213] reported numerically higher rates of indeterminate tests in the CT group versus Q-only scanning and did not report statistical significance. One study[215] reported significantly higher rates of indeterminate tests in the CT group versus the V/Q group. One study reported higher rates of technically inadequate testing in the CT group, but more similar rates if nondiagnostic V/Q scans were considered in the comparison.[220]

Another study reported numerically higher rates of indeterminate V/Q versus CT scans, with no significant difference between groups.[214] This study noted that the rates of indeterminate CT tests were five times higher in the subgroup of patients with normal chest X-ray; RR = 5.3 (95% CI 2.1 to 13.8), including when adjusted for gestational age, postpartum status, hypoxia, and chest pain.[214]

One study did not compare modalities but reported more than a quarter of tests as indeterminate for V/Q planar scintigraphy.[216] Another study reported a low rate of inconclusive (0.9%) and technically limited (20%) CT examinations.[221]

Table 16: Summary of Indeterminate or Nondiagnostic Tests

Study	CT, n/N (%)	V/Q-Based Modality, n/N (%)	*P* Value
Gruning et al., 2016[219]	1/23	0/89[a]	NR
Bajc et al., 2015[217]	6/61(10)	0/127[a]	NR
Bourjeily et al., 2012[221]	3/340 (0.9)[b]	–	–
Shahir et al., 2010[213]	6/106 (5.6)	3/99 (3.3)[c]	0.0058
Cahill et al., 2009[214]	(17)[d]	(13.2)[d]	0.38
Ridge et al., 2009[215]	10/28 (35.7)	1.25 (4)	0.0058
Scarsbrook et al., 2007[220]	1/9 (11)	7/96 (7)[e]	NR
Chan et al., 2002[216]	–	29/120 (24.2)	–

CT = computed tomography; NR = not reported; V/Q = ventilation/perfusion planar scintigraphy.
[a] V/Q SPECT.
[b] 68/340 (20%) technically limited.
[c] Perfusion-only scan.
[d] Total n not reported.
[e] 0/96 were technically inadequate.

Alternative Diagnoses and Incidental Findings

Two studies[217,219] reported on incidental findings in pregnant women. Pneumonia was detected by V/Q SPECT in 15 patients (12%), two of whom also had PE.[217] In addition, one occurrence of both airway obstruction and left heart failure was detected.[217] One study[219] reported incidental findings including atelectasis, infection, and axillary nodes in three (13%) of the CTPA scans. Incidental findings were not reported for V/Q SPECT in this study.

Safety Results

Mortality and radiation dose results are reported by outcome and modality in Table 17.

Mortality

Maternal mortality rates were rarely reported, and the rates were very low in both studies that presented data.[213,216]

Obstetrical and Pediatric Outcomes

One retrospective study of V/Q imaging reported obstetrical and pediatric outcomes in 121 pregnant women with suspected PE.[216] Gestational age was less than 12 weeks' gestation in 9.9%, between 12 and 28 weeks in 42.5%, and greater than 28 weeks in 47.6%. Seven women were already receiving anticoagulation prior to the scan, and eight received anticoagulation after scanning. The authors did not describe the comorbidity profile of the cohort.

Two women died, one during the initial scan of massive PE, and one as the result of previously diagnosed primary pulmonary hypertension after a normal scan.[216] Of the remaining 119 women, three experienced a spontaneous pregnancy loss (2.5%), one had an elective termination for unrelated reasons, and two experienced a neonatal death due to prematurity (1.7%).[216] Both women had twin pregnancies and threatened preterm labour prior to testing for PE.

Four of the 110 women with a live birth reported congenital anomalies (3.6%): hypoplastic lungs and short stature diagnosed as a genetic disorder (V/Q scan at 22 weeks' gestation, followed by low-dose heparin until delivery); duplicate ureters (V/Q scan at 11 weeks' gestation); transposition of the great arteries identified prior to the V/Q scan; and a small

hemangioma (normal V/Q scan at 28 weeks' gestation).[216] Four of the remaining 106 women (3.8%) reported developmental abnormalities. Three of the four delivered prior to 26 weeks due to premature labour, pre-eclampsia, or acute appendicitis. The fourth was delivered at term, after V/Q scanning at 26 weeks. No childhood cancers or leukemias were reported, although the mean follow-up of the mothers was less than two years (mean 20.6 months, 0.5 to 108 months).

The authors concluded that pediatric risks from V/Q scans were low, although large, prospective studies were needed for proper evaluation of suspected PE in pregnant women.

Radiation Dose

Based on the two studies,[217,219] radiation dose to maternal tissue, or to maternal breast tissue, was higher with CT than with V/Q SPECT, V SPECT, or Q SPECT. There were less pronounced differences in fetal dose between modalities. No formal comparison of radiation dose was conducted.

Table 17: Mortality and Radiation Dose Results by Modality

Study		CT, n/N (%)	V/Q, n/N (%)	*P* Value
Mortality				
Shahir et al., 2010[213a]		0/NR (0)	0/NR (0)	NR
Chan et al., 2002[216]		2/121	–	NR
Radiation Dose				
Bajc et al., 2015[217]	Maternal breast dose		0.6 mGy (V/Q SPECT) 0.25 mGy (Q SPECT only)	NR
	Fetal dose		0.34 to 0.48 mGy[b] (V/Q SPECT) 0.14 to 0.20 mGy[b] (Q SPECT only)	NR
Gruning et al., 2016[219]	Maternal effective dose (mSv)	7.8 (2 to 18)	1.4 (0.7 to 2.8) (Q SPECT) 0.82 (V SPECT) 1.6 (0.70 to 3.6) (V/Q SPECT)	NR
	Maternal breast dose (mSv)	20 (4 to 50)	0.49 (0.24 to 1.0) (Q SPECT) 0.29 (V SPECT) 0.56 (0.24 to 1.3) (V/Q SPECT)	NR
	Fetal dose (µSv)	110 (3.7 to 380)	71 (33 to 130) (Q SPECT) 22 (V SPECT) 77 (33 to 150) (V/Q SPECT)	NR

CT = computed tomography; NR = not reported; Q = perfusion only; SPECT = single-photon emission computed tomography; V = ventilation only; V/Q SPECT = ventilation/perfusion single-photon emission computed tomography.

[a] Rates not disclosed, authors stated that "none of the patients died."[213]
[b] Depending on trimester of pregnancy.[218]

Search Updates for Question 2 and 3

The meta-analysis incorporated studies retrieved to February 1, 2017. Four monthly update searches, with a latest search date of July 1, 2017, retrieved a total of 443 articles. Twenty-five articles were retrieved for full-text review, and three eligible studies were identified, reporting DTA[224] and utility outcomes.[224-226] The results of these studies were consistent with the those already identified.

Mila et al. 2017[224] compared V/Q SPECT-CT with full-dose CT, and V/Q and CT angiography using a reference standard of a complex composite consisting of clinical information, D-dimer, leg US, MRI, external CT, and three-month follow-up. A total of 380 patients with suspected PE were screened, 374 completed screening, and 314 had sufficient follow-up. Patients without contraindications received contrast media, while those with contraindications underwent imaging without contrast media (46.8%).

The sensitivity of V/Q SPECT-CT (n = 307), relative to the complex composite, was 0.995 (95% CI, 0.910 to 1.00) and the specificity, 0.971 (95% CI, 0.950 to 0.990). The sensitivity of V/Q SPECT (n = 304) was 0.919 (95% CI, 0.840 to 0.980) and the specificity, 0.924 (95% CI, 0.890 to 0.960). The sensitivity of CT (n = 162) was 0.800 (95% CI, 0.680 to 0.920), and the specificity, 0.992 (95% CI, 0.980 to 1.00). Pairwise comparison of AUC showed that V/Q SPECT-CT performed better than V/Q SPECT or CT, which is consistent with the unadjusted results we observed.

The rate of indeterminate studies was 0.022 for V/Q SPECT-CT and 0.032 for V/Q SPECT. Incidental findings and alternative diagnoses were identified in 231/314 patients (a proportion of 0.734), although only 46 patients (0.147) had new diagnostic information.

Van der Hulle et al. 2017[225] conducted a patient-level meta-analysis of test failure for four studies of a diagnostic algorithm that used Wells criteria, D-dimer, and CT to exclude PE. The combined four studies included 7,975 patients, of whom 6,148 patients were eligible for the study. The mean age was 57 years (SD 17 years), and 0.58 were male. The pretest probability of PE was “likely” in 4,254 and “unlikely” in 1,894; 1,307 were diagnosed with PE at baseline, leaving 4,421 with negative imaging results.

The three-month VTE rate ranged from 0.005 to 0.058 across the four studies. The three-month VTE rate in patients with a normal CT and score on Wells rule of 4 or less (unlikely) was 0.0085 (95% CI, 0.004 to 0.02) and for those with a score on Wells rule of more than 4 (likely) was 0.02 (0.01 to 0.04). The three-month rate for fatal PE in patients with a normal CT and score on Wells rule of 4 or less 4 (unlikely) was 0.0012 (95% CI, 0.0001 to 0.014) and for those with a score on Wells rule of more than 4 (likely) was 0.0048 (95% CI, 0.002 to 0.011).

Pelletier-Galarneau 2017[226] conducted a retrospective study of diagnostic yield of studies for V/Q in patients with suspected PE according to referral source (ED, in-patient, outpatient thrombosis clinic, and other outpatient sources). The study was conducted in Canada. Routine perfusion images were obtained using 99mTc MAA, 185 to 370 MBq. Doses were halved for pregnant patients and patients with known pulmonary hypertension. Images were interpreted using modified PIOPED criteria.

The mean age ranged from 46.3 years (SD 19.2) in the outpatient thrombosis clinic to 64.7 years (SD 19.3 years) for the in-patients. The proportion of women ranged from 0.538 for in-patients to 0.681 for the outpatient thrombosis clinic, and the proportion of women who were pregnant ranged from 0.046 in other outpatients to 0.176 to the outpatient thrombosis clinic. The proportion of patients with chronic lung disease ranged from 0.023 in ED patients to 0.191 in in-patients.

The overall rate of indeterminate studies was 0.157, with proportions ranging from 0.117 for patients in the thrombosis clinic to 0.247 for in-patients.

Economic Review

Review of Economic Studies

A review of published and grey literature was conducted to identify relevant economic evaluations that have addressed the cost-effectiveness of any component of the diagnostic pathway for PE. From this search, a recent systematic review on this topic was identified.[227] The systematic review identified 13 economic evaluations, published between 1990 and 2012, on the cost-effectiveness of diagnostic strategies that included at least one CT-based strategy. The economic evaluations were conducted for a number of jurisdictions: Europe (n = 6), US (n = 5), Canada (n = 1), and Australia (n = 1). Two additional studies were identified from our literature search : one each from Australia[228] and Canada.[229] Both of these studies were trial-based evaluations. The study from Australia compared the implementation of an evidence-based clinical diagnostic protocol (i.e., PERC > D-dimer ± diagnostic imaging) against existing practice (i.e., gestalt ± D-dimer ± diagnostic imaging),[228] while the study from Canada assessed the cost-effectiveness of different imaging modalities on a nondiagnostic V/Q lung scan (i.e., pulmonary angiography, leg US ± pulmonary angiography, or leg US ± evaluation of cardiorespiratory reserve ± pulmonary angiography or serial leg US). Appendix 24 summarizes the key aspects of each economic evaluation.

None of the identified studies completely addressed the economic research question of interest to this review. With a few exceptions,[230-233] the majority of studies compared fewer than 10 diagnostic strategies. None of the existing studies evaluated the full set of diagnostic pathways of interest. As few studies explored the same diagnostic pathways, most studies reached a different conclusion with regard to the diagnostic strategy that would be considered most likely cost-effective (Appendix 24). Furthermore, only one study formally compared CPR (e.g., Geneva/ Wells) as part of its diagnostic pathway.[228] The majority of studies were found to have adopted a short time frame (i.e., less than one year) and, in the few studies with a lifetime perspective, the approach to conduct long-term extrapolation was rarely described.[230,231]

Thus, existing economic evaluations do not fully address all possible diagnostic pathways of interest and largely fail to explore the long-term implications of a PE diagnosis. As well, there are some concerns regarding the statistical methods used to pool diagnostic test accuracy data that are then used as inputs in existing economic analyses (Meta-Analysis of Diagnostic Test Accuracy Studies). Because of these gaps, a de novo economic analysis on the cost-effectiveness of different diagnostic strategies in adults with suspected acute PE was conducted as part of the economic review. The economic models identified from the literature provided insights in conceptualizing and developing the model structure and in determining appropriate model assumptions.

Primary Economic Analysis

Methods

The objective of the economic analysis was to evaluate the lifetime costs, health outcomes, and cost-effectiveness of diagnostic pathways for adult patients with suspected acute PE who are seeking their first diagnosis within a Canadian health care system. A protocol, developed a priori, for the economic evaluation was adhered to.[100]

1. Type of analysis

Given the broad set of clinical outcomes associated with a correct diagnosis or misdiagnosis of PE, a cost-utility analysis was conducted. Health outcomes were expressed as quality-adjusted life-years (QALYs) to capture both the mortality and morbidity impacts related to the condition and treatments. The primary outcome in the economic analysis was the incremental cost per QALY gained, commonly referred to as the incremental cost-utility ratio (ICUR).

In addition, a secondary analysis was conducted to calculate the incremental cost per life-years saved.

2. Target population and settings

The target population was hemodynamically stable adults with suspected new-onset PE (i.e., no history of prior VTE). Patients with a history of PE were deemed outside the scope of this study, given that these patients have an increased risk of PE recurrence and represent a higher-risk population. The reference-case cohort were patients 55 years of age (41.4% male).[234] The underlying prevalence of PE (15.2%, 171/1126) reflected Canadian reported rates.[94] A separate analysis was conducted for a pregnant population, 30 years of age,[235] to reflect differences in the diagnostic strategies in this patient subgroup, as detailed in the section on statistical and sensitivity analyses.

It was further assumed that the initial contact with the health care system would be in an outpatient setting, although an in-patient setting was explored in further analysis. The setting for the analysis reflects a Canadian health care system in which access to all diagnostic tests was assumed to be available.

3. Time Horizon and Discount Rate

As the clinical and cost consequences of a diagnosis of PE can persist indefinitely, a lifetime time horizon was adopted. A shorter time horizon of three months was also evaluated in sensitivity analysis. Most clinical trials that have evaluated the clinical utility of diagnostic imaging and pathways, according to PE recurrence, were performed at three months, and this time point aligns with the majority of economic models with an acute time horizon.[232,233,236-240] Although the original protocol specified that the reference case would be discounted at a rate of 5% per annum, recently revised Canadian guidelines for the conduct of economic evaluations now recommend a lower discount rate of 1.5% per annum.[241] The reference case was therefore discounted at 1.5%, with a sensitivity analysis conducted to determine how the economic findings may differ under the previously recommended discount rate of 5%.[242]

4. Diagnostic Pathways

As noted in the clinical review, reliance on a single diagnostic tool has historically been problematic. Currently, the suggested diagnostic management of PE entails a multi-step sequential pathway that may include risk stratification, rule-out tests, ancillary testing, and diagnostic imaging.[243] The economic model therefore explored the cost-effectiveness of the permutations of a diagnostic pathway for PE more comprehensively than most published models that have focused on specific steps in the diagnostic pathway.

Risk stratification refers to CPRs that assign a risk score reflecting the patient's likelihood of having PE. Objective CPRs of interest to this review include the Wells rule and Geneva

score. Application of these validated CPRs allows for the determination of a pretest probability for PE. Despite this, CPRs lack the accuracy to safely rule out or establish a diagnosis of PE on their own, and treatment decisions cannot be taken on the basis of applying a CPR alone. In patients categorized as having a low pretest probability of PE (i.e., low risk), pathways will proceed to a rule-out test to establish a PE diagnosis.

As noted, if patients are deemed to have a sufficiently low risk based on one of the CPRs, the following biochemical tests or decision rules may be further applied to formally rule out PE:

- D-dimer testing: A negative D-dimer assay result, combined with a low pretest probability as determined by the CPR, is considered sufficient to rule out PE. No further workup is required.
- PERC > D-dimer: PERC is another CPR in which, if a patient scores “no” to all items, PE can be ruled out and no further diagnostic test is required. According to the clinical experts consulted as part of this review, in clinical practice, this is often followed by D-dimer testing.

If PE cannot be safely ruled out after risk stratification, patients proceed further along the diagnostic pathway to diagnostic imaging.

In patients in whom PE is still suspected after risk stratification, diagnostic imaging is offered. A variety of imaging modalities are used, and, based on the clinical review, the economic review assessed CT-, MRI-, and V/Q-based technologies (e.g., V/Q planar scintigraphy and V/Q SPECT). Thoracic US was explored in an exploratory analyses, given that this imaging modality is an intensive-care technique commonly employed in unstable patients who cannot readily be sent to diagnostic imaging and given the limitations of the clinical data, as highlighted in the clinical review (Thoracic Ultrasound: Summary of Diagnostic Test Results). As all diagnostic imaging may produce nondiagnostic findings, the model assumed that these patients with nondiagnostic findings would either be offered a CT or leg US. Specifically, leg US is a tool to diagnose DVT, as DVT is considered to fall under the broad disease condition (venous thromboembolism) that also includes PE. Research suggests that more than 70% of patients presenting with PE are found to have DVT in the legs,[5,17] and 25% to 50% of patients with PE have clinically evidence of DVT.[244]

Furthermore, seven diagnostic pathways were tested as controls in the analysis. One assumed patients would not receive any screening. On the contrary, another set of diagnostic pathways assumed all patients with suspected PE would proceed directly to diagnostic imaging without the application of a CPR or rule-out tests. Details on the clinical decision of different diagnostic findings associated with each test are described in Appendix 25. When factoring in all clinically possible permutations involving the diagnostic examinations and tests and the seven control diagnostic pathways, a total of 57 diagnostic strategies were of interest to this review (Table 18). The list of all possible diagnostic strategies of interest to this review can be found in Appendix 26.

It is important to note that leg US may be offered as an ancillary test after risk stratification and before further diagnostic imaging, especially in pregnant patients, given the concerns about the effects of radiation exposure on both the patient and the fetus. This could allow a proportion of patients to be diagnosed with DVT and treated without further imaging. A total of 57 strategies were evaluated for pregnant patients, including permutations of different CPRs, rule-out tests, ancillary tests, and diagnostic imaging (Appendix 26).

Table 18: Diagnostic Tests and Examinations Evaluated in the Reference Case

Clinical Prediction Rule	Rule-Out Test	Dx Imaging	Approach to Handle Non-Dx Findings
Wells: 3 levels versus simplified	D-dimer	CT	Leg US
Revised Geneva	PERC > D-dimer	MRI	CT (if no CT performed)
		V/Q planar scintigraphy	
		V/Q SPECT	

CT = computed tomography; Dx = diagnostic; MRI = magnetic resonance imaging; PERC = pulmonary embolism rule-out criteria; SPECT = single-photon emission computed tomography; US = ultrasound; V/Q = ventilation/perfusion.

5. Perspective

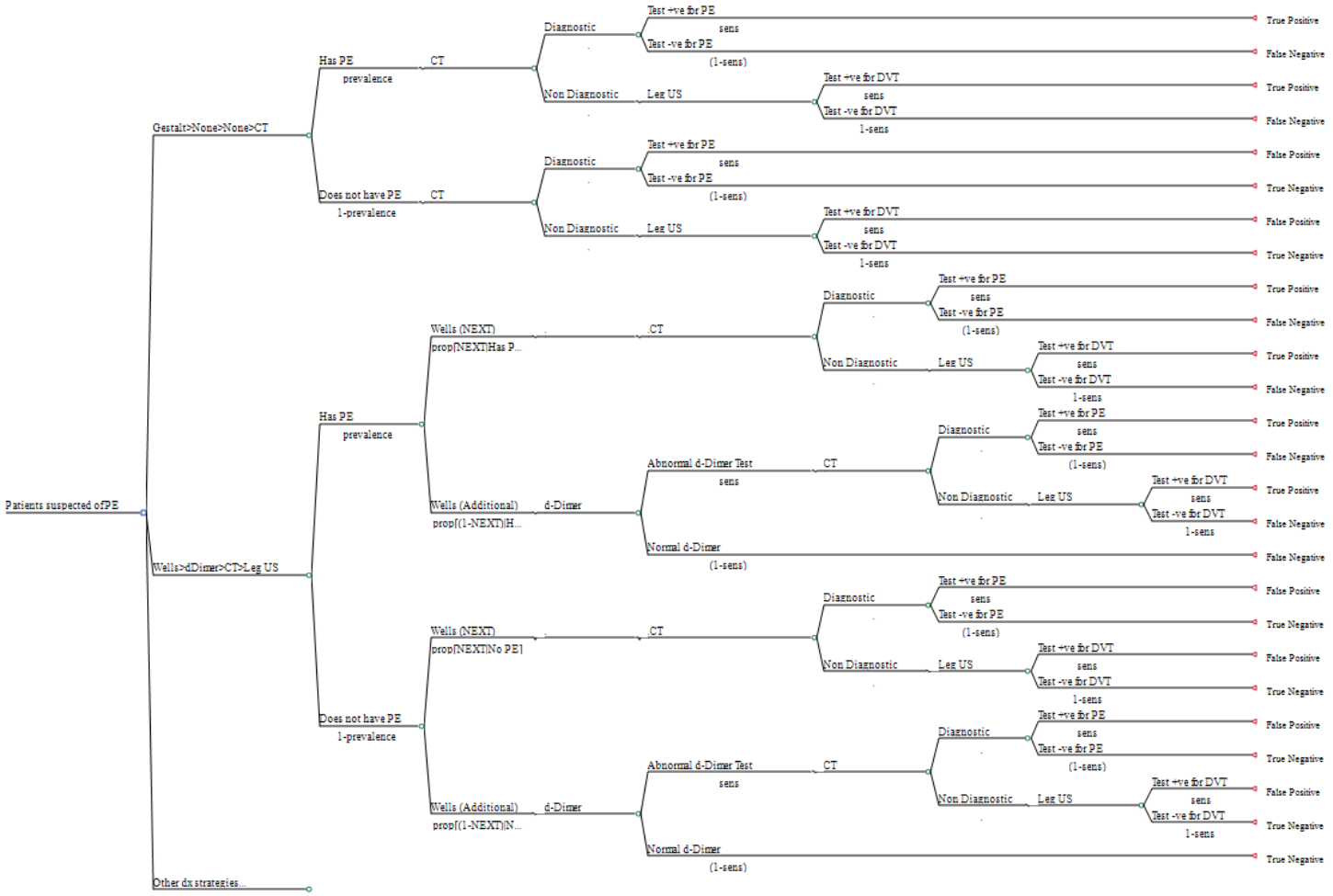
The perspective of a Canadian Ministry of Health was adopted, consistent with CADTH guidelines for the conduct of economic evaluations.[241] Accordingly, direct and indirect medical costs were captured, including the cost of laboratory and diagnostic tests, emergency visits, in-patient visits, and medical services.

6. Decision-Analytic Model

A decision-analytic hybrid model was constructed to examine the clinical outcomes and costs associated with the diagnostic management of patients suspected of acute PE. It entailed an upfront decision tree that captured the short-term screening outcomes and a downstream Markov model to capture the long-term outcomes following a correct or incorrect diagnosis. The clinical pathway and decision-analytic model were developed by reviewing existing clinical and economic literature, and the conceptualization of the model and its structure was subsequently validated by clinical experts from different medical specialties involved at different stages of the diagnostic process and clinical management of PE (e.g., radiology, emergency medicine).

Figure 23 illustrates the structure of the decision tree and presents two of the 57 diagnostic strategies evaluated in this review. The cohort of patients with suspected PE proceeds through the decision tree and, conditional on the diagnostic accuracy of upstream tests, this determines their progression through the next step of the diagnostic pathway, in terms of whether they will receive further downstream tests or whether a diagnosis or exclusion of PE can be reached. The sensitivity and specificity of each test and the test order impacts the proportion of correct diagnosis and misdiagnosis of PE.

Figure 23: Illustration of Decision Tree of Two of the 57 Diagnostic Strategies Modelled



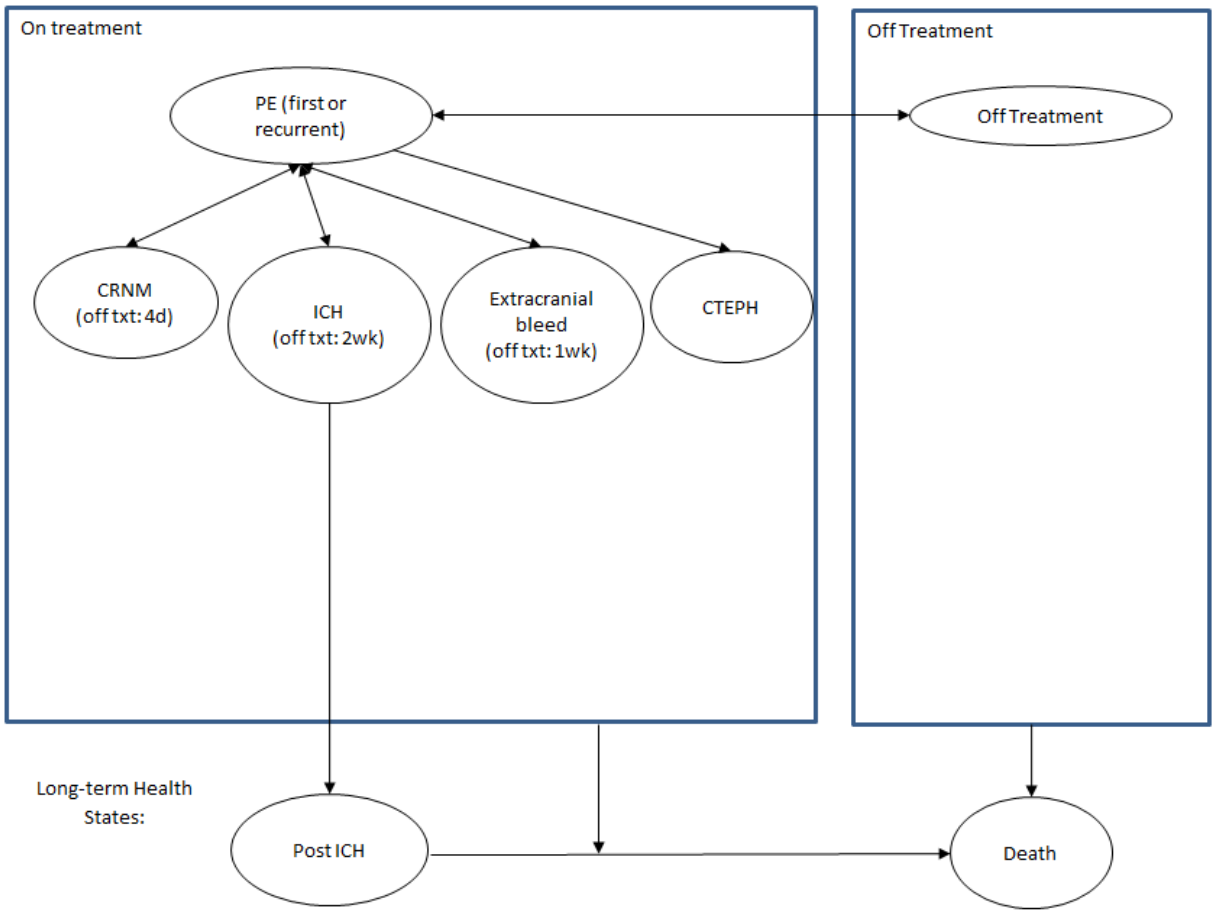
CT = computed tomography; DVT = deep vein thrombosis; PE = pulmonary embolism; sens = sensitivity; spec = specificity; US = ultrasound

Outcomes from the decision tree relating to diagnostic test performance (i.e., true-positive, false-positive, true-negative, false-negative) were then incorporated into the Markov cohort model. A recently published Markov model evaluated the cost-effectiveness of treatment for VTE in Canada. In this report, this model will be referred to as the original Markov model.[245] This was a lifetime model that followed patients presenting an index VTE as they cycled monthly through health states related to VTE and its treatment, including recurrent VTE, major bleeding (i.e., intracranial or extracranial bleeding), clinically relevant nonmajor bleeding, post-thrombotic syndrome, and chronic thromboembolic pulmonary hypertension (CTEPH). To more accurately reflect the scope of this project, the original Markov model was modified to focus on the natural history of PE solely (e.g., for instance, the probability that VTE is DVT was set to 0 in order to remove DVT) (Figure 24). Based on external validation, it was determined that the incidence of CTEPH was underestimated, as the model assumed that this complication could occur only following a recurrent PE, rather than during the index PE event. To better reflect disease prognosis and this project's scope, the original model was revised to permit the occurrence of this complication following both the index and recurrent PE event.

From the decision tree, patients classified as true-positives entered the previously described Markov treatment model. While on treatment, these patients were at risk of treatment-related complications but would also benefit from treatment due to a lowered risk of recurrent PE and PE-related mortality. Similar to the published treatment model, initial treatment upon diagnosis of the index PE event was modelled as a three-month course of anticoagulation, with recurrent PE handled by assuming lifetime anticoagulation therapy. Patients classified as true-negatives were modelled to reflect the general population (i.e., they do not receive treatment and are not at risk of PE-related morbidity and mortality). Patients classified as false-positive would have wrongly received treatment and were therefore at risk of experiencing treatment-related complications during the treatment period, resulting in negative impacts in utilities without any treatment-related benefits. Patients classified as false-negative, on the contrary, were modelled to have treatment withheld and were therefore at an increased risk of recurrent PE and PE-related mortality. Nonfatal PE recurrence (in the true-positive and false-negative arms) was assumed to be correctly diagnosed and managed.

Patients diagnosed with PE entered the "on treatment" state, while patients not diagnosed with PE enter the "off treatment" state (Figure 24). After each cycle, patients might move from one health state to the next, as indicated by the arrows, or remain in their previous state. Although not explicitly shown, all states could lead to death.

Figure 24: Conceptual Design of the Markov Component of the Economic Model



d = day; CRNM = clinically relevant nonmajor; CTEPH = chronic thromboembolic pulmonary hypertension; ICH = intracranial hemorrhage; PE = pulmonary embolism; txt = treatment; wk = week.
Adapted from CADTH, 2016.[245]

The decision-analytic model was constructed in Microsoft Excel.

7. Clinical Inputs

Diagnostic Inputs (for Decision Tree)

Inputs relating to diagnostic test accuracy and test performance were obtained from the clinical review, as described in Summary of Diagnostic Test Results and Appendix 23. There may be multiple thresholds to interpret a test, and, given the correlation between test sensitivity and specificity, a trade-off between the proportion of false-negative and false-positive results. In light of this, where data were available from the clinical review, different thresholds were tested separately as a unique diagnostic strategy.

For risk stratification, the diagnostic test accuracy data were based on the findings from pooling the clinical data, using a bivariate model that assumed perfect reference standards (Table 19). For some diagnostic tests, fewer than three clinical studies informed the pooled meta-analysis. In such instances, an external validation exercise was conducted, where

possible. The diagnostic test accuracy data from pooled studies and from individual studies were applied as inputs to the economic model to determine which scenario provided the predictions in terms of test outcomes (i.e., proportion of positive tests, proportion of negative tests, three-month risk of PE) closest to those reported in the published literature.

For diagnostic imaging, the clinical review provided both the sensitivity and specificity values according to a Bayesian HSROC latent-class model allowing for imperfect reference standards (Table 19). The HSROC curve defined the joint distribution between sensitivity and specificity to facilitate probabilistic analysis while preserving the correlation between these two parameters.

As the sensitivity and specificity values from the clinical review were based on the population of patients with definitive diagnostic test results, there remains a proportion of patients with nondiagnostic test results that had to be accounted for in the model. The proportion of nondiagnostic test results was based on pooling the rates reported in individual clinical study, as reported in the clinical review. Following advice from clinical experts, it was assumed that, in non–CT-based diagnostic management strategies, nonconfirmatory imaging results would be handled by offering patients CT or leg US. It was further assumed that this second imaging test would be confirmatory, given the low rates of nondiagnostic findings from CT scans. For CT-based diagnostic management strategies, feedback from the clinical experts suggested considerable variation in how a nonconfirmatory scan is handled. The reference case assumed patients received a repeat scan that would be confirmatory. However, sensitivity analyses were conducted to explore different approaches to handling a nonconfirmatory CT scans based on the feedback from clinical experts. One approach evaluated in sensitivity analysis was a blended strategy in which patients with low-to-moderate pretest probability of PE based on the CPR, for whom no diagnosis could be reached from rule-out tests, were not offered treatment, whereas high-risk patients were treated.

Table 19: Diagnostic Test Accuracy

		Point Estimates		HSROC Parameters (Standard Deviation)	Sources (Number of Studies)
		Sensitivity	Specificity		
Clinical Prediction Rules[a]	3-tier Wells rule	0.132	0.972	beta: -0.230 theta: –2.82 (0.37) alpha: 2.28 (0.27)	Pooled (5)[105]
	2-tier Wells rule	0.590	0.777	NA	Kabrhel et al., 2005[246]
	Revised Geneva score	0.113	0.981	NA	Chagnon et al., 2002[247]
	Gestalt (undefined)	0.883	0.446	beta: 0.214 theta: 0.60 (1.07) alpha: 1.90 (0.27)	Pooled (19)[26]
Rule-Out Test[a]	D-dimer (undefined methods, ELISA)	0.97	0.41	NA	Carrier et al., 2009[248]
	PERC	0.962	0.215	beta: 0.186 theta: 2.36 (0.39) alpha: 2.36 (0.001)	Pooled (12)[249]
Diagnostic Test Imaging	CT	0.973	0.987	beta: 0.104 theta: 0.04 (0.46) alpha: 4.54 (0.64)	Clinical review
	MRI	0.959	0.987	beta: 0.215 theta: 0.06 (0.42)	

		Point Estimates		HSROC Parameters (Standard Deviation)	Sources (Number of Studies)
		Sensitivity	Specificity		
				alpha: 4.26 (0.55)	
	Thoracic US	0.953	0.946	beta: –0.054 theta: –0.06 (0.47) alpha: 3.71 (0.71)	
	V/Q SPECT	0.974	0.9144	beta: –0.210 theta: –0.1773 (0.34) alpha: 3.61 (0.70)	
	V/Q planar scintigraphy	0.864	0.974	beta: 0.255 theta: 0.28 (0.30) alpha: 3.19 (0.56)	
	Leg US	0.410	0.960	beta: 0.013 theta: –1.84 (0.22) alpha: 2.95 (0.37)	Pooled (6)[33]
Proportion of Nondiagnostic Findings					
		Point Estimate		**95% CI**	**Sources**
CT		0.034		0.047 to 0.023	Clinical review
MRI		0.106		0.260 to 0.016	
Thoracic US		0.055[b]		Not computed	
V/Q SPECT		0.037		0.079 to 0.01	
V/Q planar scintigraphy		0.25		0.358 to 0.157	

CI = confidence interval; CT = computed tomography; ELISA = enzyme-linked immunosorbent assay; HSROC = hierarchical summary receiver operating characteristic; MRI = magnetic resonance imaging; NA = not applicable; PERC = pulmonary embolism rule-out criteria; SPECT = single-photon emission computed tomography; US = ultrasound; V/Q = ventilation/perfusion.

[a] For details, see Appendix 22.

[b] Based on one clinical study. The clinical review noted reporting issues within this single study.

Radiation Exposure

An argument in favour of a multi-step diagnostic pathway for PE that incorporates risk stratification and rule-out testing is that such a pathway can reduce radiation exposure. The expected radiation dose associated with each strategy was estimated based on a publication that provided a primer to emergency physicians on the radiation dose associated with different medical imaging tests. Table 20 presents the estimated range of radiation associated with each imaging modality. For each diagnostic strategy, the expected radiation dose (i.e., average radiation dose) was calculated by determining the proportion of patients who would undergo either CT and/or nuclear imaging modalities and factoring the estimated radiatin dose associated with the respective imaging modality.

Table 20: Radiation Exposure Associated With Each Diagnostic Test

Imaging Modality	Estimated Effective Dose of Radiation (mSv)	Reference
CT chest[a]	5.2 Range reported: 2.7 to 15	Kanal et al., 2017[250] Range from Jones et al., 2012[251] and Janbabanezhad et al., 2015[252]
Doppler US	0	Assumed
MRI	0	Assumed
Thoracic US	0	Assumed
V/Q[b]	2.2	Jones et al., 2012[251]
V/Q SPECT[b]	2.2	Assumed to be similar to V/Q

CT = computed tomography; MRI = magnetic resonance imaging; SPECT = single-photon emission computed tomography; US = ultrasound; V/Q = ventilation/perfusion.
[a] In pregnant patients, mean fetal dose from chest CT is estimated between 0.03 and 0.66 mGy.[253]
[b] In pregnant patients, mean fetal dose from V/Q-based tests is estimated between 0.32 and 0.74 mGy.[253]

Treatment Model (for Markov Model)

A detailed description relating to the clinical inputs of the treatment model have been published elsewhere.[245] Compared with the original Markov model, there were a few notable differences in this adaptation. Instead of applying a constant probability to death (i.e., 0.00267), Canadian age-specific mortality rates were incorporated as the baseline mortality rates in the revised model.[254] The decision problem for the original Markov model focused primarily on a VTE cohort, whereas the scope of this review was narrower, with an interest in patients with PE. As a result, baseline probabilities for VTE-related clinical events had to be revised to better reflect a PE-specific population. Differences in baseline probabilities between the original and re-adapted model are outlined in Table 21.

To link the diagnostic findings from the decision tree to the Markov treatment model, the original Markov model was revised to reflect the outcomes of those misdiagnosed and those without PE. Specifically, patients with false-positive results would enter the anticoagulant health state and were assumed to receive an initial course of treatment for three months. Their risks of experiencing a bleeding adverse event during this treatment period were increased to the same levels as true-positives, although their probability of a recurrent PE was set to zero. After treatment ended, the prognosis for these patients was modelled to be similar to the general population who do not have a PE diagnosis. Conversely, patients with false-negative results were at an increased risk of death and of recurrent PE in the first month because that treatment was withheld (Table 21). Thereafter, the prognosis for these patients in terms of mortality and recurrence risks was assumed to be similar to that for PE patients off anticoagulant treatment (i.e., risks were higher than a general population but lower than those with an incident PE). Patients with true-negative results were modelled to reflect a general Canadian population, with general Canadian mortality rates applied.

Table 21: Pulmonary Embolism–Specific Probabilities

Parameter		Value (Probabilistic)	References
Recurrent PE	On treatment		
	3-month probability of recurrent PE (short-term LMWH+VKA)[a]	0.017 (Beta: alpha = 14; beta = 811)	Quinlan et al., 2004[255]
	Annual probability of recurrent PE (lifetime LMWH+VKA)[b]	0.031 (Normal: mu = 0.031; sigma = 0.012)	Agnelli et al., 2003[256]
	Off treatment/ untreated		
	First month probability of recurrent PE	0.263 (Beta: alpha = 5; beta = 14)	Barritt et al., 1960[257]
	Annual probability of recurrent PE	0.041 (Normal: mu = 0.041; sigma = 0.009)	Agnelli et al., 2003[256]
Treatment-related bleeding	On treatment		
	3-month probability of major bleed (short-term LMWH+VKA)	0.014 (Beta: alpha = 14; beta = 1,009)	Quinlan et al., 2004[255]
	6-month probability of CRNM bleed (short-term LMWH+VKA)	0.082 (Beta: alpha = 1,111; beta = 12,452)	CADTH, 2016[245]
	Annual probability of major bleed (lifetime LMWH+VKA)	0.027 (Normal: mu = 0.012; sigma = 0.010)	Aujesky et al., 2005[258]
PE-related mortality[d]	On treatment		
	Case fatality rate, treated[c]	0.6 (Beta: alpha = 23,040; beta = 288,580)	Stein et al., 2002[259]
	Probability of death (short-term, month 2 to 3)	0.008 (Normal: mu = 0.008; sigma = 0.0005)	Wells et al., 2016[260]
	Off treatment		
	Case fatality rate, untreated[c]	0.263 (Beta: alpha = 5; beta = 14)	Barritt et al., 1960[257]

CRNM = clinically relevant nonmajor bleed; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; VKA = vitamin K antagonist.
[a] Applies for the first six months of the model.
[b] Applies from the seventh month onwards.
[c] Applied to the cycle of an incident PE.
[d] After PE, mortality rates return to the Canadian general population age-specific mortality rate.[254]

8. Utilities

Regardless of the diagnostic outcome, each health state in the Markov model was assigned a utility weight, adjusted to reflect the duration of that particular health state, with the value based on the original Markov model.[245] The utility impact was assumed to be one week in duration for major extracranial bleed, one month for acute PE, and permanent for major intracranial bleed and for CTEPH. Given that diagnosis of PE is rapid (i.e., in under a month), no utility weights were applied to the outcomes associated with the decision tree. Table 22 summarizes the utility values, and a more detailed description is available elsewhere.[245]

Some changes in utility weights were made from the original Markov model for this adaptation. Age-specific Canadian population utilities were used instead of applying a single utility score representing Canadian population norms for patients not experiencing an acute event or long-term consequences of a disease or treatment-related event. In addition, the utility values in the original model were reviewed to determine whether there were more suitable values since its publication. For instance, a consistent utility elicitation method for

health states is desirable, where possible. The majority of the utility values in the original model were determined through the standard gamble method, with the exception of post-intracranial bleed and CTEPH, which were obtained from a generic (i.e., EuroQoL 5-Dimensions questionnaire [EQ-5D]) and a disease-specific quality-of-life scale (i.e., Cambridge Pulmonary Hypertension Outcomes Review), respectively. In reviewing the literature, a utility weight for CTEPH based on the EQ-5D instrument was identified and deemed more suitable.[261]

Table 22: Utility Values Associated With Each Health State

Parameter Description	Description	Utility Value	Reference
Population norm	General population (n = 1,555); EQ-5D Canada	Age-specific utility value	Johnson et al., 2000[262]
PE EC bleed Major ICH	Lower extremity DVT or PE patients (n = 215); standard gamble Canada	0.75 (Beta: alpha = 161.25; beta = 53.75) 0.65 (Beta: alpha = 139.75; beta = 75.25) 0.15 (Beta: alpha = 32.25; beta = 182.75)	Hogg et al., 2013[263]
Post ICH	Population-based cohort (n = 2,425); EQ-5D UK	0.713 (Beta: alpha = 1,729.03; beta = 695.98)	Rivero-Arias et al., 2010[264]
CTEPH	CTEPH patients (n = 15); EQ-5D Spain	0.648 (Beta: alpha = 9.72; beta = 5.28)	Roman et al., 2013[261]
Death		0	Assumption

CTEPH = chronic thromboembolic pulmonary hypertension; DVT = deep vein thrombosis; EC = extracranial; EQ-5D = EuroQoL 5-Dimensions questionnaire; ICH = intracranial hemorrhage; PE = pulmonary embolism.

9. Costs

Costs are described in Table 23. Given the model's perspective (i.e., public health care payer), only direct medical costs were considered. Whenever possible, the most current Canadian cost estimates were used, with all prices reflecting the 2016/2017 Canadian dollar. As treatment and event costs were available in the original Markov model, these costs were reviewed to determine whether more recent prices were available. If 2016/2017 valuation was not available, prices were adjusted to 2016/2017 values using the health care component of the consumer price index inflation calculator from the Bank of Canada.[265] If Canadian costs were unavailable, costs were estimated from comparable health systems. Conversion of currency was conducted using the Bank of Canada currency converter.[266]

For resources with equal rates of utilization across all diagnostic strategies (i.e., initial physician examination), such costs were omitted from the analysis. Given that the symptoms of PE may be undifferentiated, the costs of other tests performed for differential diagnosis that are unrelated to PE (e.g., chest X-ray, ECG) were considered outside of the scope of the model.

Diagnostic Costs

Diagnostic costs included both the diagnostic tests and the physician's fee for interpretation of the test. The costs for diagnostic tests were taken from the Ontario Case Costing Initiative (2010/2011 fiscal year inflated to 2016 Canadian dollar values),[267] with the exception of the

cost of D-dimer, which came from a published Canadian paper.[268] Physician fees were obtained from the Ontario Schedule of Benefit for Physician Services.[269]

The clinical experts consulted in this project said that CT scans are interpreted immediately and, if a scan appears nondiagnostic, it is repeated during the same session. For the reference case, it was therefore assumed that the cost of CT in CT-based diagnostic strategies would be applied only once, even if the scan had to be performed more than once due to an initial nondiagnostic scan.

Table 23: Diagnostic Costs (2017 $)

Imaging Modality	Diagnostic Test Costs ($, Per Test)	Physician Interpretation ($)	Reference
CT	580 (Gamma: alpha = 4.35; beta = 133.24)	75.85	OCCI, OSB
Doppler US	585 (Gamma: alpha = 2.38; beta = 245.54)	17.30	OCCI, OSB
MRI	900 (Gamma: alpha = 1; beta = 900)	73.35	Canada Diagnostics; OSB
V/Q	581 (Gamma: alpha = 2.71; beta = 214.47)	219.55	OCCI, OSB
V/Q SPECT	864 (Gamma: alpha = 3.87; beta = 223.06)	322.80	OCCI, OSB

CT = computed tomography; MRI = magnetic resonance imaging; OCCI = Ontario Case Costing Initiative; OSB = Ontario Schedule of Benefits; SPECT = single-photon emission computed tomography; US = ultrasound; V/Q = ventilation/perfusion.

Treatment Costs

The treatment costs for patients with positive test results for PE included anticoagulant therapy (including drugs, laboratory tests for monitoring anticoagulant therapy, and physician fees). In alignment with the findings of a recent CADTH therapeutic review,[245] the most cost-effective treatment was selected for the reference-case analysis: initial parenteral anticoagulation (i.e., low-molecular-weight heparin [LMWH]) followed by at least three months of oral administration of vitamin K antagonists (VKAs) with LMWH, provided until systemic anticoagulation is achieved. Drug costs were determined using the Ontario Drug Benefit Formulary and based on recommended dosages.[270] No additional markup or dispensing fee was applied. VKA requires monitoring of international normalized ratio (INR) and dose titration. Laboratory tests for monitoring anticoagulant therapy were based on an existing published Markov model, and further details can be found elsewhere.[245]

Event Costs

Costs to manage PE and treatment-related complications were based on the original Markov model.[245] The cost of PE management reflected a weighted cost based on an assumption that 67% would be in an in-patient setting (i.e., average length of hospital stay of 7.8 days) while the remaining would be managed as an outpatient service.

10. Statistical Analysis and Sensitivity Analysis

The reference case reflects the probabilistic results based on 5,000 Monte Carlo simulations. The probabilistic results characterize the extent to which parameter uncertainty affects the cost-effectiveness estimates in the model. Standard distributional forms were taken to describe the probability distribution functions relating to input parameters: transition

probabilities and relative risks were characterized by beta and normal distributions, utility was characterized by beta distribution, and costs were characterized by gamma distributions. Where possible, DTA (i.e., sensitivity and specificity) was sampled by the joint distribution function described by the HSROC curve. For some of the diagnostic tests, it was not possible to define the joint distribution between sensitivity and specificity, given a lack of data (i.e., D-dimer, most CPRs with the exception of the three-tier Wells rule). This may result in greater certainty in the findings.

The incremental cost-utility ratio was calculated according to convention and, in most cases, the sequential ICUR was presented unless otherwise specified. Strategies that were dominated (i.e., another strategy has lower expected costs and higher expected QALYs) or extendedly dominated (i.e., at least one possible combination of two treatment strategies would be less costly and results in higher QALYs) were identified and did not inform the calculation of the efficiency frontier (the set of optimal strategies that, for varying costs, produce the highest health benefits). Results of the probabilistic analysis are presented on a cost-effectiveness acceptability curve, on which diagnostic pathways on the efficiency frontier are highlighted. This graph presents the probability that each treatment is optimal, given different willingness-to-pay values for an additional QALY gained. Interpretation of the economic findings was based on setting a willingness-to-pay threshold of $50,000 per QALY.

Sensitivity analyses were conducted to evaluate how much uncertainty in the model parameters (i.e., parameter uncertainty) and its assumptions (i.e., structural uncertainty) would affect the results. These include:

- Time horizon: The reference case presents the lifetime cost-effectiveness associated with different diagnostic strategies for PE. By selecting this time horizon, the focus was on lifetime implications of diagnosis. To explore the immediate short-term outcomes associated with different diagnostic strategies, a shorter model duration of three months was also explored. This was selected because it reflects the commonly selected time horizon used in economic models conducted for this topic to capture the immediate impact of diagnostic strategies.[232,233,236-240]
- Discount rate: The reference case selected the most recently recommended discount rate of 1.5%,[241] with sensitivity analyses conducted on the previously recommended discount rate of 5% and an undiscounted scenario (i.e., discount rate = 0%).[242]
- Risk of PE: In the reference case, the general population prevalence of PE was 0.15.[94] However, some patients are at increased risk of PE for reasons such asrecent surgery, hormonal contraception, or thrombophilia.[271] As many economic models of diagnostic testing are sensitive to the underlying risk of the disease, both higher and lower prevalence of PE were tested to evaluate the robustness of the model to this model input.
- Proportion of nondiagnostic findings for V/Q and MRI: While the reference case incorporated the pooled data for the proportion of nondiagnostic findings, the clinical review highlighted considerable heterogeneity in these pooled estimates for V/Q-based imaging techniques and MRI. Sensitivity analyses were conducted to explore an optimistic estimate that would favour these imaging modalities. For each, the smallest estimate reported in an individual study was selected.[121,138,182]
- Management of nondiagnostic findings: In the reference case, it was assumed that, if the initial CT was nondiagnostic, a second imaging procedure (CT or leg US) would be conducted. According to the clinical experts consulted as part of this review, an alternative approach in clinical practice would be to treat patients with high pretest risk of PE and nondiagnostic findings while withholding treatment in patients with low pretest risk of PE and nondiagnostic findings.

- Treatment duration for PE: According to most treatment guidelines for PE, the duration of treatment should be dictated by the nature of the event and the clinical context. Anticoagulation therapy is recommended for at least three months[244] and, in the therapeutic review that the long-term Markov model was adapted from, the duration of treatment with anticoagulation was evaluated at three months, six months, and lifelong. The reference case in this review assumed three months' treatment duration, with sensitivity analyses conducted for the other longer time horizons.
- Utilities from original model: As noted, the original Markov model applied a single utility score to healthy patients.[245] In the reference case, baseline utility values were based on age-specific utility values. A sensitivity analysis was conducted in which the utility values from the original Markov model were applied.
- Treatment by newer anticoagulant: The original Markov model for treatment for VTE found that the historical standard of care (LMWH with VKA) was the most likely cost-effective intervention under a willingness-to-pay threshold of $170,00 per QALY. This was therefore selected under the reference case. However, given interest in newer anticoagulation therapy, sensitivity analysis was conducted exploring apixaban as the anticoagulation regimen.

The clinical review reported subgroup effects of different diagnostic tests. Given the limited evidence, meta-analyses by subgroup could not be performed to evaluate potential heterogeneity and, similarly, the economic evaluation is constrained in terms of evaluating the cost-effectiveness of different subgroups. However, the clinical experts consulted as part of this review noted that leg US may be offered as an ancillary test before diagnostic imaging in pregnant patients as a means to avoid unnecessary radiation exposure, given that treatment of patients diagnosed with DVT is similar to treatment of those diagnosed with PE (i.e., initiation of anticoagulant therapy). As noted in the clinical review, PE, together with DVT, is considered a single disease entity (VTE). These conditions often co-occur. Thus, offering leg US prior to imaging as a potential diagnostic strategy was explored specifically in pregnant patients. It is important to note that the CPRs and rule-out tests have not been validated among pregnant patients, and the economic analysis assumed similar diagnostic test accuracy between pregnant and nonpregnant patients, which may not hold true upon further research in this area.

The implementation review did suggest that some patients may be contraindicated for CT. A subgroup analysis was therefore conducted, removing all CT-based strategies. Given that mortality differs by age, and the expected benefits of anticoagulation may differ based on the expected lifespan of patients, subgroup analysis were conducted by exploring different age groups.

An in-patient setting was evaluated, given that the reference case assumed a patient's initial contact with the health care system would be in an outpatient setting but 67% of patients are subsequently admitted to hospital.

Given concerns noted in the clinical review with regards to the pooled DTA data for thoracic US, an exploratory analysis was conducted incorporating this imaging modality to determine whether different conclusions could be reached if it were incorporated. The pooled HSROC curve and the pooled proportion of nondiagnostic findings from the clinical review were incorporated into the analysis. By including thoracic US as a potential imaging test for PE, an additional 30 diagnostic pathways of interest were included, resulting in a total of 150 diagnostic pathways.

11. Model Validation

The model structure and data inputs were presented to two Canadian clinical experts to ensure that the model, its parameters, and its assumptions reflected Canadian clinical practice and the available body of literature (i.e., face validity). Internal validity was assessed by ensuring that the mathematical calculations were performed correctly and were consistent with the model specification and that logical discrepancies were assessed by evaluating the model under hypothetical and extreme conditions. The model further underwent external technical peer review.

The long-term component of the Markov model was previously external validated.[245] However, given that the model was restructured for a different application, further external validation was conducted to ensure the revised model remained valid. Validation was done by comparing rates of recurrent PE and death reported in other independently published studies.[272,273] To externally validate the decision tree, the model's outputs in terms of diagnostic accuracy (i.e., true-positive, true-negative, false-positive, and false-negative) and short-term outcomes (i.e., three-month PE recurrence) was compared with diagnostic management studies identified in the clinical review.[107,108,114,116,274-279]

12. Model Assumptions

The reference case economic analysis was conducted under the following assumptions (Table 24).

Table 24: Assumptions Used to Populate the Economic Model (applied to all diagnostic strategies evaluated)

Assumption	Sensitivity Analysis Description
Base-case cohort represented patients 55 years of age, with 41% males and an underlying prevalence of 15.2%. It was further assumed that patients had no prior history of PE.	Varied prevalence of PE at both ends of the estimated range; subgroup analysis by age
Initial contact by patients with the health care system is in an outpatient setting.	Initial contact with the health care system in an in-patient setting.
Time horizon in the model was set as lifetime. In addition, discounting was set at 1.5% per annum for both costs and benefits.	Shorter 3-month time horizon was tested. Discounting was also tested at 0% and 5%.
Performance of a test does not depend on previous tests performed or on the prevalence of PE.	
The tests for nondiagnostic findings were assumed to provide confirmatory findings. For a repeat CT, it was assumed to be performed immediately and, if the preceding diagnostic test was a CT, only a single billing fee was applied.	Patients deemed at high-risk for PE would receive treatment; patients deemed at low-to-moderate risk would have treatment withheld.
Time between diagnosis and initiation of treatment was not explicitly modelled. In other words, the duration required to reach diagnosis was assumed to have no effect on patient prognosis.	
Anticoagulation therapy is initiated only after a diagnosis is complete.	
Treatment following an established diagnosis of PE involved LMWH with VKA.	Treatment entailed apixaban, a direct oral anticoagulant therapy. The regimen involved apixaban 10 mg b.i.d. in the first week followed by 5 mg b.i.d. thereafter.
Treatment was three months in duration. Recurrent PE would lead to indefinite anticoagulant therapy.	Following initial diagnosis of PE, patients would receive six months or lifetime anticoagulant therapy.
Patients with false-positive diagnosis and on treatment are assumed to be at the same risk of adverse bleeding events as those with PE	

Assumption	Sensitivity Analysis Description
who are on anticoagulant therapy.	
Treatment compliance was not explicitly captured in the model, and it was assumed that patients remained perfectly compliant with their treatment regimen.	
Patients with nonfatal recurrent PE initially classified as false-negative were assumed to receive a correct diagnosis upon recurrence and to initiate lifetime anticoagulant therapy.	

b.i.d. = twice daily; CT = computed tomography; LMWH = low molecular weight heparin; PE = pulmonary embolism; VKA = vitamin K antagonist.

Results

1. Validation

Before analyzing the results of the economic model, a series of external validation tests were conducted, comparing results with independent studies that had not informed the development of the economic model. Table 25 summarizes the key findings from this exercise.

Markov Model

Mortality rates reported in patients with PE differ considerably by study design. As summarized by Meyer et al.,[280] the risk of death at three to six months in patients with PE is below 5% in most RCTs evaluating therapeutic strategies, whereas, in cohort and registry studies, this can range from 10% to 15%, given the selective inclusion criteria imposed in therapeutic trials. As cohort and registry studies have fewer restrictions on study inclusion and the economic model is meant to reflect a general Canadian population, the model's predictions for mortality were compared with these clinical studies. At three months after diagnosis, the cumulative mortality rate in cohort and registry studies are reported to range from 5.07% to 10.3%.[272,273] The observed range may reflect differences in patient baseline characteristic (e.g., age, comorbidities). Lobo et al.[273] recruited patients with symptomatic acute PE without coexisting chronic lung disease or chronic heart failure while Pengo et al.[272] included first-time acute PE patients without pre-existing exertional dyspnea or pre-existing conditions that can cause nonthromboembolic pulmonary hypertension. The model predicted a three-month cumulative mortality of 7.87%. Over a 10-year period, the model predictions slightly underestimated mortality, although it remained within the reported 95% confidence interval (Table 24).[272]

In terms of other clinical outcomes, the model closely predicted the three-month cumulative incidence of several clinical events reported in Lobo et al.[273] (major bleeding: 1.39% [reported] versus 1.34% [predicted] and recurrent PE: 1.71% [reported] versus 1.62% [predicted]). However, Pengo et al.[272] reported recurrent PE at the same time period, and found incidence higher than our model's predictions (i.e., 4.9%; 95% CI, 1.9 to 7.9 [reported] versus 1.61% [predicted]). Over a longer duration, the model's predictions aligned closer to the reported rate.

Only one study reported on the incidence of CTEPH.[272] In using the original published model,[245] its prediction was found to be nearly 100-fold lower than the reported incidence. The rationale is partly explained by the model structure. The modelled disease pathway assumed patients develop CTEPH only upon recurrent PE whereas, in reality, CTEPH is a complication after PE regardless of whether PE is incident or recurrent. The Markov model structure was revised to reflect this, and, although this improved the model's predictions, the revised model underestimates CTEPH incidence (six months: 1.0%; 95% CI, 0.0 to 2.4,

versus 0.59%). As CTEPH is a relatively rare complication (probability after PE = 3.1%), no further changes were made to the model structure. Rather, extensive sensitivity analyses were conducted in which the incidence of CTEPH was changed to determine its impact on the robustness of the model.

Table 25: Comparison of Markov Model's Prediction on Disease Progression With Published Studies

Parameter	Study Description	Reported Results (95% CI)	Model Prediction
Major bleeding	Lobo et al., 2006[273] Registry of 4,145 patients Age NR; 43.0% males Setting: Spain Total follow-up: 3 months after hospital discharge	**Cumulative Incidence** 3 months: 1.39%	**Cumulative Incidence** 3 months: 1.34%
All-cause mortality		**Cumulative Mortality** 3 months: 5.07%	**Cumulative Mortality** 3 months: 7.86%
	Pengo et al., 2006[272] Case study involving 223 patients Age 60.8; 42.2% males (anticoagulant was minimum of 6 months and extended on an individualized decision) Setting: Italy Total follow-up: 10 years	**Cumulative Mortality** 3 months: 10.3% (6.3 to 14.4) 6 months: 12.5% (8.1 to 17) 1 year: 13.4% (8.9 to 17.9) 5 years: 20.1% (14.2 to 26) 10 years: 25.1% (14.2 to 36)	**Cumulative Mortality [in true positive cohort]** 3 months: 7.86% 6 months: 8.74% 1 year: 9.21% 5 years: 13.54% 10 years: 20.77%
CTEPH		**Cumulative Incidence** 6 months: 1.0% (0.0 to 2.4) 1 year: 3.1% (0.7 to 5.5) 2 years: 3.8% (1.1 to 6.5) No reports of CTEPH thereafter	**Cumulative Incidence** 6 months: 0.59% 1 year: 0.61% 2 years: 0.69% 10 years: 2.44%
Recurrent PE		**Cumulative Incidence** 3 months: 4.9% (1.9 to 7.9) 6 months: 6.5% (3.1 to 9.9) 1 year: 8.0% (4.2 to 11.8) 5 years: 22.1% (13.5 to 30.7) 10 years: 29.1% (16.9 to 41.3)	**Cumulative Incidence** 3 months: 1.61% 6 months: 3.15% 1 year: 5.26% 5 years: 18.21% 10 years: 28.94%
	Lobo et al., 2006[273]	**Cumulative Incidence** 3 months: 1.71%	**Cumulative Incidence:** 3 months: 1.93%

CI = confidence interval; CTEPH = chronic thromboembolic pulmonary hypertension; NR = not reported; PE = pulmonary embolism.

Decision Tree

As previously noted, the clinical review included diagnostic management studies. Given that these studies evaluated different diagnostic strategies, and no two studies evaluated the same diagnostic strategy, indirect comparison and network meta-analyses were not possible to compare across different diagnostic strategies. These clinical studies can, however, be useful to assess the accuracy of the predictions of the decision tree that incorporated, to the extent possible, pooled diagnostic test accuracy data (i.e., sensitivity, specificity).

In conducting these external validation exercises, three studies[107,108,116] provided sufficient details to validate each step of the diagnostic pathway. The remaining publications permitted

validation of one step or reported the findings at an aggregate level for the entire pathway (i.e., the total number of positive and total negative results). Overall, for diagnostic tools and imaging tests in which the clinical review provided robust meta-analytic DTA data (e.g., CT, V/Q, three-level Wells rule), the model predictions were found to align closely to each study's reported outcomes. However, the predictions were more divergent for diagnostic tools for which pooled sensitivity/specificity were based on fewer than three studies (e.g., two-level Wells rule, revised Geneva score, gestalt (< 20%)). Given this observation, when more than two clinical studies were available for a particular diagnostic tool, we compared the modelled prediction using both the pooled and unpooled DTA data from individual studies. Across multiple clinical studies, better model predictions were observed when the DTA was taken from Kabrhel et al.[246] for two-level Wells rule and by Chagnon et al.[247] for revised Geneva score. The diagnostic test accuracies from both these studies were therefore taken toward our reference case. As only one study provided gestalt (< 20%), we conducted the same exercise, and although Carrier et al. 2006[281] resulted in better predictions, the pooled analysis was selected for the reference case, with a sensitivity analyses conducted using this DTA reported by Carrier et al.

It is important to note that no clinical pathway studies involving PERC or MRI were identified that could be used to compare with the model predictions.

Table 26: Comparison of Decision Tree Prediction on Diagnostic Results Against Clinical Studies

Study	Pathway	Outcomes Reported	Model Prediction	
			Based on Pooled DTA	DTA From Single Source (If Applicable)
Righini et al., 2008[116a] Prevalence: 20.6%	Revised Geneva→ D-dimer→ leg US→ CT (n = 916)	Prediction positive (i.e., TP + FP): 189 Prediction negative (i.e., TN + FN): 722 3-month VTE risk: 0.28% (2/722) Low/Intermediate Geneva:	Prediction positive: 204 Prediction negative: 712 3-month VTE risk: 0.56%	Chagnon et al., 2002 Prediction positive: 203 Prediction negative: 713 3-month VTE risk: 0.53%
	Revised Geneva→ D-dimer→ CT (n = 903)	Prediction positive: 186 Prediction negative: 715 3-month VTE risk: 0.3% (2/673)	Prediction positive: 182 (176+6) Prediction negative: 721 (711+10) 3-month VTE risk: 0.65% (4.7)	Chagnon et al., 2002 Prediction positive: 181 Prediction negative: 721 3-month VTE risk: 0.67%
Perrier et al., 2005[114] Prevalence: 26%[b]	Geneva→D-dimer→leg US→ CT (n = 756) [Strategy 66 in model]	Prediction positive: 190 Prediction negative: 554 3-month VTE risk: 5/554 (0.9%)	Prediction positive: 206 (188+18) Prediction negative: 550 (542+8) 3-month VTE risk: 0.73% (4.04)	Chagnon et al., 2002 Prediction positive: 205 Prediction negative: 550 3-month VTE risk: 0.73%
Bosson et al., 2007[107 a] Prevalence: 20%	3-level Wells→ D-dimer→ leg US→V/Q (n = 997)	Prediction positive: 210 Prediction negative: 787 3-month VTE risk: 7/787 (0.9%)	Prediction positive: 212 Prediction negative: 785 3-month VTE risk: 1.06%	
Galipienzo et al.[108 a] Prevalence: 23.6% (95% CI, 18.2 to 29.6%)	[Dichotomized] Wells→ D-dimer→ CT (n = 241)	Predictive positive: 57 Predictive negative: 179 3-month VTE risk: 0	Predictive positive: 57 Predictive negative: 184 3-month VTE risk: 0.43%	Kabrhel et al., 2005 Predictive positive: 56 Predictive negative: 185 3-month VTE risk: 0.43%
Hendriksen et al., 2016[277] Prevalence: 12.04%	Gestalt (<20%) (n = 598)	Gestalt <20%: 196 Gestalt >20%: 402 TP: 66 TN: 189 FP: 336 FN: 7	Gestalt <20%: 144 Gestalt >20%: 454 TP: 64 TN:136 FP: 390 FN: 8	Carrier et al., 2009 Gestalt <20%: 211 Gestalt >20%: 387 TP: 62 TN: 201 FP: 325 FN: 10

Study	Pathway	Outcomes Reported	Model Prediction	
			Based on Pooled DTA	DTA From Single Source (If Applicable)
	[Dichotomized] Wells (n = 598)	Wells ≤ 4: 422 Wells >4: 176 TP: 52 TN: 401 FP: 124 FN: 21	Wells ≤ 4: 339 Wells >4: 259 TP: 52 TN: 319 FP: 207 FN: 19	Kabrhel et al., 2005 Wells ≤ 4: 439 Wells >4: 160 TP: 42 TN: 409 FP: 118 FN: 30
Di Marca et al., 2015[278] Prevalence: 21.6%	3-level Wells→ D-dimer→ CT (n = 102)	Wells, Low + Intermediate: 94 Wells, High: 8 *Probability of PE based on pretest results* High: 88% Intermediate/Low: 16%	Low + Intermediate: 97 (19+78) High: 5 (3+2) *Probability of PE based on pretest results* High: 55.5% Intermediate/Low: 19.2%	
	Revised Geneva → D-dimer→ CT (n = 102)	rGeneva, Low + Intermediate: 89 rGeneva, High: 13 *Probability of PE based on pretest results* High: 54% Intermediate/Low: 16.9%	rGeneva, Low + Intermediate: 96 rGeneva, High: 6 *Probability of PE based on pretest results* High: 57.7% Intermediate/Low: 18.8%	Chagnon et al., 2002 rGeneva, Low + Intermediate: 98 rGeneva, High: 4 *Probability of PE based on pretest results* High: 60.3% Intermediate/Low: 19.4%
Prevalence: 23.8%	3-level Wells→ D-dimer→ CT (n = 101)	Wells, Low + Intermediate: 92 Wells, High: 9 *Probability of PE based on pretest results* High: 100% Intermediate/Low: 16%	Low + Intermediate: 96 High: 5 *Probability of PE based on pretest results* High: 58.4% Intermediate/Low: 21.1%	
	Revised Geneva → D-dimer→ CT (n = 101)	rGeneva, Low + Intermediate: 85 rGeneva, High: 16 *Probability of PE based on pretest results* High: 56% Intermediate/Low: 17%	Low + Intermediate: 95 High: 6 *Probability of PE based on pretest results* High: 60.6% Intermediate/Low: 20.7%	Chagnon et al., 2002 Low + Intermediate: 96 High: 5 *Probability of PE based on pretest results* High: 63.1% Intermediate/Low: 21.4%

Study	Pathway	Outcomes Reported	Model Prediction	
			Based on Pooled DTA	DTA From Single Source (If Applicable)
Klok et al., 2008[279] Prevalence: 16%	3-level Wells (n = 300)	Low+Intermediate: 287 High:13	Low+Intermediate: 287 High:13	
	Revised Geneva (n = 300)	Low+Intermediate: 293 High: 7	Low+Intermediate: 284 High: 16	Chagnon et al., 2002 Low+Intermediate: 290 High: 10

CT = computed tomography; DTA = diagnostic test accuracy; FN = false-negative; FP = false-positive; PE = pulmonary embolism; rGeneva = revised Geneva; TN = true-negative; TP = true-positive; US = ultrasound; VTE = venous thrombus embolism.

[a] In these studies, each step of the diagnostic pathway could be performed between the model's predictions and the observed number.

[b] In this study, physicians could override Geneva score by clinical judgment.

2. Reference-case Findings

Cost-Utility Analysis

Lifetime probabilistic results of the reference-case analysis — displaying the diagnostic strategies that form the efficiency frontier — are presented in Table 27 and Figure 25, with disaggregated clinical outcomes and costs presented in Table 28 and Table 29, respectively. More detailed findings of all 57 diagnostic imaging strategies can be found in Appendix 27. Most non-CT strategies were ruled out by dominance (i.e., more expensive and provided worse clinical outcomes compared with another diagnostic strategy) or extended dominance (i.e., more expensive and provide worse clinical outcomes than a combination of two diagnostic strategies). This was expected, given that the clinical review suggested that CT had better diagnostic test accuracy compared with other imaging modalities, was associated with one of the lowest rates of nondiagnostic findings, and had the lowest technical costs.

Not providing patients suspected of PE with a diagnostic test formed the reference with which all diagnostic strategies were compared, as it was the least costly but also the least effective option. Five strategies provided better clinical outcomes but at greater costs (Table 27). All of the strategies included CT as the diagnostic imaging modality but differed in terms of the risk stratification performed. The diagnostic strategy with the lowest costs was revised Geneva score > PERC > D-dimer > CT > CT. Clinically, this strategy would involve providing revised Geneva score to all patients in whom PE is suspected to classify their risk. In those considered at low-to-moderate pretest probability of PE, PERC followed by D-dimer is used to rule out PE and, in those in whom PE could not be ruled out or in patients with high pretest probability of PE according to revised Geneva score, CT is offered. Further, in patients who have nondiagnostic findings following CT imaging, a repeat CT scan would be conducted (it was assumed a diagnostic decision can be made with the second scan).

Employing risk stratification was less costly than a corresponding strategy that involved only the diagnostic imaging modality. The use of systematic risk stratification can result in the avoidance of further diagnostic imaging in a proportion of the population (Table 28). For instance, PERC-based strategies were associated with the lowest expected costs and, consequently, lower ICUR values, as PE could be ruled out in patients with negative PERC results without incurring additional costs for imaging. D-dimer testing was present in the five diagnostic strategies, but on the lower end of the cost-effectiveness frontier. Only the strategy with the highest ICUR value, “all CT” (ICUR = $57,097 per QALY), did not include any risk stratification but resulted in all patients in whom PE was suspected proceeding to CT.

Therefore, upon ordering strategies by ascending ICUR values, a trade-off was observed between false-positive and false-negative findings. Diagnostic strategies with higher ICURs had fewer false-negative but more false-positive findings (Table 27). These findings reflect the implications of incorrectly missing a PE diagnosis (i.e., false-negative), as withholding treatment in patients with PE is associated with considerable morbidity and mortality consequences.

The largest difference in incremental costs between diagnostic strategies was observed in the short-term — arising from the cost of diagnosis and the cost of treatment during the three months after diagnosis. The incremental difference in QALYs among strategies was small. For instance, between the diagnostic strategy with the lowest expected costs (i.e., revised Geneva score > PERC > D-dimer > CT > CT) and the strategy with the highest

ICUR (i.e., all CT), the QALY difference was only 0.034, which can be interpreted as 12 additional days of perfect health. The small differences among strategies with respect to QALYs may reflect the small differences in the number of recurrent PE and CTEPH adverted and the number of adverse bleeding events (Table 28). Figure 25 presents the incremental cost-effectiveness plane highlighting, when factoring in parameter uncertainty, the diagnostic pathways that were most likely cost-effective across different willingness-to-pay values. It allows identification of the preferred strategy based on willingness to pay. At a willingness-to-pay threshold of $50,000 per QALY, the strategy of Wells rule (two-tier) > D-dimer > CT > CT was the most likely cost-effective diagnosis pathway (probability = 72.3%).

Cost-Effectiveness Analysis

Results, based on the incremental cost per life-years saved, are presented in Table 30. The findings were very similar to those in which QALYs were the clinical outcome.

Table 27: Lifetime Costs and QALYs of Different Diagnostic Strategies (Reference Case) — Sequential Incremental Cost-Utility Ratio

The 51 strategies that were dominated or extendedly dominated are not presented below.

Strategy				Diagnostic Test Accuracy				Costs ($)	QALYs	Incremental		ICUR ($/QALYs)
Risk Stratification		Dx Imaging	Test for Non-Dx Findings	TP	FP	TN	FN			Costs ($)	QALYs	
No imaging				0	0	0.848	0.152	2,997	16.8286	Reference		
Revised Geneva	PERC > D-dimer	CT	CT	0.133	0.039	0.809	0.018	3,937	17.4632	940	0.6346	1,481
Wells: 3 tier	PERC > D-dimer	CT	CT	0.134	0.040	0.809	0.018	3,945	17.4655	9	0.0023	3,706
Wells: 2 tier	PERC > D-dimer	CT	CT	0.137	0.047	0.801	0.014	4,073	17.4822	128	0.0167	7,661
Wells: 2 tier	D-dimer	CT	CT	0.139	0.054	0.794	0.013	4,183	17.4903	110	0.0081	13,556
None		CT	CT[†]	0.141	0.079	0.769	0.011	4,571	17.4971	388	0.0068	57,097

CT = computed tomography; Dx = diagnostic; FN = false-negative; FP = false-positive; ICUR = incremental cost-utility ratio; PERC = pulmonary embolism rule-out criteria; QALY = quality-adjusted life-year; TN = true-negative; TP = true positive.

[a] This diagnostic strategy is also referred throughout the report as “All CT”.

Table 28: Expected Clinical Outcomes — Diagnostic Strategies on the Efficiency Frontier

Strategy				Short-term		Long-term		
Risk Stratification		Dx Imaging	Test for Non-Dx Findings	Number of Patients Undergoing CT	Expected Effective Dose of Radiation (mSv)	Number of Recurrent PEs	Number of Adverse Bleeding Events	Number of CTEPH
No Imaging				0	0	0.180	0.072	0.027
Revised Geneva	PERC > D-dimer	CT	CT	0.56	3.04	0.143	0.044	0.020
Wells: 3 tier	PERC > D-dimer	CT	CT	0.57	3.07	0.143	0.044	0.020
Wells: 2 tier	PERC > D-dimer	CT	CT	0.66	3.54	0.142	0.044	0.020
Wells: 2 tier	D-dimer	CT	CT	0.73	3.93	0.142	0.043	0.019
None		CT	CT[a]	1	5.39	0.141	0.044	0.019

CT = computed tomography; CTEPH = chronic thromboembolic pulmonary hypertension; Dx = diagnostic; PE = pulmonary embolism; PERC = pulmonary embolism rule-out criteria.

[a] This diagnostic strategy is also referred throughout the report as “All CT”

Table 29: Expected Lifetime Costs in Selected Categories — Diagnostic Strategies on the Efficiency Frontier

Strategy				Diagnostic Costs ($)	Treatment and Management Costs ($)		Total Costs ($)
Risk Stratification		Dx Imaging	Test for Non-Dx Findings		First Three Months	Long-Term	
No Imaging				0	484	2,513	2,997
Revised Geneva	PERC > D-dimer	CT	CT	483	1,264	2,189	3,936
Wells: 3 tier	PERC > D-dimer	CT	CT	488	1,269	2,188	3,945
Wells: 2 tier	PERC > D-dimer	CT	CT	556	1,335	2,183	4,074
Wells: 2 tier	D-dimer	CT	CT	617	1,385	2,181	4,183
None		CT	CT[a]	824	1,557	2,189	4,570

CT = computed tomography; Dx = diagnostic; PERC = pulmonary embolism rule-out criteria.
[a] This diagnostic strategy is also referred throughout the report as "All CT"

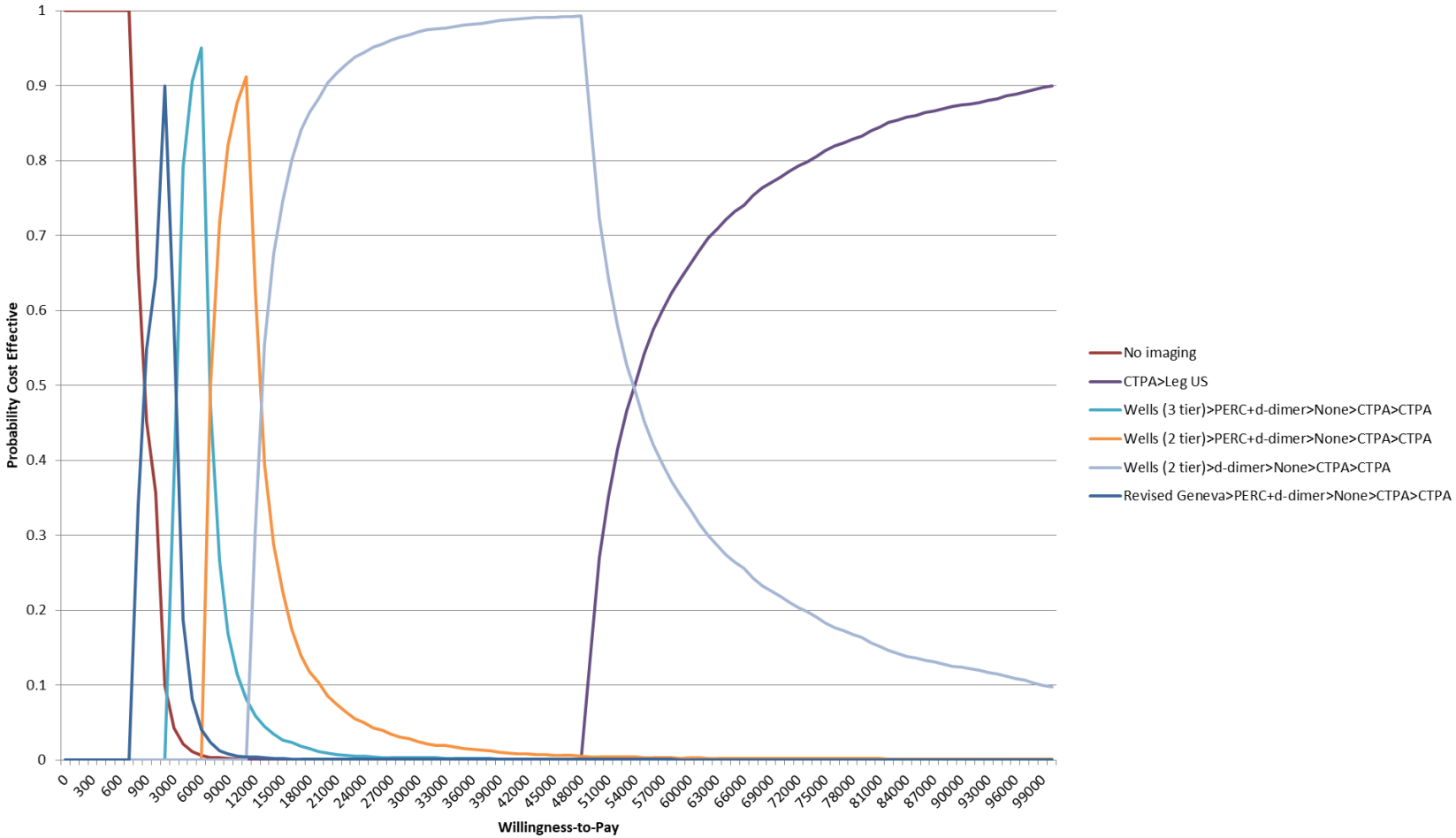
Table 30: Lifetime Costs and Life-Years of Different Diagnostic Strategies — Sequential Incremental Cost-Effectiveness Ratio

The 51 strategies that were dominated or extendedly dominated are not presented below.

Strategy				Diagnostic Test Accuracy				Costs ($)	Life Years	Incremental		ICER ($/LYs)
Risk stratification		Dx Imaging	Test for Non-Dx findings	TP	FP	TN	FN			Costs ($)	LYs	
No Imaging				0	0	0.848	0.152	2,997	21.690	Reference		
Revised Geneva	PERC > D-dimer	CT	CT	0.133	0.039	0.809	0.018	3,937	22.417	940	0.727	1,292
Wells: 3 tier	PERC > D-dimer	CT	CT	0.134	0.040	0.809	0.018	3,945	22.420	9	0.003	3,212
Wells: 2 tier	PERC > D-dimer	CT	CT	0.137	0.047	0.801	0.014	4,073	22.439	128	0.020	6,561
Wells: 2 tier	D-dimer	CT	CT	0.139	0.054	0.794	0.013	4,183	22.449	110	0.010	11,435
None		CT	CT[a]	0.141	0.079	0.769	0.011	4,571	22.458	388	0.009	42,513

CT = computed tomography; Dx = diagnostic; FN = false-negative; FP = false-positive; ICER = incremental cost-effectiveness ratio; LY = life-year; PERC = pulmonary embolism rule-out criteria; TN = true-negative; TP = true positive.
[a] This diagnostic strategy is also referred throughout the report as "All CT"

Figure 25: Cost-Effectiveness Acceptability Curve, Clinical Outcome Defined as QALYs (Reference Case)



CTPA = computed tomography pulmonary angiography; PERC = pulmonary embolism rule-out criteria.
At different willingness-to-pay thresholds (x-axis), the y-axis highlights the proportion of simulations (n = 5,000) in which a particular strategy emerged as cost-effective in the economic model.

3. Sensitivity Analysis

Selected results of the sensitivity analysis are shown in Table 31, Table 33, and Table 35. Sensitivity analyses with minimal impact on the ICUR or conclusion included the proportion of nondiagnostic findings in V/Q-based modalities and MRI, alternative approaches to the management of nondiagnostic CT findings, duration of anticoagulation therapy for the index PE event, and alternative therapies for anticoagulation (see Appendix 28).

Prevalence of PE: The model was sensitive to the population prevalence of PE, although the order of strategies on the cost-effectiveness frontier remained identical. With lower PE prevalence, the ICURs increased for most diagnostic strategies while, with higher PE prevalence, the ICURs decreased. This observation reflects the fact that there is less overall benefit from screening when fewer patients are expected to be at risk of PE, whereas the opposite holds true when more patients are at risk. At a willingness-to-pay threshold of $50,000 per QALY, Wells rule (two-tier) > D-dimer > CT > CT was the most likely cost-effective intervention (probability = 97.0%) in patients with lower disease prevalence (9%); while screening all patients with CT was considered cost-effective when the baseline prevalence in the population with suspected PE was higher (i.e., 28%). Having all patients with suspected PE proceed directly to CT was considered cost-effective if the willingness-to-pay threshold was $24,462 per QALY.

Patients contraindicated for CT (all other imaging modalities): In the reference-case analysis, all strategies on the cost-effectiveness frontier involved CT as the diagnostic imaging modality. However, as the implementation review notes, not all patients may be suitable for CT imaging. An analysis was therefore conducted to explore this scenario, by removing all strategies involving CT (Table 31). In terms of diagnostic imaging modalities, at willingness-to-pay threshold of $10,562 per QALY, MRI-based strategies emerged as cost-effective, while strategies involving V/Q SPECT were cost-effective at a willingness-to-pay threshold of $10,562 per QALY. This was expected, given the trade-off in costs (MRI, $383 versus V/Q SPECT, $932) and test sensitivity (MRI, 0.959 versus V/Q SPECT, 0.974). Similar to the reference case, rule-out test involving PERC and D-dimer were cost-effective at the lower end of the willingness-to-pay threshold ($23,438 per QALY), D-dimer alone was cost-effective when the willingness-to-pay threshold was between $23,438 per QALY and $113,187 per QALY, and applying a rule-out test would not be cost-effective beyond a willingness-to-pay of $113,187/QALY. As these patients were assumed to be contraindicated for CT, the diagnostic test following an initial nondiagnostic imaging test would always involve leg US. At a willingness to pay of $50,000 per QALY, Wells rule (two-tier) > D-dimer > V/Q SPECT > leg US was the most likely cost-effective strategy for the diagnosis of PE (probability = 95.2%) (Figure **26**) in patients who are unable to undergo CT imaging.

Patient contraindicated for CT (nuclear imaging modalities only): As noted in the clinical review, the use of MRI for the diagnosis of PE is not currently part of routine clinical practice. In existing clinical guidelines, for patients contraindicated for CT, nuclear imaging modalities are accepted as the imaging modality within the diagnostic algorithm. An analysis exploring only diagnostic strategies involving nuclear imaging (i.e., V/Q planar scintigraphy and V/Q SPECT) was therefore evaluated. The findings were similar to the reference case, although, for the diagnostic imaging modality, CT was replaced by V/Q SPECT, whereas, for the additional test to manage nondiagnostic findings, CT was replaced by leg US. At a willingness to pay of $50,000 per QALY, Wells rule (two-tier) > D-dimer > V/Q SPECT > leg

US was the most likely cost-effective strategy (probability = 95.4%) (Figure 26) in patients who are unable to undergo CT imaging.

Table 31: General Sensitivity Analyses Results (Diagnostic Strategies That Are Dominated Are Not Shown)

Strategy				ICUR ($/QALYs)
Risk Stratification		Dx Imaging	Test for Non-Dx Findings	
Prevalence of PE (9%)				
No imaging				Reference
Revised Geneva	PERC > D-dimer	CT	CT	2,290
Wells: 3 tier	PERC > D-dimer	CT	CT	6,592
Wells: 2 tier	PERC > D-dimer	CT	CT	14,254
Wells: 2 tier	D-dimer	CT	CT	25,904
None		CT	CT[a]	131,151
Prevalence of PE (28%)				
No imaging				Reference
Revised Geneva	PERC > D-dimer	CT	CT	876
Wells: 3 tier	PERC > D-dimer	CT	CT	1,875
Wells: 2 tier	PERC > D-dimer	CT	CT	3,718
Wells: 2 tier	D-dimer	CT	CT	6,471
None		CT	CT[a]	24,462
Patients contraindicated for CT (all other imaging modalities)				
No imaging				Reference
Revised Geneva	PERC > D-dimer	MRI	Leg US	2,025
Wells: 3 tier	PERC > D-dimer	MRI	Leg US	5,125
Wells: 3 tier	PERC > D-dimer	V/Q SPECT	Leg US	10,562
Wells: 2 tier	PERC > D-dimer	V/Q SPECT	Leg US	13,337
Wells: 2 tier	D-dimer	V/Q SPECT	Leg US	23,438
None		V/Q SPECT[b]	Leg US	113,187
Patients contraindicated for CT (nuclear imaging modalities only)				
No imaging				Reference
Revised Geneva	PERC > D-dimer	V/Q SPECT	Leg US	2,348
Wells: 3 tier	PERC > D-dimer	V/Q SPECT	Leg US	6,333
Wells: 2 tier	PERC > D-dimer	V/Q SPECT	Leg US	13,337
Wells: 2 tier	D-dimer	V/Q SPECT	Leg US	23,438
None		V/Q SPECT	Leg US	113,187

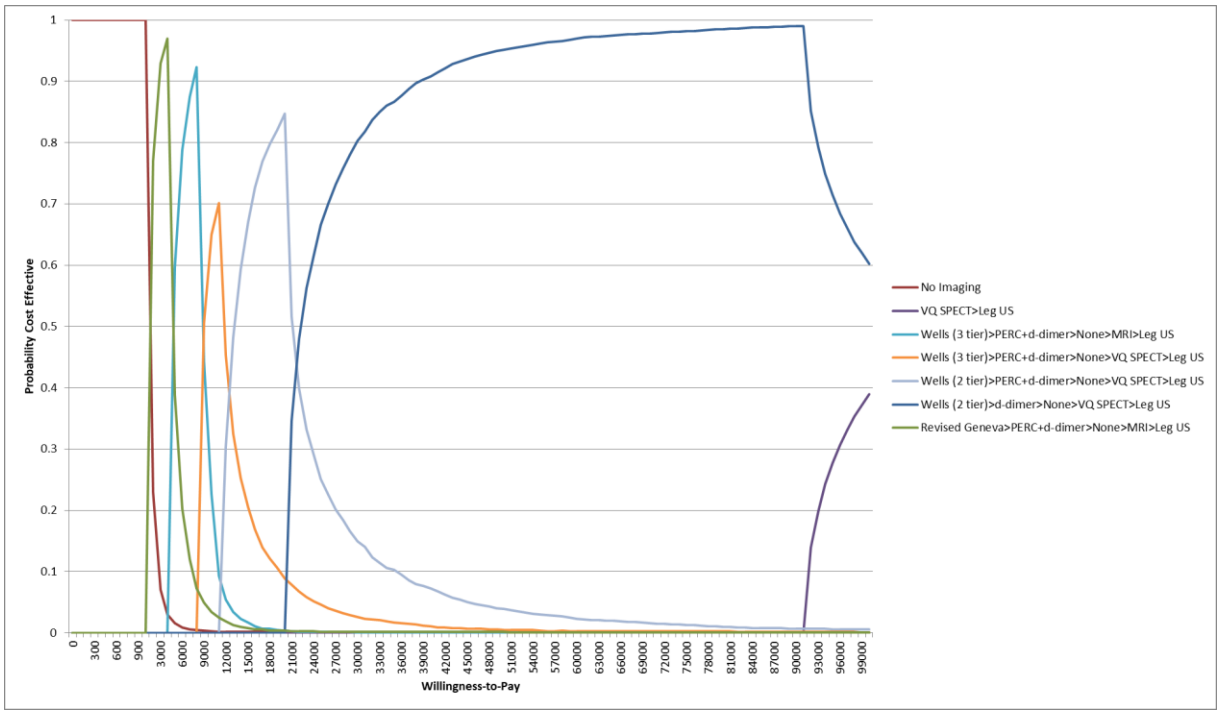
CT = computed tomography; Dx = diagnostic; ICUR = incremental cost-utility ratio; MRI = magnetic resonance imaging; PERC = pulmonary embolism rule-out criteria; QALY = quality-adjusted life-year; SPECT = single-photon emission computed tomography; US = ultrasound; V/Q = ventilation/perfusion.

[a] This diagnostic strategy is also referred throughout the report as "All CT."

[b] This strategy involves all patients undergoing V/Q SPECT if suspected of PE.

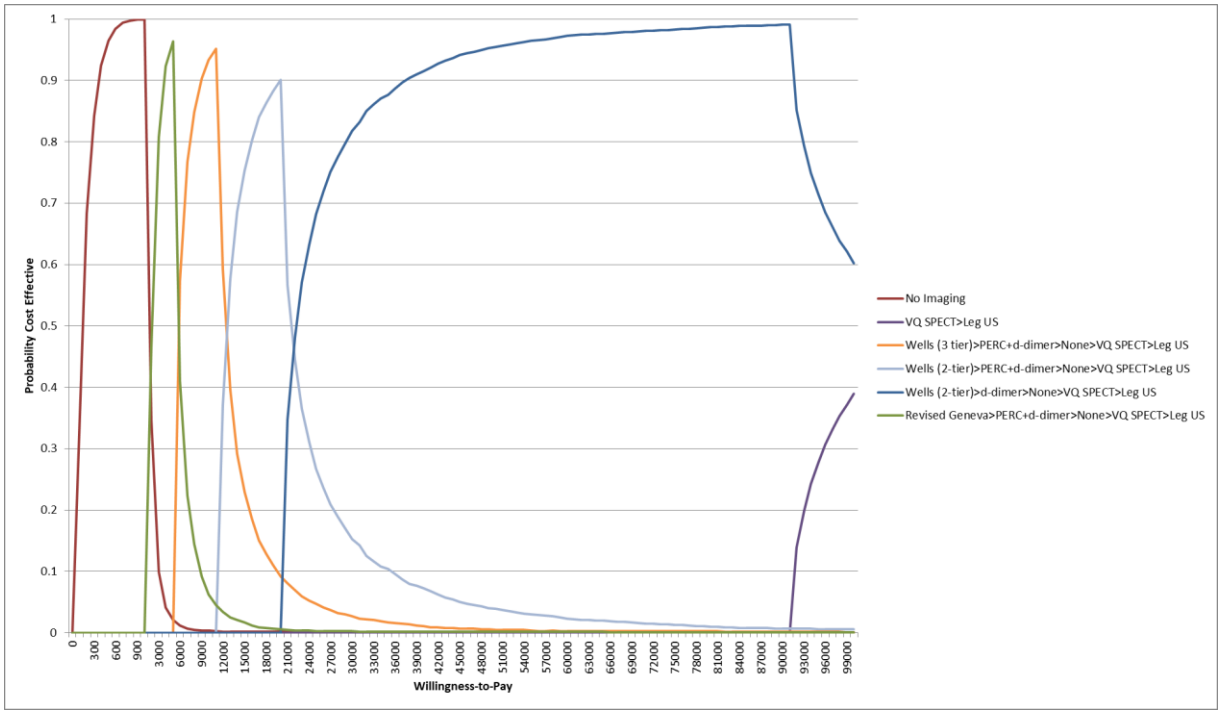
Figure 26: Cost-Effectiveness Acceptability Curve (Patients Contraindicated for Computed Tomography)

A. All Other Imaging Modalities



MRI = magnetic resonance imaging; PERC = pulmonary embolism rule-out criteria; SPECT = single-photon emission computed tomography; US = ultrasound; V/Q = ventilation/perfusion.

B. Nuclear Imaging Modalities Only



MRI = magnetic resonance imaging; PERC = pulmonary embolism rule-out criteria; SPECT = single-photon emission computed tomography; US = ultrasound; V/Q = ventilation/perfusion.

Scenario Analysis

Several structural and methodological uncertainties were evaluated. It was found that the model was not sensitive to the discount rate selected or to applying the utility values from the original Markov model[245] (see Appendix 28). The economic model was sensitive to the following structural or methodological uncertainties:

Different analytical time horizons: By truncating the time horizon to three months, as commonly observed in many economic evaluations in this topic area, not offering screening was the most likely cost-effective strategy when the willingness to pay was under $230,524 per QALY. Although the order of diagnostic strategies considered cost-effective remained mostly the same compared with the reference case (with the exception that the strategy involving imaging all patients with CT became dominated), the ICUR values associated with each diagnostic strategy were much higher (Table 32). These findings were expected, as much of the difference in incremental costs between strategies lay primarily in the cost of diagnosis, while the incremental benefits were lower, given that the overall benefits of imaging tend to be realized over a longer time period as a result of avoiding PE-related morbidity and mortality and of preventing recurrent PE.

Pooled DTA data: As noted in the external validation section, the inputs for DTA for revised Geneva score and Wells rule (two-tier) were selected based on comparing the outputs of the model's prediction with clinical studies of diagnostic pathways. As predicted, outcomes were better aligned when DTA data were taken from Kabrhel et al.[246] for Wells rule (two-tier) and

by Chagnon et al[247] for revised Geneva score. These were selected for the reference-case analyses. When using the pooled sensitivity and specificity values instead, one set of diagnostic strategy differed on the efficiency frontier. Wells rule (two-tier) > PERC > D-dimer > CT > CT was extendedly dominated, given that Wells rule (three-tier) > D-dimer > CT > CT appeared on the efficiency frontier (Table 32). Between a willingness-to-pay threshold of $8,393 per QALY to $17,391 per QALY, Wells rule (three-tier) > D-dimer > CT > CT was the most likely cost-effective diagnostic strategy. At a willingness-to-pay threshold of $50,000 per QALY, Wells rule (two-tier) > D-dimer > CT > CT remained the most likely cost-effective intervention (*P* = 98.5%).

Management of moderate pretest probability: Under the Wells rule (three-tier), patients can be divided into low, moderate, and high pretest risk of PE. In the reference case, it was assumed that patients deemed moderate risk would proceed with a rule-out test before undergoing diagnostic imaging. However, clinical practice does vary, as some clinicians may manage patients at moderate pretest risk in a similar fashion to those at high pretest risk — by proceeding directly to diagnostic imaging. A scenario was explored in which the sensitivity and specificity values of Wells rule (three-tier) reflected this alternative approach to clinical management for patients classified as moderate pretest risk. Under these circumstances, the order of Wells rule (three-tier) and Wells rule (two-tier) reversed, as Wells rule (two-tier) was found to be cost-effective from a willingness to pay of $7,173 to $26,266 per QALY, whereas Wells rule (three-tier) was the most likely cost-effective CPR, with a willingness to pay from $26,266 to $82,529 per QALY.

Table 32: Lifetime Results of Different Scenario Analyses

Strategy				ICUR ($/QALYs)
Risk Stratification		**Dx Imaging**	**Test for Non-Dx Findings**	
Time horizon: 3 months				
No imaging				Reference
Revised Geneva	PERC > D-dimer	CT	CT	230,524
Wells: 3 tier	PERC > D-dimer	CT	CT	538,925
Wells: 2 tier	PERC > D-dimer	CT	CT	1,305,785
Wells: 2 tier	D-dimer	CT	CT	3,379,345
Pooled diagnostic test accuracy (pooled sensitivity for 2-level Wells and revised Geneva)				
No imaging				Reference
Revised Geneva	PERC > D-dimer	CT	CT	1,489
Wells: 3 tier	PERC > D-dimer	CT	CT	1,543
Wells: 3 tier	D-dimer	CT	CT	8,393
Wells: 2 tier	D-dimer	CT	CT	17,391
None		CT	CT[a]	68,930
Management of patients with moderate pretest probabilities from Wells 3-tier (proceed directly to imaging) (sensitivity = 0.174; specificity = 0.968)				
No imaging				Reference
Revised Geneva	PERC > D-dimer	CT	CT	1,481
Wells: 2 tier	PERC > D-dimer	CT	CT	7,173
Wells: 2 tier	D-dimer	CT	CT	13,556
Wells: 3 tier	D-dimer	CT	CT	26,266
None		CT	CT[a]	82,529

CT = computed tomography; Dx = diagnostic; ICUR = incremental cost-utility ratio; PERC = pulmonary embolism rule-out criteria; QALY = quality-adjusted life-year.
[a] This diagnostic strategy is also referred throughout the report as "All CT."

Subgroup Analysis

Age: Under the assumption that the prevalence of PE remains constant at 15.2%, the findings for subgroups at the age of 40 or 70 remained similar to the reference case, although the ICURs were systematically higher (Table 33). Of note, a trend was observed when comparing the same strategies across these two age cohorts: younger patients incurred higher costs but also had a greater gain in QALY improvement. This reflects the impact of being diagnosed with PE, as it would lead to proper treatment with greater gains in QALYs — especially in those who are younger — but this is offset by the higher costs, as younger patients may require a longer duration of anticoagulation therapy, especially as the overall numbers of recurrent PE are higher.

The model did not explore the relationship between age and PE prevalence and how it may affect cost-effectiveness. Clinical studies have suggested that the prevalence of PE is linearly related to age, with older patients presenting a higher prevalence of PE.[282] Under these circumstances, it is suspected that the economic findings would remain even more similar to those observed in the reference case. As shown under Sensitivity Analyses, with higher disease prevalence, the diagnostic strategies have lowered ICURs. The interaction between the ICER increasing for age but decreasing for prevalence would likely mean that in factoring in age and PE prevalence, the model findings should remain robust.

Table 33: Lifetime Results, By Varied Patients' Age (Diagnostic Strategies That Are Dominated Are Not Shown)

Strategy				ICUR ($/QALYs)
Risk Stratification		Dx Imaging	Test for Non-Dx Findings	
Age: 40 years				
No imaging				Reference
Revised Geneva	PERC > D-dimer	CT	CT	2,495
Wells: 3 tier	PERC > D-dimer	CT	CT	7,319
Wells: 2 tier	PERC > D-dimer	CT	CT	15,500
Wells: 2 tier	D-dimer	CT	CT	26,563
None		CT	CT[a]	114,110
Age: 70 years				
No imaging				Reference
Revised Geneva	PERC > D-dimer	CT	CT	2,488
Wells: 3 tier	PERC > D-dimer	CT	CT	6,445
Wells: 2 tier	PERC > D-dimer	CT	CT	13,590
Wells: 2 tier	D-dimer	CT	CT	24,482
None		CT	CT[a]	117,071

CT = computed tomography; Dx = diagnostic; ICUR = incremental cost-utility ratio; PERC = pulmonary embolism rule-out criteria; QALY = quality-adjusted life-year.
[a] This diagnostic strategy is also referred throughout the report as "All CT."

Pregnant patients: According to the clinical experts consulted as part of this review, leg US may be a suitable ancillary test for patients who are pregnant as a means to avoid radiation exposure. Indeed, by assuming a cohort of pregnant patients 30 years of age under a lifetime-analysis time frame, leg US as an ancillary test became a cost-effective option before offering CT imaging if willingness-to-pay was greater than $7,882 per QALY. This would allow a subset of patients to be diagnosed with DVT and receive anticoagulant therapy, without needing to proceed with further imaging. Although this suggests there may be economic value in introducing leg US for pregnant patients, these findings should be interpreted with caution, as the analysis assumed identical DTA properties between pregnant and nonpregnant cohorts.

Table 34: Lifetime Results for Pregnant Patients (Diagnostic Strategies That Are Dominated Are Not Shown)

Strategy					ICUR ($/QALYs)
Risk Stratification		Ancillary Testing	Dx Imaging	Test for Non-Dx Findings	
No imaging					Reference
Revised Geneva	PERC > D-dimer	None	CT	Leg US	2,162
Wells: 3 tier	PERC > D-dimer	None	CT	Leg US	5,892
Wells: 3 tier	PERC > D-dimer	Leg US	CT	CT	7,882
Wells: 2 tier	PERC > D-dimer	Leg US	CT	CT	14,859
None		Leg US	CT	CT	65,076

CT = computed tomography; Dx = diagnostic; ICUR = incremental cost-utility ratio; PERC = pulmonary embolism rule-out criteria; QALY = quality-adjusted life-year; US = ultrasound.

In-patient setting: If PE were diagnosed and managed in an in-patient setting (changing the proportion of patients treated from 0.67 to 1.00 and the prevalence of PE to 20%), this would have a minimal impact compared with the reference-case analysis. The order of diagnostic strategies on the cost-effectiveness frontier remained the same, although the ICUR for each respective diagnostic strategy was reduced (Table 35).

Table 35: Lifetime Results From an In-Patient Setting (Diagnostic Strategies That Are Dominated Are Not Shown)

Strategy				Diagnostic Test Accuracy				Costs ($)	QALYs	Incremental		ICUR ($/QALYs)
Risk Stratification		Dx Imaging	Test for Non-Dx Findings	TP	FP	TN	FN			Costs ($)	QALYs	
No imaging				0	0	0.800	0.200	4,235	16.5105			Reference
Revised Geneva	PERC > D-dimer	CT	CT	0.176	0.037	0.763	0.024	5,599	17.3238	1,364	0.8134	1,677
Wells: 3 tier	PERC > D-dimer	CT	CT	0.176	0.037	0.763	0.024	5,610	17.3268	11	0.0030	3,561
Wells: 2 tier	PERC > D-dimer	CT	CT	0.181	0.045	0.755	0.019	5,759	17.3484	149	0.0215	6,907
Wells: 2 tier	D-dimer	CT	CT	0.183	0.051	0.749	0.017	5,883	17.3589	124	0.0105	11,793
None		CT	CT[a]	0.186	0.074	0.726	0.014	6,312	17.3681	429	0.0092	46,664

CT = computed tomography; Dx = diagnostic; FN = false-negative; FP = false-positive; ICUR = incremental cost-utility ratio; PERC = pulmonary embolism rule-out criteria; QALY = quality-adjusted life-year; TN = true-negative; TP = true positive.
[a] This diagnostic strategy is also referred throughout the report as "All CT."

4. Exploratory Analysis

As noted in the clinical and implementation review, thoracic US is not used widespread outside of an intensive care setting. By adding the 14 potential thoracic US-based strategies, the cost-effectiveness findings remained identical to the reference-case findings. There were multiple interwoven factors that resulted in this finding. First, the clinical review highlighted that the DTA (i.e., sensitivity and specificity) of CT was superior to thoracic US. In addition, the proportion of nondiagnostic findings were lower with CT than thoracic US (mean proportion = 0.034 [CT] versus. 0.055 [thoracic US]). Second, the cost of performing CT was lower than that of thoracic US. Combined, this resulted in the observation that the economic findings remain constant, even after adding thoracic US strategies.

Summary of Findings

Over a lifetime time frame, based on the economic model, a small difference in health benefits (QALYs and life years gained) was estimated between different diagnostic strategies for PE. The rank order of strategies, by increasing ICUR (Table 27), can be explained by the properties of each test in terms of diagnostic performance and costs. For instance, employing risk stratification and rule-out tests was less costly than a corresponding strategy involving only the diagnostic imaging modality, as risk stratification and rule-out tests can result in avoiding further diagnostic imaging in a proportion of the population. However, in the proportion of the population who in fact have an incident PE, avoidance of imaging is not optimal, as it may lead to misdiagnosis (i.e., false-negative results). A trade-off emerged between false-positive and false-negative results, as diagnostic strategies with higher ICURs had fewer false-negative results but were associated with more false-positive findings that would lead to unnecessary anticoagulant therapy. These findings were not

surprising, given the implicit trade-off between sensitivity and specificity within each diagnostic test and the morbidity and mortality implications of incorrectly missing a PE diagnosis. The economic analysis was based primarily on procedure costs and physician billings from the province of Ontario. Although these costs do vary by provinces, the findings that CT imaging was the dominant imaging modality should hold constant, so long as the cost of performing CT is lower than the cost to perform other imaging modalities.

At a willingness-to-pay of $50,000 per QALY, the diagnostic strategy involving Wells rule (two-tier) > D-dimer > CT > CT was found to be the most likely cost-effective strategy (probability = 72.3%) (Table 27, Figure 25). This strategy would be cost-effective at a willingness to pay ranging from $13,556 per QALY to $57,097 per QALY. Clinically, this entails employing the Wells rule (two-tier) to determine the pretest PE risk in all patients with suspected PE. In those deemed at low risk (i.e., Wells rule score 4 or lower), D-dimer is offered to rule out PE and, of those in whom PE could not be ruled out by D-dimer or in patients with high pretest probability of PE (i.e., Wells rule score greater than 4), CT is employed as the diagnostic imaging modality to reach a conclusive diagnosis. A repeat CT is performed, if necessary, in cases with nondiagnostic findings, and the model assumed that the second CT would enable clinicians to reach a diagnosis.

The efficiency frontier was comprised of only CT-based strategies. This was not unexpected: the clinical review highlighted that CT was associated with greater sensitivity and specificity than other imaging modalities and, according to the fee schedules, CT has the lowest cost compared with other imaging modalities. The emergence of CT-based strategies on the efficiency frontier is important when understanding the economic results in the context of rural and remote communities. The Canadian Medical Imaging Inventory[42] has highlighted that, in rural and remote areas, CT is the most common modality across Canada. As a result, no further exploration of rural and remote settings was performed, given that the imaging modality most likely cost-effective was also the most readily accessible one in these communities.

With increasing willingness to pay, the analysis found that a strategy of offering all patients CT imaging had an ICER of $57,097 per QALY. Although this strategy may appear attractive if willingness to pay for an incremental gain in QALY is greater than $57,094, it is important to note that this strategy goes against the Canadian ”Choosing Wisely” statements and general principles of keeping radiation exposure as low as reasonably achievable. Caution is required in interpreting this finding, given that the economic analysis did not consider capacity constraints explicitly. It assumed that there would be unlimited availability of CT testing to diagnose patients with suspected PE in a timely fashion and did not evaluate the potential impacts of waiting for access to imaging on a patient’s clinical outcomes. However, as the clinical and implementation review notes, the value of conducting risk stratification lies partly in capacity considerations, by reducing the number of patients requiring imaging and, thus, preventing a long wait list of patients requiring imaging.

The economic results were found to be sensitive to the analysis time horizon, the prevalence of PE, and the management of patients with moderate pretest probability of PE based on the Wells criteria. These parameters had a more pronounced impact on cost-effectiveness, given its influence on shifting the costs and benefits of diagnosing and treating PE. For instance, in truncating the analysis to three months, as is commonly done in most economic evaluation in this area,[232,233,236-240] the initial cost of diagnosis is more prominent compared with the long-term benefit of anticoagulation therapy to reduce PE recurrence. With a lower prevalence of PE, the cost-effectiveness increased, as there is less benefit from more costly

screening, as fewer cases would be identified. The opposite argument can be applied when the prevalence of PE is suspected to be higher, as more intense, and thus more costly, screening strategies become more preferred (i.e., lower ICUR), given that the cost and clinical impact of missing a diagnosis of PE become greater.

Patient Perspectives and Experiences

Study Design

A rapid review of the published qualitative literature was conducted to gain an understanding of patients', family members', and nonclinical caregivers' perspectives and experiences of the process of undergoing diagnosis for acute PE.

Research Questions

The research questions were developed in response to the policy issues and in consultation with subject and content matter experts. As is typical in qualitative research, the questions were refined in an iterative process through the course of the review to respond to the quantity and nature of relevant published literature. The goal was to provide a relevant response to the policy concern based on the available qualitative literature. The first research question, listed below, focuses on the experience of diagnostic processes for PE as well as experiences with the technologies of interest. Following an initial literature search, it was deemed there was insufficient literature to answer the stated question, and so an additional research question, and corresponding literature search, was added to broaden the focus to the experiences of diagnosis in any setting, including the emergency department, for any condition.

1. What are the experiences with the diagnostic process from the perspective of those who have undergone testing for acute PE, in any setting, including the emergency department, from the perspective of patients, their family members, and nonclinical caregivers?
2. What are the experiences with diagnostic imaging for any reason and in any setting, including the emergency department, from the perspective of patients, their family members, and/or their nonclinical caregivers?

Methods

Literature Search Methods

The literature search was performed by an information specialist, using a search strategy peer-reviewed according to the PRESS checklist — an evidence-based checklist for the peer review of electronic search strategies.[79]

Patient experiences information was identified by searching the following bibliographic databases: MEDLINE (1946–), with in-process records and daily updates, via Ovid; Embase (1974–) via Ovid; PsycINFO (1967–) via Ovid; CINAHL (1981–) via EBSCO; PubMed; and Scopus. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH terms, and keywords. The main search concept was medical imaging modalities and terms related to patient experiences, perspectives, beliefs, and values. Methodological filters were applied to limit retrieval qualitative studies. Retrieval was limited to documents published since January 1, 2006. Results were limited to English- or French-language publications. Conference abstracts were excluded from the search results. The detailed strategy can be found in Appendix 1.

The search was completed on December 14, 2016. Regular alerts were established to update the search until the publication of the final report. Regular search updates were

performed on databases that do not provide alert services. A supplemental search was conducted on December 16, 2016 for qualitative studies on anticoagulant drugs.

Grey literature (literature that is not commercially published) was identified by searching sources identified in the Grey Matters checklist (https://www.cadth.ca/grey-matters), which includes the websites of clinical trial registries, regulatory agencies, Health Technology Assessment agencies, clinical guideline repositories, and professional associations. Google and other Internet search engines were used to search for additional Web-based materials.

Eligibility Criteria

All English- and French-language reports of studies of any qualitative design that describe the perspectives of adults who 1) have undergone testing for acute pulmonary embolism; 2) have experience with diagnostic imaging technologies for any reason and in any setting, including the emergency department, were eligible for this review. We were also interested in reports describing related perspectives and experiences of family members and other nonclinical caregivers. To be eligible, studies must have explored or assessed the perspectives of patients and caregivers directly rather than indirectly, for example, through another person. Studies that assessed only clinician perspectives were excluded. The following types of publications were also excluded: theses and dissertations, data presented in abstract form only, book chapters, editorials, and letters to the editor. Typically, in quantitative syntheses, only primary studies are included to avoid the issue of double-counting or giving undue weight to one set of study findings. As double-counting is less of an issue in qualitative research, in which the analytical focus is interpretive rather than aggregative, individual studies that have already been included in systematic reviews remain eligible for inclusion in our review. The eligibility criteria are listed in Table 36 below.

Table 36: Eligibility Criteria

Population	Adults (≥ 18 years), and their nonclinical caregivers (e.g., partners and family members), who have either: • undergone testing for suspected acute PE using any diagnostic strategy OR • experienced diagnostic imaging technologies for any reason and in any setting, including the emergency department
Intervention	Any pathway used for diagnosing acute PE (e.g., Wells, D-dimer, imaging) or any imaging technologies including CT technologies, MRI technologies, V/Q-based technologies, PET/CT, thoracic ultrasound
Comparator	No comparator necessary
Outcomes	Experiences of benefits and harms; expectations versus actual experiences; outcomes of importance to patients and caregivers; value of outcomes from the perspective of patients and caregivers; any other outcome of importance to patients and caregivers that might emerge from the literature
Study Designs	Systematic reviews of qualitative studies of any design, primary qualitative studies of any design, and the qualitative component of mixed methods studies

CT = computed tomography; MRI = magnetic resonance imaging; PE = pulmonary embolism; PET = positron emission tomography; V/Q = ventilation/perfusion.

Screening and Selecting Studies for Inclusion

One reviewer screened citations identified through the literature search. In the first level of screening, titles and abstracts were reviewed, and the full text of potentially relevant articles was retrieved and assessed for inclusion by the same reviewer. The final selection of full-text articles was based on the eligibility criteria in Table 36.

Critical Appraisal of Individual Studies

The included primary qualitative studies were critically appraised by one reviewer using the Critical Appraisal Skills Programme (CASP) Qualitative Checklist[283] as a guide. Systematic reviews of qualitative studies were appraised using the CASP Systematic Review Checklist. Summary scores were not calculated for the included studies; rather, the results of the quality-assessment process are reported narratively and summarized to highlight the strengths and limitations of each study. Quality assessment was not used as a basis for excluding any studies deemed to be of low quality.

Data Collection and Extraction

From each eligible article, descriptive data were extracted by one reviewer into a standardized electronic form developed a priori. Descriptive data included such items as first author, article title, study objectives, participant characteristics, and study design. Further, result statements from all eligible articles relevant to the research question were captured for analysis, or coded, using NVivo qualitative data analysis software (QSR International Pty Ltd. Version 11,2015).

Data Analysis

Descriptive Analysis

A descriptive analysis was performed to characterize the included studies in terms of important study and patient characteristics (e.g., sample size, inclusion criteria). Study and patient characteristics are summarized in tables and accompanied by a narrative description.

Thematic Analysis

A thematic analysis was conducted by a single reviewer using NVivo 11.3.2. To begin, the data were coded line by line for meaning and content, starting with an a priori list of codes that was developed based on the research questions. The start list included, for example, harms and benefits of testing and expected outcomes of testing. During the coding process, other codes that were not on the start list emerged from the data and were included, for example, to capture the personal emotional experience of the diagnostic imaging process. When new codes emerged, all data were recoded to search for further instances of the meaning captured by that code.

Once all data were coded, the codes were organized into related areas to construct descriptive themes. In this process, the reviewer looked for similarities and differences among codes and grouped together similar codes. Once descriptive themes were identified, the reviewer wrote a summary of the results across the studies organized by each theme. A group discussion then took place, involving other researchers with experience in qualitative research, to review and discuss the emergent themes and identify further analytic ideas.

Preliminary results were presented to the CADTH Health Technology Expert Review Panel (HTERP), in a manner similar to peer debriefing. This impartial, multidisciplinary panel helped to raise new and relevant areas to consider in the final analysis. For example, the panel discussed the challenge of using a shared decision-making model or obtaining informed consent, given the urgent circumstances when diagnosing PE. Also, the finding that some patients preferred to have emotional support from another person during the imaging process led to a discussion of the perspectives of health care providers on the feasibility of implementing routines that would meet the emotional and information needs of patients and their family members. The panel also questioned the strength of the link between the reported results and the original research questions, following which, the data were revisited to assess the credibility of the results, and subsequent revisions were made to increase the clarity of those linkages.

The results presented below represent a synthesis that remains close to the original results of the included studies, with minimal interpretation.

Summary of Evidence

Quantity of Research Available

A total of 1,891 citations were identified in the literature search. Following screening of titles and abstracts by one reviewer, 1,858 citations were excluded, and 34 potentially relevant articles from the electronic search were retrieved for full-text review. Of these potentially relevant articles, 27 were excluded, as they did not fit the study criteria, and the remaining seven were selected for inclusion in this report. All seven studies are relevant to the second research question.[284-290] No eligible studies were identified that addressed the first research question. The study selection process is presented in a PRISMA flow chart (Appendix 29).

Summary of Study Characteristics

Study Design

Seven studies of various designs were included as relevant to this report (Appendix 30). One was a systematic literature review,[289] two used a phenomenological design,[287,290] while four did not report a study design[284-286,288] and appeared to follow a descriptive approach with no theoretical orientation.

Place and Time of Studies

The systematic review was conducted in Australia,[289] while three primary studies were conducted in Sweden,[284,287,290] two in the UK,[285,286] and one in the US.[288] Two studies were published in 2014[284,286] and one study each in 2015,[288] 2013,[287] 2012,[285] 2011,[289] and 2006.[290]

Patient Population

A range of patient populations and experiences with diagnostic imaging technologies were covered in the studies included in this review. One study included women and their partners who had experienced a near-miss event in childbirth (defined as “severe maternal illnesses which, without urgent medical attention, would have led to a mother’s death”).[286] Of the 35 women included in this study, five women had experienced a PE. Three studies included adults who presented at the MRI department to undergo a scan where the head was to be fully inside the tunnel.[284,287,290] One study included adults who had undergone a SPECT-CT

examination,[285] and another study included adults who were diagnosed with colorectal, breast, testicular, thoracic, and lung cancers, and who underwent diagnostic imaging examinations that involved the use of ionizing radiation.[288] The systematic review included literature describing the patient experience of high-technology imaging.[289]

Types of Technologies

Three studies included patients who underwent MRI,[284,287,290] one included individuals who had undergone SPECT-CT,[285] and one study explored perspectives on a range of strategies to diagnose cancer, including X-ray, CT, PET mammography, and MRI.[288] The study including women who experienced near-miss events in childbirth did not report the types of technologies used in their diagnosis.[286] The focus of the systematic review was on high-technology imaging, including MRI, CT, PET, and SPECT; however, each of the five included studies focused on either MRI or CT.[289]

Summary of Critical Appraisal

Overall, studies included in this report are of moderate to high quality. There are, however, a few exceptions, described later. All studies were well conducted and demonstrated congruence between the research methods and objectives. A summary of the strengths and limitations is included below, and details are available in Appendix 31.

Primary Studies

Each of the six included primary studies provided a clear statement of the research objectives or purpose, and all study objectives fit well with a qualitative inquiry and synthesis. Four studies did not report a study design, although they appeared to follow a qualitative descriptive design, which was appropriate for the descriptive intentions of the study.[284-286,288] Two primary studies described using a phenomenological approach, thereby applying a stronger theoretical orientation to guide data collection, analysis, and interpretation.[287,290]

Three of the six primary studies identified using a purposive sampling strategy,[286-288] which is appropriate for qualitative research of all designs. No mention, however, was made within any primary study report regarding data saturation. It is therefore unclear whether the final samples could represent the diversity of participants' experiences. The final three primary studies[284,285,290] made no mention of a particular sampling strategy; however, one did report including men and women of different ages and with different experiences of their MRI scans.[290] This description therefore appears to follow a maximum variation strategy, which is appropriate to ensure that a broad range of experiences can be represented.

Both focus groups and interviews were used across the included primary studies. Four studies described using semi-structured interviews,[284-287] and one used focus groups and an interview guide.[288] In each case, the approach allowed a consistent set of topics to be raised with all individual and focus group participants. One study used unstructured interviews to allow the issues experienced by participants to emerge.[290] Three studies reported that the interviews were conducted by a researcher; however, none of the studies discussed how rapport was built with the participants, thus making it unclear whether a rapport was built at all. [286,287,290] The five studies that used interviews as their data-collection method, identified using content analysis,[284,285] a systematic text-condensation approach,[287] a qualitative interpretive approach,[286] and a hermeneutic phenomenological analysis[290] to analyze their data. The study using focus groups described an iterative, thematic, textual-analysis

process, which allowed for the emergence of inductive themes.[288] All six studies described strategies to enhance rigour; these primarily focused on reliability in coding, including coding by more than one researcher and consensus meetings among the researchers with regard to the final code list.[284-288,290]

Reflexivity refers to the process of systematically reflecting and collecting data throughout the research process to determine the potential effect of the researcher on the data collected and analyzed. It is important to consider reflexivity, as it is aimed at the threat to the confirmability of qualitative research results. One of the six primary studies detailed the researchers' backgrounds and efforts to put aside personal beliefs during data collection and analysis,[284] while the remaining five were silent on the issue.[285-288,290] Further, the same study included a discussion of the relationship between the researcher and the participants, and the researcher and the topic,[284] while, again, the remaining five were silent.[285-288,290]

Systematic Review

There was one systematic review that met the eligibility criteria for this review.[289] The authors of this review outlined a clear objective for their study that is well suited to a systematic review of primary qualitative research studies. The research question falls clearly from the objective, and the eligibility criteria are congruent with each. A comprehensive literature search was conducted that included both grey and published literature, with no date limits. The search was, however, limited to articles published in the English language, which means relevant studies published in other languages would not have been identified. Quality appraisal of all included studies was conducted using the Joanna Briggs Institute–Qualitative Assessment and Review Instrument (JBI-QARI) tool and was conducted independently by two reviewers, which enhanced the reliability of the assessments. It is unclear, however, whether citation screening and study identification were conducted by more than one reviewer, which raises the potential for some studies to be inappropriately classified. Similarly, it is unclear whether data extraction and analysis involved more than one reviewer. In particular, for data synthesis, involving more than one reviewer would help to ensure reliability in coding and ultimately credibility in the emergent synthesis. A detailed list of 11 synthesized results are presented, however, alongside all 127 result statements that were extracted from the primary study reports, which allows for an assessment of the comprehensiveness of the synthesized results. Based on this assessment, it appears that the emergent synthesis dependably reflects the primary study results. An important limitation of this review is the authors' failure to speak to any efforts seeking to enhance rigour within the review process. For example, no description was provided of the researchers' background and their relationship to the topic, and no other attempts were made to remain reflexive and aware of their influence on data collection, synthesis, or interpretation. Similarly, no mention was made of team meetings or peer debriefing, or the maintenance of an audit trail. While it is unclear whether strategies to enhance rigour were not conducted or simply not reported, it remains possible that the synthesis lacks credibility as a result.

Results

Perceived Benefits and Risks of Diagnostic Imaging

All but one of the studies included participants who spoke to the perceived benefits of a range of diagnostic imaging techniques.[284,285,287-290] In one study, some participants even tied their lives to these technologies stating "I might not be here [without that CT scan]" or "I owe my life to an X-ray" (p. 5).[288]

In most cases, however, benefits were articulated in terms of the technology's noninvasive potential to peer within[288] and deliver images capable of mapping out current or prospective health concerns. Strand et al.[284] point to one individual who could find nothing positive about their experience with an MRI scan for neoplasm metastases in their spine, aside from it offering the potential to "get help and know what can be done" (p. 194). Whether the resulting images indicated a positive or negative diagnosis, this ability to "know" was often perceived as valuable in and of itself,[287] so much so that several individuals indicated that reminding themselves of this potential helped to mitigate varied levels of discomfort experienced during their actual examination.[284,287,288,290]

While these perceived benefits of imaging technologies tended to be discussed more often than risks, Thornton et al.'s[288] study with individuals navigating cancer care from a variety of perspectives (i.e., lung cancer screening, chemotherapy for stage IV colorectal carcinoma, thoracic cancer survivorship) also explored perceptions of risk. The cumulative ionizing radiation risks of repeated CT scans during chemotherapy treatments, the potential for kidney damage from intravenous contrast material, or safety concerns about excretion of radioactive tracers weighed heavily.[288] For some individuals in Nightingale et al.'s study on experiences with cardiac SPECT-CT, perceptions of risks emanated from an association of terms like "nuclear" with "atom bombs."[285] Nonetheless, for both studies, individuals expressed that the value of imaging strategies far outweighed any long-term risks of ionizing radiation.[285,288]

Experience of Diagnostic Testing

The primary themes to emerge from the literature regarding patient or partner experience with diagnostic imaging were identified as "threats to self-control," "the importance of family or staff," the importance of "clear and honest communication," and "long-term psychological effects." While perceived benefits and risks of undergoing imaging revolved around the post-examination experience, this section focuses much more on "heat-of-the-moment" experience. As individual interviews for all of the primary studies (except Hinton et al.[286]) occurred on the same day as examination, it is possible to understand them as presenting a visceral glimpse into what it could be like on the examining table.

Threat to Self-Control

Some patients stated that the experience of undergoing diagnostic imaging examinations challenged their self-control and their ability to manage the situation.[287,289,290] Patients attributed this feeling of loss of control to being isolated, confined, and dependent on others, and they also reported a loss of control over their thoughts and reactions.[289,290] In one study, outpatients undergoing an MRI indicated that this feeling of loss of control started before even coming into the MRI department.[290] Some stated that the sight of the MRI machine (often noted as one of the more claustrophobia-provoking imaging technologies due to the elongated and narrow tunnel) triggered the feeling. One participant described feeling calm

before the scan, but that the procedure triggered stressful memories of being buried in a previous accident, which was unexpected.[290] One author reported that the variation in experiences highlights the need for individualized support to manage feelings of threats to self-control.[290]

While no specific imaging technologies are discussed in Hinton et al.'s study on near-miss events or "severe life-threatening obstetric complications" during childbirth [286] the pregnant patient's partners likewise described feeling out of control watching their partner in the emergency situation. Unable to help on their own and feeling powerless, these partners often described the experience as shocking and distressing.[286] Because of the nature of the emergency situation, partners also described feeling excluded by the health care team as the team worked to save the patient.[286]

Importance of Support from Family or Staff

Similar to the way in which the spatial confines of these technologies had the ability to pull at one's sense of self-control, several individuals indicated feeling unmoored from reality both during and leading up to their examination. Whether causing the perception of time to slow[285,287] or ushering the individual to "another world,"[290] the unfamiliarity of the setting could increase anxiety or fear for some people. In an extreme example, Tornqvist et al. noted some individuals associated their MRI scan with being in a coffin or "lying almost as for cremation"(p. 957).[290] Perhaps little more than a passing comment, by drawing upon these spaces reserved for dead and inert bodies as a means of explanation, some participants seem to signal a form of isolation or reality separated from the living.

In order to be drawn back, several individuals spoke to the importance of knowing someone was sharing this space with them.[284,285,287,290] Again in Tornqvist et al., reminiscing on his own experience, one participant said, "My wife is there with me now. I can feel her hand on my leg, and then I know there is someone, she is there. It's an enormous support" (p. 958).[290] By simply laying a hand on her husband's leg, this woman was able to pull him back and help him remain calm. For others, radiographers tended to play the role of anchor. Whether counting down remaining time aloud,[285] providing an emergency buzzer in case the participant needed to prematurely end the exam,[284,287,289,290] or simply reminding the participant that they were there,[290] radiographers could act as mediators between reality and the individual.

Another form of support, this one before the actual examination, took the form of spending time customizing the experience for each participant. Individuals in Strand et al.'s study note this customizability as valuable due to the potentially painful positions required in MRI scanning for potential neoplasm metastasis in the spine.[284] By providing pillows or thicker mattresses to suit individual needs, radiographers were able to add a certain level of humanity to such a surreal experience.

Support appears to enable patients to relax during the procedure and increase their feeling of control over the situation.[290] There also appears to be a link between threat to self-control and the need for support; those feeling a greater threat to self-control were more likely to need support from others, and conversely the availability of support could improve the ability to cope.[290]

For some families who had experienced near-misses in childbirth, the pregnant patient's partners similarly acknowledged the importance of family and staff support.[286] One husband, telling the story of his family's near-miss, recounted the empathy shown by a staff member after their daughter had been delivered. As he held his daughter and wife who was "down for

the count," he remembered the way in which the anesthetist "put her arm around [me] and she was stroking [my wife's] hair as well" (p.5)[286] Although unable to completely resolve the partner's feelings of powerlessness or distress throughout the imaging and intervention processes (as discussed in the previous section), showing a keen awareness of these feelings was experienced as both appreciated and calming.

Clear, honest communication from medical staff was highly valued by patients and their partners.

Support could also come in the form of clinicians or radiographers taking time to talk about the examination before the actual procedure.[285,287-289] While patients in Carlsson and Carlsson's study reported being satisfied with the written information they received regarding their upcoming MRI scan, the same patients emphasized the importance of reviewing this information in person, as several realized, once undergoing the examination, that they had not fully understood the written information.[287]

Nightingale et al.[285] similarly report that patients appreciated pre-appointment conversations with their radiologists. For those patients who were quite anxious to even attend the imaging procedure, this background and being on a first-name basis with the radiographers was beneficial.

The synthesized findings from the systematic review by Munn and Jordan[289] indicate that being aware of what to expect during a MRI scan (i.e., the sound during MRI and invasive aspects of the scan) helped patients to deal with the anxiety they experience during the test. Where participants reported receiving information from their health care providers, some also indicated being dissatisfied with it and turning to self-directed Internet searches for further information.[288,289] In particular, participants in the systematic review[289] as well as a further primary study[288] expressed a desire for information regarding the availability of different diagnostic imaging options and the risks and benefits associated with each.

Several participants in the study by Thornton et al.[288] reported benefit–risk discussions about ionizing radiation from medical imaging as rare and seldom initiated by clinicians. While some indicated this would be a valuable conversation, perceptions of the importance seemed to vary, based on stage of illness and personal feelings toward imaging technologies. For instance, patients with advanced-stage cancer reported preferring to leave all decision-making responsibility about imaging tests to their physician during active phases of therapy, whereas others had low interest in shared decision-making processes when they understood the importance of an imaging test.[288] Several participants indicated a lesser need for discussion of the benefits and risks of diagnostic imaging because they had trust and the confidence that their physician or hospital would protect them by using the best imaging equipment and protocols.[288]

Although, in each study, patients expressed the need for clear communication and information, the circumstances or local format of the imaging procedures may prevent optimal communication or shared decision-making. Variation in hospital or clinic procedures, and the circumstances of the suspected PE, could account for why some patients felt satisfied and others did not.

Although the partners of women facing imaging for near-misses understood that it was an emergency situation and information needed to be moved along quickly, sometimes without their knowledge, they explained that having clear and honest communication from the health care professionals made a difference in their experience.[286] For instance, one partner

recalled walking into the intensive care unit where his wife was and thinking that she was dead for an hour before being told that she was on life support and would be fine.[286]

Long-Term Emotional Effects

Psychological distress, including anxiety, uncertainty, dread, and fear that lasted until the results of the scan were known, was also expressed in two studies.[288,289] In Hinton et al.'s study on near-miss events in childbirth, many of the partners and patients were interviewed several years after the emergency experience, and some reported suffering from posttraumatic stress disorder as a result of their overall experience. Others explained they were unable to re-visit the past experience through recollections with their family members or clinician.[286]

Summary of Findings

Of those individual experiences explored within the studies included in this review, several spoke to the ways in which the power of these diagnostic technologies to map out both current and prospective health concerns helped to mitigate various levels of discomfort felt throughout their respective exam. Nonetheless, however powerful this prognostic potential "to know" may be, many participants still framed their experience in terms of their concerns with self-control, isolation, and lack of preparation.

Self-control could be placed under threat at any point throughout the imaging process. Whether beginning somewhere during the move toward the imaging room or rising and falling throughout the actual examination, these feelings of powerlessness could heighten levels of anxiety or discomfort for both patients and their caregivers (or partners). At times, this discomfort could be expressed through metaphors related to death, dying, or other forms of extreme alienation. More than merely signalling a basic sense of isolation, the use of these extreme metaphors seems to indicate feelings of disconnection or unmooring from reality.

With that in mind, physical reminders of the presence of loved ones or more verbal or visual reminders of a radiographer's presence could serve as anchors throughout the imaging process and help alleviate related concerns. Similarly, although potentially irrelevant to the emergency department diagnostic process for PE, clear lines of communication between individual and clinicians before the examination could help to alleviate these concerns. While reading material was noted as helpful when preparing for an upcoming scan, many participants felt that spending time with a clinician before undergoing the actual examination would provide a greater level of comfort.

Implementation Issues

This section addressed the following research question:

Research Question 7: What are the issues associated with implementing the optimal use of diagnostic strategies, including imaging, for acute PE in adults in urban, rural, and remote settings?

Methods

Data Collection

Survey

A survey was developed to provide information and context on this topic, and conducted as part of a CADTH Environmental Scan.[291] The objectives of the Environmental Scan were to identify current practice related to diagnostic strategies for PE in Canada; identify which tests, scans, and tools are available across Canadian jurisdictions and settings (i.e., urban, rural, and remote health care centres) to diagnose PE; and identify challenges and enablers to the diagnosis of PE, including relevant implementation issues in Canada. The survey (Appendix 32) consisted of 13 questions that were close-ended (single or multiple responses) or open-ended in nature. The final survey was distributed via email to potential respondents.

Potential survey respondents (e.g., clinicians, directors of diagnostic imaging, medical directors, hospital department heads) were identified by CADTH Liaison Officers, through professional and clinical networks, or through referrals by other respondents. The survey was pilot-tested by a clinical expert on the project and was administered to potential respondents in January 2017.

Expert Interview

To supplement the findings of the survey and the literature search, an interview with a clinical expert in the field of emergency medicine was conducted. This interview centred on the expert's views of the approach to diagnosing PE, including challenges to diagnosis and the Canadian context. A semi-structured interview approach was used. Interview questions related to the general approach to diagnosing PE, challenges and supports to the diagnosis of PE, and gaps in the literature.

Literature Search

A targeted literature search was conducted to identify information on issues relevant to implementation of diagnostic strategies for PE in Canada.

Search Strategy

The literature search was performed by an information specialist, using a search strategy peer-reviewed according to the PRESS checklist — an evidence-based checklist for the peer review of electronic search strategies.[79]

Implementation issues information was identified through targeted literature searches of the following bibliographic databases: MEDLINE (1946–), with in-process records and daily updates, via Ovid; Embase (1974–) via Ovid; CINAHL (1981–) via EBSCO; Scopus; and PubMed. The search strategy comprised both controlled vocabulary, such as the National

Library of Medicine's MeSH terms, and keywords. The main search concepts were medical imaging, pulmonary embolism, and Canada, and key terms for implementation issues. No methodological filters were applied to limit retrieval by study design. Retrieval was limited to documents published since January 1, 2006. Results were limited to English- and French-language publications. The detailed strategy can be found in Appendix 1.

The search was completed on October 7, 2016. Regular alerts were established to update the search until the publication of the final report. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching sources identified in the *Grey Matters* checklist (https://www.cadth.ca/grey-matters), which includes the websites of clinical trial registries, regulatory agencies, HTA agencies, clinical guideline repositories, and professional associations. Google and other Internet search engines were used to search for additional Web-based materials.

Screening and Selecting Articles for Inclusion

One reviewer included English- and French-language reports that described implementation and context issues, including barriers (or challenges) and facilitators (or enablers), associated with tests, tools, or scans used for the diagnosis of PE. Titles and abstracts from the literature were screened by the reviewer for information related to implementation issues. The full text of all potentially relevant reports was retrieved for determination of eligibility by the same reviewer. Articles were deemed relevant and included for summary if they reported information on the implementation and context domains, according to the INTEGRATE-HTA model.[292]

Data Extraction

From each relevant article, the bibliographic details (i.e., author, date of publication), implementation issue under review, and other relevant study information pertaining to barriers or facilitators (e.g., clinical setting, geographical setting) were captured by one reviewer. The information from the literature was used to supplement and augment the information provided by the survey, and to address any potential information gaps around implementation.

Data Analysis

For the survey, quantitative responses that were dichotomous (for example, Yes/No) and nominal (for example, a list of options) were summarized descriptively (see Environmental Scan[291]). Open-ended qualitative responses were categorized by theme and summarized narratively by one reviewer.

Survey data, interview data, and findings from the literature were coded into categories based on the domains of implementation and context identified by the *Guidance for the Assessment of Context and Implementation in Health Technology Assessments (HTA) and Systematic Reviews of Complex Interventions: The Context and Implementation of Complex Interventions (CICI) Framework* (INTEGRATE-HTA framework).[292] Using this framework, four domains of implementation, i.e., “provider,” “organization and structure,” “policy,” and “funding,” as well as the additional domain of “patient” were used to further guide the categorization of identified strategies, barriers, or supports as they relate to the implementation of diagnostic strategies across the various levels of health care service delivery. The domains of context, i.e., “socio-economic,” “socio-cultural,” “setting,” “political,”

"legal," "geographical," "ethical," and "epidemiological," were also used to guide the categorization of information.

Survey data and the literature were read through for initial familiarization before coding. Data were coded by one researcher. Data could be coded to more than one domain, if relevant. The information from all sources was summarized narratively and presented by domain. The summary includes a brief description of the domain and how the identified issues relate to the implementation of PE diagnosis.

Results

One or more survey respondents from each province and territory, with the exception of the Northwest Territories where no potential respondent was identified, were contacted to complete the survey. Seventy people were initially sent the survey, and survey recipients were asked to further distribute the survey to their colleagues, as appropriate. Twelve survey responses (from clinicians, directors of diagnostic imaging, a medical director, and a department head) were received from five jurisdictions. Four responses were received from Manitoba, three from New Brunswick, two from Prince Edward Island, two from Saskatchewan, and one from Ontario. No responses were received from the remaining Canadian jurisdictions. Appendix 33 provides additional information on the survey respondents.

Nine English-language primary studies[36,293-300] were included in the summary of the literature. Appendix 34 presents the study characteristics for the articles included in this review. Year of publication ranged from 2008[36] to 2015.[296,298] Five studies were retrospective chart reviews,[36,294,295,297,300] one was a survey,[298] one was a survey and retrospective chart review,[293] one was a retrospective chart review and review of physician characteristics,[296] and one was a survey, with interviews and global information systems mapping components.[299] Regarding geographical location of study sites, one study was pan-Canadian,[299] one study was Canadian but did not specify which provinces and territories information was from,[298] while the remainder were from Ontario.[36,293-297,300] For clinical setting, one study specifically reported on the experiences of a rural emergency department.[295] Six studies were conducted in an academic, tertiary care centre.[36,293,294,296,297,300] One study[298] looked at practices in 48 nuclear medicine departments, while one study[299] surveyed 658 acute care hospitals. Five studies[293,295,296,298,300] reported solely on patients with suspected or confirmed PE, while the remainder[36,294,297,299] reported on patients with suspected or confirmed VTE (but reported PE-specific information).

Domains of Implementation

Provider

At the provider level, both the included studies and survey respondents identified provider knowledge and choice as relevant to the diagnosis of PE.

Risk Stratification and Pretest Probability

Provider factors may influence the assessment of patients when they present with PE-like symptoms. Issues that emerged related to physician factors and the risk stratification and pretest probability (PTP) assessment (including CPRs) for the diagnosis of PE were familiarity and knowledge of PTP (including documentation of PTP testing), the consideration of PE as a diagnosis, and the concern about missing a PE diagnosis. These factors may influence the use of these tests.

Some survey respondents, when asked which CPRs (e.g., Wells criteria, Geneva score, etc.) are used to diagnosis PE, indicated that the choice is driven by physician choice, with some providers choosing whichever is more familiar to them. The study by Smith et al.[36] listed reasons why physicians do not apply CPRs, including medicolegal concerns (not specified further); challenges with memorizing and applying the rule; perception that clinical gestalt is better; perception that none of the rules have been validated to the physician's standards.[36] Provider knowledge and familiarity may be a support if the implementation of a particular PTP tool is the one the provider uses. A barrier could be the implementation of an unfamiliar PTP tool that may require additional provider education.

In the interview with a clinical expert, challenges to PTP testing were discussed (Dr. Eddy Lang, Academic Department Head and Professor at the University of Calgary Cumming School of Medicine, Calgary, AB: personal communication, April 21, 2017). The issue was raised that PTP is typically not memorized by physicians, and it can be difficult to incorporate into a busy ED; this is a barrier to the implementation of PTP assessment. Findings from several of the studies suggest that PTP, if done, is poorly documented in patient charts.[36,294,295,297] This appears to be the case for large, academic, tertiary care hospitals[36,294] as well as small, rural hospitals.[295] Additionally, it was noted that there is not much literature regarding clinical gestalt to diagnose PE compared with the structured approach of PTP.

In addition to PTP choice and documentation, the survey respondents and the clinical expert indicated that the main challenge is in considering PE as a diagnosis. A diagnosis of PE may be overlooked when patients experience chest complaints, which may then be attributed to other conditions. In the interview, the clinical expert discussed general challenges in diagnosing PE, specifically that most patients with PE present atypically, and that it can be difficult to diagnose. It was suggested that most patients with PE are not diagnosed on their first visit to their doctor or the ED. Failure to consider PE as a diagnosis is a challenge; this lack of consideration could result in near-misses or potential fatalities when patients fail to be appropriately diagnosed with PE. The fear of missing PE may also cause physicians to start treating patients with anticoagulants, as a bleeding complication of treatment is thought by some to be preferable to a PE (Dr. Eddy Lang: personal communication, 2017 April).

Rule-Out and Ancillary Testing

Provider factors may also influence the use of rule-out and ancillary testing. This may include knowledge of D-dimer testing, including how it should be used and interpreted. Based on the survey responses and the literature identified in the review, D-dimer may be used as a screening tool, and changing this behaviour may be challenging for the implementation of judicious D-dimer use. A barrier may also be provider education regarding the interpretation and appropriate use of D-dimer.

Regarding rule-out and ancillary testing, a few studies focused on the use of D-dimer testing, or, more specifically, the overuse of D-dimer testing. In the study by Smith et al.,[36] the study authors determined that D-dimer was not being used as recommended by their facility or was being misinterpreted by emergency clinicians. The study by Ingber et al.[297] also evaluated the use of D-dimer testing and suggested that clinicians may have inaccurately filled out PTP forms in order to gain access to the test. Additionally, the study by Arnason et al.[294] regarded the use of appropriate diagnostic strategies for VTE and reviewed 863 charts of patients for whom D-dimer had been ordered. The authors reviewed diagnostic imaging for patients who had had D-dimer testing and suspected that D-dimer

was being used as an initial screening tool for patients with chest pain, regardless of their clinical presentation.[294] The study authors noted that the prevalence of PE was lower than expected, and thought this may have been due to the use of D-dimer in patients before PE had been considered a possible diagnosis.[294]

From the survey, one participant indicated that D-dimer may be used as a screening tool. Other participants more generally indicated that D-dimer may be required if clinically indicated, as a rule-out test, based on the initial clinical suspicion of PE.

Diagnostic Imaging

As with the clinical prediction rules and rule-out testing, provider factors may influence the choice and use of diagnostic imaging modalities. Much of the literature related to clinician utilization or preference for certain modalities, although choice of imaging test could be related to contextual issues such as access, not just provider knowledge. Depending on the diagnostic strategy, provider knowledge or preference for one imaging modality may be either a barrier or a support.

Limited information was provided by survey participants about provider factors influencing diagnostic imaging; one participant stated that there was an over-reliance on imaging for PE diagnosis. However, over-testing may not always be the case, as the study by Aranson et al.[294] found that testing strategies for VTE (including PE) are more likely to be classified as inappropriate due to a provider failing to perform imaging than due to overuse of diagnostic imaging; in their study, they found that 220 of 230 PE patients had inappropriate testing strategies (based on the Wells criteria) due to the underuse of diagnostic imaging.

In the study by Ahn et al., emergency physicians (n = 43) had a general knowledge that a V/Q scan exposed patients to less radiation than CTPA, and they preferentially chose V/Q scans for younger patients (< 50 years old), females, and patients with a history of recent, multiple CT scans.[293] However, physicians had limited knowledge of precise radiation doses, and the study authors did not explore whether radiation risk had been discussed with the patients.[293] The study by Ballantine et al. noted that physicians seemed to prefer CT to diagnose PE; however, they were not certain whether this was because of the perceived ease of access to CT.[295]

One study examined CTPA utilization rate among 26 emergency physicians, with training in either a three-year Canadian College of Family Physicians Certificate of Special Competence in Emergency Medicine or a five-year Fellowship of the Royal College of Physicians in Emergency Medicine.[296] Physician gender, years of practice, and training certification were not correlated with CTPA utilization rate or with PE positivity rate.[296] However, CTPA utilization rates differed among physicians, with a range of 0.21 to 0.77 scans per 100 patient visits (average of 0.48 scans per 100 patient visits).[296] The authors of this study listed several factors that may influence how often CTPA is used, including physicians' knowledge of guidelines, risk tolerance, prior training, prior experiences, and the "need to know."[296] While the authors did not specifically look at appropriate use of CTPA and the source of the inter-physician variation in use rates, they speculated that there were differences in adherence to guidelines; they suggest future efforts be focused on physician education.[296]

In the study looking at the use of SPECT in Australia, France, and Canada, the study authors noted some resistance to the adoption of SPECT technology (not specific to Canada but a trend in the overall study), which they suspected was due to several reasons, including reluctance to change, more experience and familiarity with planar imaging, concerns related

to time for SPECT, lack of appropriate imaging agents, or resistance from other colleagues.[298] These are barriers to using SPECT technology.

Policy

At the policy level, survey participants and the literature identified policies, or potential policies, that would support the implementation of diagnostic strategies for PE.

Although it appears that PTP assessment is rarely documented, if done, it could be made mandatory. This would require collaboration across hospital departments, and the initial implementation could be challenging. Once in place, it could be a support to providers. The study by Ballantine et al.[295] stated that there was a lack of documented PTP and suggested implementing a protocol that required the use of the Wells rule before any further testing or imaging was ordered. In the study by Ingber et al.,[297] the study authors investigated the initiation of mandatory PTP algorithms (based on Wells criteria). The authors were primarily interested in the use of D-dimer and imaging tests in the pre- and post-intervention periods, but they also demonstrated that the initiation of mandatory PTP testing was feasible, given a high degree of compliance. This required collaboration with the ED and with its laboratory; D-dimer samples had to have a PTP score sheet in order to be tested, and those without one would not be tested.[297]

The study by Le Roux et al.[298] explored the use of SPECT or SPECT/CT instead of V/Q planar scintigraphy for the diagnosis of PE at 48 Canadian sites (provinces or territories not specified). Compared with France and Australia where 58% and 42%, respectively, of facilities using V/Q SPECT also acquired CT images, only 11% of Canadian facilities did this. The study authors hypothesized several reasons for this, including different cost and reimbursement policies, but this was not explored further. This same study examined the way V/Q planar scintigraphy was interpreted and found that it was primarily interpreted using the EANM criteria (60%), followed by binary one subsegment (17%), probabilistic Prospective Investigation of PE Diagnosis study criteria (17%), or no standardized criteria (7%).[298] Existing guidance for the interpretation of SPECT is a potential support for implementation of its use.

From the survey, one participant stated that clear protocols for diagnosing PE are needed for small and medium-sized communities. Another mentioned the use of American College of Chest Physician guidelines (no further details provided). No other participants stated the use of guidelines for PE diagnosis, although this may only reflect the facility or particular respondent, rather than their jurisdiction. There may be a need for consistent protocols, and these may vary depending on the resources available to the facility.

The lack of clarity around guidelines or protocols for diagnosing PE was also noted in the literature. Chen et al. indicated that, although there have been guidelines developed regarding when to use CTPA, the implementation of these guidelines has been inconsistent, and suggested overuse in some settings (not specified) and underuse in others.[296] The study by Southern et al. found that there was considerable variation in the use of decision-support tools (e.g., diagnostic critical pathways or computer prompts); it was noted that most provinces had at least some hospitals that used such tools, but Prince Edward Island and the territories did not have decision-support tools for the diagnosis of VTE at the time of their survey.[299]

Patient

Diagnostic approaches may differ depending on characteristics of and factors related to the patient (e.g., contrast allergy, pregnancy, morbid obesity).

The clinical expert also mentioned that D-dimer may have high rates of false-positive results in certain populations (e.g., the elderly, patients with autoimmune or inflammatory disease) (Dr. Eddy Lang: personal communication, 2017 April). The literature also notes the difficulty in using D-dimer in critically ill patients.[297] Use of D-dimer in these populations may be challenging. While our survey attempted to address what type of D-dimer was being used (e.g., age-adjusted), the response rate was too low to determine what is being used across Canada; this is an information gap.

Survey participants were asked whether the diagnostic approach may vary based on particular patient populations. Seven participants indicated that CT imaging may be difficult if patients have renal dysfunction or an allergy or contraindication to the contrast used. Two participants mentioned that V/Q scans, echocardiography, or leg ultrasounds are available in this case. One participant mentioned that, if patients are not able to have contrast CT and are presumed to be high risk for PE, they may be treated if treatment is deemed less risky than investigation. As well, one participant stated that patients are sometimes too unstable to get a CT scan if needed. Two participants indicated that pregnant women are a special population, although alternative diagnostic strategies were not specified. One participant indicated that patients with morbid obesity may be beyond the weight limit of imaging scanners; no alternative diagnostic method was specified. In the literature, it was specified that patients with poor renal function (defined as an estimated glomerular filtration rate of 60 mL/min), contrast allergies, asthma, other malignancies, a previous DVT, or previous PE were more likely to have a V/Q scan.[293]

It is uncertain how use of imaging modalities differs by patient gender. The study by Chen et al.[296] examined CTPA utilization rates by patient gender and age. CTPA utilization was higher for females compared with males, and CTPA utilization rates increased with increasing patient age; the increase in CTPA use in females and older patients did not correspond to an increase in PE positivity rate for gender or age cohorts.[296] The authors suspected there was a gender-related bias in the use of CTPA.[296] For older patients, the authors suspected the increased imaging was related to more ambiguous clinical examinations.[296] However, in the study by Ahn et al.,[293] females were more likely to receive V/Q scans than CT. This was also noted in the provider factors, and the extent to which the patient or the physician influences this choice was not explored.

There may also be unintended consequences of imaging in certain patient populations. Spencer Netto et al.[300] assessed the use of contrast-enhanced chest CT as part of trauma assessment. The increased use of CT for imaging of trauma patients increased the diagnosis of asymptomatic PE.[300] Management of coincidental PE may be different than the assessment and management in patients with suspected PE.

Organization and Structure

Issues of organization and structure that emerged from the survey involved staffing and after-hours access to resources. One respondent indicated that nuclear scans are a limiting step, as only one radiologist is available to read them, and that having more staff after hours may enable them to do more nuclear scans. One respondent stated that they are generally

satisfied with their tools to diagnose PE, but that access to V/Q scans is limited after hours. Adequate staffing may be a barrier to implementing interventions for the diagnosis of PE.

In the literature, issues of organization and structure were related to referral of patients outside of centres for diagnostic imaging, physician education, the documentation of PTP assessment in patient charts, and regional programs.

The study by Ballantine et al.[295] described the referral patterns for patients with suspected PE to be transferred out of their facility, if they need CT or V/Q scans. Patients can be sent up to 55 km away to receive diagnostic imaging, as there is no CT or V/Q scanning available in the small, rural facility. One survey participant indicated that V/Q scans are not available after hours in the province, but that if patients need this, it is a 45-minute transfer away. Establishing when patients need to transfer, and which facility they will be transferred to, requires coordination between facilities and clear protocols in place. This also ties into the section on setting and geographical influences for diagnostic strategies for PE.

The study by Chen et al.[296] explored the differences in CTPA usage among physicians who have completed either the five-year emergency medicine Fellowship of the Royal College of Physicians, or the two-year family emergency medicine program of the Canadian College of Family Physicians. CTPA usage for the diagnosis of PE did not differ between physicians with either training. On average, it had been 15 years since the completion of their residency for the physicians in the study, and the authors suspected that the effects of training had waned, while other organizational factors may be more influential, such as interaction with patients, work environment, the emergency physician's practice pattern, and continuing education.[296]

As previously mentioned in the section on provider factors for implementation, PTP assessment was seen to be poorly documented in patient charts, and the clinical expert had stated that it was difficult to use formal PTP in busy clinical settings. The study by Ingber et al.[297] explored the establishment of mandatory PTP assessment before D-dimer testing. To implement mandatory PTP assessment and documentation before D-dimer testing would require system-wide changes and direction from the organization to facilitate the change, in addition to any provider or policy changes.

There was some exploration into regional resources and clinics, such as outpatient clinics and home monitoring for VTE (PE-specific programs not specified, detail regarding the programs was also lacking).[299] Southern et al. found that Alberta, Saskatchewan, Manitoba, Quebec, New Brunswick, and Nova Scotia had early outpatient clinics for VTE (but not every region within the jurisdiction had these services). At least one region in Alberta, Saskatchewan, Manitoba, Quebec, New Brunswick, and Nova Scotia had long-term outpatient clinics. For home programs, Alberta, New Brunswick, and Nova Scotia had programs in at least one region. One region in Saskatchewan had a home monitoring program.[299] Although this was not PE-specific, it does provide some insight into the limited availability of additional support services and clinics.

Funding

There was little information identified explicitly related to funding or lack of funding for the implementation of strategies to diagnose PE. Again, the study by Le Roux et al.[298] suspected that a difference in cost and reimbursement policies may have contributed to differential use of SPECT versus SPECT/CT in Australia, France, and Canada, but this was not explored further. One survey participant indicated that, if patients with suspected PE

needed to be transferred from one health care facility to another, the costs are covered by the province.

A detailed economic model is explored in a separate chapter of this HTA. This section more fully explores which pathways are economically favourable, although this also depends on certain willingness-to-pay thresholds (e.g., more pathways, or certain pathways, will be acceptable at higher willingness-to-pay thresholds). Intuitively, adequate funding for interventions is a support; however, lack of funding for diagnostic strategies is a barrier.

Domains of Context

Socioeconomic

None of the identified relevant articles, survey participants, or clinical expert identified issues explicitly related to socioeconomic factors for the implementation of strategies to diagnose PE.

Sociocultural

Sociocultural factors, such as language and communication, as well as lifestyle and social resources, may influence the approaches to the diagnosis of PE. Patient-related factors, including knowledge and perceptions, are explored in this HTA in a separate chapter. The following explores the relevant sociocultural factors, as identified in the literature found during the implementation search.

For clinicians, the choice of diagnostic imaging for PE may depend, in part, on the surrounding sociocultural context. The study by Chen et al.[296] found that CTPA was disproportionately used in females at their tertiary, academic hospital emergency department. The authors suspected that this may be due to patient histories of oral contraceptive use (which is a risk factor for PE), but they also stated that this risk factor may be overestimated by clinicians.[296] Use and trends in oral contraceptive use may influence approaches to the diagnosis of PE.

Perceptions of imaging modalities within the clinical community can change over time. The study by Le Roux[298] discusses the change in perception of V/Q SPECT. The author observed that V/Q SPECT had largely replaced traditional planar imaging at facilities in Australia, France, and Canada. They suspected that the changing perceptions of the nuclear medicine community, with a more favourable view of SPECT, was a factor in this change.[298] For the facilities still using planar V/Q scintigraphy rather than SPECT, the authors proposed that clinician resistance to change, a greater familiarity with planar imaging, concerns with the technology, and lack of a suitable ventilation agent were barriers to use.[298] While SPECT is one example, the perception of different PTP assessments, ancillary and rule-out tests, and imaging modalities may influence their use among clinicians.

Setting and Geographical

Issues of setting (according to INTEGRATE-HTA[292]) refer to region, “country” (e.g., urban and rural), type of facility, etc. whereas issues of geography refer to infrastructure (e.g., transport), access to health care, geographical isolation, etc. The questions of this HTA combine the issues of setting and geography as the diagnostic strategies are considered in urban, rural, and remote settings.

Regarding modalities for diagnostic imaging, CADTH’s Canadian Medical Imaging Inventory[42] provides recent data on the number of CT, MRI, PET, and SPECT units across the country (with information on the number of hours these units are available per day and

per week). However, whether these are indicated for use in patients with suspected PE is not known. As of the 2015 data, there are 538 CT, 340 MRI, 264 SPECT, and 214 SPECT-CT units across Canada; for all of these imaging modalities, the most units were found in Ontario and Quebec. There are also two PET-MRI units in Canada, both of which are in Ontario and used for research purposes only.

Patient location may influence the appropriateness of the diagnostic strategy; patients with suspected PE presenting to the ED were more likely than in-patients to undergo appropriate diagnostic testing in one study.[294] Regarding treatment, from the interview with a clinical expert, patients in the north or from remote areas may be treated with anticoagulants in the interim, before they can be transported for further workup (Dr. Eddy Lang: personal communication, April 2017). Survey participants also indicated that high-risk patients may be started on treatment while investigations are still being done.

The Environmental Scan[291] related to this project reports in more detail the availability of tests and diagnostic imaging across Canada. As a general trend, provinces with small populations were more likely to collect samples for D-dimer testing and send them to centralized facilities to be analyzed, whereas provinces with large populations had more hospitals with on-site D-dimer testing. CT appeared to be more common than other imaging modalities, such as MRI and V/Q, in smaller centres,[299] although CT units may still be limited in rural or remote centres.[42,295]

In the survey, participants were asked whether they were aware of instances when their diagnostic strategy may differ depending on location within their jurisdiction (e.g., urban, rural, or remote hospitals). Seven respondents indicated that how a diagnosis is made may change depending on the availability of tools and tests within their jurisdictions. Some stated the diagnostic strategy may differ depending on availability of D-dimer, V/Q, and CT scanning or nuclear medicine. One respondent suspected that larger facilities may have different approaches, and another respondent stated that some facilities do not have CT scanning or nuclear medicine departments. Respondents were aware that rural hospitals may not have the same tools and tests as urban hospitals; this may require transfer of patients to other centres. Two respondents indicated that patients seen in rural sites requiring CT scans would need to be transferred to a hospital with CT scans. Similarly, one respondent mentioned that rural sites do not have CT or V/Q scanning available.

Survey respondents were also asked about the availability of rule-out and ancillary tests in their jurisdiction, including arterial blood gas, capnography, chest X-ray, D-dimer testing, echocardiography, electrocardiography, and leg compression US. All provinces that provided responses had access to at least some of these tests. New Brunswick and Saskatchewan, based on responses from survey respondents, did not have capnography, although this may reflect the facilities where the respondents were located and not the provinces as a whole.

Survey respondents were asked about the availability of imaging tests in their jurisdiction, including V/Q scintigraphy, V/Q SPECT, V/Q SPECT-CT, CT, thoracic ultrasound, MRI, and PET. All jurisdictions had access to at least some of these tests. Only the hospital in Ontario had access to all of the imaging modalities. New Brunswick was the jurisdiction with responses from both an urban teaching hospital and a rural hospital; only CT and MRI were available at the rural hospital, while the urban, teaching hospital had V/Q modalities, CT, and MRI.

Political

None of the identified relevant articles, survey participants, or clinical expert identified issues explicitly related to political factors for the implementation of strategies to diagnose PE.

Legal

Few sources identified relevant legal issues regarding strategies for the diagnosis of PE. When exploring imaging test ordering and imaging utilization, the study by Chen et al.[296] cited physician concerns over litigation (presumably due to a missed PE diagnosis) as an influencing factor.

Related to the section on ethical issues, informing patients of radiation risk (from imaging modalities such as CT) is a potential legal issue. One study[293] surveyed 31 physicians and found that 58% of them informed all patients about the radiation risks of diagnostic imaging tests, 35% informed only high-risk patients ("pregnant patients and females of childbearing age"), one physician stated they told patients there was a risk but that the degree of risk is uncertain, and another physician never informed patients about radiation risks. One survey respondent also addressed the issue of consent; they indicated that pregnant women are asked to give consent after being informed of their risk. There is a possibility that patients who feel they were not properly informed of risks related to the modalities used to diagnose PE may file a legal suit.

Ethical

While ethics is one of the INTEGRATE-HTA domains, this HTA also contains a chapter on ethical issues that provides a more detailed exploration of this topic area. For the implementation review, relevant ethical issues were related to the issues of informed consent around, and exposure to, radiation (specifically for CTPA).[293,296,297] The section on legal issues, in this HTA chapter, provides more detailed study findings of physician disclosure of radiation risks.

Epidemiological

Relevant epidemiological factors (e.g., subgroups of interest) related to the diagnosis of PE are explored in more detail in the clinical section of the report; however, few epidemiological issues were found for this component of the HTA. Patient factors are also explored in a previous section of this report (e.g., special populations such as pregnant women, females, and older persons).

The establishment and use of local cut-off values for D-dimer may aid in the appropriate diagnostic workup of patients with suspected PE and support further implementation strategies. The study by Ingber et al.[297] explored other findings related to D-dimer use (latex immunoassay – HemosIL D-dimer, Instrumentation Laboratory Company, Bedford, MA) after mandatory PTP assessment. Despite efforts to curb inappropriate test usage, the use of diagnostic imaging for VTE did not decrease in this study, even though PTP was now required for D-dimer testing.[297] The authors suspected that this might be partly due to the high false-positive rates of the test they were using and further emphasized using a local cut-off value (rather than the manufacturer cut-off), as well as an age-adjusted cut-off.[297] Use of more appropriate cut-offs may have resulted in more low PTP patients in whom VTE might have been ruled out.[297]

Summary of Results

This section of the HTA reported on issues related to the implementation of diagnostic strategies for PE, based on a survey of stakeholders, a literature review, and an interview with an expert clinician. The following summarizes the main findings from the analysis of the information from all sources.

Provider knowledge and choice, as well as patient factors, may influence the initial assessment, and subsequent investigation, of suspected PE. Clinicians play a large role in carrying out the diagnostic strategies for PE, including recognition of PE as a possible diagnosis during the initial patient assessment. Depending on knowledge and familiarity, a physician may use certain PTP tests over others. It was found that PTP assessment is poorly documented in patient charts, possibly because PTP assessment is not typically memorized by physicians and because it is difficult to integrate into a busy work environment such as the ED.

Provider knowledge of D-dimer may influence how it is used and interpreted. Additionally, D-dimer may have high rates of false-positive results in certain populations, such as the elderly, the critically ill, or patients with autoimmune or inflammatory disease. The need for local cut-off values for D-dimer tests was also expressed, as high false-positive rates did not decrease unnecessary diagnostic imaging.

Choice of diagnostic imaging was also related to provider knowledge and patient factors. For example, a physician's knowledge of radiation risk may influence whether they order V/Q or CT for certain populations; women, younger patients, and those with a recent history of multiple CT scans were more likely to receive V/Q scans than CT. Physician knowledge and perception of SPECT also influenced whether it was used.

Policies and protocols can be used to support the diagnostic strategies for PE. It is possible to establish policies and protocols to implement a particular diagnostic strategy for PE. For example, mandatory PTP assessment before D-dimer testing was feasible, as evidenced by one study, although this required collaboration from those involved, such as the laboratory and the ED. There is also the possibility of additional support for PE diagnosis, such as clinical guidelines and protocols and tools such as computer prompts. However, these policies and protocols may not be the same in every facility, as a need was expressed for tools specific to small and medium-sized centres. This may also relate to the need for protocols for the transfer of patients out of a facility for further testing. Policies and protocols to aid PE diagnosis are possible but require clarity on their use and collaboration from those involved.

Resources, including staffing and access to tests, scans, and imaging, are differentially located across the country. As evidenced in the literature, the survey, and expert interview, access to tools and tests used to diagnosis PE varies across Canada and differs depending on whether a site is urban, rural, or remote. Urban centres tended to have more availability and access to tests and imaging modalities than rural or remote centres. Northern jurisdictions also had less access to certain tests (e.g., one CT for Nunavut). Access was also related to whether certain services were available after hours or 24-hours, seven days a week and whether staff were available to provide these services.

Environmental Impact

Objective

To assess the potential environmental effects associated with the use of diagnostic strategies for suspected pulmonary embolism.

Literature Search

The literature search was performed by an information specialist, using a search strategy peer-reviewed according to the PRESS checklist — an evidence-based checklist for the peer review of electronic search strategies.[79]

Information on the environmental impact was identified through targeted literature searches of the following bibliographic databases: MEDLINE (1946–), with in-process records and daily updates, via Ovid; Embase (1974–) via Ovid; CINAHL (1981–) via EBSCO; Scopus; and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH terms, and keywords. The main search concepts were medical imaging and key terms for environmental impact. No methodological filters were applied to limit retrieval by study design. Retrieval was limited to documents published since January 1, 2007. Results were limited to English- and French-language publications. The detailed strategy can be found in Appendix 1.

The search was completed on April 7, 2017. Regular alerts were established to update the search until the publication of the final report. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching sources identified in the *Grey Matters* checklist (https://www.cadth.ca/grey-matters), which includes the websites of clinical trial registries, regulatory agencies, HTA agencies, clinical guideline repositories, and professional associations. Google and other Internet search engines were used to search for additional Web-based materials.

Study Selection Criteria

Two reviewers screened the titles and abstracts of all citations retrieved from the literature search for relevant studies and reports. Full-text articles were retrieved and assessed for inclusion by the two reviewers if either of them considered a citation potentially relevant to the research question. Articles and reports were considered eligible if they published from 2007 onwards, provide insights into the potential environmental impact associated with diagnostic imaging modality for PE. Papers reporting on the effects of ionizing radiation from imaging devices on patients undergoing imaging studies or clinical staff operating the equipment and articles that were not published in English or French were excluded.

Data Extraction

The reviewers planned to extract from each relevant article the bibliographic details (i.e., authors, year of publication, and country of origin), population, and intervention information, and to identify issues related to the environmental impact. The environmental factors were to be classified as follows:

a) source media (e.g., air, water, soil);
b) receptor-macro (e.g., flora, fauna);
c) receptor-micro (e.g., fish, wildlife, vegetation);
d) receptor-specific (list name);
e) impact-macro (e.g., contamination, effect); and
f) impact-specific (describe).

Content Analysis

Two phases of analysis were planned. First, one reviewer planned to conduct a content analysis to identify issues related to the environmental impact from the use of diagnostic imaging modalities for PE. After review of extracted data, a list of codes would be developed, tested for appropriateness, and expanded or merged into themes. A constant comparative technique would be applied to identify all instances and appropriateness of the coding framework, and to determine how to expand or merge the codes into themes. A sample text passage to illustrate their application the codes and a narrative summary of the themes would be provided. Second, the extracted information would be organized into the key steps of an ecological risk assessment, namely hazard identification, exposure assessment, toxicology, and risk characterization.

Results

Quantity of Research Available

A total of 3,317 citations were identified: 3,237 from the main literature search and 77 from alerts. Following screening of titles and abstracts, 3,310 citations were excluded and seven potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search. None of these seven potentially relevant articles met the inclusion criteria for this report. Six of the articles did not have environmental impact outcomes. The remaining article was published in a language other than English or French. Appendix 35 describes the PRISMA flowchart of the study selection.

Summary of Findings

The literature search did not find any studies or reports that evaluated the environmental impact of imaging modalities for PE.

Ethics

This ethics section identifies key ethical considerations in the diagnosis of PE for patients presenting in the ED in urban, rural, and remote settings in Canada. It provides a framework for the ethical development, implementation, and provision of practices related to the diagnosis of PE. Necessarily, the ethical issues presented in this section go beyond narrowly defined ethical concerns in the clinical context to also encompass broader legal and social considerations. It is common in the ethics literature, across a broad range of health-related issues, to refer to ethical, legal, and social issues when addressing broader values-related considerations. While the primary emphasis here will be on ethical considerations, legal and social issues may also be relevant to ethics analyses.

The relevant perspectives considered in identifying and addressing the ethical issues associated with the various strategies for diagnosing acute PE include those of patients, family members or informal caregivers, health care providers, and the health system, more generally.

Research Question

The ethical question explored in this section has developed since the creation of this HTA protocol. In this section, we ask:

What are the key ethical considerations related to the diagnosis of acute PE within the ED in remote, rural, and urban settings in Canada?

The report aims to identify and analyze explicit and implicit ethical issues in the literature concerning the diagnosis of PE in EDs.

Methods

Literature Search

Search Strategy

The literature search was performed by an information specialist, using a search strategy peer-reviewed according to the PRESS checklist — an evidence-based checklist for the peer review of electronic search strategies.[79]

Ethics-related information was identified through targeted literature searches of the following bibliographic databases: MEDLINE (1946–), with in-process records and daily updates, via Ovid; Embase (1974–) via Ovid; PsycINFO (1967–) via Ovid; CINAHL (1981–) via EBSCO; and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH terms, and keywords. The main search concepts were medical imaging and pulmonary embolism, and key terms for ethics concepts. No methodological filters were applied to limit retrieval by study design. Retrieval was limited to documents published since January 1, 2006. Results were limited to English- and French-language publications. Conference abstracts were excluded from the search results. The detailed strategy can be found in Appendix 1.

The search was completed on October 12, 2016. Regular alerts were established to update the search until the publication of the final report. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching sources identified in the Grey Matters checklist (https://www.cadth.ca/grey-matters), which includes the websites of clinical trial registries, regulatory agencies, HTA agencies, clinical guideline repositories, and professional associations. Google and other Internet search engines were used to search for additional Web-based materials.

A review of the empirical and bioethics literature was conducted to identify potential ethical issues related to the diagnosis of acute PE in the ED context. This includes an analysis of literature that explicitly and specifically raises ethical issues, as well as literature that provides data related to PE that, when read through an ethics lens, implicitly raises or points to potential ethical issues. The relevant literature includes issues related to diagnostic strategies for PE and diagnostic testing for other conditions that may present possible analogies for the ethical issues related to the diagnosis of PE.

Search Results

In the first level of screening, titles and abstracts were reviewed and the full text of potentially relevant articles was retrieved and assessed for inclusion by the same reviewer. Articles were categorized as “retrieve” or “do not retrieve” according to whether they meet the following inclusion criteria:

- Provides information (explicit) on or is relevant to identification (implicit) of an ethical issue related to diagnosing PE.

In the second stage of screening, two reviewers independently assessed the relevance of the full-text reports for all citations classified as “retrieve” in the first stage of screening. The relevance of the full-text reports was assessed according to the following criteria:

- Relevant diagnostic strategy for PE
- Explicitly or implicitly mention ethical issues

Reports meeting all criteria were included in the analysis. Reports that did not meet these criteria were excluded from analysis. The results of the study selection process are presented in a flow chart (Appendix 36).

The database search results yielded 590 records. Ethics experts also identified an additional 14 articles from a Google search for ethical issues related to radiology and DVT, more generally. After reviewing record titles and abstracts, 422 articles were removed and the remaining 182 full-text articles were reviewed. These full-text articles were assessed based on the inclusion criteria. Articles that did not meet these inclusion criteria were excluded. A total of 42 articles were included in this study. Of these 42 articles, two articles explicitly acknowledge “ethics” related to the diagnosis of PE [301,302] Gosner and Nau[301] considered the ethical implications related to the care of elderly patients with suspected PE, while Amaro et al.[302] explored the ethics related to overutilization of diagnostic imaging for PE and health care reform responsibilities. In addition, four articles[303-306] identified by the ethics experts explicitly considered ethical issues related to radiology, more broadly (Appendix 37). Thus, a total of six articles included in this study make explicit mention of ethical issues relevant to the diagnosis of PE. The remaining 36 articles[19,21,195,213,230,295,299,307-335] included in this study contain implicit information that bears ethical relevance to the diagnosis of PE.

No articles included in this study answered our research question. Furthermore, no articles compared the ethical risks and benefits of the various diagnostic pathways for PE.

Ethically relevant issues mentioned earlier in this report in the clinical, economic, patient experience, and implementation sections were also included in our ethical analysis. In addition, we identified and drew upon additional articles that consider analogous medical contexts that are relevant to understanding the ethical issues surrounding the diagnosis of PE in the ED.

In this report, we do not provide normative arguments in favour of or against any specific diagnostic pathway or imaging modality. Rather, we offer an ethical framework for considering the various ethical implications related to the use or nonuse of various diagnostic pathways for PE within the ED. This framework can be used to support the ethical provision of diagnostic imaging for PE.

Summary of Findings and Ethics Analysis

Several key themes emerged from our analysis of the implicit and explicit ethical issues in the literature related to use or nonuse of the various diagnostic pathways for PE within the ED context. We found that ethical considerations were related to the following basic ethical principles:

- beneficence and nonmaleficence, which are related to benefits and risks of diagnosis, misdiagnosis, or treatment;
- autonomy, which is related to informed consent and clinical decision-making;
- system efficiency and professional responsibilities; and
- issues of justice related to costs and economic implications of treatment or nontreatment, and issues that are unique to certain subpopulations and public health.

Our ethics analysis organizes our findings by the relevant ethical interests of and implications for, the key stakeholder groups, including patients, clinicians, health care organizations, and society, more generally. We describe 1) patient-related issues, 2) clinician-related issues, and 3) organization-related issues, and 4) systemic and social issues. There is some overlap of the ethical considerations discussed both within and between each of these categories. For example, concerns related to risks to patients will have implications not only for individual patients, but also for clinicians and the organization. Such overlap is to be expected given the relational nature of health care practices. Nevertheless, the demarcation of ethical issues within these four categories encourages shifts in perspectives when considering the ethics of diagnostic pathways for PE. It prompts one to ask: What are the ethical concerns for patients, for clinicians, for the organization, or for the health care system and society, more generally?

a) Patient-Related Issues

How might patients benefit from the diagnosis of PE?

Patients who present to the ED with PE or suspected PE have an interest in receiving timely and appropriate care. These patients benefit from the diagnosis of PE, in which case they may receive potentially life-saving treatment. The use of risk stratification tools can help ensure that only patients who require diagnostic imaging receive it. Furthermore, the use of imaging modalities can confirm the presence of PE, with some degree of confidence, before initiating anticoagulant therapy. Similarly, the use of diagnostic imaging to rule out PE helps

to ensure that patients are not given anticoagulant medications unnecessarily. Patients benefit from receiving the treatment that they need and from not receiving unnecessary treatment.

Patients may also benefit from the use of diagnostic imaging modalities that result in incidental findings, that is, images that help to detect and diagnose other health concerns. For example, a CT scan for PE may inadvertently reveal other medical concerns, such as lung cancer.

Finally, the use of CPRs and diagnostic imaging may be reassuring to patients who are presenting in the ED with unspecified symptoms. For example, patients who have a CT scan that is negative for PE may feel more confident in a physician's determination that they do not have PE than if PE was ruled out using CPRs and/or D-dimer testing. The Patient Perspectives and Experience Section in this report found several perceived benefits of diagnostic imaging techniques, more generally. For example, in one study,[288] patients credited imaging with saving their lives and, in most cases, benefits were articulated in terms of "the technology's noninvasive potential to peer within and deliver images capable of mapping out current or prospective health concerns." (Patient Perspectives and Experience section). The ability "to know" was often valued by patients.

How might patients be harmed from the diagnosis of PE?

First, patients with PE who are not diagnosed will go untreated. This can lead to pulmonary hypertension, post-thrombotic syndrome, right ventricular failure, or death. Patients who have an obstructed blood vessel in the lungs are at risk of having their lung tissue damaged because of lack of oxygen. As mentioned in the clinical review, approximately 30% of untreated PE cases are fatal.[12] With treatment, the mortality rate is reduced to 10%.[230]

In addition, false-positive results can cause patients to worry. According to the Patient Perspectives and Experience Section of this report, some patients saw the use of diagnostic imaging at a threat to their self-control and ability to manage the situation, and they had concerns about isolation, confinement, and dependence on others, particularly with the use of MRI.

Second, there are also risks associated with diagnostic testing for PE. The risks differ for different modalities. As an example, we will review the risks associated with the use of CTPA. Although most patients complete CTPA with no adverse events, there are risks related to radiation and to the contrast material used. Radiation is absorbed by the body during CTPA, with the highest doses being absorbed by the liver, skin, esophagus, heart, breast, and lungs. This radiation exposure has been linked to an increased risk of cancer, especially at younger ages.[331] Patients who undergo CTPA are also at risk of allergic reaction to the iodinated contrast media used. The mortality rate for adverse reactions to the contrast media is of one to three per 100,000 cases of use.[331] Other reactions to the contrast media include urticaria, nausea, vomiting, bronchospasm, dyspnea, angioedema, and anaphylactic shock.[331] Patients with kidney problems are at risk of kidney damage from the iodinated contrast material.[336] There is also a risk that the contrast material will leak from the vein in which it is being injected, causing damage to the surrounding skin, blood vessels, and nerves. This often leads to repeating CTPA and requires exposing patients to additional radiation.[331] If CTPA is overused for the diagnosis of PE, some patients may be at risk of receiving unnecessary radiation.[309]

Some patient populations face increased or unique risks in the diagnosis of PE. For example, PE is the leading cause of death among pregnant women.[315] Pregnant and

lactating women who undergo CTPA or other diagnostic imaging tests, such as V/Q scintigraphy, face additional risks related to radiation. Many argue that the risks to women and the fetus must be considered in the context of diagnostic imaging.[213,315] Some suggest that preference should be given to the mother over the fetus when considering options for diagnostic imaging to detect for PE.[316]

The imaging of elderly patients presents unique risks for this group.[302] For example, imaging strategies may have to be adjusted to meet the needs of elderly frail patients with respect "to mobility and breath holds." In addition, some older patients may need supervision while waiting in radiology, more time for positioning, and additional help during testing.[302]

Other patient groups may be at high risk for PE but may fail to be diagnosed for PE when they present to the ED. These patients are at a higher risk of not receiving necessary anticoagulant treatment. For example, in patients with chronic obstructive pulmonary disease presenting to the ED with chest pain, PE may not be considered if their symptoms are attributed to their chronic disease.

Given the sensitivity of CTPA, as described in the clinical review, as with other imaging modalities, there is risk of false-positive results.[307] As a result, some patients may be misdiagnosed with PE, which may cause them unnecessary concern and anxiety. According to the Patient Perspectives and Experience review, some patients viewed the use of diagnostic imaging at a threat to their self-control and ability to manage the situation, and had concerns about isolation, confinement, and dependence on others, particularly with the use of MRI. Patients who are misdiagnosed with PE may then undergo unnecessary anticoagulant treatment for PE. It has been found that nearly a third of patients with suspected PE who have a low likelihood of PE and a normal D-dimer test may have anticoagulant therapy safely withheld.[19]

What are the concerns related to patient decision-making in the context of PE diagnosis?

At a minimum, informed consent requires that patients understand the risks and benefits of the proposed treatment or intervention and also appreciate the consequences of receiving or not receiving the treatment or intervention. Patients must provide consent to all medical interventions and health care treatments, except in emergencies. Informed consent can be challenging to obtain for urgent testing or interventions proposed in the ED. Often, in this context, consent to testing is taken as implied. According to clinical experts consulted for this review, in some provinces, such as Alberta, (nonemergent) patients presenting to the ED sign a general waiver in which they give their consent to the evaluation and treatment within the ED. This may also include consent to receiving care by trainees. Although general consent to diagnosis or treatment is often given (or implied upon admission), some interventions may require additional or explicit consent. In the context of the diagnostic pathway for PE, patients need not consent to the use of risks stratification and CPRs. However, consent (explicit or implied) is required for diagnostic imaging.

For consent to be informed, patients need an understanding of the risks and benefits of the medical intervention. Consent, as a dialectic process, also gives clinicians opportunities to address patients' questions and concerns and counsel them on the risks and benefits of imaging.[328] Patients' understanding should be confirmed by asking them to acknowledge the key points as they are explained and, if appropriate, by asking them to explain the risks and benefits in their own words.[328] The consent process could give patients an opportunity to choose their imaging modality, if the physician were to propose more than one option. For

example, this may be a factor if there are different risks and benefits (increased sensitivity but increased risk).

Pregnant patients need additional information during the informed consent process. There are concerns related to whether breastfeeding should be temporarily halted after intravenous administration of the iodizing contrast material used in CTPA.[328] It has been recommended that radiologists inquire about the possibility of pregnancy for any women of reproductive age and conduct a verbal screening and obtain consent before diagnostic imaging.[328] When feasible and medically indicated, modalities that do not use ionizing radiation, such as MRI, may be preferable for pregnant or lactating patients.[328] It has also been suggested that radiologists should strive to minimize risks of radiation and facilitate shared decision-making with patient and her family. Matthews (2006)[337] describe the difficulties related to the diagnosis and imaging of PE, pointing to the lack of guidelines concerning imaging protocols for pregnant women. The absence of policies, consensus on level of risk, etc., can make discussions of informed consent challenging. The authors describe a 2003 survey of members of the Society of Thoracic Radiology, which found that 53% of responding radiologists would use CTPA as a first-line investigation for excluding PE in pregnant patients, but only 60% of radiologists obtained informed consent from any pregnant patient undergoing CTPA.[338]

Diagnostic imaging is typically seen as a routine intervention. In practice, it is rare for someone to refuse diagnostic imaging. When someone presents to the ED, they have either been referred by their family doctor or have come because they are concerned about their symptoms. Emergency wait times are often long, and patients are usually happy and relieved to receive imaging results to confirm or rule out their diagnosis. If a patient refused a particular diagnostic imaging modality, physicians could document their refusal and suggest another testing modality or intervention. It is possible that some patients with suspected PE may choose to leave the hospital against medical advice, but this is extremely unlikely.

The process of informed choice is connected to patient medical literacy. For example, within the context of consent to CTPA, patients may have assumptions or misconceptions related to “radioactivity.”[306] The noncritical reading of patient advocacy literature can pose tremendous ethical challenges. There may also be risks from reading other biased information available to patients, as we see in the context of vaccines. It is unclear whether such information informs decisions related to PE diagnosis. It could, however, influence patient’s beliefs about other aspects of care in the ED. As mentioned in the Patient Perspectives and Experience Section in relation to some patients’ experiences with cardiac SPECT-CT, perceptions of risks emanated from an association of terms such as “nuclear” with “atom bombs.” As such, literacy and social privilege are entangled with informed consent.[306] This can make decision-making around diagnostic imaging challenging in some cases. Furthermore, informed consent can be compromised when patients fail to fully understand or appreciate the proposed diagnostic or treatment intervention due to time constraints and the urgency of PE diagnosis.

What are the concerns related to patients’ access to testing for PE?

The geographical size of Canada and the distribution of its population has resulted in some challenges in accessing timely diagnostic imaging for some rural or remote patients. In larger urban hospitals, CTPA is available 24 hours a day, seven days a week, but patients visiting a smaller rural or remote hospital may need to wait for diagnostic imaging or need to travel to a larger hospital. Patients who require a V/Q scan, such as pregnant patients, may

need to return the next day if they present after hours and V/Q testing is not available. These patients may be given a single-dose anticoagulant treatment if PE is suspected. Issues of access to diagnostic imaging may influence what is considered optimal for different populations. For instance, provision of timely diagnosis may be less feasible in rural and remote facilities due to lack of access to certain testing and imaging modalities and specialist expertise, as well as geographical barriers to care. Inability to access optimal diagnostic testing in a timely manner could increase the risk of missed diagnoses, as well as unnecessary anticoagulation due to either false-positive results or long wait times to receive assessment.[7]

In addition, although cost is not typically an issue for individual patients who have provincial or territorial health care insurance because they do not need to pay out-of-pocket for diagnosis or treatment of PE, it may be an issue for uninsured patients, such as those visiting from outside of Canada who are billed for their visit to the ED. In these cases, the cost of various diagnostic pathways may factor into decision-making.

As mentioned previously, an accurate estimate of PE incidence is difficult to obtain, because a large proportion of PEs are detected on autopsy. In approximately 80% of patients in whom a PE was identified at autopsy, the PE was unsuspected or undiagnosed before death.[7]

b) Clinician-Related Ethical Considerations

What are clinician's obligations in relation to the diagnosis of PE?

The clinician duty to do no harm is arguably one of the most fundamental principles of medical ethics. In the context of diagnosing PE, there are concerns about the possibility of harming patients with testing modalities or unnecessary treatments, as discussed earlier. Some worry about the iatrogenic harm from the overtreatment of PE.[311] A commitment to the duty to do no harm, a fear of missing a PE, and concerns about the professional repercussion for clinicians can contribute to the practice of "defensive medicine," which causes excessive use or overuse of diagnostic imaging and other tests.[309,310,326] Factors such as ''request from the patient or his/her relatives'' or ''fear of being sued'' played a role in the US.[326] The practice of defensive medicine is common in the US health care contexts, where clinicians fear lawsuits if PE is missed or misdiagnosed.[310] This may not be as common in Canada, given the difference in health care systems and social and medical cultures. Nevertheless, it may indicate clinicians' concerns related to the professional repercussions of making a diagnostic error related to PE. "Defensive behaviour" is frequent and is associated with decreased odds of positive CTPA results.[326] In other words, many patients are subjected to unnecessary diagnostic imaging because of the practice of defensive medicine.

Some literature suggests that radiologists have a unique duty to notify patients of any diagnostic errors; however, current disclosure rates are low.[303] For example, if a radiologist missed a PE diagnosis, or another incidental finding from imaging, for that matter, they should notify the patient or the most responsible physician of this error. The disclosure of errors by radiologists or other clinicians can help ensure that patients ultimately receive accurate diagnostic information and can support a health care culture of trust and transparency.

There are also ethical concerns related to the challenges surrounding the accurate documentation of the testing and diagnosis of PE. The Economic section of this report found

that there is poor documentation of PE in patient charts. Inadequate reporting and poor communication among health care providers can put patients at risk. Failure to accurately document PE raises concerns about clinicians' transparency and accountability.

What are the concerns related to clinician's decision-making in the context of PE?

As discussed in the Clinical Section, the nonspecific nature of common PE symptoms can make the consideration of a PE diagnosis challenging for physicians. As professionals, physicians often exercise their clinical judgment in the diagnosis of PE. This may be in tension with a commitment to evidence-based medicine. According to the Implementation Section of this report, clinicians may order the imaging modality with which they are most comfortable, despite what the evidence indicates. In a 2002 poll of American physicians, 79% of respondents indicated that they order more tests than they otherwise would, ''based *only* on professional judgment of what is medically needed'' (emphasis added) It has been found that intuition alone is unreliable for evaluating the utility of policies in complex diagnostic scenarios.[230] Duriseti et al. 2006 suggest that experienced clinicians can use clinical judgment ("gestalt") to assign a clinical pretest probability for the diagnosis of PE with "reasonable accuracy."[230] They suggest that structured CPRs perform equally well, but have an advantage because they can be used by less experienced clinicians.[104]

In exercising clinical judgment, clinicians may exhibit personal biases with respect to patients in different patient populations groups that influence the likelihood of receiving diagnostic imaging or testing.

Yan et al., 2016,[329] examined the overuse of CTPA for PE in the ED. The odds of finding an acute PE nearly doubled when providers adhered to evidence presented in clinical decision-making tools. Most clinician overrides were due to the lack of D-dimer testing in patients unlikely to have PE. Similarly, Alhassan et al. 2016 found that suboptimal implementation of assessment tools can result in the overuse of CTPA.[331] It has also been found that clinicians seldom use all nine data elements of the PERC rule in patients whom they deem PERC-negative. These data suggest the need for paper or electronic aids to support use of the PERC rule.[318]

Several barriers to improving the utilization of CTPA in the ED have been identified, including litigation and defensive medicine; pressure for quick turnover; and patient demands.[309] There is pressure from access and flow that might lead to demand for rapid patient turnover in the ED, which, in turn, can lead to "blanket ordering" to obtain a diagnosis as quickly as possible.[309] As individuals, physicians' tolerance of risk may vary, and this can result in differences in ordering tests and in the diagnostic pathway for PE. The fundamental issue for physicians in the diagnosis of PE is often not wanting to miss PE. Diagnosing PE can be extremely difficult because it presents with nonspecific symptoms. Some physicians may also worry about the legal implications of having missed a PE diagnosis. In some jurisdictions, campaigns, such as the "Choosing Wisely" have been implemented to support clinicians to make appropriate use of diagnostic imaging. The clinical review in this PE report found that combining a clinical decision tool with D-dimer testing is a good rule-out strategy for PE.

Variations have been found in the diagnostic pathway for PE based on physician specialty.[308] For example, cardiologists are more likely to use echocardiography and cardiac perfusion imaging in the diagnosis of PE, while pulmonologists are more likely to use CT.

It has been shown that physicians who disclose their biases with respect to their specialty and their preferred treatment can increase patient trust in their recommended treatment

plan. Moreover, physicians who disclose their bias have increased confidence in their treatment recommendations to patients. During the disclosure of bias, physicians afforded patients with the opportunity to seek a consultation with a physician from a different specialty.[333] This could be challenging in the ED setting. This finding suggests that physician disclosure of biases with respect to the pathway for diagnostic testing for PE may increase patient trust in the proposed testing pathway.

Survey respondents and the clinical expert indicated that the main challenge is in considering PE as a diagnosis. A diagnosis of PE may be overlooked when patients experience chest complaints, which may be attributed to other conditions. In the interview, the clinical expert discussed general challenges to diagnosing PE, specifically that most patients with PE present atypically, and that PE can be difficult to diagnose. It was suggested that most patients with PE are not diagnosed on their first visit to their doctor or the ED. Failure to consider PE as a diagnosis is a challenge; this lack of consideration could result in near-misses or potential fatalities when patients fail to be appropriately diagnosed with PE. This fear of missing PE may also cause physicians to start treating patients with anticoagulants, as a bleeding complication from being treated is thought by some to be preferable to having PE (Dr. Eddy Lang: personal communication, April 2017).

What are the risks to clinicians in the diagnosis of PE?

There may be some health risks to clinicians related to the administration of radiologic imaging. A study by Vano and colleagues (2013) found posterior subcapsular lens changes characteristic of ionizing radiation exposure in 50% of interventional cardiologists and 41% of nurses and technicians. They suggest that most lens injuries are the result of several years of work in radiology without eye protection.[339]

c) Organization-Related Issues

How is the diagnosis of PE related to quality of care?

At the hospital level, there are serious concerns about crowded or overcrowded EDs. Lee-Lawandrowski and colleagues (2009) found that the use of a rapid D-dimer test for patients in the ED was associated with a shorter ED length of stay and fewer hospital admissions.[340] Mourad and Adler (2011) found that care for PE on the weekends or nights is less aggressive, and there is variation in the quality of patient care.[341] This means that patients presenting to the ED with PE during off-peak hours may not undergo diagnostic imaging and, as a result, a PE may be missed and necessary treatment may not be started. Further, quality of care can be compromised during off-peak hours because of the lack of radiologists or other clinicians needed to interpret diagnostic images for PE testing.

The Implementation Section of this report found that provider factors may influence the assessment of patients as they present with PE-like symptoms. Emerging issues related to physician factors and the risk stratification and pretest probability (PTP) assessment for the diagnosis of PE were familiarity and knowledge of PTP assessment (including documentation of PTP testing), the consideration of PE as a diagnosis, and the concern of missing a PE diagnosis. These factors may influence the use of these tests. For example, the implementation of an unfamiliar PTP tool that may require additional provider education could be a barrier to quality of care. As with the CPRs and rule-out testing, provider factors may influence the choice and use of diagnostic imaging modalities. Much of the literature is related to clinician utilization or preference for certain modalities, although choice of imaging test could be related to contextual issues such as access, not just provider knowledge.

Depending on the diagnostic strategy, provider knowledge or preference for one imaging modality may be either a barrier or a support.

One proposed solution is the use of an iPad as a mobile device for CT display and interpretation in identifying PE.[317] The use of this mobile device would allow for remote image interpretation and consults during off-peak hours when the radiologist is not on duty, for example. This use of technology could help to reduce the waiting time for diagnostic imaging results and speed up the diagnosis of PE. It could also help to reduce the need to call patients back after a revised interpretation of results by a specialist.[317] Although the use of such a technology may be beneficial and increase accessibility, it may also raise ethical concerns with respect to patient privacy. The implementation of this new technology may also have practical and ethical implications for the operation of the ED and coordination and communication among health care professionals.

Itri and colleagues (2015) provide suggestions for humanizing the patient care environment within radiology, by using certain lighting, colours, etc. They maintain that a patient's experience of illness includes the emotional and psychological consequences of being ill. They argue that health care providers must adequately address these subjective aspects of illness to provide the most effective care. [335]

What are the ethical issues related to interprofessional collaborations and clinician education?

Clinicians' awareness of PE (or VTE) diagnosis and adherence to associated best practices within the ED can help ensure quality patient care and reduce health care costs. Nurse education can be effective at increasing compliance with VTE awareness and could lead to reductions in associated health care costs.[314]

d) Health Care System and Social Issues

The diagnosis of PE also has implications for systems-level and population-level ethics. For systems-level ethics, instead of asking, "Does this technology benefit the patient?" and "Does this technology disadvantage vulnerable individuals?" we ask, "Does this technology create overall benefit for the population?" and "Does this technology disadvantage marginalized groups?"

What are the financial burdens on the health care system?

As mentioned earlier in this report, of the total population of patients who are evaluated for suspected PE, few are confirmed to have the condition, indicating a low diagnostic yield of current evaluation methods. High-cost imaging modalities are overutlilized.[301,309,310] Further, the overuse of diagnostic imaging modalities can place a heavy economic burden on the health care system.[313] The costs associated with the diagnosis and treatment of PE may include nursing, pharmacy, radiology, ED laboratory, blood bank, and practice fees. The Economic Section of this report found that CT provides the best value for imaging modalities. It also found that it is most cost-effective to treat a patient who does not have PE than to miss treating a patient who does have PE, given the increased risks of recurring PE and mortality.

Given regional variation in infrastructure for the diagnosis and treatment of PE, there is sometimes a need to move samples or images between facilities for testing. Similarly, there may be a need to transfer patients to another hospital for testing or treatment. This need for transfers increases the financial burden of PE on the health care system. At the systemic

level, there is also a concern about the practice of "imaging up," that is, ordering a more advanced, risky, and costly testing modality when a lesser intervention may be sufficient or more appropriate. This practice has been associated with the health care system costs related to PE.[305]

The optimal diagnostic strategy for suspected PE can differ based on factors related to the health care setting (i.e., urban, rural, or remote) because there are variations in the availability of imaging technologies and the relevant clinical expertise across the country. According to the Economic section of this report, the diagnostic strategy with the lowest costs was revised Geneva score > PERC > D-dimer > CTPA. Clinically, this strategy involves providing the revised Geneva score to all patients with suspected PE to classify their risk. In those considered of low-to-intermediate risk, PERC followed by D-dimer was used to rule out PE and, of those in whom PE could not be ruled out or of those with high probability of PE according to revised Geneva score, CT is offered. Eight strategies provided better clinical outcomes but at greater costs (balancing needs of individual patients and the system as a whole). Greater cost in this area may limit availability of other health care services within a publicly funded health care model. Further, a trade-off was observed between false-positive and false-negative findings. Diagnostic strategies with higher ICERs had fewer false-negative but more false-positives findings. These findings reflect the implications of incorrectly missing a PE diagnosis (i.e., false-negative), as withholding treatment in patients with PE is associated with considerable morbidity and mortality consequences.

What are the concerns related to equity in access for diagnosing PE?

There was considerable variation across Canada in the availability of key infrastructure for the diagnosis and management of VTE disease, in general, and PE, in particular.[299,308] Provinces with higher populations tended to have a large proportion of hospitals with the capability to measure D-dimer levels. In contrast, less populated provinces were more likely to send samples to centralized analysis facilities for D-dimer testing. All provinces and territories have some facilities offering advanced diagnostic imaging; however, there are variations in the availability of diagnostic imaging equipment and specialists across the country. Typically, access to testing modalities is limited in some rural and remote hospitals. Patients with suspected PE should be assessed using appropriate diagnostic tests in a timely manner, and the timing of access to diagnostic test results may affect the management of the condition and the effective use of health care resources.[7]

In Canada, CT is the most prevalent imaging modality. As of 2015, across the country there were 538 CT machines, 340 MRI machines, 264 SPECT machines, 214 SPECT-CT machines, and 2 PET-MRI machines.[342] Most imaging machines are in large urban hospitals, with the greatest number in Ontario, Quebec, British Columbia, and Alberta. Nova Scotia, Manitoba, Saskatchewan, Newfoundland and Labrador, and New Brunswick have a relatively moderate number of machines, while the less populated jurisdictions have a relatively low number of machines. Less populated jurisdictions in Canada often have limited imaging modalities. Some of the less populated jurisdictions have a greater number of some modalities (CT and MRI) per population, but the population is spread out, so the machines may still be difficult for patients to access. The Northwest Territories have only CT; Yukon has only CT and MRI; and Nunavut has only CT.[342] For this reason, the diagnosis of PE and availability of testing varies greatly across Canada.

What are the public health considerations in relation to PE?

Estimates suggest that PE afflicts 0.1% to 1% of the Canadian population.[7] Certain subpopulations, such as pregnant women and older adults, are disproportionately affected by PE due to a higher risk. Indeed, PE rarely occurs in the absence of risk factors, and the likelihood of occurrence increases progressively where multiple risk factors are present. As mentioned in the Clinical Section, factors associated with the development of PE can be inherited or acquired and include malignancies, immobilization, surgery, extremity paresis, hormone replacement therapy or oral contraception, factor V Leiden mutation or other acquired thrombophilia conditions, DVT, pregnancy, and the use of medications that alter coagulation of the blood. There are public health concerns related to the increasing cumulative radiation exposure of population because of medical imaging tests.[330] Although the risk of PE increases with age, it has been found that the prevention of PE in young adults may be a worthwhile.[343] The prevention of PE begins with the prevention of DVT. For patients who are at risk of DVT or PE, their risk can be reduced by exercising or moving after extended periods of sitting, surgery, or illness. Certain prescription medications (anticoagulants) can help to reduce the risk of clotting. In addition, leg elevation, compression stockings, or pneumatic compression may help to prevent swelling in the legs and improve circulation.[344] The promotion of healthy lifestyles aimed at reducing risk factors related to PE or a public health campaign aimed at making at risk populations aware of the symptoms of PE so that they seek the appropriate medical care may be worthwhile. However, some individuals who develop PE have no risk factors.

Summary

The diagnosis of acute PE in the ED setting raises several ethical issues related to patients, clinicians, health care organizations, the health care system, and society more generally. These ethical issues are grounded in several principles, among them beneficence, nonmaleficence, autonomy, and justice. Our findings suggest that there is variation in the clinically and ethically appropriate diagnostic pathway for individual patients, given their unique histories, location, and medical needs. The ethical considerations related to the diagnosis of PE will vary to some degree for clinicians across different specialties. There are likely to be similar ethical considerations for different health care organizations, but the ways to address these ethical challenges may vary across organizations. At a systems level, there appears to be a greater ethical difference among the various diagnostic pathways and imaging modalities for the diagnosis of PE. According to the economic models and clinical sections described previously, the use of CT seems to be the most likely candidate for the ethical provision of PE diagnosis.

Discussion

Overall Summary of Findings

This report assessed the optimal diagnostic strategy for acute PE among different imaging modalities; the report included the clinical and cost-effectiveness analyses, patient perspectives and experience, implementation issues, environmental issues, and ethical considerations.

The results of the overview of systematic reviews indicated that the Wells rule for predicting PE probability, regardless of cut-off (<2 or ≤4), showed greater specificity than both the Geneva score and the revised Geneva score. There were insufficient data or consistencies in trends to allow a conclusive statement about which CPR had the best sensitivity. The systematic reviews[26,103,106] in the clinical overview of reviews did not show a consistent diagnostic advantage of one of CPRs over the others, with respect to the dichotomized Wells rule, the Geneva score, or the revised Geneva score. This is in agreement with a publication by the American Academy of Family Physicians, which states that no single CPR has proven superior.[76]

The most economically favourable CPR depended on willingness to pay. At a willingness-to-pay threshold between $1,481 per QALY and $3,706 per QALY, the revised Geneva score was the most likely cost-effective CPR; at a willingness-to-pay threshold between $3,706 per QALY and $57,097, the Wells criteria emerged instead. Both a three-tier and two-tier model may be acceptable for the Wells rule to define the cut-offs for pretest risk although, with higher willingness-to-pay values (i.e., between $7,661 per QALY and $57,097 per QALY), the two-tier Wells was the most likely cost-effective CPR. In terms of rule-out tests (predicated on low pretest PE risk based on CPR), if willingness to pay was between $1,481 and $7,661 per QALY, the rule-out test that was most likely cost-effective was PERC followed by D-dimer. However, if willingness to pay was between $7,661 per QALY and $57,097 per QALY, D-dimer alone was the rule-test that was most likely cost-effective. In total, six strategies formed the efficiency frontier (i.e., the set of strategies that, for varying costs, produces the highest health benefits).

No DTA information was available for pathway studies. Sufficient information was available for individual DTA meta-analysis for CT, MRI, US, V/Q, and V/Q SPECT. The meta-analysis included an adjustment for the use of variable and imperfect reference standards in the pooled studies. With the exception of V/Q (sensitivity 0.864), all imaging modalities had pooled sensitivity greater than 0.950, and, with the exception of V/Q SPECT (specificity 0.914), all imaging modalities had pooled specificity greater than 0.940. CT and V/Q SPECT both offer similarly high estimates for sensitivity, and therefore the lowest number of missed diagnoses when used for rule-out testing. Furthermore, proportions with test failure for both CT and V/Q modalities were below the accepted threshold of 3% VTE risk over three months;[41] however, there were more cases of VTE in patients with negative CT results for PE. Most comparative studies reported numerically higher proportions of nondiagnostic tests for CT-based versus V/Q-based modalities, although this is offset by the higher proportion of indeterminate tests for V/Q. Previous DTA meta-analyses used models that assume a perfect reference standard. One meta-analysis addressed threshold effects by comparing calculated ROC curves for CT, V/Q, and V/Q SPECT. They found no difference between V/Q SPECT (10 studies) and CT (9 studies), and found that both were significantly superior to V/Q planar scintigraphy.[59] V/Q SPECT was associated with the lowest radiation exposure and CT with the highest.[59] Another article compared V/Q SPECT-CT with CT, but the

method of pooling was potentially inappropriate for diagnostic test data, and the pool of studies was small.[345]

Previous meta-analyses of MRI found lower sensitivity but comparable specificity to our analysis,[80,81,346,347] and a published meta-analysis of V/Q SPECT found higher specificity and comparable specificity.[348] Published analyses of US found lower sensitivity and specificity,[82,349,350] which we also saw in our meta-analysis of the data without adjustment for an imperfect reference standard. In our review, there was greater uncertainty in the estimates for US, V/Q, and V/Q SPECT, and the results for thoracic US, in particular, varied widely according to the choice of the statistical model. We were unable to explain the heterogeneity with the available patient and study covariate data, although for V/Q and V/Q SPECT, the individual studies' differing interpretation criteria and handling of indeterminate (nondiagnostic) values may have contributed.

The economic analysis found that employing strategies of risk stratification and diagnostic imaging to diagnose patients with PE was generally cost-effective if willingness to pay was greater than $1,481 per QALY. In patients suspected of PE, a diagnostic strategy involving risk stratification followed by CT was most likely cost-effective, so long as there were no contraindications to CT, as this imaging modality was found to have the highest sensitivity and specificity values, lowest proportion of nondiagnostic findings, and lowest costs to perform.

The economic model was robust to most sensitivity analyses, including scenarios that explored different approaches to clinical management of nondiagnostic test findings and alternative parameter inputs for DTA. Analyses that affected the model involved those that had a more pronounced impact in shifting the cost-benefit ratio, such as the analyzed time horizon, the prevalence of PE, and the management of patients with moderate pretest probability of PE based on the Wells criteria. The economic analysis found that, in pregnant patients, leg US introduced earlier in the diagnostic pathway as an ancillary test before proceeding to diagnostic imaging could be a potentially cost-effective strategy if willingness to pay was greater than $7,882 per QALY.

At least one study reported proportion with test failure for CT, MRI, Q SPECT, V/Q, and V/Q SPECT. Test failure was low for all modalities; all but MRI (proportion 0.034) were below the accepted proportions of 3% over three months.[41] Moreover, proportions with test failure from diagnostic pathways consisting of combinations of CPR, D-dimer, CT, and V/Q, were below 3% for eight of 10 pathways. The low proportions with test failure of diagnostic algorithms that incorporate D-dimer help support current practice and argue for its inclusion in the workup of patients at intermediate risk of PE who have positive imaging results or patients at high risk but have false-negative or indeterminate findings on imaging.

Reducing radiation exposure is important for younger patients, women, and people who have undergone or will undergo repeated imaging, for example, for monitoring cancer. Younger patients have greater lifetime risk; breast tissue receives a high organ-specific dose in thoracic imaging, and risk is believed to be additive over a lifetime. Few studies reported radiation dose for their study cohort, and the clinical search excluded phantom or modelling studies, but most studies involving a comparison of CT with other modalities featured a discussion of other research and its implications for radiation safety. CT imaging resulted in substantially higher doses than the other modalities, with lower exposure from V/Q, V/Q SPECT, and V/Q SPECT-CT (with low-dose CT). Radiation exposure, which was lower using V/Q modalities, is of particular concern for pregnant patients. Radiation exposure, frequency of incidental findings, and other contextual factors are considerations when

selecting a diagnostic imaging modality. Given the lack of data, the role of other imaging modalities in pregnancy is unclear.

There remains a need to understand how surreal an experience diagnostic imaging can be for individuals unfamiliar with the technologies or settings. While the potential benefits of a scan may be well understood and at times serve as a calming mechanism throughout the imaging process, reminders of human presence throughout the examination could help ground the patient in reality, and explicit conversations before the examinations could allow for greater levels of comprehension. In addition to patient factors, provider knowledge and choice may influence the initial assessment and subsequent investigation of suspected PE. Many studies drew from an in-patient population who were sicker and, therefore, at increased risk of adverse events. It is therefore difficult to anticipate how much the risk of adverse events in the study population might differ from the general clinical population. Due to the insufficient safety data available, we were unable to assess long-term safety concerns, such as consequences of radiation exposure.

In the context of PE, there are several diagnostic pathways, each with its own set of benefits and risks, for the various stakeholders. The diagnosis of PE is further complicated by the diversity in the patient populations, treating clinicians, health care organizations, and access to tools and tests across Canada. There may be conflicting values in the diagnosis of PE within and between each of the relevant stakeholder groups. For example, while an individual patient may benefit from the relief associated with the use of CTPA to rule out PE, they may also experience harm from the iodizing contrast used in this test, while the health care organization and health care system, more generally, incur the financial cost of this testing modality.

The diagnosis of PE, like many health care interventions, also requires balancing the ethical considerations for relevant stakeholders. The weight of these ethical considerations, in part, relies on the availability of empirical evidence and on the value which we ascribe to the interests of the relevant stakeholders. As well, it could be possible to establish policies and protocols to implement a particular diagnostic strategy for PE, although this may require clarity on their use and collaboration from those involved. In terms of the implementation issues review, the selected studies, survey responses, and expert interview are all from a Canadian perspective. As technological advancements in the context of PE diagnosis and the broader health care and social environments change, the ethics of various PE diagnostic pathways will also evolve. In determining the optimal pathway for diagnosing PE, clinicians, health care organizations, and the relevant policy-makers must take the various stakeholder's values/interests and the ethical considerations into account.

Strengths

To our knowledge, this is the most comprehensive evaluation of the clinical and cost-effectiveness of diagnostic strategies for PE. Furthermore, this is the first report aimed at understanding more about the patient perspectives and experiences, implementation issues, and ethical considerations associated with PE diagnostic imaging. For instance, the review of implementation issues of the PE diagnostic pathway from a pan-Canadian perspective drew on information in the literature, from survey participants, and from a clinical expert. This report considered a pathway approach to the diagnosis of PE, and considered issues for urban, rural, and remote settings. The ethics sections not only drew from the published literature, but also raised important considerations based on the findings from the other sections in this report.

The review was not focused simply on comparing diagnostic imaging modalities but evaluated the full diagnostic pathway, consisting of risk stratification, ancillary testing, and diagnostic imaging. Our analysis was based on publicly available evidence. In particular, for the DTA parameters for imaging modalities, the approach taken by the clinical review addresses some of the methodological concerns with past meta-analyses in this discipline by using a statistical model that adjusted for a variable and imperfect reference standard.

In our economic model, external validation was conducted both separately for each submodel and together in evaluating the three-month PE risk in individuals with a negative diagnosis of PE. The external validation exercise provided confidence in the model's predictions and, therefore, the costs and health benefits predicted. Where possible, Canadian data were used as inputs to the model.

When there were concerns with the diagnostic data (e.g., inputs for CPRs), extensive sensitivity analyses were conducted in the economic model to explore its robustness by testing alternative values.

Limitations

Although the intention of the clinical review was to evaluate treatment pathways as a whole, the number of studies that reported the performance of well-defined treatment pathways was relatively small, and most studies described single components of the treatment pathways. In the clinical analyses, we therefore assumed that the diagnostic performance of each test was independent of the test before it, an assumption that may not be valid.[92] We also did not compare the utility of imaging with no imaging, or examine the patient experience of those who did not undergo imaging.

The review included all imaging modalities used for the diagnosis of PE. CT, V/Q, and V/Q SPECT have all been used as part of routine clinical practice, while US has limited use, and the optimal imaging conditions for MRI are still being investigated. Treatment for patients in studies involving US and MRI, in particular, does not reflect the index test results, but rather the results of the standard-of-care reference test, which will affect the failure rate.

There is no agreed-upon gold standard for the diagnosis of PE, and studies used variable reference standards, some of which were anticipated to have lower anatomic resolution than the index test. In this analysis, a latent-class statistical model was used to adjust for the imperfection and variability of the reference class, but it is not possible to determine whether the underlying assumptions of a statistical model have been met. Clinical and statistical heterogeneity was evident in the study pools, and final estimates were, in most cases, associated with substantial uncertainty. Sources of the uncertainty could not be identified from the available information. Although the CrIs of sensitivity and specificity overlapped for CT, V/Q, and V/Q SPECT, significant difference between modalities could not be excluded. Too few eligible studies were retrieved for meta-analysis of V/Q SPECT-CT, a hybrid modality that offers potentially faster imaging with lower radiation dose.

One study was identified in the implementation issues section that reported on imaging for PE in a rural hospital, and no information was captured on what information might be used in the decision to transfer a patient with suspected PE for further investigation and care in these settings. This is an important limitation, given the policy question, which reflects the geographical spread of Canada. Although the economic analysis did not explore this issue of cost-effectiveness across different settings explicitly, the findings were hypothesized to be similar in rural and remote settings. As the most recent Canadian Medical Imaging

Inventory[42] noted, CT is the most common imaging modality in rural and remote areas, and the economic evaluation found that CT was less costly and more clinically effective than other imaging techniques. The reference-case findings of the economic analysis are therefore likely to remain consistent in rural and remote areas. Of note, the cost of transportation to a medical facility was not factored in the evaluation and may be significant in rural and remote settings.

A number of subgroups that were of particular interest were not well described. Age was represented by the covariate of mean age, which did not appear to be associated with diagnostic test performance, and by three studies that described stratified results. One study reported results stratified by gender. Other subgroups were excluded from studies for reasons of safety and feasibility, including elderly patients, obese patients, patients with pre-existing renal disease, or patients who were hemodynamically unstable at the time of presentation.

Safety was sparsely reported, although the immediate procedures were not associated with serious adverse events. There was insufficient information on long-term adverse effects, such as cancer risks associated with radiation dose. It is important to note, given the scope of this project, that the economic model ignored the indirect effects, such as the potential clinical benefit of prophylactic anticoagulation in patients with false-positive results (to prevent VTE) or the impact of incidental findings emerging from imaging to diagnose other conditions. In addition, the relationship between radiation exposure from PE diagnostic strategies and cancer was limited in literature and, therefore, not modelled.

With respect to the economic analysis, there was only deterministic value for the sensitivity and specificity of D-dimer and some of the CPRs. The correlation between sensitivity and specificity could not be derived from the HSROC curve, given a lack of primary studies and difficulties in deriving the 2 × 2 tables from the published systematic reviews (Appendix 23). A separate analysis was conducted on diagnostic strategies with the three-tier Wells rule to compare the expected costs and outcomes when either the deterministic estimates or the probabilistic inputs were employed. The expected costs and outcomes were similar for each diagnostic strategy, regardless of whether the deterministic or probabilistic values were used. This highlights that, by using the deterministic input for the majority of risk stratification inputs and for D-dimer, the impact is expected to be less on the overall ordering of the diagnostic strategy on the efficiency frontier but more on the quantification of uncertainty.

The economic evaluation further assumed perfect treatment compliance. This may be reasonable for the incident PE event, when the duration of a treatment course varies from three to six months. However, the economic model did not explore the impact of discontinuation in patients on lifelong anticoagulation therapy (i.e., subsequent PE cases). In RCTs, rates of treatment discontinuation are high,[351] although the impact of including treatment compliance in the economic model may be marginal, as only a small portion of patients (i.e., 14.3%) experienced a recurrent PE in our model and would have required lifelong anticoagulation therapy (Table 28).

It is important to note that the economic evaluation did not factor in the impacts of wait time or delays to diagnosis. This was deemed outside the scope of the review, although, in reality, this can have significant clinical implications that can be costly. Instead, the economic analysis made a simplifying assumption that, if imaging was required, there would be no delays to access. It is therefore important to interpret the ICER of $57,097 per QALY for imaging all patients with a suspected PE cautiously, given that this likely represents an underestimate of the true economic consequences associated with this diagnostic strategy.

Furthermore, such a diagnostic strategy would have other consequences; as the economic model found, this strategy was expected to be associated with highest dose of radiation exposure (Table 28). Furthermore, point-of-care D-dimer may be used. Although a rapid review was recently conducted on point-of-care D-dimer, the evidence was limited and, therefore, could not be incorporated into the economic model.

While the results for the patient perspectives and experience review demonstrated the value patients place on diagnostic imaging's ability to "peer within" and "know" what was happening, regardless of associated or perceived risks, we were unable to explore perspectives of individuals who had been ruled out before receiving diagnostic imaging (e.g., through CPRs). Although this gap is a result of the direction of our research questions, which focused on post-imaging perspectives, further exploring these experiences of patients for whom imaging has been ruled out is relevant to address the policy question. It is important to note how our findings on the value of imaging are echoed in Munn and Jordan's systematic review[284] on patients' experiences with high-technology medical imaging. In this review, the authors note that receiving a diagnosis was so important for one individual that they deliberately withheld information in order to not be excluded from imaging. While this could have had potentially dangerous consequences, this individual was "prepared to take the chance" (p.643). Similarly, one of Munn and Jordan's larger, synthesized findings was that imaging could be perceived as a way of legitimizing or delegitimizing an individual's symptoms. These results echo our conversation on the power to "peer within": receiving a visual image has the power to turn an abstract symptom into very real malady. While none of the literature included in our review directly addresses experiences with being denied diagnostic imaging, understanding the value individuals place on receiving an image could help inform a more theoretical conversation on how CPRs should be implemented and their results discussed with individuals.

To date, few studies have addressed patient perspectives, implementation issues, and ethical considerations related to the diagnosis of PE. For the implementation issues review, only Canadian studies were searched and included. While this was done to increase relevancy and generalizability, studies from other countries may have been applicable to the Canadian setting. Therefore, it is possible that relevant information was not captured or retrieved. As well, 12 survey responses were received from five provinces. This offers limited perspectives from persons involved in the diagnosis of PE, as the respondents' answers cannot speak for all health care providers. These responses cannot be further generalized to the whole province and are specific to the facility the respondent represents.

Directions for Future Research

Given the concern about exposure to radiation, particularly for certain susceptible patient populations, there are opportunities for development of reduced-dose protocols, more sensitive detectors, and imaging modalities that do not involve ionizing radiation, e.g., MRI. The use of imaging modalities capable of higher resolution leads to the identification of smaller and more peripheral emboli. Research is required to identify their clinical significance and determine the risk–benefit of treatment.

There are insufficient data to conduct formal subgroup analyses to evaluate whether the clinical effectiveness differs for patients in rural or remote settings, patients who are pregnant, population or patients with cancer. This may emerge as an important issue if evidence suggests clinical heterogeneity in the DTA of different diagnostic tests and imaging modalities between these subgroups. Consequently, the economic analysis did not evaluate two of these subgroups, as there was no evidence or indication to support where economic

differences may exist. Although the economic analysis did look at pregnant populations, given a different set of diagnostic strategies may be relevant to this subgroup (i.e., offering leg US as ancillary test before imaging), it is important to note that this analysis is limited. There was a paucity of clinical literature on the DTA of these tests in a pregnant population, and the analysis relied on the assumption that the diagnostic tests performed identically in a pregnant and nonpregnant population. CPRs have not been validated in pregnancy, although tools such as the modified Wells rule have been proposed.[352] It has been suggested that D-dimer tests perform differently in pregnant patients, as pregnancy is known to increase D-dimer concentration above the conventional thresholds, leading to higher false-positive tests; trimester-specific cut-offs have been proposed.[352]

On a related note, the DTA inputs for D-dimer were based on the pooled analyses from two different publications.[33,248] However, emerging data suggest differences may exist between the type of assay used for D-dimer tests. There is increasing interest in employing age-adjusted D-dimer, given that D-dimer levels increase with age. Greater research in this area and appropriate meta-analyses would permit analysis to evaluate whether the clinical and cost-effectiveness differs according to the assay type or the patient's age for D-dimer testing.

The economic analysis did not evaluate all imaging modalities of interest to the clinical review, as there was limited data on some CPRs and imaging tests. In particular, V/Q SPECT-CT represents a potentially promising technology that could not be evaluated, given the lack of clinical data to parameterize the economic model. A recent study undertaken from the perspective of a US health plan payer suggested that the total cost of a SPECT-CT diagnostic strategy could be lower than a CTPA-based diagnostic strategy and could result in more lives saved, given improved DTA and lower nondiagnostic rates over a six-month duration.[353] However, these findings should be interpreted with caution as, in their study, DTA data were pooled by weighting the inputs according to the sample size and assumed perfect reference standards, regardless of the reference standard used. The clinical review in this HTA undertook a more sophisticated statistical approach to adjust for imperfect and composite reference standards in order to estimate sensitivity and specificity of V/Q SPECT-CT, and, despite using a nearly identical set of publications, found high instability in the pooled estimates.

The use of clinical decision support tools and computer-assisted diagnosis was out of the scope for this HTA. As these tools may play a role in diagnosis and may influence the outcome of screening, additional research may be warranted. Moreover, the clinical review focused on patients with suspected acute PE. While PE is part of the spectrum of VTE, evidence that focused on patients with suspected DVT or suspected broader VTE without PE-specific outcomes available was not included. Some of this evidence may be relevant to the general clinical area, so further research is required.

As little has been done to explore experiences or perspectives of individuals undergoing diagnostic imaging for PE, it would be interesting to see how PE-specific experiences align with those included within this report. While there is value in understanding the perceived benefits, harms, and experiences outlined in this report, a more diverse representation may be possible with further research. We were unable to fully explore the question of how patients perceive being assessed as having a low risk for PE and therefore being ruled out for further imaging, but the value patients placed on imaging technologies' capacity to help know what was going on, regardless of risks, demonstrates further need to explore these types of questions. As all of these studies were conducted outside of Canada, to gain a

greater understanding of PE imaging within the Canadian context and its range of urban, semi-urban, and rural populations, further research should be conducted in Canada. The Canadian Medical Imaging Inventory update will provide current information regarding where medical imaging units are located across the country. This report will provide updated information on access to imaging modalities in the provinces and territories, especially as it relates to type and placement of imaging units. It may also provide insight on access to these units for those in rural or remote settings. In addition to this, future research efforts could focus on hospital or province-wide policies and procedures for the diagnosis of PE (e.g., travel policies for patients transported out of centre), and the supports and barriers to the implementation of these practices. The focus of future research can also explore areas of the INTEGRATE-HTA framework (e.g., funding, socioeconomic) for which little was found.

We were unable to identify relevant literature on the potential environmental impact of PE diagnostic imaging, such the use of radioisotopes and the disposal of radioactive waste, based on the literature search conducted. Future research can examine the most effective approaches and opportunities to decrease the environmental footprint and improve resource efficiencies of imaging modalities, such as energy savings, waste and toxicity reduction, and waste management, across various health care settings.[354]

There remains a need for more research concerning the impact of PE diagnostic pathways on both the environment and population health. Furthermore, there are opportunities for deeper exploration of the ethical analyses related to certain patient populations and comparison of the implementation and provision of the various diagnostic pathways and imaging modalities in different jurisdictions in Canada.

Conclusions

The findings in the overview of reviews indicate that, while similar, the clinical decision rules differ in their ability to identify a low-risk group of patients. Therefore, the economic analysis found that their cost-effectiveness varies depending on the trade-off between sensitivity and specificity. There is a risk of misdiagnosis with more false-negative findings and, with increasing willingness to pay, PERC as part of the diagnostic pathway is not cost-effective. With respect to imaging modalities, CT had the highest DTA and was the most cost-effective imaging modality. However, CT also involved higher radiation exposure than all the other modalities and is not appropriate for all patients, for example, patients who are pregnant, who have severe kidney disease, or who have an allergy to contrast. For these patients, V/Q SPECT may be an appropriate alternative as the diagnostic imaging modality within the diagnostic pathway, as seen in the clinical and economic evidence.

Patient factors and provider knowledge and choice can influence the initial assessment and subsequent investigation of suspected PE. As well, the variability of access to PE diagnostic tools and tests used across Canada and in urban, rural, and remote settings may influence PE diagnosis. More specifically, resources, including staffing and access to tests, scans, and imaging, are differentially located across the country. Policies and protocols can be established to support diagnostic strategies for PE. Additional support for PE diagnosis can also come from clinical guidelines and other tools, such as computer prompts. The ethical issues associated with patients, clinicians, health care organizations, the health care system, and society are grounded in several principles, including beneficence, nonmaleficence, autonomy, and justice. The use of CT seems to be the most likely candidate for the ethical provision of PE diagnosis, as the results indicated that it was the most cost-effective modality compared with the others.

References

1. Sadigh G, Kelly A, Cronin P. Challenges, controversies, and hot topics in pulmonary embolism imaging. AJR Am J Roentgenol [Internet]. 2011 [cited 2016 Jul 19];196(3):497-515. Available from: http://www.ajronline.org/doi/full/10.2214/AJR.10.5830
2. Ma Y, Yan S, Zhou L, Yuan DT. Competitive assessments of pulmonary embolism: noninvasiveness versus the gold standard. Vascular. 2016;24(2):217-24.
3. Thompson B. Patient education: pulmonary embolism (beyond the basics). In: Post TW, editor. UpToDate [Internet]. Waltham (MA): UpToDate; 2016 [cited 2016 Sep 9]. Available from: http://www.uptodate.com/contents/pulmonary-embolism-beyond-the-basics Subscription required.
4. Tapson VF. Acute pulmonary embolism. N Engl J Med. 2008 Mar 6;358(10):1037-52.
5. Moser KM, Fedullo PF, LitteJohn JK, Crawford R. Frequent asymptomatic pulmonary embolism in patients with deep venous thrombosis. JAMA. 1994 Jan 19;271(3):223-5.
6. Sweet PH, III, Armstrong T, Chen J, Masliah E, Witucki P. Fatal pulmonary embolism update: 10 years of autopsy experience at an academic medical center. JRSM Short Rep [Internet]. 2013 [cited 2016 Aug 17];4(9). Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3767072
7. Canadian Agency for Drugs and Technologies in Health. Detection of pulmonary embolsim [Internet]. Ottawa: CADTH; 2012. [cited 2016 Jul 19]. Available from: https://www.cadth.ca/resources/detection-pulmonary-embolism
8. Masotti L, Ray P, Righini M, Le GG, Antonelli F, Landini G, et al. Pulmonary embolism in the elderly: a review on clinical, instrumental and laboratory presentation. Vasc Health Risk Manag [Internet]. 2008 [cited 2016 Sep 9];4(3):629-36. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2515422
9. Kline JA, Hernandez-Nino J, Jones AE, Rose GA, Norton HJ, Camargo CA, Jr. Prospective study of the clinical features and outcomes of emergency department patients with delayed diagnosis of pulmonary embolism. Acad Emerg Med. 2007 Jul;14(7):592-8.
10. Goldhaber SZ, Visani L, De RM. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet. 1999 Apr 24;353(9162):1386-9.
11. Laporte S, Mismetti P, Decousus H, Uresandi F, Otero R, Lobo JL, et al. Clinical predictors for fatal pulmonary embolism in 15,520 patients with venous thromboembolism: findings from the Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) Registry. Circulation. 2008 Apr 1;117(13):1711-6.
12. Thaler J, Pabinger I, Ay C. Anticoagulant Treatment of Deep Vein Thrombosis and Pulmonary Embolism: The Present State of the Art. Front Cardiovasc Med [Internet]. 2015 [cited 2016 Aug 8];2:30. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4671349
13. Pollack CV, Schreiber D, Goldhaber SZ, Slattery D, Fanikos J, O'Neil BJ, et al. Clinical characteristics, management, and outcomes of patients diagnosed with acute pulmonary embolism in the emergency department: initial report of EMPEROR (Multicenter Emergency Medicine Pulmonary Embolism in the Real World Registry). J Am Coll Cardiol. 2011 Feb 8;57(6):700-6.
14. Konstantinides SV. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J [Internet]. 2014 Dec 1 [cited 2016 Aug 9];35(45):3145-6. Available from: http://eurheartj.oxfordjournals.org/content/ehj/35/45/3145.full.pdf
15. White RH. The epidemiology of venous thromboembolism. Circulation. 2003 Jun 17;107(23 Suppl 1):I4-I8.
16. Skinner S. Pulmonary embolism: assessment and imaging. Aust Fam Physician [Internet]. 2013;42(9):628-32. Available from: http://www.racgp.org.au/download/Documents/AFP/2013/Sep/201309skinner.pdf
17. Kearon C. Natural history of venous thromboembolism. Circulation. 2003 Jun 17;107(23 Suppl 1):I22-I30.
18. Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton LJ, III. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. Ann Intern Med. 2005 Nov 15;143(10):697-706.
19. Pasha SM, Klok FA, Snoep JD, Mos IC, Goekoop RJ, Rodger MA, et al. Safety of excluding acute pulmonary embolism based on an unlikely clinical probability by the Wells rule and normal D-dimer concentration: a meta-analysis. Thromb Res. 2010 Apr;125(4):e123-e127.
20. Boka K. Pulmonary embolism clinical scoring systems [Internet]. New York: Medscape; 2015. [cited 2016 Jul 20]. Available from: http://emedicine.medscape.com/article/1918940-overview
21. Raja AS, Greenberg JO, Qaseem A, Denberg TD, Fitterman N, Schuur JD, et al. Evaluation of Patients With Suspected Acute Pulmonary Embolism: Best Practice Advice From the Clinical Guidelines Committee of the American College of Physicians. Ann Intern Med. 2015 Nov 3;163(9):701-11.
22. Kabrhel C, Camargo CA, Jr., Goldhaber SZ. Clinical gestalt and the diagnosis of pulmonary embolism: does experience matter? Chest. 2005 May;127(5):1627-30.
23. Thompson BT. Clinical presentation, evaluation, and diagnosis of the adult with suspected acute pulmonary embolism. In: Post TW, editor. UpToDate [Internet]. Waltham (MA): UpToDate; 2016 Aug 8 [cited 2016 Nov 23]. Available from: www.uptodate.com Subscription required.
24. Shen JH, Chen HL, Chen JR, Xing JL, Gu P, Zhu BF. Comparison of the Wells score with the revised Geneva score for assessing suspected pulmonary embolism: a systematic review and meta-analysis. J Thromb Thrombolysis. 2016 Apr;41(3):482-92.
25. Wang RC, Bent S, Weber E, Neilson J, Smith-Bindman R, Fahimi J. The Impact of Clinical Decision Rules on Computed Tomography Use and Yield for Pulmonary Embolism: A Systematic Review and Meta-analysis. Ann Emerg Med. 2016 Jun;67(6):693-701.

26. Lucassen W, Geersing GJ, Erkens PM, Reitsma JB, Moons KG, Büller H, et al. Clinical decision rules for excluding pulmonary embolism: a meta-analysis. Ann Intern Med. 2011 Oct 4;155(7):448-60.

27. Screaton NJ, Karia S. Commentary on " Ten years of imaging for pulmonary embolism: too many scans or the tip of an iceberg?". Clin Radiol. 2016;70:1355-6.

28. Riley RS, Gilbert AR, Dalton JB, Pai S, McPherson RA. Widely Used Types and Clinical Applications of D-Dimer Assay. Lab Med. 2016 May;47(2):90-102.

29. Geersing GJ, Janssen KJ, Oudega R, Bax L, Hoes AW, Reitsma JB, et al. Excluding venous thromboembolism using point of care D-dimer tests in outpatients: a diagnostic meta-analysis. Bmj [Internet]. 2009 [cited 2016 Jul 8];339:b2990. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2727580

30. Lucassen WA, Erkens PM, Geersing GJ, Buller HR, Moons KG, Stoffers HE, et al. Qualitative point-of-care D-dimer testing compared with quantitative D-dimer testing in excluding pulmonary embolism in primary care. J Thromb Haemost. 2015 Jun;13(6):1004-9.

31. Kline JA, Mitchell AM, Kabrhel C, Richman PB, Courtney DM. Clinical criteria to prevent unnecessary diagnostic testing in emergency department patients with suspected pulmonary embolism. J Thromb Haemost [Internet]. 2004 Aug [cited 2017 Jun 1];2(8):1247-55. Available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1538-7836.2004.00790.x/abstract

32. Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galie N, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J [Internet]. 2014 Nov 14 [cited 2016 Aug 12];35(43):3033-69. Available from: http://eurheartj.oxfordjournals.org/content/ehj/35/43/3033.full.pdf

33. Da Costa Rodrigues J, Alzuphar S, Combescure C, Le Gal G, Perrier A. Diagnostic characteristics of lower limb venous compression ultrasonography in suspected pulmonary embolism: a metaanalysis. J Thromb Haemost. 2016 Sep;14(9):1765-72.

34. Squizzato A, Galli L, Gerdes V. Point-of-care ultrasound in the diagnosis of pulmonary embolism [Internet]. Crit Ultrasound J. 2016 [cited 2016 Jul 20];7(7). Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4447771/pdf/13089_2015_Article_25.pdf

35. Van der Pol LM, Mairuhu ATA, Tromeur C, Couturaud F, Huisman MV, Klok FA. Use of clinical prediction rules and D-dimer tests in the diagnostic management of pregnant patients with suspected acute pulmonary embolism. Blood Rev. 2017 Mar;31(2):31-36.

36. Smith C, Mensah A, Mal S, Worster A. Is pretest probability assessment on emergency department patients with suspected venous thromboembolism documented before SimpliRED D-dimer testing? CJEM. 2008 Nov;10(6):519-23.

37. Corwin MT, Donohoo JH, Partridge R, Egglin TK, Mayo-Smith WW. Do emergency physicians use serum D-dimer effectively to determine the need for CT when evaluating patients for pulmonary embolism? Review of 5,344 consecutive patients. AJR Am J Roentgenol. 2009 May;192(5):1319-23.

38. Choosing Wisely. [Internet]. Philadelphia (PA): ABIM Foundation. Avoid CT pulmonary angiography in emergency department patients with a low-pretest probability of pulmonary embolism and either a negative Pulmonary Embolism Rule-Out Criteria (PERC) or a negative D-dimer; 2014 Oct 27 [cited 2016 Jul 27]. Available from: http://www.choosingwisely.org/clinician-lists/acep-ct-pulmonary-angiography-in-ed-patients/

39. Emergency medicine: ten things physicians and patients should question [Internet]. Toronto (ON): Choosing Wisely Canada; 2017. [cited 2017 Oct 16]. Available from: https://choosingwiselycanada.org/emergency-medicine/ Question 7.

40. Dogan H, DE RA, Geleijins J, Huisman MV, Kroft LJ. The role of computed tomography in the diagnosis of acute and chronic pulmonary embolism. Diagn Interv Radiol [Internet]. 2015 Jul [cited 2016 Aug 8];21(4):307-16. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4498425

41. van Beek EJ, Brouwerst EM, Song B, Stein PD, Oudkerk M. Clinical validity of a normal pulmonary angiogram in patients with suspected pulmonary embolism--a critical review. Clin Radiol. 2001 Oct;56(10):838-42.

42. Canadian medical imaging inventory [Internet]. Ottawa (ON): CADTH; 2016 Mar 31. [cited 2017 Jul 27]. Available from: https://www.cadth.ca/imaginginventory

43. Computed tomography [Internet]. Geneva (CH): World Health Organization (WHO); 2017. [cited 2017 Jul 27]. Available from: http://www.who.int/diagnostic_imaging/imaging_modalities/dim_comptomography/en/

44. Ionizing radiation in pregnant women: a review of the safety and guidelines [Internet]. Ottawa (ON): CADTH; 2015 Jun 9. [cited 2017 Jul 27]. (CADTH rapid response report: summary with critical appraisal). Available from: https://www.cadth.ca/sites/default/files/pdf/htis/june-2015/RC0665-IonizingRadiation-Pregnancy-Final.pdf

45. Radiation emissions from computed tomography: a review of the risk of cancer and guidelines [Internet]. Ottawa (ON): CADTH; 2014 Jun 4. [cited 2017 Jul 27]. (CADTH rapid response report: summary with critical appraisal). Available from: https://www.cadth.ca/sites/default/files/pdf/htis/jul-2014/RC0558%20CT%20Radiation%20Emission%20Final.pdf

46. Magnetic resonance imaging [Internet]. Geneva (CH): World Health Organization (WHO); 2017. [cited 2017 Jul 27]. Available from: http://www.who.int/diagnostic_imaging/imaging_modalities/dim_magresimaging/en/

47. Consiglio N. MRI and patient safety. J Med Imaging Radiat Sci. 2006;37(2):5-9.

48. Shellock FG. MRIsafety.com [Internet]. [Playa Del Ray (CA)]: Shellock R & D Services, Inc.; 2017. [cited 2017 Jul 27]. Available from: http://www.mrisafety.com/SafetyInfog.asp

49. Shellock FG, Crues JV, Karacozoff AM. MRI bioeffects, safety, and patient management. Los Angeles (CA): Biomedical Research Publishing Group; [2014].

50. Nuclear medicine [Internet]. Geneva (CH): World Health Organization (WHO); 2017. [cited 2017 Jul 27]. Available from: http://www.who.int/diagnostic_imaging/imaging_modalities/dim_nuclearmed/en/

51. Wongwaisayawan S, Suwannanon R, Sawatmongkorngul S, Kaewlai R. Emergency Thoracic US: The Essentials. Radiographics. 2016 May;36(3):640-59.

52. Hunsaker AR, Lu MT, Goldhaber SZ, Rybicki FJ. Imaging in acute pulmonary embolism with special clinical scenarios. Circ Cardiovasc Imaging. 2010 Jul;3(4):491-500.

53. Mos I, Klok F, Kroft L, de Roos A, Huisman M. Imaging tests in the diagnosis of pulmonary embolism. Semin Respir Crit Care Med. 2012;33:138-43.

54. Schiebler ML, Nagle SK, Francois CJ, Repplinger MD, Hamedani AG, Vigen KK, et al. Effectiveness of MR angiography for the primary diagnosis of acute pulmonary embolism: clinical outcomes at 3 months and 1 year. J Magn Reson Imaging [Internet]. 2013 Oct [cited 2016 Oct 7];38(4):914-25. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3970266

55. Le Roux PY, Robin P, Delluc A, Abgral R, Duc-Pennec AL, Nowak E, et al. V/Q SPECT interpretation for pulmonary embolism diagnosis: Which criteria to use? J Nucl Med [Internet]. 2013 [cited 2016 Oct 7];54(7):1077-81. Available from: http://jnm.snmjournals.org/content/54/7/1077.full.pdf+html

56. Sheh S, Bellin E, Freeman K, Haramati L. Pulmonary embolism diagnosis and mortality with pulmonary CT angiography versus ventilation-perfusion scintigraphy: evidence of overdiagnosis with CT? AJR Am J Roentgenol [Internet]. 2012 [cited 2016 Nov 17];198:1340-5. Available from: http://www.ajronline.org/doi/pdf/10.2214/AJR.11.6426

57. Anderson DR, Kahn SR, Rodger MA, Kovacs MJ, Morris T, Hirsch A, et al. Computed tomographic pulmonary angiography vs ventilation-perfusion lung scanning in patients with suspected pulmonary embolism: a randomized controlled trial. JAMA. 2007 Dec 19;298(23):2743-53.

58. Smith-Bindman R, Lipson J, Marcus R, Kim KP, Mahesh M, Gould R, et al. Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. Arch Intern Med [Internet]. 2009 Dec 14 [cited 2016 Jul 27];169(22):2078-86. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4635397

59. Phillips JJ, Straiton J, Staff RT. Planar and SPECT ventilation/perfusion imaging and computed tomography for the diagnosis of pulmonary embolism: A systematic review and meta-analysis of the literature, and cost and dose comparison. Eur J Radiol. 2015 Jul;84(7):1392-400.

60. Robert-Ebadi H, Le Gal G, Righini M. Evolving imaging techniques in diagnostic strategies of pulmonary embolism. Exp Rev Cardiovasc Therapy. 2016;14(4):495-503.

61. Morgan DJ, Dhruva SS, Coon ER, Wright SM, Korenstein D. 2017 Update on Medical Overuse: A Systematic Review. JAMA Intern Med. 2018 Jan 1;178(1):110-115.

62. Le Gal G, Bounameaux H. Diagnosing pulmonary embolism: running after the decreasing prevalence of cases among suspected patients. J Thromb Haemost. 2004 Aug;2(8):1244-6.

63. Schissler AJ, Rozenshtein A, Kulon ME, Pearson GD, Green RA, Stetson PD, et al. CT pulmonary angiography: increasingly diagnosing less severe pulmonary emboli. PLoS ONE [Internet]. 2013 [cited 2016 Nov 17];8(6):e65669. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3680477

64. Walen S, Leijstra MA, Uil SM, Boomsma MF, van den Berg JW. Diagnostic yield of CT thorax angiography in patients suspected of pulmonary embolism: independent predictors and protocol adherence. Insights Imaging [Internet]. 2014 Apr [cited 2016 Oct 12];5(2):231-6. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3999363

65. Mamlouk MD, vanSonnenberg E, Gosalia R, Drachman D, Gridley D, Zamora JG, et al. Pulmonary embolism at CT angiography: implications for appropriateness, cost, and radiation exposure in 2003 patients. Radiology. 2010 Aug;256(2):625-32.

66. Shankar S, Gour A, Khanijao S, Taha O, Kitchloo K, Gorukanti P, et al. The diagnostic yield of computed tomographic pulmonary angiography (CTPA) for pulmonary diseases [abstract]. Chest [Internet]. 2016 [cited 2016 Aug 30];149(4 Suppl):A521. Available from: http://journal.publications.chestnet.org/article.aspx?articleid=2511929

67. Stein PD, Fowler SE, Goodman LR, Gottschalk A, Hales CA, Hull RD, et al. Multidetector computed tomography for acute pulmonary embolism. N Engl J Med. 2006 Jun 1;354(22):2317-27.

68. Miller WT, Marinari LA, Mahne A. Frequency and causes of false-positive CTPA exams in community hospitals [abstract]. Chest [Internet]. 2009 [cited 2016 Aug 30];136(4 Suppl):14S. Available from: http://journal.publications.chestnet.org/article.aspx?articleid=1095863

69. Hutchinson B, Navin P, Marom E, Truong M, Bruzzi J. Overdiagnosis of pulmonary embolism by pulmonary CT angiography. AJR Am J Roentgenol [Internet]. 2015;205:271-7.

70. Hogg K, Brown G, Dunning J, Wright J, Carley S, Foex B, et al. Diagnosis of pulmonary embolism with CT pulmonary angiography: a systematic review. Emerg Med J. 2006 Mar [cited 2016 Oct 13];23(3):172-8. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2464412

71. Lucassen WA, Beenen LF, Buller HR, Erkens PM, Schaefer-Prokop CM, van den Berk I, et al. Concerns in using multi-detector computed tomography for diagnosing pulmonary embolism in daily practice. A cross-sectional analysis using expert opinion as reference standard. Thromb Res [Internet]. 2013 Feb [cited 2016 Oct 7];131(2):145-9. Available from: http://www.sciencedirect.com/science/article/pii/S0049384812008481

72. Stein PD, Goodman LR, Hull RD, Dalen JE, Matta F. Diagnosis and management of isolated subsegmental pulmonary embolism: review and assessment of the options. Clin Appl Thromb Hemost. 2012 Jan;18(1):20-6.

73. Wiener RS, Schwartz LM, Woloshin S. Time trends in pulmonary embolism in the United States: evidence of overdiagnosis. Arch Intern Med. 2011 May 9;171(9):831-7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3140219

74. Glassroth J. Imaging of pulmonary embolism: too much of a good thing? JAMA. 2007 Dec 19;298(23):2788-9.

75. Burge AJ, Freeman KD, Klapper PJ, Haramati LB. Increased diagnosis of pulmonary embolism without a corresponding decline in mortality during the CT era. Clin Radiol. 2008 Apr;63(4):381-6.

76. Wilbur J, Shian B. Diagnosis of deep venous thrombosis and pulmonary embolism. Am Fam Physician [Internet]. 2012 [cited 2016 Jul 19];86(10):913-9. Available from: http://www.aafp.org/afp/2012/1115/p913.pdf

77. Stein P, Sostman D, Dalen J, Bailey D, Bajc M, Goldhaber S, et al. Controversies in diagnosis of pulmonary embolism. Clin Appl Thromb Hemost. 2011;17(2):140-9.

78. Tapson VF. Overview of the treatment, prognosis, and follow-up of acute pulmonary embolism in adults. In: Post TW, editor. UpToDate [Internet]. Waltham (MA): UpToDate; 2016 Jul 19 [cited 2016 Jul 27]. Available from: http://www.uptodate.com/contents/overview-of-the-treatment-prognosis-and-follow-up-of-acute-pulmonary-embolism-in-adults

79. PRESS peer review electronic search strategies: 2015 guideline explanation and elaboration (PRESS E&E) [Internet]. Ottawa: CADTH; 2016 Jan. [cited 2016 Sep 13]. (CADTH methods and guidelines). Available from: https://www.cadth.ca/sites/default/files/pdf/CP0015_PRESS_Update_Report_2016.pdf

80. Zhou M, Hu Y, Long X, Liu D, Liu L, Dong C, et al. Diagnostic performance of magnetic resonance imaging for acute pulmonary embolism: a systematic review and meta-analysis. J Thromb Haemost. 2015 Sep;13(9):1623-34.

81. Squizzato A, Pomero F, Allione A, Priotto R, Riva N, Huisman MV, et al. Diagnostic accuracy of magnetic resonance imaging in patients with suspected pulmonary embolism: a bivariate meta-analysis. Thromb Res. 2017 Apr 7;154:64-72.

82. Squizzato A, Rancan E, Dentali F, Bonzini M, Guasti L, Steidl L, et al. Diagnostic accuracy of lung ultrasound for pulmonary embolism: a systematic review and meta-analysis. J Thromb Haemost. 2013 Jul;11(7):1269-78.

83. Whiting P, Savovic J, Higgins JP, Caldwell DM, Reeves BC, Shea B, et al. ROBIS: A new tool to assess risk of bias in systematic reviews was developed. J Clin Epidemiol [Internet]. 2016 Jan [cited 2016 Jul 27];69:225-34. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4687950

84. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011 Oct 18;155(8):529-36.

85. Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions [Internet]. Version 5.1.0. London (England): The Cochrane Collaboration; 2011 Mar. 8: Assessing risk of bias in included studies. [cited 2016 Jul 27]. Available from: http://handbook.cochrane.org/chapter_8/8_assessing_risk_of_bias_in_included_studies.htm

86. Sterne JAC, Higgins JPT, Reeves BC, on behalf of the development group. The ROBINS-I tool (Risk of bias in non-randomized studies - of Interventions) [Internet]. [Oxford, United Kingdom]: The Cochrane Collaboration. 2016 Mar [cited 2016 Jul 27]. Available from: http://www.riskofbias.info

87. Moga C, Guo B, Schopflocher D, Harstall C. Development of a quality appraisal tool for case series studies using a modified Delphi technique [Internet]. Edmonton (AB): Institute of Health Economics; 2012 Mar 7. [cited 2017 Aug 29]. Available from: https://www.ihe.ca/publications/development-of-a-quality-appraisal-tool-for-case-series-studies-using-a-modified-delphi-technique

88. Rutter CM, Gatsonis CA. A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. Stat Med. 2001 Oct 15;20(19):2865-84.

89. Dendukuri N, Schiller I, Joseph L, Pai M. Bayesian meta-analysis of the accuracy of a test for tuberculous pleuritis in the absence of a gold standard reference. Biometrics [Internet]. 2012 Dec [cited 2016 Jul 27];68(4):1285-93. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3728030

90. Sinclair A, Xie X, Teltscher M, Dendukuri N. Systematic review and meta-analysis of a urine-based pneumococcal antigen test for diagnosis of community-acquired pneumonia caused by Streptococcus pneumoniae. J Clin Microbiol [Internet]. 2013 Jul [cited 2016 Jul 27];51(7):2303-10. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3697702

91. Novielli N, Sutton AJ, Cooper NJ. Meta-analysis of the accuracy of two diagnostic tests used in combination: application to the ddimer test and the wells score for the diagnosis of deep vein thrombosis. Value Health. 2013 Jun;16(4):619-28.

92. Novielli N, Cooper NJ, Sutton AJ. Evaluating the cost-effectiveness of diagnostic tests in combination: is it important to allow for performance dependency? Value Health. 2013 Jun;16(4):536-41.

93. Wang Z, Dendukuri N, Joseph L. Understanding the effects of conditional dependence in research studies involving imperfect diagnostic tests. Stat Med. 2017 Feb 10;36(3):466-80.

94. Kearon C, Ginsberg JS, Douketis J, Turpie AG, Bates SM, Lee AY, et al. An evaluation of D-dimer in the diagnosis of pulmonary embolism: a randomized trial. Ann Intern Med. 2006 Jun 6;144(11):812-21.

95. Macaskill P, Gatsonis C, Deeks J, Harbord R, Takwoingi Y. Cochrane handbook for systematic reviews of diagnostic test accuracy [Internet]. Version 1.0. London: The Cochrane Collaboration; 2010. Chapter 10. Analysing and presenting results. [cited 2016 Aug 9]. Available from: http://methods.cochrane.org/sdt/sites/methods.cochrane.org.sdt/files/uploads/Chapter%2010%20-%20Version%201.0.pdf

96. Spiegelhalter DJ, Best NG, Carlin BP, van der Linde A. Bayesian measures of model complexity and fit (with discussion). J R Statist Soc B. 2002;64(Part 4):583-639.

97. The R project for statistical computing [Internet]. Vienna: R Foundation; 2016. [cited 2016 Aug 9]. Available from: https://www.r-project.org/

98. Lunn DJ, Thomas A, Best N, Spiegelhalter D. WinBUGS - A Bayesian modelling framework: concepts, structure, and extensibility. Statistics and Computing. 2000 Oct;10(4):325-37.

99. Doebler P. Mada: meta-analysis of diganostic accuracy [Internet]. Version 0.5.7. [place uknown]: Comprehensive R Archive Network; 2015. [cited 2016 Aug 9]. Available from: https://cran.r-project.org/web/packages/mada/index.html

100. Optimal strategies for the diagnosis of acute pulmonary embolism: a health technology assessment - project protocol [Internet]. Ottawa: CADTH; 2016 Sep 29. [cited 2017 Jun 28]. (CADTH optimal use report vol. 6, no. 3a). Available from: https://www.cadth.ca/optimal-strategies-diagnosis-acute-pulmonary-embolism-health-technology-assessment-project-protocol

101. Higgins JP. Cochrane handbook for systematic reviews of interventions [Internet]. Version 5.1.0. London (England): The Cochrane Collaboration; 2011. [cited 2016 Aug 9]. Available from: http://handbook.cochrane.org/

102. Conducting meta-analyses in R with the metafor package. Journal of Statistical Software [Internet]. 2010 [cited 2016 Aug 8];36(3). Available from: https://www.jstatsoft.org/article/view/v036i03

103. Siccama RN, Janssen KJ, Verheijden NA, Oudega R, Bax L, van Delden JJ, et al. Systematic review: diagnostic accuracy of clinical decision rules for venous thromboembolism in elderly. Ageing Res Rev. 2011 Apr;10(2):304-13.

104. van Es N, van der Hulle T, van Es J, den Exter PL, Douma RA, Goekoop RJ, et al. Wells Rule and d-Dimer testing to rule out pulmonary embolism: a systematic review and individual-patient data meta-analysis. Ann Intern Med. 2016 Aug 16;165(4):253-61.

105. Sanders S, Doust J, Glasziou P. A systematic review of studies comparing diagnostic clinical prediction rules with clinical judgment. PLoS ONE [Internet]. 2015;10(6):e0128233. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4454557

106. Pernod G, Maignan M, Marlu R. Questioning the use of an age-adjusted D-dimer threshold to exclude venous thromboembolism: analysis of individual patient data from two diagnostic studies: comment. J Thromb Haemost. 2016;14(12):2553-4.

107. Bosson JL, Pernod G, Joubin E, Hamidfar R, Bricault I, Hugon V, et al. Non-conform diagnostic management of pulmonary embolism suspected patients is responsible for a higher risk of thrombotic event occurrence. J Mal Vasc. 2007;32(1):15-22.

108. Galipienzo J, Garcia de Tena J, Flores J, Alvarez C, Garcia-Avello A, Arribas I. Effectiveness of a diagnostic algorithm combining clinical probability, D-dimer testing, and computed tomography in patients with suspected pulmonary embolism in an emergency department. Rom J Intern Med. 2012 Jul;50(3):195-202.

109. Ghanima W, Almaas V, Aballi S, Dorje C, Nielssen BE, Holmen LO, et al. Management of suspected pulmonary embolism (PE) by D-dimer and multi-slice computed tomography in outpatients: an outcome study. J Thromb Haemost. 2005 Sep;3(9):1926-32.

110. Hogg K, Dawson D, kway-Jones K. Outpatient diagnosis of pulmonary embolism: the MIOPED (Manchester Investigation Of Pulmonary Embolism Diagnosis) study. Emerg Med J [Internet]. 2006 Feb [cited 2016 Oct 13];23(2):123-7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2564034

111. Jouveshomme S, Bohn I, Cazaban A. Diagnosis of pulmonary embolism in hospitalised patients: retrospective survey of an institutional standard. Eur Respir J [Internet]. 2007 Dec [cited 2016 Oct 6];30(6):1117-23. Available from: http://erj.ersjournals.com/content/erj/30/6/1117.full.pdf

112. Miniati M, Monti S, Bauleo C, Scoscia E, Tonelli L, Dainelli A, et al. A diagnostic strategy for pulmonary embolism based on standardised pretest probability and perfusion lung scanning: a management study. Eur J Nucl Med Mol Imaging. 2003 Nov;30(11):1450-6.

113. Miron MJ, Perrier A, Bounameaux H, de Moerloose P, Slosman DO, Didier D, et al. Contribution of noninvasive evaluation to the diagnosis of pulmonary embolism in hospitalized patients. Eur Respir J [Internet]. 1999 Jun [cited 2016 Dec 6];13(6):1365-70. Available from: http://erj.ersjournals.com/content/erj/13/6/1365.full.pdf

114. Perrier A, Roy PM, Sanchez O, Le Gal G, Meyer G, Gourdier AL, et al. Multidetector-row computed tomography in suspected pulmonary embolism. N Engl J Med [Internet]. 2005 Apr 28;352(17):1760-8. Available from: http://www.nejm.org/doi/pdf/10.1056/NEJMoa042905

115. Vigo M, Pesavento R, Bova C, Porro F, Ghirarduzzi A, Bazzan M, et al. The value of four-detector row spiral computed tomography for the diagnosis of pulmonary embolism. Semin Thromb Hemost. 2006 Nov;32(8):831-7.

116. Righini M, Le Gal G, Aujesky D, Roy PM, Sanchez O, Verschuren F, et al. Diagnosis of pulmonary embolism by multidetector CT alone or combined with venous ultrasonography of the leg: a randomised non-inferiority trial. Lancet. 2008 Apr 19;371(9621):1343-52.

117. Lechleitner P, Riedl B, Raneburger W, Gamper G, Theurl A, Lederer A. Chest sonography in the diagnosis of pulmonary embolism: a comparison with MRI angiography and ventilation perfusion scintigraphy. Ultraschall Med. 2002 Dec;23(6):373-8.

118. Galipienzo J, Garcia de Tena J, Flores J, Álvarez C, Alonso-Viteri S, Ruiz A. Safety of withholding anticoagulant therapy in patients with suspected pulmonary embolism with a negative multislice computed tomography pulmonary angiography. Eur J Intern Med. 2010 Aug;21(4):283-8.

119. Lu GM, Luo S, Meinel FG, McQuiston AD, Zhou CS, Kong X, et al. High-pitch computed tomography pulmonary angiography with iterative reconstruction at 80 kVp and 20 mL contrast agent volume. Eur Radiol. 2014 Dec;24(12):3260-8.

120. Thieme SF, Graute V, Nikolaou K, Maxien D, Reiser MF, Hacker M, et al. Dual Energy CT lung perfusion imaging - correlation with SPECT/CT. Eur J Radiol. 2012;81(2):360-5.

121. Wang F, Fang W, Lv B, Lu JG, Xiong CM, Ni XH, et al. Comparison of lung scintigraphy with multi-slice spiral computed tomography in the diagnosis of pulmonary embolism. Clin Nucl Med. 2009 Jul;34(7):424-7.

122. Reinartz P, Wildberger JE, Schaefer W, Nowak B, Mahnken AH, Buell U. Tomographic imaging in the diagnosis of pulmonary embolism: a comparison between V/Q lung scintigraphy in SPECT technique and multislice spiral CT. J Nucl Med [Internet]. 2004 Sep [cited 2016 Dec 1];45(9):1501-8. Available from: http://iv.iiarjournals.org/content/19/5/873.long

123. Winer-Muram HT, Rydberg J, Johnson MS, Tarver RD, Williams MD, Shah H, et al. Suspected acute pulmonary embolism: evaluation with multi-detector row CT versus digital subtraction pulmonary arteriography. Radiology [Internet]. 2004 Dec [cited 2016 Dec 1];233(3):806-15. Available from: http://pubs.rsna.org/doi/pdf/10.1148/radiol.2333031744

124. Nilsson T, Soderberg M, Lundqvist G, Cederlund K, Larsen F, Rasmussen E, et al. A comparison of spiral computed tomography and latex agglutination D-dimer assay in acute pulmonary embolism using pulmonary arteriography as gold standard. Scand Cardiovasc J. 2002 Dec;36(6):373-7.

125. Qanadli SD, Hajjam ME, Mesurolle B, Barre O, Bruckert F, Joseph T, et al. Pulmonary embolism detection: prospective evaluation of dual-section helical CT versus selective pulmonary arteriography in 157 patients. Radiology [Internet]. 2000 Nov [cited 2016 Dec 1];217(2):447-55. Available from: http://pubs.rsna.org/doi/pdf/10.1148/radiology.217.2.r00nv01447

126. Coche E, Verschuren F, Keyeux A, Goffette P, Goncette L, Hainaut P, et al. Diagnosis of acute pulmonary embolism in outpatients: comparison of thin-collimation multi-detector row spiral CT and planar ventilation-perfusion scintigraphy. Radiology [Internet]. 2003 Dec [cited 2016 Dec 1];229(3):757-65. Available from: http://pubs.rsna.org/doi/pdf/10.1148/radiol.2293020889

127. Mahdavi R, Caronia J, Fayyaz J, Panagopoulos G, Lessnau KD, Scharf SC, et al. Agreement between SPECT V/Q scan and CT angiography in patients with high clinical suspicion of PE. Ann Nucl Med. 2013 Nov;27(9):834-8.

128. Gutte H, Mortensen J, Jensen CV, Johnbeck CB, von der RP, Petersen CL, et al. Detection of pulmonary embolism with combined ventilation-perfusion SPECT and low-dose CT: head-to-head comparison with multidetector CT angiography. J Nucl Med [Internet]. 2009 Dec [cited 2016 Oct 12];50(12):1987-92. Available from: http://jnm.snmjournals.org/content/50/12/1987.full.pdf+html

129. Okada M, Kunihiro Y, Nakashima Y, Nomura T, Kudomi S, Yonezawa T, et al. Added value of lung perfused blood volume images using dual-energy CT for assessment of acute pulmonary embolism. Eur J Radiol. 2015 Jan;84(1):172-7.

130. Megyeri B, Christe A, Schindera ST, Horkay E, Sikula J, Cullmann JL, et al. Accuracy of computed tomography angiography in the detection of pulmonary embolism in patients with high body weight. Eur J Intern Med. 2014 Oct;25(8):724-30.

131. He J, Wang F, Dai HJ, Li M, Wang Q, Yao Z, et al. Chinese multi-center study of lung scintigraphy and CT pulmonary angiography for the diagnosis of pulmonary embolism. Int J Cardiovasc Imaging. 2012 Oct;28(7):1799-805.

132. Blachere H, Latrabe V, Montaudon M, Valli N, Couffinhal T, Raherisson C, et al. Pulmonary embolism revealed on helical CT angiography: comparison with ventilation-perfusion radionuclide lung scanning. AJR Am J Roentgenol [Internet]. 2000 Apr [cited 2017 Jan 16];174(4):1041-7. Available from: http://www.ajronline.org/doi/pdf/10.2214/ajr.174.4.1741041

133. Stein PD, Beemath A, Quinn DA, Olson RE, Goodman LR, Gottschalk A, et al. Usefulness of multidetector spiral computed tomography according to age and gender for diagnosis of acute pulmonary embolism. Am J Cardiol. 2007 May 1;99(9):1303-5.

134. Gupta A, Raja AS, Khorasani R. Examining clinical decision support integrity: is clinician self-reported data entry accurate? J Am Med Inform Assoc [Internet]. 2014 Jan [cited 2016 Oct 4];21(1):23-6. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3912709

135. Li H, Cheng Y, Liu B, Lv Y, Guo Y, Wang G, et al. Diagnostic value of three-dimensional contrast-enhanced MR pulmonary angiography with liver acquisition volume acceleration sequence on a 3-T MR system for acute pulmonary embolism. International Journal of Clinical and Experimental Medicine [Internet]. 2017 [cited 2017 Feb 16];10(1):872-80. Available from: http://www.ijcem.com/files/ijcem0038614.pdf

136. Pasin L, Zanon M, Moreira J, Moreira AL, Watte G, Marchiori E, et al. Magnetic resonance imaging of pulmonary embolism: diagnostic accuracy of unenhanced MR and influence in mortality rates. Lung. 2017 Apr;195(2):193-199.

137. Nyrén S, Nordgren Rogberg A, Vargas Paris R, Bengtsson B, Westerlund E, Lindholm P. Detection of pulmonary embolism using repeated MRI acquisitions without respiratory gating: a preliminary study. Acta Radiol. 2017 Mar;58(3):272-278.

138. Zhang LJ, Luo S, Yeh BM, Zhou CS, Tang CX, Zhao Y, et al. Diagnostic accuracy of three-dimensional contrast-enhanced MR angiography at 3-T for acute pulmonary embolism detection: comparison with multidetector CT angiography. Int J Cardiol. 2013 Oct 12;168(5):4775-83.

139. Revel MP, Sanchez O, Lefort C, Meyer G, Couchon S, Hernigou A, et al. Diagnostic accuracy of unenhanced, contrast-enhanced perfusion and angiographic MRI sequences for pulmonary embolism diagnosis: results of independent sequence readings. Eur Radiol. 2013 Sep;23(9):2374-82.

140. Revel MP, Sanchez O, Couchon S, Planquette B, Hernigou A, Niarra R, et al. Diagnostic accuracy of magnetic resonance imaging for an acute pulmonary embolism: results of the 'IRM-EP' study. J Thromb Haemost [Internet]. 2012 May [cited 2017 Feb 8];10(5):743-50. Available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1538-7836.2012.04652.x/epdf

141. Kluge A, Luboldt W, Bachmann G. Acute pulmonary embolism to the subsegmental level: diagnostic accuracy of three MRI techniques compared with 16-MDCT. AJR Am J Roentgenol [Internet]. 2006 Jul [cited 2016 Oct 31];187(1):W7-14. Available from: http://www.ajronline.org/doi/pdf/10.2214/AJR.04.1814

142. Grist TM, Sostman HD, MacFall JR, Foo TK, Spritzer CE, Witty L, et al. Pulmonary angiography with MR imaging: preliminary clinical experience. Radiology. 1993 Nov;189(2):523-30.

143. Oudkerk M, van Beek EJ, Wielopolski P, van Ooijen PM, Brouwers-Kuyper EM, Bongaerts AH, et al. Comparison of contrast-enhanced magnetic resonance angiography and conventional pulmonary angiography for the diagnosis of pulmonary embolism: a prospective study. Lancet. 2002 May 11;359(9318):1643-7.

144. Gupta A, Frazer CK, Ferguson JM, Kumar AB, Davis SJ, Fallon MJ, et al. Acute pulmonary embolism: diagnosis with MR angiography. Radiology. 1999 Feb;210(2):353-9.

145. Meaney JF, Weg JG, Chenevert TL, Stafford-Johnson D, Hamilton BH, Prince MR. Diagnosis of pulmonary embolism with magnetic resonance angiography. Abstract presented at: 1997 May 15. Department of Internal Medicine, University of Michigan Hospitals, Ann Arbor 48109, USA.

146. Stein PD, Chenevert TL, Fowler SE, Goodman LR, Gottschalk A, Hales CA, et al. Gadolinium-enhanced magnetic resonance angiography for pulmonary embolism: a multicenter prospective study (PIOPED III). Ann Intern Med [Internet]. 2010 Apr 6 [cited 2016 Oct 4];152(7):434-43. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3138428

147. Ohno Y, Higashino T, Takenaka D, Sugimoto K, Yoshikawa T, Kawai H, et al. MR angiography with sensitivity encoding (SENSE) for suspected pulmonary embolism: comparison with MDCT and ventilation-perfusion scintigraphy. AJR Am J Roentgenol [Internet]. 2004 Jul [cited 2016 Dec 1];183(1):91-8. Available from: http://www.ajronline.org/doi/pdf/10.2214/ajr.183.1.1830091

148. Erdman WA, Peshock RM, Redman HC, Bonte F, Meyerson M, Jayson HT, et al. Pulmonary embolism: comparison of MR images with radionuclide and angiographic studies. Radiology. 1994 Feb;190(2):499-508.

149. Pleszewski B, Chartrand-Lefebvre C, Qanadli SD, Déry R, Perreault P, Oliva VL, et al. Gadolinium-enhanced pulmonary magnetic resonance angiography in the diagnosis of acute pulmonary embolism: a prospective study on 48 patients. Clin Imaging. 2006 May;30(3):166-72.

150. Abootalebi A, Golshani K, Karami M, Masoumi B, Aliasgharlou M. Diagnostic validity of ultrasonography in evaluation of pulmonary thromboembolism. Adv Biomed Res [Internet]. 2016 [cited 2016 Oct 4];5:4. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4763566

151. Nazerian P, Vanni S, Volpicelli G, Gigli C, Zanobetti M, Bartolucci M, et al. Accuracy of point-of-care multiorgan ultrasonography for the diagnosis of pulmonary embolism. Chest. 2014 May;145(5):950-7.

152. Comert SS, Caglayan B, Akturk U, Fidan A, Kiral N, Parmaksiz E, et al. The role of thoracic ultrasonography in the diagnosis of pulmonary embolism. Ann Thorac Med [Internet]. 2013 Apr [cited 2016 Oct 4];8(2):99-104. Available from: http://www.thoracicmedicine.org/temp/AnnThoracMed8299-5029393_135813.pdf

153. Pfeil A, Reissig A, Heyne JP, Wolf G, Kaiser WA, Kroegel C, et al. Transthoracic sonography in comparison to multislice computed tomography in detection of peripheral pulmonary embolism. Lung. 2010 Jan;188(1):43-50.

154. Reißig A, Heyne JP, Kroegel C. Ancillary lung parenchymal findings at spiral CT scanning in pulmonary embolism. Relationship to chest sonography. Eur J Radiol. 2004 Mar;49(3):250-7.

155. Mohn K, Quiot JJ, Nonent M, Lacut K, Le Gall G, Couturaud F, et al. Transthoracic sonography of the lung and pleura in view of a suspected pulmonary embolism: a pilot study. J Ultrasound Med [Internet]. 2003 Jul [cited 2016 Dec 1];22(7):673-8. Available from: http://www.jultrasoundmed.org/content/22/7/673.full.pdf+html

156. Reissig A, Heyne JP, Kroegel C. Sonography of lung and pleura in pulmonary embolism: sonomorphologic characterization and comparison with spiral CT scanning. Chest. 2001 Dec;120(6):1977-83.

157. Mathis G, Metzler J, Fussenegger D, Sutterlutti G, Feurstein M, Fritzsche H. Sonographic observation of pulmonary infarction and early infarctions by pulmonary embolism. Eur Heart J. 1993 Jun [cited 2016 Dec 1];14(6):804-8.

158. Lechleitner P, Raneburger W, Gamper G, Riedl B, Benedikt E, Theurl A. Lung sonographic findings in patients with suspected pulmonary embolism. Ultraschall Med. 1998 Apr;19(2):78-82.

159. Kim PS, Gasparis AP, Probeck K, Elitharp D, Tassiopoulos A, Labropoulos N. Accuracy of venous thromboembolism assessment and compliance to prophylaxis in a tertiary care center. Phlebology. 2016;31(8):541-5.

160. Watanabe N, Fettich J, Kucuk NO, Kraft O, Mut F, Choudhury P, et al. Modified PISAPED criteria in combination with ventilation scintigraphic finding for predicting acute pulmonary embolism. World J Nucl Med [Internet]. 2015 Sep [cited 2016 Oct 4];14(3):178-83. Available from: http://www.wjnm.org/temp/WorldJNuclMed143178-4442071_122020.pdf

161. Skarlovnik A, Hrastnik D, Fettich J, Grmek M. Lung scintigraphy in the diagnosis of pulmonary embolism: Current methods and interpretation criteria in clinical practice. Radiol Oncol [Internet]. 2014 [cited 2016 Oct 7];48(2):113-9. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4078029/pdf/rado-48-02-113.pdf

162. Tondeur MC, Mols PG, Ham HR. Is the perfusion lung-scan still useful for the diagnosis approach towards lung embolism suspicion in the emergency department? JEUR. 2007;20(4):153-7.

163. Lu Y, Lorenzoni A, Fox JJ, Rademaker J, Vander Els N, Grewal RK, et al. Noncontrast perfusion single-photon emission CT/CT scanning: a new test for the expedited, high-accuracy diagnosis of acute pulmonary embolism. Chest. 2014 May;145(5):1079-88.

164. Sostman HD, Miniati M, Gottschalk A, Matta F, Stein PD, Pistolesi M. Sensitivity and specificity of perfusion scintigraphy combined with chest radiography for acute pulmonary embolism in PIOPED II. J Nucl Med [Internet]. 2008 Nov [cited 2016 Oct 7];49(11):1741-8. Available from: http://jnm.snmjournals.org/content/49/11/1741.full.pdf+html

165. Rubini G, Niccoli AA, Stabile Ianora AA, Rubini D, Gaudiano A, Angelelli G, et al. Acute pulmonary embolism: comparison and integration of perfusion lung scintigraphy with multislice spiral CT. Radiol Med (Torino). 2007 Mar;112(2):174-84.

166. Mazurek A, Dziuk M, Witkowska-Patena E, Piszczek S, Gizewska A. The Utility of Hybrid SPECT/CT Lung Perfusion Scintigraphy in Pulmonary Embolism Diagnosis. Respiration. 2015;90(5):393-401.

167. van Es J, Douma RA, Hezemans REL, Penaloza A, Motte S, Erkens PGM, et al. Accuracy of X-ray with perfusion scan in young patients with suspected pulmonary embolism. Thromb Res. 2015;136(2):221-4.

168. Miniati M, Pistolesi M, Marini C, Di Ricco G, Formichi B, Prediletto R, et al. Value of perfusion lung scan in the diagnosis of pulmonary embolism: results of the Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA-PED). Am J Respir Crit Care Med. 1996 Nov;154(5):1387-93.

169. Collart JP, Roelants V, Vanpee D, Lacrosse M, Trigaux JP, Delaunois L, et al. Is a lung perfusion scan obtained by using single photon emission computed tomography able to improve the radionuclide diagnosis of pulmonary embolism? Nucl Med Commun. 2002 Nov;23(11):1107-13.

170. Ishiyama M, Matsusako M, Oikado K, Nishi Y, Ohi K, Hirano M, et al. Three-dimensional T2-weighted imaging using the dark blood method for detecting pulmonary embolisms: comparison with computed tomography angiography. Jpn J Radiol. 2011 Nov;29(9):667-72.

171. Kumamaru KK, Kumamaru H, Bateman BT, Gronsbell J, Cai T, Liu J, et al. Limited hospital variation in the use and yield of CT for pulmonary embolism in patients undergoing total hip or total knee replacement surgery. Radiology. 2016 May 26;152765.

172. Casals-Sole J, Bernaudo D, Camp J, Lozano N, Ballester E, Escolar G. A normal D-Dimer value, measured by a high sensitivity assay, rule out a suspected Venous Thromboembolism episode independently of pretest clinical probability [abstract]. Haematologica. 2009;94:408-9. (Presented at 14th Congress of the European Hematology Association; 2009 Jun 4-7; Berlin, Germany).

173. Bajc M, Miniati M, Jogi J, Stein PD. Perfusion SPECT in patients with suspected pulmonary embolism. European Journal of Nuclear Medicine and Molecular Imaging. 2013;40(9):1432-7.

174. Le Roux PY, Robin P, Delluc A, Abgral R, Palard X, Tissot V, et al. Additional value of combining low-dose computed tomography to V/Q SPECT on a hybrid SPECT-CT camera for pulmonary embolism diagnosis. Nucl Med Commun. 2015 Sep;36(9):922-30.

175. Kumar N, Xie K, Mar W, Anderson TM, Carney B, Mehta N, et al. Software-based hybrid perfusion SPECT/CT provides diagnostic accuracy when other pulmonary embolism imaging is indeterminate. Nucl Med Mol Imaging. 2015 Dec;49(4):303-11.

176. Gutte H, Mortensen J, Jensen CV, von der Recke P, Petersen CL, Kristoffersen US, et al. Comparison of V/Q SPECT and planar V/Q lung scintigraphy in diagnosing acute pulmonary embolism. Nucl Med Commun. 2010 Jan;31(1):82-6.

177. PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). JAMA. 1990 May 23;263(20):2753-9.

178. Gray HW, McKillop JH, Bessent RG, Fogelman I, Smith ML, Moran F. Lung scanning for pulmonary embolism: clinical and pulmonary angiographic correlations. Poster presented at: 1990 Nov. Department of Nuclear Medicine, Royal Infirmary, Glasgow.

179. Woods ER, Iles S, Jackson S. Comparison of scintigraphic diagnostic criteria in suspected pulmonary embolism. Can Assoc Radiol J. 1989 Aug;40(4):194-7.

180. Sostman HD, Stein PD, Gottschalk A, Matta F, Hull R, Goodman L. Acute pulmonary embolism: sensitivity and specificity of ventilation-perfusion scintigraphy in PIOPED II study. Radiology [Internet]. 2008 Mar [cited 2016 Nov 16];246(3):941-6. Available from: http://pubs.rsna.org/doi/pdf/10.1148/radiol.2463070270

181. Stein PD, Terrin ML, Gottschalk A, Alavi A, Henry JW. Value of ventilation/perfusion scans versus perfusion scans alone in acute pulmonary embolism. Am J Cardiol. 1992 May 1;69(14):1239-41.

182. Quirce R, Ibanez-Bravo S, Jimenez-Bonilla J, Martinez-Rodriguez I, Martinez-Amador N, Ortega-Nava F, et al. Contribution of V/Q SPECT to planar scintigraphy in the diagnosis of pulmonary embolism. Rev Esp Med Nucl Imagen Mol [Internet]. 2014 May [cited 2016 Oct 4];33(3):153-8. Available from: http://www.elsevier.es/es-revista-revista-espanola-medicina-nuclear-e-125-linkresolver-contribution-v-q-spect-planar-scintigraphy-S2253654X14000067

183. Miles S, Rogers KM, Thomas P, Soans B, Attia J, Abel C, et al. A comparison of single-photon emission CT lung scintigraphy and CT pulmonary angiography for the diagnosis of pulmonary embolism. Chest. 2009 Dec;136(6):1546-53.

184. Bajc M, Olsson B, Palmer J, Jonson B. Ventilation/Perfusion SPECT for diagnostics of pulmonary embolism in clinical practice. J Intern Med. 2008 Oct;264(4):379-87.

185. Harris B, Bailey D, Miles S, Bailey E, Rogers K, Roach P, et al. Objective analysis of tomographic ventilation-perfusion scintigraphy in pulmonary embolism. Am J Respir Crit Care Med. 2007 Jun 1;175(11):1173-80.

186. Reinartz P, Kaiser HJ, Wildberger JE, Gordji C, Nowak B, Buell U. SPECT imaging in the diagnosis of pulmonary embolism: automated detection of match and mismatch defects by means of image-processing techniques. J Nucl Med [Internet]. 2006 Jun [cited 2016 Oct 13];47(6):968-73. Available from: http://jnm.snmjournals.org/content/47/6/968.full.pdf+html

187. Weinmann P, Moretti JL, Brauner MW. Usefulness of tomographic versus planar lung scintigraphy in suspected pulmonary embolism in a daily practice. The Open Medical Imaging Journal [Internet]. 2008 [cited 2016 Oct 21];9(2):49-55. Available from: http://benthamopen.com/contents/pdf/TOMIJ/TOMIJ-2-49.pdf

188. Ibáñez-Bravo S, Banzo I, Quirce R, Martínez-Rodríguez I, Jiménez-Bonilla J, Martínez-Amador N, et al. Ventilation/Perfusion SPECT lung scintigraphy and computed tomography pulmonary angiography in patients with clinical suspicion of pulmonary embolism. Revista Espanola de Medicina Nuclear e Imagen Molecular. 2016;35(4):215-20.

189. Bajc M, Olsson CG, Olsson B, Palmer J, Jonson B. Diagnostic evaluation of planar and tomographic ventilation/perfusion lung images in patients with suspected pulmonary emboli. Clin Physiol Funct Imaging. 2004 Sep;24(5):249-56.

190. Le Duc-Pennec A, Le Roux PY, Cornily JC, Jaffrelot M, Delluc A, de Saint-Martin L, et al. Diagnostic accuracy of single-photon emission tomography ventilation/perfusion lung scan in the diagnosis of pulmonary embolism. Chest. 2012 Feb;141(2):381-7.

191. Ling IT, Naqvi HA, Siew TK, Loh NK, Ryan GF. SPECT ventilation perfusion scanning with the addition of low-dose CT for the investigation of suspected pulmonary embolism. Intern Med J. 2012 Nov;42(11):1257-61.

192. Bhatia KD, Ambati C, Dhaliwal R, Paschkewitz R, Hsu E, Ho B, et al. SPECT-CT/VQ versus CTPA for diagnosing pulmonary embolus and other lung pathology: Pre-existing lung disease should not be a contraindication. J Med Imaging Radiat Oncol. 2016 Aug;60(4):492-7.

193. Bourriot K, Couffinhal T, Bernard V, Montaudon M, Bonnet J, Laurent F. Clinical outcome after a negative spiral CT pulmonary angiographic finding in an inpatient population from cardiology and pneumology wards. Chest. 2003 Feb;123(2):359-65.

194. Donato AA, Scheirer JJ, Atwell MS, Gramp J, Duszak R. Clinical outcomes in patients with suspected acute pulmonary embolism and negative helical computed tomographic results in whom anticoagulation was withheld. Arch Intern Med. 2003 Sep 22;163(17):2033-8.

195. Gimber LH, Travis RI, Takahashi JM, Goodman TL, Yoon HC. Computed tomography angiography in patients evaluated for acute pulmonary embolism with low serum D-dimer levels: a prospective study. Perm J [Internet]. 2009 [cited 2016 Oct 6];13(4):4-10. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2911823

196. Hantous-Zannad S, Esseghaier S, Ridène I, Zidi A, Ben Romdhane K, Baccouche I, et al. Acute pulmonary embolism: epidemiologic and tomodensitometric study. Tunis Med. 2010 Dec;88(12):880-4.

197. Huisman MV. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. JAMA. 2006;295(2):172-9.

198. Meier A, Higashigaito K, Martini K, Wurnig M, Seifert B, Keller D, et al. Dual energy CT pulmonary angiography with 6g iodine-A propensity score-matched study. PLoS ONE [Internet]. 2016 [cited 2016 Jan 4];11(12):e0167214. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5132396/pdf/pone.0167214.pdf

199. Moores L, Kline J, Portillo AK, Resano S, Vicente A, Arrieta P, et al. Multidetector computed tomographic pulmonary angiography in patients with a high clinical probability of pulmonary embolism. J Thromb Haemost. 2016;14(1):114-20.

200. Ost D, Rozenshtein A, Saffran L, Snider A. The negative predictive value of spiral computed tomography for the diagnosis of pulmonary embolism in patients with nondiagnostic ventilation-perfusion scans. Am J Med. 2001 Jan;110(1):16-21.

201. Pérez De Llano LA, Veres Racamonde A, Ortiz Piquer M, López Diaz MJ, Janeiro Amela M, Méndez Maroto L, et al. Safety of withholding anticoagulant therapy in patients who have clinically suspected pulmonary embolism and negative results on helical computed tomography. Respiration. 2006;73(4):514-9.

202. Pesavento R, De Conti G, Minotto I, Filippi L, Mongiat M, de Faveri D, et al. The value of 64-detector row computed tomography for the exclusion of pulmonary embolism. Thromb Haemost. 2011 May;105(5):901-7.

203. Revel MP, Petrover D, Hernigou A, Lefort C, Meyer G, Frija G. Diagnosing pulmonary embolism with four-detector row helical CT: prospective evaluation of 216 outpatients and inpatients[1]. Radiology [Internet]. 2005 Jan [cited 2016 Dec 8];234(1):265-73. Available from: http://pubs.rsna.org/doi/pdf/10.1148/radiol.2341031880

204. Sodhi KS, Gulati M, Aggarwal R, Kalra N, Mittal BR, Jindal SK, et al. Computed tomographic pulmonary angiography: utility in acute pulmonary embolism in providing additional information and making alternative clinical diagnosis. Indian J Med Sci. 2010 Jan;64(1):26-32.

205. Woo JK, Chiu RY, Thakur Y, Mayo JR. Risk-benefit analysis of pulmonary CT angiography in patients with suspected pulmonary embolus. AJR Am J Roentgenol. 2012 Jun;198(6):1332-9.

206. Mitchell AM, Kline JA. Contrast nephropathy following computed tomography angiography of the chest for pulmonary embolism in the emergency department. J Thromb Haemost. 2007 Jan;5(1):50-4.

207. Yazici S, Kiris T, Emre A, Ceylan US, Akyuz S, Uzun AO, et al. Relation of contrast nephropathy to adverse events in pulmonary emboli patients diagnosed with contrast CT. Am J Emerg Med. 2016 Jul;34(7):1247-50.

208. Niemann T, Zbinden I, Roser HW, Bremerich J, Remy-Jardin M, Bongartz G. Computed tomography for pulmonary embolism: assessment of a 1-year cohort and estimated cancer risk associated with diagnostic irradiation. Acta Radiol. 2013 Sep;54(7):778-84.

209. Kluge A, Mueller C, Strunk J, Lange U, Bachmann G. Experience in 207 combined MRI examinations for acute pulmonary embolism and deep vein thrombosis. AJR Am J Roentgenol [Internet]. 2006 Jun [cited 2016 Oct 13];186(6):1686-96. Available from: http://pubs.rsna.org/doi/pdf/10.1148/radiol.2392050118

210. Kyrtatos PG, Navalkissoor S, Burniston M, Wagner T. Planar images reprojected from SPECT V/Q data perform similarly to traditional planar V/Q scans in the diagnosis of pulmonary embolism. Nucl Med Commun. 2013 May;34(5):445-50.

211. Leblanc M, Leveillée F, Turcotte E. Prospective evaluation of the negative predictive value of V/Q SPECT using ^{99m}Tc-Technegas. Nucl Med Commun. 2007 Aug;28(8):667-72.

212. Rhee KH, Iyer RS, Cha S, Naidich DP, Rusinek H, Jacobowitz GR, et al. Benefit of CT venography for the diagnosis of thromboembolic disease. Clin Imaging. 2007 Jul;31(4):253-8.

213. Shahir K, Goodman LR, Tali A, Thorsen KM, Hellman RS. Pulmonary embolism in pregnancy: CT pulmonary angiography versus perfusion scanning. AJR Am J Roentgenol. 2010 Sep;195(3):W214-W220.

214. Cahill AG, Stout MJ, Macones GA, Bhalla S. Diagnosing pulmonary embolism in pregnancy using computed-tomographic angiography or ventilation-perfusion. Obstet Gynecol. 2009 Jul;114(1):124-9.

215. Ridge CA, Mcdermott S, Freyne BJ, Brennan DJ, Collins CD, Skehan SJ. Pulmonary embolism in pregnancy: comparison of pulmonary CT angiography and lung scintigraphy. AJR Am J Roentgenol. 2009 Nov;193(5):1223-7.

216. Chan WS, Ray JG, Murray S, Coady GE, Coates G, Ginsberg JS. Suspected pulmonary embolism in pregnancy: clinical presentation, results of lung scanning, and subsequent maternal and pediatric outcomes. Arch Intern Med. 2002 May 27;162(10):1170-5.

217. Bajc M, Olsson B, Gottsater A, Hindorf C, Jogi J. V/P SPECT as a diagnostic tool for pregnant women with suspected pulmonary embolism. Eur J Nucl Med Mol Imaging [Internet]. 2015 Jul [cited 2017 Mar 6];42(8):1325-30. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4480826

218. Browne AM, Cronin CG, NiMhuircheartaigh J, Donagh C, Morrison JJ, Lohan DG, et al. Evaluation of imaging quality of pulmonary 64-MDCT angiography in pregnancy and puerperium. AJR Am J Roentgenol [Internet]. 2014 Jan [cited 2017 Mar 6];202(1):60-4. Available from: http://www.ajronline.org/doi/pdf/10.2214/AJR.12.9917

219. Grüning T, Mingo RE, Gosling MG, Farrell SL, Drake BE, Loader RJ, et al. Diagnosing venous thromboembolism in pregnancy. Br J Radiol. 2016 Jun;89(1062):20160021.

220. Scarsbrook AF, Bradley KM, Gleeson FV. Perfusion scintigraphy: diagnostic utility in pregnant women with suspected pulmonary embolic disease. Eur Radiol. 2007 Oct;17(10):2554-60.

221. Bourjeily G, Khalil H, Raker C, Martin S, Auger P, Chalhoub M, et al. Outcomes of negative multidetector computed tomography with pulmonary angiography in pregnant women suspected of pulmonary embolism. Lung. 2012 Feb;190(1):105-11.

222. van Mens TE, Scheres LJ, de Jong PG, Leeflang MM, Nijkeuter M, Middeldorp S. Imaging for the exclusion of pulmonary embolism in pregnancy. Cochrane Database Syst Rev. 2017 Jan 26;1:CD011053.

223. Kalb B, Sharma P, Tigges S, Ray GL, Kitajima HD, Costello JR, et al. MR imaging of pulmonary embolism: diagnostic accuracy of contrast-enhanced 3D MR pulmonary angiography, contrast-enhanced low-flip angle 3D GRE, and nonenhanced free-induction FISP sequences. Radiology [Internet]. 2012 Apr [cited 2016 Oct 4];263(1):271-8. Available from: http://pubs.rsna.org/doi/pdf/10.1148/radiol.12110224

224. Mila M, Bechini J, Vazquez A, Vallejos V, Tenesa M, Espinal A, et al. Acute pulmonary embolism detection with ventilation/perfusion SPECT combined with full dose CT: What is the best option? Revista Espanola de Medicina Nuclear e Imagen Molecular. 2017;36(3):139-45.

225. van der HT, van EN, den EP, van EJ, Mos ICM, Douma RA, et al. Is a normal computed tomography pulmonary angiography safe to rule out acute pulmonary embolism in patients with a likely clinical probability? A patient-level meta-analysis. Thromb Haemost. 2017 Jun 1;117(8).

226. Pelletier-Galarneau M, Zannier E, Zuckier LS, Le GG. Referral Patterns and Diagnostic Yield of Lung Scintigraphy in the Diagnosis of Acute Pulmonary Embolism. Thrombosis [Internet]. 2017 [cited 2017 Jun 12]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5405392/pdf/THROMBOSIS2017-1623868.pdf

227. Raymakers AJ, Mayo J, Marra CA, FitzGerald M. Diagnostic strategies incorporating computed tomography angiography for pulmonary embolism: a systematic review of cost-effectiveness analyses. J Thorac Imaging. 2014 Jul;29(4):209-16.

228. Gospodarevskaya E, V, Goergen SK, Harris AH, Chan T, de Campo JF, Wolfe R, et al. Economic evaluation of a clinical protocol for diagnosing emergency patients with suspected pulmonary embolism. Cost Effectiveness and Resource Allocation [Internet]. 2006 Jun 27 [cited 2016 Jul 14];4(12). Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1550258/pdf/1478-7547-4-12.pdf

229. Hull RD, Pineo GF, Stein PD, Mah AF, Butcher MS. Cost-effectiveness of currently accepted strategies for pulmonary embolism diagnosis. Semin Thromb Hemost. 2001;27(1):15-23.

230. Duriseti RS, Shachter RD, Brandeau ML. Value of quantitative D-dimer assays in identifying pulmonary embolism: implications from a sequential decision model. Acad Emerg Med [Internet]. 2006 [cited 2016 Nov 17];13(7):755-66. Available from: http://onlinelibrary.wiley.com/doi/10.1197/j.aem.2006.02.011/abstract

231. Duriseti RS, Brandeau ML. Cost-effectiveness of strategies for diagnosing pulmonary embolism among emergency department patients presenting with undifferentiated symptoms. Ann Emerg Med [Internet]. 2010 Oct [cited 2016 Oct 5];56(4):321-32. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3699695

232. van Erkel AR, Pattynama PM. Cost-effective diagnostic algorithms in pulmonary embolism: an updated analysis. Acad Radiol. 1998 Sep;5 Suppl 2:S321-S327.

233. van Erkel AR, van Rossum AB, Bloem JL, Kievit J, Pattynama PM. Spiral CT angiography for suspected pulmonary embolism: a cost-effectiveness analysis. Radiology. 1996 Oct;201(1):29-36.

234. Stein PD, Matta E. Noninvasive imaging in pulmonary embolism according to age and gender. Clin Appl Thromb Hemost. 2014;20(2):143-6.

235. Fertility: overview, 2009 to 2011 [Internet]. Ottawa: Statistics Canada; 2015 Nov 30. [cited 2017 Oct 19]. Available from: https://www.statcan.gc.ca/pub/91-209-x/2013001/article/11784-eng.htm

236. Lee JA, Zierler BK, Liu CF, Chapko MK. Cost-effective diagnostic strategies in patients with a high, intermediate, or low clinical probability of pulmonary embolism. Vasc Endovascular Surg. 2011;45(2):113-21.

237. Righini M, Nendaz M, Gal G, Bounameaux H, Perrier A. Influence of age on the cost-effectiveness of diagnostic strategies for suspected pulmonary embolism. J Thromb Haemost [Internet]. 2007 [cited 2016 Oct 5];5(9):1869-77. Available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1538-7836.2007.02667.x/epdf

238. Paterson DI, Schwartzman K. Strategies incorporating spiral CT for the diagnosis of acute pulmonary embolism: a cost-effectiveness analysis. Chest. 2001 Jun;119(6):1791-800.

239. Elias A, Molinier L, Bauvin E, Elias M, Duru G, Colin C. Integrating complete lower limb venous ultrasound into diagnostic strategies for pulmonary embolism: a cost-effectiveness analysis. Thromb Haemost. 2004 Jan;91(1):205-7.

240. Perrier A, Nendaz MR, Sarasin FP, Howarth N, Bounameaux H. Cost-effectiveness analysis of diagnostic strategies for suspected pulmonary embolism including helical computed tomography. Am J Respir Crit Care Med. 2003 Jan 1;167(1):39-44.

241. Guidelines for the economic evaluation of health technologies: Canada [Internet]. 4th ed. Ottawa: CADTH; 2017. [cited 2017 Jun 28]. Available from: https://www.cadth.ca/guidelines-economic-evaluation-health-technologies-canada-4th-edition

242. Guidelines for the economic evaluation of health technologies: Canada [Internet]. Ottawa: CADTH; 2006. [cited 2016 Aug 2]. Available from: https://www.cadth.ca/media/pdf/186_EconomicGuidelines_e.pdf

243. Huisman MV, Klok FA. Diagnostic management of clinically suspected acute pulmonary embolism. J Thromb Haemost [Internet]. 2009 Jul [cited 2017 Jun 28];7 Suppl 1:312-7. Available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1538-7836.2009.03386.x/pdf

244. Pulmonary embolism: diagnosis and management [Internet]. Hamilton (ON): Thrombosis Canada; 2013. [cited 2017 Jun 28]. Available from: http://thrombosiscanada.ca/guides/pdfs/PE.pdf

245. Direct oral anticoagulants for the treatment of venous thromboembolic events: economic evaluation [Internet]. Ottawa: CADTH; 2016 Mar. [cited 2016 Aug 2]. (CADTH Technology review; no. 3). Available from: https://www.cadth.ca/sites/default/files/pdf/TR0005_DOACS_for_DVT_and_PE_Report.pdf

246. Kabrhel C, McAfee AT, Goldhaber SZ. The contribution of the subjective component of the Canadian Pulmonary Embolism Score to the overall score in emergency department patients. Acad Emerg Med [Internet]. 2005 Oct [cited 2017 Jun 1];12(10):915-20. Available from: http://onlinelibrary.wiley.com/doi/10.1197/j.aem.2005.05.030/abstract

247. Chagnon I, Bounameaux H, Aujesky D, Roy PM, Gourdier AL, Cornuz J, et al. Comparison of two clinical prediction rules and implicit assessment among patients with suspected pulmonary embolism. Am J Med. 2002 Sep;113(4):269-75.

248. Carrier M, Righini M, Djurabi RK, Huisman MV, Perrier A, Wells PS, et al. VIDAS D-dimer in combination with clinical pre-test probability to rule out pulmonary embolism. A systematic review of management outcome studies. Thromb Haemost. 2009 May;101(5):886-92.

249. Singh B, Mommer SK, Erwin PJ, Mascarenhas SS, Parsaik AK. Pulmonary embolism rule-out criteria (PERC) in pulmonary embolism--revisited: a systematic review and meta-analysis. Emerg Med J [Internet]. 2013 Sep [cited 2016 Nov 17];30(9):701-6. Available from: http://emj.bmj.com/content/30/9/701.full.pdf+html

250. Kanal KM, Butler PF, Sengupta D, Bhargavan-Chatfield M, Coombs LP, Morin RL. U.S. Diagnostic Reference Levels and Achievable Doses for 10 Adult CT Examinations. Radiology. 2017 Jul;284(1):120-33.

251. Jones JG, Mills CN, Mogensen MA, Lee CI. Radiation dose from medical imaging: a primer for emergency physicians. West J Emerg Med [Internet]. 2012 May [cited 2017 Jul 26];13(2):202-10. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3415811

252. Janbabanezhad TA, Shabestani-Monfared A, Deevband MR, Abdi R, Nabahati M. Dose Assessment in Computed Tomography Examination and Establishment of Local Diagnostic Reference Levels in Mazandaran, Iran. J Biomed Phys Eng [Internet]. 2015 Dec [cited 2017 Aug 25];5(4):177-84. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4681462

253. Leung AN, Bull TM, Jaeschke R, Lockwood CJ, Boiselle PM, Hurwitz LM, et al. An official American Thoracic Society/Society of Thoracic Radiology clinical practice guideline: evaluation of suspected pulmonary embolism in pregnancy. Am J Respir Crit Care Med [Internet]. 2011 Nov 15 [cited 2017 Aug 25];184(10):1200-8. Available from: http://www.atsjournals.org/doi/pdf/10.1164/rccm.201108-1575ST

254. Life tables, Canada, provinces and territories 2009 to 2011 [Internet]. Ottawa: Statistics Canada; 2015. [cited 2017 Jun 28]. Available from: http://www.statcan.gc.ca/pub/84-537-x/84-537-x2013005-eng.htm

255. Quinlan DJ, McQuillan A, Eikelboom JW. Low-molecular-weight heparin compared with intravenous unfractionated heparin for treatment of pulmonary embolism: a meta-analysis of randomized, controlled trials. Ann Intern Med. 2004 Feb 3;140(3):175-83.

256. Agnelli G, Prandoni P, Becattini C, Silingardi M, Taliani MR, Miccio M, et al. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. Ann Intern Med. 2003 Jul 1;139(1):19-25.

257. BARRITT DW, JORDAN SC. Anticoagulant drugs in the treatment of pulmonary embolism. A controlled trial. Lancet. 1960 Jun 18;1(7138):1309-12.

258. Aujesky D, Smith KJ, Cornuz J, Roberts MS. Cost-effectiveness of low-molecular-weight heparin for treatment of pulmonary embolism. Chest. 2005 Sep;128(3):1601-10.

259. Stein PD, Matta F, Alrifai A, Rahman A. Trends in case fatality rate in pulmonary embolism according to stability and treatment. Thromb Res. 2012 Dec;130(6):841-6.

260. Wells GA, Kelly S, Elliott J, Carrier M, Hsieh S, Chen L. Direct oral anticoagulants for the treatment of venous thromboembolic events: a systematic review and network meta-analysis [Internet]. Ottawa: University of Ottawa Heart Institute; 2016. [cited 2017 Jun 28]. Available from: https://www.ottawaheart.ca/sites/default/files/uploads/documents/Researchers/gwells-doac-vte-scientific-report-2015-2016.pdf

261. Roman A, Barbera JA, Castillo MJ, Munoz R, Escribano P. Health-related quality of life in a national cohort of patients with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension. Arch Bronconeumol. 2013 May;49(5):181-8.

262. Johnson JA, Pickard AS. Comparison of the EQ-5D and SF-12 health surveys in a general population survey in Alberta, Canada. Med Care. 2000 Jan;38(1):115-21.

263. Hogg K, Kimpton M, Carrier M, Coyle D, Forgie M, Wells P. Estimating quality of life in acute venous thrombosis. JAMA Intern Med. 2013 Jun 24;173(12):1067-72.

264. Rivero-Arias O, Ouellet M, Gray A, Wolstenholme J, Rothwell PM, Luengo-Fernandez R. Mapping the modified Rankin scale (mRS) measurement into the generic EuroQol (EQ-5D) health outcome. Med Decis Making. 2010 May;30(3):341-54.

265. Consumer price index, health and personal care, by province (Canada) [Internet]. Ottawa: Statistics Canada; 2017. [cited 2017 Jun 28]. Available from: http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/econ161a-eng.htm

266. Exchange rates [Internet]. Ottawa: Bank of Canada; 2017. [cited 2017 Jun 28]. Available from: http://www.bankofcanada.ca/rates/exchange/?page_moved=1

267. Ontario Ministry of Health and Long-term Care OCCI costing analysis tool. In: Health data branch web portal [Internet]. Toronto: Ontario Ministry of Health and Long-Term Care; 2015 [cited 2017 Jun 28]. Available from: https://hsim.health.gov.on.ca/hdbportal/ Registration required.

268. Wilbur K, Lynd LD, Sadatsafavi M. Low-molecular-weight heparin versus unfractionated heparin for prophylaxis of venous thromboembolism in medicine patients--a pharmacoeconomic analysis. Clin Appl Thromb Hemost. 2011 Oct;17(5):454-65.

269. Schedule of benefits: physician services under the Health Insurance Act (December 22, 2015 (effectiveMar 1, 2016)) [Internet]. Toronto: Ontario Ministry of Health and Long-Term Care; 2015. [cited 2017 Jun 28]. Available from: http://www.health.gov.on.ca/en/pro/programs/ohip/sob/physserv/sob_master20160401.pdf

270. Ontario drug benefit formulary/comparative drug index. effective from May 31, 2017 [Internet]. Toronto: Ontario Ministry of Health and Long-Term Care; 2017 [cited 2017 Jun 28].

271. Wu O, Robertson L, Twaddle S, Lowe GD, Clark P, Greaves M, et al. Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study. Health Technol Assess. 2006 Apr;10(11):1-110.

272. Pengo V, Lensing AW, Prins MH, Marchiori A, Davidson BL, Tiozzo F, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Engl J Med. 2004 May 27;350(22):2257-64.

273. Lobo JL, Zorrilla V, Aizpuru F, Uresandi F, Garcia-Bragado F, Conget F, et al. Clinical syndromes and clinical outcome in patients with pulmonary embolism: findings from the RIETE registry. Chest. 2006 Dec;130(6):1817-22.

274. van Erkel AR, Pattynama PM. Cost-effective diagnostic algorithms in pulmonary embolism: an updated analysis. Acad Radiol. 1998 Sep;5 Suppl 2:S321-S327.

275. Wilts IT, Le GG, den Exter PL, van EJ, Carrier M, Planquette B, et al. Performance of the age-adjusted cut-off for D-dimer in patients with cancer and suspected pulmonary embolism. Thromb Res. 2017;152:49-51.

276. Righini M, Le GG, Perrier A, Bounameaux H. More on: clinical criteria to prevent unnecessary diagnostic testing in emergency department patients with suspected pulmonary embolism. J Thromb Haemost [Internet]. 2005 Jan [cited 2017 Jun 1];3(1):188-9. Available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1538-7836.2004.01097.x/epdf

277. Hendriksen JM, Lucassen WA, Erkens PM, Stoffers HE, van Weert HC, Buller HR, et al. Ruling Out Pulmonary Embolism in Primary Care: Comparison of the Diagnostic Performance of "Gestalt" and the Wells Rule. Ann Fam Med [Internet]. 2016 May [cited 2017 Jun 28];14(3):227-34. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4868561

278. Di MS, Cilia C, Campagna A, D'Arrigo G, Abd ES, Tripepi G, et al. Comparison of Wells and Revised Geneva Rule to Assess Pretest Probability of Pulmonary Embolism in High-Risk Hospitalized Elderly Adults. J Am Geriatr Soc. 2015 Jun;63(6):1091-7.

279. Klok FA, Kruisman E, Spaan J, Nijkeuter M, Righini M, Aujesky D, et al. Comparison of the revised Geneva score with the Wells rule for assessing clinical probability of pulmonary embolism. J Thromb Haemost. 2008 Jan;6(1):40-4.

280. Meyer G, Planquette B, Sanchez O. Long-term outcome of pulmonary embolism. Curr Opin Hematol. 2008 Sep;15(5):499-503.

281. Carrier M, Wells PS, Rodger MA. Excluding pulmonary embolism at the bedside with low pre-test probability and D-dimer: safety and clinical utility of 4 methods to assign pre-test probability. Thromb Res. 2006;117(4):469-74.

282. Stein PD, Huang H, Afzal A, Noor HA. Incidence of acute pulmonary embolism in a general hospital: relation to age, sex, and race. Chest. 1999 Oct;116(4):909-13.

283. CASP qualitative research checklist: 10 questions to help you make sense of qualitative research. Oxford (United Kingdom): Critical Appraisal Skills Programme (CASP); 2017 Mar 13. [cited 2017 Nov 7]. Available from: http://docs.wixstatic.com/ugd/dded87_25658615020e427da194a325e7773d42.pdf

284. Strand T, Tornqvist E, Rask M, Roxberg A. The experience of patients with neoplasm metastasis in the spine during a magnetic resonance imaging examination. J RADIOL NURS. 2014;33(4):191-8.

285. Nightingale JM, Murphy FJ, Blakeley C. 'I thought it was just an x-ray': a qualitative investigation of patient experiences in cardiac SPECT-CT imaging. Nucl Med Commun. 2012 Mar;33(3):246-54.

286. Hinton L, Locock L, Knight M. Partner experiences of "near-miss" events in pregnancy and childbirth in the UK: a qualitative study. PLoS ONE [Internet]. 2014 [cited 2017 Feb 8];9(4):e91735. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3981658

287. Carlsson S, Carlsson E. 'The situation and the uncertainty about the coming result scared me but interaction with the radiographers helped me through': a qualitative study on patients' experiences of magnetic resonance imaging examinations. J Clin Nurs. 2013 Nov;22(21-22):3225-34.

288. Thornton RH, Dauer LT, Shuk E, Bylund CL, Banerjee SC, Maloney E, et al. Patient perspectives and preferences for communication of medical imaging risks in a cancer care setting. Radiology [Internet]. 2015 [cited 2017 Feb 2];275(2):545-52. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4976442/pdf/nihms804378.pdf

289. Munn Z, Jordan Z. The patient experience of high technology medical imaging: a systematic review of the qualitative evidence. Radiography. 2011;17(4):323-31.

290. Törnqvist E, Mansson A, Larsson EM, Hallstrom I. It's like being in another world--patients' lived experience of magnetic resonance imaging. J Clin Nurs. 2006 Aug;15(8):954-61.

291. Garland S, Severn M. Approaches to diagnosing acute pulmonary embolism in Canada: current practice, challenges, and availability of testing. [Internet]. Ottawa: CADTH. Forthcoming 2017. [cited 2017 Jul 28]. Available from: https://www.cadth.ca/approaches-diagnosing-acute-pulmonary-embolism-canada-current-practice-challenges-and-availability

292. Pfadenhauer L, Rohwer A, Burns J, Booth A, Bakke Lysdahl K, HJofmann B, et al. Guidance for the assessment of context and implementation in Health Technology Assessments (HTA) and systematic reviews of complex interventions: the Context and Implementation of Complex Interventions (CICI) Framework [Internet]. place unknown: Integrated Health Technology Assessment for Evaluating Complex Technologies (INTEGRATE-HTA); 2016. [cited 2017 Jan 19]. Available from: http://www.integrate-hta.eu/wp-content/uploads/2016/02/Guidance-for-the-Assessment-of-Context-and-Implementation-in-HTA-and-Systematic-Reviews-of-Complex-Interventions-The-Co.pdf

293. Ahn JS, Edmonds ML, McLeod SL, Dreyer JF. Familiarity with radiation exposure dose from diagnostic imaging for acute pulmonary embolism and current patterns of practice. CJEM Can J Emerg Med [Internet]. 2014 Sep [cited 2016 Nov 30];16(5):393-404. Available from: https://www.cambridge.org/core/services/aop-cambridge-core/content/view/S1481803500003079

294. Arnason T, Wells PS, Forster AJ. Appropriateness of diagnostic strategies for evaluating suspected venous thromboembolism. Thromb Haemost. 2007 Feb;97(2):195-201.

295. Ballantine M, Bhimani M, Milne WK. Diagnostic approach to pulmonary embolism in a rural emergency department. Can j rural med [Internet]. 2012 [cited 2016 Nov 15];17(1):17-20. Available from: http://www.srpc.ca/PDF/cjrm/vol17n1/pg17.pdf

296. Chen YA, Gray BG, Bandiera G, MacKinnon D, Deva DP. Variation in the utilization and positivity rates of CT pulmonary angiography among emergency physicians at a tertiary academic emergency department. Emerg Radiology. 2015 Jun;22(3):221-9.

297. Ingber S, Selby R, Lee J, Geerts W, Brnjac E. Combination pretest probability assessment and D-dimer did not reduce outpatient imaging for venous thromboembolism in a tertiary care hospital emergency department. CJEM Can J Emerg Med [Internet]. 2014 Jan [cited 2016 Dec 1];16(1):53-62. Available from: https://www.cambridge.org/core/services/aop-cambridge-core/content/view/E554192410CD97381E3D0F418682EB1A/S1481803500003328a.pdf/combination-pretest-probability-assessment-and-d-dimer-did-not-reduce-outpatient-imaging-for-venous-thromboembolism-in-a-tertiary-care-hospital-emergency-department.pdf

298. Le Roux PY, Pelletier-Galarneau M, De Laroche R, Hofman MS, Zuckier LS, Roach P, et al. Pulmonary scintigraphy for the diagnosis of acute pulmonary embolism: a survey of current practices in Australia, Canada, and France. J Nucl Med [Internet]. 2015 Aug [cited 2016 Dec 2];56(8):1212-7. Available from: http://jnm.snmjournals.org/content/56/8/1212.full.pdf+html

299. Southern DA, Poole J, Patel A, Waters N, Pilote L, Hull RD, et al. Health system capacity and infrastructure for adopting innovations to care for patients with venous thromboembolic disease. Open medicine : a peer-reviewed, independent, open-access journal [Internet]. 2014 [cited 2016 Nov 15];8(2):e46-e53. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4085085/pdf/OpenMed-08-46.pdf

300. Spencer Netto F, Tien H, Ng J, Ortega S, Scarpelini S, Rizoli SB, et al. Pulmonary emboli after blunt trauma: timing, clinical characteristics and natural history. Injury. 2012 Sep;43(9):1502-6.

301. Armao D, Semelka RC, Elias J. Radiology's ethical responsibility for healthcare reform: tempering the overutilization of medical imaging and trimming down a heavyweight. Journal of Magnetic Resonance Imaging. 2012;35(3):512-7.

302. Gossner J, Nau R. Geriatric chest imaging: When and how to image the elderly lung, age-related changes, and common pathologies. Radiology Research and Practice [Internet]. 2013; 584793. [cited 2016 Nov 15]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3713368/pdf/RRP2013-584793.pdf

303. Berlin L, Murphy DR, Singh H. Breakdowns in communication of radiological findings: an ethical and medico-legal conundrum. Diagnosis (Berl). 2014 Dec;1(4):263-8. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4799785

304. Blumenthal-Barby JS, Cantor SB, Russell HV, Naik AD, Volk RJ. Decision aids: when 'nudging' patients to make a particular choice is more ethical than balanced, nondirective content. Health Aff (Millwood). 2013 Feb;32(2):303-10.

305. Keefer R. Ethical dilemmas in radiology and the vow to do no harm. ACR Radiology [Internet]. 2012 Mar 9 [cited 2017 Aug 22]. Available from: https://www.acr.org/News-Publications/News/News-Articles/2012/ACR-Bulletin/201203-Do-No-Harm

306. Rosenthal MS. Patient misconceptions and ethical challenges in radioactive iodine scanning and therapy. J Nucl Med Technol. 2006 Sep;34(3):143-50.

307. Adams DM, Stevens SM, Woller SC, Evans RS, Lloyd JF, Snow GL, et al. Adherence to PIOPED II investigators' recommendations for computed tomography pulmonary angiography. Am J Med. 2013 Jan;126(1):36-42.

308. Bhargavan M, Sunshine JH, Lewis RS, Jha S, Owen JB, Vializ J. Frequency of use of imaging tests in the diagnosis of pulmonary embolism: Effects of physician specialty, patient characteristics and region. Am J Roentgenol [Internet]. 2010 [cited 2016 Nov 14];194(4):1018-26. Available from: http://www.ajronline.org/doi/pdf/10.2214/AJR.09.3215

309. Booker MT, Johnson JO. Optimizing CT Pulmonary Angiogram Utilization in a Community Emergency Department: A Pre- and Postintervention Study. J Am Coll Radiol. 2017 Jan;14(1):65-71.

310. Bozarth AL, Bajaj N, Wessling MR, Keffer D, Jallu S, Salzman GA. Evaluation of the pulmonary embolism rule-out criteria in a retrospective cohort at an urban academic hospital. Am J Emerg Med. 2015 Apr;33(4):483-7.

311. D'Apuzzo MR, Keller TC, Novicoff WM, Browne JA. CT pulmonary angiography after total joint arthroplasty: overdiagnosis and iatrogenic harm? Clin Orthop [Internet]. 2013 Sep [cited 2016 Nov 15];471(9):2737-42. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3734436

312. Daley J, Grotberg J, Pare J, Medoro A, Liu R, Hall MK, et al. Emergency physician performed tricuspid annular plane systolic excursion in the evaluation of suspected pulmonary embolism. Am J Emerg Med. 2017 Jan;35(1):106-111.

313. Fanikos J, Rao A, Seger AC, Carter D, Piazza G, Goldhaber SZ. Hospital costs of acute pulmonary embolism. Am J Med. 2013;126(2):127-32.

314. Gaston S, White S. Venous thromboembolism (VTE) risk assessment: rural nurses' knowledge and use in a rural acute care hospital. Int J Nurs Pract. 2013;19(1):60-4.

315. Goodacre S, Nelson-Piercy C, Hunt B, Chan WS. When should we use diagnostic imaging to investigate for pulmonary embolism in pregnant and postpartum women? Emerg Med J. 2015;32(1):78-82.

316. Groves AM, Yates SJ, Win T, Kayani I, Gallagher FA, Syed R, et al. CT pulmonary angiography versus ventilation-perfusion scintigraphy in pregnancy: implications from a UK survey of doctors' knowledge of radiation exposure. Radiology [Internet]. 2006 Sep;240(3):765-70. Available from: http://pubs.rsna.org/doi/pdf/10.1148/radiol.2403050910

317. Johnson PT, Zimmerman SL, Heath D, Eng J, Horton KM, Scott WW, et al. The iPad as a mobile device for CT display and interpretation: diagnostic accuracy for identification of pulmonary embolism. Emerg Radiol. 2012 Aug;19(4):323-7.

318. Kline JA, Peterson CE, Steuerwald MT. Prospective evaluation of real-time use of the pulmonary embolism rule-out criteria in an academic emergency department. Acad Emerg Med [Internet]. 2010 Sep [cited 2017 Jun 1];17(9):1016-9. Available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1553-2712.2010.00826.x/epdf

319. Kodadek LM, Haut ER. Screening and Diagnosis of VTE: The More You Look, The More You Find? Current Trauma Reports [Internet]. 2016 [cited 2016 Nov 16];2(1):29-34. Available from: http://download.springer.com/static/pdf/991/art%253A10.1007%252Fs40719-016-0038-y.pdf?originUrl=http%3A%2F%2Flink.springer.com%2Farticle%2F10.1007%2Fs40719-016-0038-y&token2=exp=1479311548~acl=%2Fstatic%2Fpdf%2F991%2Fart%25253A10.1007%25252Fs40719-016-0038-y.pdf%3ForiginUrl%3Dhttp%253A%252F%252Flink.springer.com%252Farticle%252F10.1007%252Fs40719-016-0038-y*~hmac=b345c990d20fc2a92c052bb22bd597a6e03a13a8f12e1c3d41c1d303c367c25f

320. Long B, Koyfman A. Best Clinical Practice: Current Controversies in Pulmonary Embolism Imaging and Treatment of Subsegmental Thromboembolic Disease. J Emerg Med. 2017 Feb;52(2):184-193.

321. Matthews S. Essay negates code of patient rights. Nurs N Z. 2006 Jun;12(5):6.

322. Mitchell AM, Kline JA. Systematic bias introduced by the informed consent process in a diagnostic research study. Acad Emerg Med. 2008 Mar;15(3):225-30.

323. Mourad M, Adler J. Safe, high quality care around the clock: What will it take to get us there? J Gen Intern Med [Internet]. 2011 [cited 2016 Nov 16];26(9):948-50. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3157519/pdf/11606_2011_Article_1795.pdf

324. Henzler T, Schoenberg SO, Schoepf UJ, Fink C. Diagnosing acute pulmonary embolism: systematic review of evidence base and cost-effectiveness of imaging tests. J Thorac Imaging. 2012 Sep;27(5):304-14.

325. Raja AS, Ip IK, Dunne RM, Schuur JD, Mills AM, Khorasani R. Effects of Performance Feedback Reports on Adherence to Evidence-Based Guidelines in Use of CT for Evaluation of Pulmonary Embolism in the Emergency Department: A Randomized Trial. AJR Am J Roentgenol [Internet]. 2015 Nov [cited 2016 Nov 14];205(5):936-40. Available from: http://www.ajronline.org/doi/pdf/10.2214/AJR.15.14677

326. Rohacek M, Buatsi J, Szucs-Farkas Z, Kleim B, Zimmermann H, Exadaktylos A, et al. Ordering CT pulmonary angiography to exclude pulmonary embolism: defense versus evidence in the emergency room. Intensive Care Med. 2012 Aug;38(8):1345-51.

327. Sheard L, Prout H, Dowding D, Noble S, Watt I, Maraveyas A, et al. The ethical decisions UK doctors make regarding advanced cancer patients at the end of life-The perceived (in) appropriateness of anticoagulation for venous thromboembolism: A qualitative study. BMC Medical Ethics [Internet]. 2012 [cited 2016 Nov 15];13, ArtID 22. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3459796/pdf/1472-6939-13-22.pdf

328. Tirada N, Dreizin D, Khati NJ, Akin EA, Zeman RK. Imaging pregnant and lactating patients. Radiographics. 2015 Oct;35(6):1751-65.

329. Yan Z, Ip IK, Raja AS, Gupta A, Kosowsky JM, Khorasani R. Yield of CT Pulmonary Angiography in the Emergency Department When Providers Override Evidence-based Clinical Decision Support. Radiology. 2016 Sep 30;151985.

330. Albrecht MH, Bickford MW, Nance JW, Jr., Zhang L, De Cecco CN, Wichmann JL, et al. State-of-the-Art Pulmonary CT Angiography for Acute Pulmonary Embolism. AJR Am J Roentgenol. 2017 Mar;208(3):495-504.

331. Alhassan S, Sayf A, Arsene C, Krayem H. Suboptimal implementation of diagnostic algorithms and overuse of computed tomography-pulmonary angiography in patients with suspected pulmonary embolism. Annals of Thoracic Medicine [Internet]. 2016 [cited 2017 Feb 1];11(4):254-60. Available from: http://www.thoracicmedicine.org/temp/AnnThoracMed114254-4993048_135210.pdf

332. Mountain D, Keijzers G, Chu K, Joseph A, Read C, Blecher G, et al. RESPECT-ED: Rates of Pulmonary Emboli (PE) and Sub-Segmental PE with Modern Computed Tomographic Pulmonary Angiograms in Emergency Departments: A Multi-Center Observational Study Finds Significant Yield Variation, Uncorrelated with Use or Small PE Rates. PLoS ONE [Internet]. 2016 [cited 2017 Jan 31];11(12):e0166483. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5137866

333. Sah S, Fagerlin A, Ubel P. Effect of physician disclosure of specialty bias on patient trust and treatment choice. Proc Natl Acad Sci U S A. 2016 Jul 5;113(27):7465-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4941435

334. Calder KK, Herbert M, Henderson SO. The mortality of untreated pulmonary embolism in emergency department patients. Ann Emerg Med. 2005 Mar;45(3):302-10.

335. Itri JN. Patient-centered Radiology. Radiographics. 2015 Oct;35(6):1835-46.

336. Browne AM, Cronin CG, English C, NiMhuircheartaigh J, Murphy JM, Bruzzi JF. Unsuspected pulmonary emboli in oncology patients undergoing routine computed tomography imaging. J Thorac Oncol [Internet]. 2010 Jun [cited 2016 Oct 7];5(6):798-803. Available from: http://ac.els-cdn.com/S1556086415305062/1-s2.0-S1556086415305062-main.pdf?_tid=3f376638-8cc1-11e6-bef2-00000aab0f6b&acdnat=1475867409_ff68ac277eb054c81cab4c1450043bab

337. Matthews S. Imaging pulmonary embolism in pregnancy: What is the most appropriate imaging protocol? Br J Radiol. 2006;79(941):441-4.

338. Schuster ME, Fishman JE, Copeland JF, Hatabu H, Boiselle PM. Pulmonary embolism in pregnant patients: a survey of practices and policies for CT pulmonary angiography. AJR Am J Roentgenol. 2003 Dec;181(6):1495-8.

339. Vano E, Kleiman NJ, Duran A, Romano-Miller M, Rehani MM. Radiation-associated lens opacities in catheterization personnel: results of a survey and direct assessments. J Vasc Interv Radiol. 2013 Feb;24(2):197-204.

340. Lee-Lewandrowski E, Nichols J, Van CE, Grisson R, Louissaint A, Benzer T, et al. Implementation of a rapid whole blood D-dimer test in the emergency department of an urban academic medical center: impact on ED length of stay and ancillary test utilization. Am J Clin Pathol [Internet]. 2009 Sep [cited 2016 Nov 14];132(3):326-31. Available from: http://ajcp.oxfordjournals.org/content/ajcpath/132/3/326.full.pdf

341. Brockbank J, Wolowacz S. Economic evaluations of new oral anticoagulants for the prevention of venous thromboembolism after total hip or total knee replacement [abstract]. Value in Health Conference. 2015;18(7):A392. (Presented at ISPOR 18th Annual European Congress; 2015 Nov 7-11; Milan, Italy).

342. Canadian medical imaging inventory: 2015 [Internet]. Ottawa (ON): CADTH; 2016 Mar 31. [cited 2017 Nov 10]. (In brief a summary of the evidence). Available from: https://www.cadth.ca/sites/default/files/pdf/cmii_in_brief_e.pdf

343. Chenaghlou M, Parizad R, Jafarabadi MA. Risk factors and prevention of pulmonary embolism in young adults. Crescent Journal of Medical and Biological Sciences. 2017 Jan;4(1):7-12.

344. Goldhaber SZ, Fanikos J. Prevention of deep vein thrombosis and pulmonary embolism. Circulation. 2004;110:e445-7.

345. Hess S, Frary EC, Gerke O, Madsen PH. State-of-the-art Imaging in pulmonary embolism: ventilation/perfusion single-photon emission computed tomography versus computed tomography angiography - controversies, results, and recommendations from a systematic review. Semin Thromb Hemost. 2016 Nov;42(8):833-845.

346. Yue K. Diagnosis efficiency for pulmonary embolism using magnetic resonance imaging method: a meta-analysis. Int J Clin Exp Med [Internet]. 2015 [cited 2016 Nov 25];8(8):14416-23. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4613114

347. Li J, Feng L, Li J, Tang J. Diagnostic accuracy of magnetic resonance angiography for acute pulmonary embolism - a systematic review and meta-analysis. VASA. 2016;45(2):149-54.

348. Kan Y, Yuan L, Meeks JK, Li C, Liu W, Yang J. The accuracy of V/Q SPECT in the diagnosis of pulmonary embolism: a meta-analysis. Acta Radiol. 2015 May;56(5):565-72.

349. Niemann T, Egelhof T, Bongartz G. Transthoracic sonography for the detection of pulmonary embolism--a meta-analysis. Ultraschall Med. 2009 Apr;30(2):150-6.

350. Jiang L, Ma Y, Zhao C, Shen W, Feng X, Xu Y, et al. Role of Transthoracic Lung Ultrasonography in the Diagnosis of Pulmonary Embolism: A Systematic Review and Meta-Analysis. PLoS ONE [Internet]. 2015 [cited 2016 Jul 6];10(6):e0129909. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4468196

351. Kneeland PP, Fang MC. Current issues in patient adherence and persistence: focus on anticoagulants for the treatment and prevention of thromboembolism. Patient Prefer Adherence [Internet]. 2010 [cited 2017 Dec 11];4:51-60. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2846139/pdf/ppa-4-051.pdf

352. Parilla BV, Fournogerakis R, Archer A, Sulo S, Laurent L, Lee P, et al. Diagnosing Pulmonary Embolism in Pregnancy: Are Biomarkers and Clinical Predictive Models Useful? AJP Rep [Internet]. 2016 Apr [cited 2017 Jul 17];6(2):e160-e164. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4844549

353. Toney LK, Kim RD, Palli SR. The economic value of hybrid single-photon emission computed tomography with computed tomography imaging in pulmonary embolism diagnosis. Acad Emerg Med. 2017 Sep;24(9):1110-1123.

354. Onabola CO. Greening Medical Imaging in BC's Lower Mainland Health Authorities [Internet]. Vancouver: University of British Columbia; 2017. [cited 2017 Nov 6]. Available from: https://sustain.ubc.ca/sites/sustain.ubc.ca/files/Sustainability%20Scholars/2017_Sustainability_Scholars/Final_Reports/Greening%20Medical%20Imaging%20in%20BC%20Lower%20Mainland%20Health%20Authorities_Onabola_%202017%20SS

355. Addendum to optimal strategies for the diagnosis of acute pulmonary embolism: a health technology assessment - project protocol. Ethics review [Internet]. Ottawa: CADTH; 2016 Oct. [cited 2016 Nov 23]. (CADTH optimal use, vol. 6, no. 3a). Available from: https://www.cadth.ca/addendum-optimal-strategies-diagnosis-acute-pulmonary-embolism-health-technology-assessment-project

356. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med [Internet]. 2009 Jul 21 [cited 2016 Aug 8];6(7):e1000097. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2707599

357. van Es N, van der Hulle T, Büller H, Klok FA, Huisman MV, Galipienzo J, et al. Stand-alone D-dimer testing to rule out acute pulmonary embolism. J Thromb Haemost. 2017 Feb;15(2):323-328.

358. Adams D, Welch JL, Kline JA. Clinical utility of an age-adjusted D-dimer in the diagnosis of venous thromboembolism. Ann Emerg Med. 2014;64(3):232-4.

359. Akgul O, Uyarel H. D-dimer: a novel predictive marker for cardiovascular disease. Int J Cardiol. 2013;168(5):4930-1.

360. Ayaram D, Bellolio MF, Murad MH, Laack TA, Sadosty AT, Erwin PJ, et al. Triple rule-out computed tomographic angiography for chest pain: a diagnostic systematic review and meta-analysis. Acad Emerg Med. 2013 Sep;20(9):861-71.

361. Barnes GD, Izzo B, Conte ML, Chopra V, Holbrook A, Fagerlin A. Use of decision aids for shared decision making in venous thromboembolism: A systematic review. Thromb Res. 2016 Jul;143:71-5.

362. Becattini C, Lignani A, Masotti L, Forte MB, Agnelli G. D-dimer for risk stratification in patients with acute pulmonary embolism. J Thromb Thrombolysis. 2012 Jan;33(1):48-57.

363. Ceriani E, Combescure C, Le GG, Nendaz M, Perneger T, Bounameaux H, et al. Clinical prediction rules for pulmonary embolism: a systematic review and meta-analysis. J Thromb Haemost. 2010 May;8(5):957-70.

364. Carrier M, Righini M, Wells PS, Perrier A, Anderson DR, Rodger MA, et al. Subsegmental pulmonary embolism diagnosed by computed tomography: incidence and clinical implications. A systematic review and meta-analysis of the management outcome studies. J Thromb Haemost. 2010 Aug;8(8):1716-22.

365. Challen K, Goodacre SW. Predictive scoring in non-trauma emergency patients: a scoping review. Emerg Med J. 2011;28(10):827-37.

366. Crawford F, Andras A, Welch K, Sheares K, Keeling D, Chappell FM. D-dimer test for excluding the diagnosis of pulmonary embolism. Cochrane Database Syst Rev. 2016;8:CD010864.

367. Douketis J. Review: Positive D-dimer results predict recurrence after first unprovoked VTE regardless of test timing or cutpoint, or patient age. Ann Intern Med. 2011;154(2):JC1-JC5.

368. Current evidence does not support the use of a negative d-dimer to rule out suspected pulmonary embolism in pregnancy. Emerg Med J. 2011;28(3):245-6.

369. Graham SM, Mwilu R, Liles WC. Clinical utility of biomarkers of endothelial activation and coagulation for prognosis in HIV infection: a systematic review. Virulence. 2013 Aug 15;4(6):564-71.

370. Hallifax RJ, Talwar A, Rahman NM. The role of computed tomography in assessing pleural malignancy prior to thoracoscopy. Curr Opin Pulm Med. 2015 Jul;21(4):368-71.

371. Hendriksen JM, Geersing GJ, Lucassen WA, Erkens PM, Stoffers HE, van Weert HC, et al. Diagnostic prediction models for suspected pulmonary embolism: systematic review and independent external validation in primary care. Bmj [Internet]. 2015 [cited 2016 Oct 14];351:h4438. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4561760

372. Corrigendum to prognostic clinical prediction rules to identify a low-risk pulmonary embolism: a systematic review and meta-analysis. J Thromb Haemost. 2013;11(1):218-20.

373. Klok FA, Mos IC, Huisman M, V. Brain-type natriuretic peptide levels in the prediction of adverse outcome in patients with pulmonary embolism: a systematic review and meta-analysis. Am J Respir Crit Care Med. 2008;178(4):425-30.

374. Kohn CG, Mearns ES, Parker MW, Hernandez AV, Coleman CI. Prognostic accuracy of clinical prediction rules for early post-pulmonary embolism all-cause mortality: a bivariate meta-analysis. Chest. 2015 Apr;147(4):1043-62.

375. Manara A, D'hoore W, Thys F. Capnography as a diagnostic tool for pulmonary embolism: a meta-analysis. Ann Emerg Med. 2013 Dec;62(6):584-91.

376. Mos IC, Klok FA, Kroft LJ, DE RA, Dekkers OM, Huisman MV. Safety of ruling out acute pulmonary embolism by normal computed tomography pulmonary angiography in patients with an indication for computed tomography: systematic review and meta-analysis. J Thromb Haemost. 2009 Sep;7(9):1491-8.

377. Mos IC, Douma RA, Erkens PM, Kruip MJ, Hovens MM, van Houten AA, et al. Diagnostic outcome management study in patients with clinically suspected recurrent acute pulmonary embolism with a structured algorithm. Thromb Res. 2014 Jun;133(6):1039-44.

378. Ouatu A, Tanase DM, Ionescu SD, Rezus C, Ambarus V, Arsenescu-Georgescu C. The importance of clinical prediction models in non-fatal pulmonary embolism: an analysis of the best known clinical scores. Rev Med Chir Soc Med Nat Iasi. 2014 Oct;118(4):932-41.

379. Pulivarthi S, Gurram MK. Effectiveness of D-Dimer as a screening test for venous thromboembolism: an update. N A J Med Sci (Hamilt) [Internet]. 2014 Oct [cited 2016 Oct 4];6(10):491-9. Available from: http://www.najms.org/temp/NorthAmJMedSci610491-4195742_113917.pdf

380. Rehnberg JV, Vondy A. Towards evidence-based emergency medicine: Best BETs from the Manchester Royal Infirmary. BET 3: Pulmonary embolism rule-out criteria (PERC) for excluding pulmonary embolism. Emerg Med J. 2014 Jan;31(1):81-2.

381. Schouten HJ, Geersing GJ, Koek HL, Zuithoff NP, Janssen KJ, Douma RA, et al. Diagnostic accuracy of conventional or age adjusted D-dimer cut-off values in older patients with suspected venous thromboembolism: systematic review and meta-analysis. Bmj [Internet]. 2013;346:f2492. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3643284

382. Self WH, Barrett TW. Annals of Emergency Medicine journal club. Is "PERC negative" adequate to rule out pulmonary embolism in the emergency department? Evaluating meta-analysis for studies of clinical prediction models. Ann Emerg Med. 2012 Jul;60(1):129-31.

383. Self WH, Barrett TW. Is "PERC negative" adequate to rule out pulmonary embolism in the emergency department? Evaluating meta-analysis for studies of clinical prediction models. Ann Emerg Med. 2012;60(1):129-31.

384. Sharma A, Chatterjee S, Lichstein E, Mukherjee D. Extended thromboprophylaxis for medically ill patients with decreased mobility: does it improve outcomes? J Thromb Haemost. 2012;10(10):2053-60.

385. Singh B, Parsaik AK, Agarwal D, Surana A, Mascarenhas SS, Chandra S. Diagnostic accuracy of pulmonary embolism rule-out criteria: a systematic review and meta-analysis. Ann Emerg Med. 2012 Jun;59(6):517-20.

386. Squizzato A, Donadini MP, Galli L, Dentali F, Aujesky D, Ageno W. Prognostic clinical prediction rules to identify a low-risk pulmonary embolism: a systematic review and meta-analysis. J Thromb Haemost. 2012 Jul;10(7):1276-90.

387. Stevens SM. 2011 - Review: Gestalt or clinical decision rules have limited sensitivity and specificity for detecting acute PE [Philadelphia, Pennsylvania]. ACP J Club. 2012 Jan 17;156(1):1. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=cin20&AN=104527902&site=ehost-live

388. Tafur A. Systematic review: a low wells score and a negative D-dimer was not safe in patients with cancer for ruling out DVT. Evid Based Med. 2014;19(5):188.

389. van Es N, van der Hulle T, van Es J, den Exter PL, Douma RA, Goekoop RJ, et al. Excluding pulmonary embolism in cancer patients using the Wells rule and age-adjusted D-dimer testing: an individual patient data meta-analysis. Thromb Res. 2016 Apr;140 Suppl 1:S179.

390. van Es N, Kraaijpoel N, Klok FA, Huisman MV, den Exter PL, Mos IC, et al. The original and simplified Wells rules and age-adjusted D-dimer testing to rule out pulmonary embolism: an individual patient data meta-analysis. J Thromb Haemost. 2017 Apr;15(4):678-684.

391. van Leent MW, Stevanovic J, Jansman FG, Beinema MJ, Brouwers JR, Postma MJ. Cost-Effectiveness of Dabigatran Compared to Vitamin-K Antagonists for the Treatment of Deep Venous Thrombosis in the Netherlands Using Real-World Data. PLoS ONE [Internet]. 2015 [cited 2016 Oct 4];10(8):e0135054. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4524689

392. Wessler BS, Lai YL, Kramer W, Cangelosi M, Raman G, Lutz JS, et al. Clinical prediction models for cardiovascular disease: The Tufts PACE CPM database. Circ Cardiovasc Qual Outcomes [Internet]. 2015 Jul [cited 2016 Oct 4];8(4):368-75. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4512876/pdf/nihms-692018.pdf

393. Witt DM. Review: Positive D-dimer results predict recurrence after first unprovoked VTE regardless of test timing or cutpoint, or patient age [Philadelphia, Pennsylvania]. ACP J Club. 2011 Jan 18;154(1):4.

394. Zhou XY, Ben SQ, Chen HL, Ni SS. The prognostic value of pulmonary embolism severity index in acute pulmonary embolism: a meta-analysis. Respir Res [Internet]. 2012;13:111. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3571977

395. Abujudeh HH, Kaewlai R, Farsad K, Orr E, Gilman M, Shepard JA. Computed tomography pulmonary angiography. An assessment of the radiology report. Acad Radiol. 2009;16(11):1309-15.

396. Albrizio M, Mizzi A. Rate of computed tomography pulmonary angiographies (CTPA) positive for pulmonary embolism and predictive scores. Radiol Med. 2007 Oct;112(7):982-7.

397. Alhadad A, Miniati M, Alhadad H, Gottsater A, Bajc M. The value of tomographic ventilation/perfusion scintigraphy (V/PSPECT) for follow-up and prediction of recurrence in pulmonary embolism. Thromb Res. 2012 Dec;130(6):877-81.

398. Summaries for patients. Evaluation of patients with suspected acute pulmonary embolism: best practice advice from the Clinical Guidelines Committee of the American College of Physicians. Ann Intern Med. 2015 Nov 3;163(9):I34.

399. Summaries for patients. Diagnosis of pulmonary embolism with magnetic resonance angiography. Ann Intern Med. 2010 Apr 6;152(7):I44.

400. Arnason T, Wells PS, Forster AJ. Appropriateness of diagnostic strategies for evaluating suspected venous thromboembolism. Thromb Haemost. 2007;97(2):195-201.

401. Astani SA, Davis LC, Harkness BA, Supanich MP, Dalal I. Detection of pulmonary embolism during pregnancy: comparing radiation doses of CTPA and pulmonary scintigraphy. Nucl Med Commun. 2014 Jul;35(7):704-11.

402. Bajc M. Potential of hybrid V/P SPECT-low-dose CT in lung diagnostics. Breathe [Internet]. 2012 [cited 2016 Oct 12];9(1):49-60. Available from: http://breathe.ersjournals.com/content/breathe/9/1/48.full.pdf

403. Baliga RR. Diagnosis of pulmonary embolism by multidetector CT alone or combined with venous ultrasonography of the leg. ACC Cardiosource Rev J. 2008;17(6):31-2.

404. Bannas P, Schiebler ML, Motosugi U, Francois CJ, Reeder SB, Nagle SK. Pulmonary MRA: differentiation of pulmonary embolism from truncation artefact. Eur Radiol [Internet]. 2014 Aug [cited 2016 Oct 4];24(8):1942-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4362685

405. Bates DD, Tkacz JN, LeBedis CA, Holalkere N. Suboptimal CT pulmonary angiography in the emergency department: a retrospective analysis of outcomes in a large academic medical center. Emerg Radiol. 2016 Dec;23(6):603-607.

406. Begic A, Opankovic E, Cukic V, Rustempasic M, Basic A, Miniati M, et al. Impact of ventilation/perfusion single-photon emission computed tomography on treatment duration of pulmonary embolism. Nucl Med Commun [Internet]. 2015 Feb [cited 2016 Oct 4];36(2):162-7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4280272

407. Blackmore CC. Evidence-based imaging and cost-effectiveness analysis in cardiopulmonary imaging. J Thorac Imaging. 2012;27(5):272-6.

408. Blum AG, Delfau F, Grignon B, Beurrier D, Chabot F, Claudon M, et al. Spiral-computed tomography versus pulmonary angiography in the diagnosis of acute massive pulmonary embolism. Am J Cardiol. 1994 Jul 1;74(1):96-8.

409. Boldt BM, Cox CW, Dedekam EA, Tsytsik B, Mysliwiec V. Pulmonary embolism at follow-up outpatient CT pulmonary angiography: implications on patient risk stratification. Blood Coagul Fibrinolysis. 2013 Sep;24(6):633-7.

410. Bova C, Greco F, Misuraca G, Serafini O, Crocco F, Greco A, et al. Diagnostic utility of echocardiography in patients with suspected pulmonary embolism. Am J Emerg Med. 2003 May;21(3):180-3.

411. Stawicki SP, Seamon MJ, Kim PK, Meredith DM, Chovanes J, Schwab CW, et al. Transthoracic echocardiography for pulmonary embolism in the ICU: finding the "right" findings. J Am Coll Surg. 2008 Jan;206(1):42-7.

412. Branch KR, Strote J, Shuman WP, Mitsumori LM, Busey JM, Rue T, et al. Diagnostic accuracy and clinical outcomes of ECG-gated, whole chest CT in the emergency department. PLoS ONE [Internet]. 2013 [cited 2016 Oct 4];8(4). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3629052/pdf/pone.0061121.pdf

413. Cereser L, Bagatto D, Girometti R, Como G, Zuiani C, Bazzocchi M. Chest multidetector computed tomography (MDCT) in patients with suspected acute pulmonary embolism: diagnostic yield and proportion of other clinically relevant findings. Radiol Med (Torino). 2011 Mar;116(2):219-29.

414. Christiansen F. Diagnostic imaging of acute pulmonary embolism. Acta Radiol Suppl. 1997;410:1-33.

415. Callejas MF, Errazuriz JI, Castillo F, Otarola C, Riquelme C, Ortega C, et al. Incidental venous thromboembolism detected by PET-CT in patients with cancer: prevalence and impact on survival rate. Thromb Res. 2014 May;133(5):750-5.

416. Cueto SM, Cavanaugh SH, Benenson RS, Redclift MS. Computed tomography scan versus ventilation-perfusion lung scan in the detection of pulmonary embolism. J Emerg Med. 2001 Aug;21(2):155-64.

417. Darze ES, Braghiroli JF, Almeida RV, Araujo EP, Toscano SM, Araujo-Neto CA. Clinical outcomes after investigation for pulmonary embolism using CT angiography and venography. Arq Bras Cardiol [Internet]. 2012 Aug [cited 2016 Oct 4];99(2):740-6. Available from: http://www.scielo.br/pdf/abc/v99n2/en_aop05512.pdf

418. Douma RA, Hofstee HM, Schaefer-Prokop C, van Waesberghe JH, Lely RJ, Kamphuisen PW, et al. Comparison of 4- and 64-slice CT scanning in the diagnosis of pulmonary embolism. Thromb Haemost. 2010 Jan;103(1):242-6.

419. Douma RA, Hofstee HM, Schaefer-Prokop C, van Waesberghe JH, Lely RJ, Kamphuisen PW, et al. Comparison of 4- and 64-slice CT scanning in the diagnosis of pulmonary embolism. Thromb Haemost. 2010 Jan;103(1):242-6.

420. Drucker EA, Rivitz SM, Shepard JA, Boiselle PM, Trotman-Dickenson B, Welch TJ, et al. Acute pulmonary embolism: assessment of helical CT for diagnosis. Radiology. 1998 Oct;209(1):235-41.

421. Duralde XA, McClelland WB, Jr. The clinical results of arthroscopic transtendinous repair of grade III partial articular-sided supraspinatus tendon tears. Arthroscopy. 2012 Feb;28(2):160-8.

422. Easther S, Langdana F, Beasley R, Maharaj D, Entwisle J, Abels P. The diagnostic role of ventilation/perfusion scans versus computed tomography pulmonary angiography in obstetric patients investigated for pulmonary embolism at Wellington Hospital from 2010 to 2012. N Z Med J. 2016;129(1433):62-8.

423. Elias A, Cazanave A, Elias M, Chabbert V, Juchet H, Paradis H, et al. Diagnostic management of pulmonary embolism using clinical assessment, plasma D-dimer assay, complete lower limb venous ultrasound and helical computed tomography of pulmonary arteries. A multicentre clinical outcome study. Thromb Haemost. 2005 May;93(5):982-8.

424. Emet M, Ozucelik DN, Sahin M, Oran M, Sivri B. Computed tomography pulmonary angiography in the diagnosis of acute pulmonary embolism in the emergency department. Adv Ther. 2007 Nov;24(6):1173-80.

425. Engelke C, Rummeny EJ, Marten K. Pulmonary embolism at multi-detector row CT of chest: one-year survival of treated and untreated patients. Radiology [Internet]. 2006 May [cited 2016 Oct 13];239(2):563-75. Available from: http://pubs.rsna.org/doi/pdf/10.1148/radiol.2392050118

426. Ersoy H, Goldhaber SZ, Cai T, Luu T, Rosebrook J, Mulkern R, et al. Time-resolved MR angiography: a primary screening examination of patients with suspected pulmonary embolism and contraindications to administration of iodinated contrast material. AJR Am J Roentgenol [Internet]. 2007 May [cited 2016 Oct 6];188(5):1246-54. Available from: http://www.ajronline.org/doi/pdf/10.2214/AJR.06.0901

427. Fabiá Valls MJ, van der Hulle T, den Exter PL, Mos IC, Huisman MV, Klok FA. Performance of a diagnostic algorithm based on a prediction rule, D-dimer and CT-scan for pulmonary embolism in patients with previous venous thromboembolism. A systematic review and meta-analysis. Thromb Haemost. 2015 Feb;113(2):406-13.

428. Feragalli B, Galluzzo M, Scaglione M. MDCT venography in patients with suspected pulmonary embolism: diagnostic impact of pelvic vein evaluation in thromboembolic disease detection. Panminerva Med. 2012 Dec;54(1 Suppl 4):67-72.

429. Ferreira EV, Gazzana MB, Sarmento MB, Guazzelli PA, Hoffmeister MC, Guerra VA, et al. Alternative diagnoses based on CT angiography of the chest in patients with suspected pulmonary thromboembolism. J Bras Pneumol [Internet]. 2016 Jan;42(1):35-41. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4805385

430. Ferretti GR, Bosson JL, Buffaz PD, Ayanian D, Pison C, Blanc F, et al. Acute pulmonary embolism: role of helical CT in 164 patients with intermediate probability at ventilation-perfusion scintigraphy and normal results at duplex US of the legs. Radiology. 1997 Nov;205(2):453-8.

431. Flavell RR, Behr SC, Brunsing RL, Naeger DM, Pampaloni MH. The incidence of pulmonary embolism and associated FDG-PET findings in IV contrast-enhanced PET/CT. Acad Radiol. 2014 Jun;21(6):718-25.

432. Friera A, Olivera MJ, Suárez C, Ruiz-Giménez N, Caballero P, Thromboembolic Study Group of La Princesa Hospital. Clinical validity of negative helical computed tomography for clinical suspicion of pulmonary embolism. Respiration. 2004 Jan;71(1):30-6.

433. Garg KC, Das KM. 64-slice CT diagnosis of pulmonary embolism. Journal of Emergency Medicine, Trauma and Acute Care. 2008;8(1):38-41.

434. Garg K, Welsh CH, Feyerabend AJ, Subber SW, Russ PD, Johnston RJ, et al. Pulmonary embolism: diagnosis with spiral CT and ventilation-perfusion scanning--correlation with pulmonary angiographic results or clinical outcome. Radiology. 1998 Jul;208(1):201-8.

435. Garg K, Sieler H, Welsh CH, Johnston RJ, Russ PD. Clinical validity of helical CT being interpreted as negative for pulmonary embolism: implications for patient treatment. AJR Am J Roentgenol [Internet]. 1999 Jun [cited 2017 Jan 16];172(6):1627-31. Available from: http://www.ajronline.org/doi/pdfplus/10.2214/ajr.172.6.10350303

436. Ghazvinian R, Gottsater A, Elf J. Is it safe to withhold long-term anticoagulation therapy in patients with small pulmonary emboli diagnosed by SPECT scintigraphy? Thrombosis Journal [Internet]. 2016 [cited 2016 Oct 7];14:12. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4886445/pdf/12959_2016_Article_86.pdf

437. Glaser JE, Chamarthy M, Haramati LB, Esses D, Freeman LM. Successful and safe implementation of a trinary interpretation and reporting strategy for V/Q lung scintigraphy. J Nucl Med [Internet]. 2011 [cited 2016 Oct 7];52(10):1508-12. Available from: http://jnm.snmjournals.org/content/52/10/1508.full.pdf+html

438. Gleeson FV, Turner S, Scarsbrook AF. Improving the diagnostic performance of lung scintigraphy in suspected pulmonary embolic disease. Clin Radiol. 2006 Dec;61(12):1010-5.

439. Goodman LR, Lipchik RJ, Kuzo RS, Liu Y, McAuliffe TL, O'Brien DJ. Subsequent pulmonary embolism: risk after a negative helical CT pulmonary angiogram--prospective comparison with scintigraphy. Radiology [Internet]. 2000 May [cited 2016 Dec 1];215(2):535-42. Available from: http://pubs.rsna.org/doi/pdf/10.1148/radiology.215.2.r00ma23535

440. Remy-Jardin M, Remy J, Deschildre F, Artaud D, Beregi JP, Hossein-Foucher C, et al. Diagnosis of pulmonary embolism with spiral CT: comparison with pulmonary angiography and scintigraphy. Radiology. 1996 Sep;200(3):699-706.

441. Grimm LJ, Coleman RE. Assessing the utility of the ventilation phase in ventilation-perfusion imaging for acute pulmonary embolism. Nucl Med Commun. 2013 Jan;34(1):1-4.

442. Gruettner J, Fink C, Walter T, Meyer M, Apfaltrer P, Schoepf UJ, et al. Coronary computed tomography and triple rule out CT in patients with acute chest pain and an intermediate cardiac risk profile. Part 1: Impact on patient management. Eur J Radiol. 2013;82(1):100-5.

443. Gruettner J, Walter T, Bolte M, Haghi D, Sudarski S, Henzler T. Incidence of pulmonary embolism in an emergency department cohort evaluated with a simple symptom-based diagnostic algorithm. In Vivo. 2013 Mar;27(2):215-20.

444. Hansch A, Betge S, Poehlmann G, Neumann S, Baltzer P, Pfeil A, et al. Combined magnetic resonance imaging of deep venous thrombosis and pulmonary arteries after a single injection of a blood pool contrast agent. Eur Radiol. 2011;21(2):318-25.

445. Hata T, Ikeda M, Nakamori S, Suzuki R, Kim T, Yasui M, et al. Single-photon emission computed tomography in the screening for postoperative pulmonary embolism. Dig Dis Sci. 2006 Nov;51(11):2073-80.

446. Hayes SA, Soff GA, Zabor EC, Moskowitz CS, Liu CC, Ginsberg MS. Clinical consequences of an indeterminate CT pulmonary angiogram in cancer patients. Clin Imaging [Internet]. 2014 Sep [cited 2016 Oct 4];38(5):637-40. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4431545

447. Hirsch AM, Kahn SR, Morris T, Wells PS, Rodger M, Kovacs MJ, et al. PEDS (pulmonary embolism diagnosis study) a randomized controlled trial of CT pulmonary angiography and V/Q scanning in patients with suspected pulmonary embolism. Proc Am Thorac Soc. 2006;A783p.

448. Hochuli M, Duewell S, Frauchiger B. Quantitative d-dimer levels and the extent of venous thromboembolism in CT angiography and lower limb ultrasonography. VASA. 2007 Nov;36(4):267-74.

449. Hofman MS, Beauregard JM, Barber TW, Neels OC, Eu P, Hicks RJ. ^{68}Ga PET/CT ventilation-perfusion imaging for pulmonary embolism: a pilot study with comparison to conventional scintigraphy. J Nucl Med [Internet]. 2011 Oct [cited 2016 Oct 7];52(10):1513-9. Available from: http://jnm.snmjournals.org/content/52/10/1513.full.pdf+html

450. Holmquist F, Hansson K, Pasquariello F, Bjork J, Nyman U. Minimizing contrast medium doses to diagnose pulmonary embolism with 80-kVp multidetector computed tomography in azotemic patients. Acta Radiol. 2009 Mar;50(2):181-93.

451. Hou DJ, Tso DK, Davison C, Inacio J, Louis LJ, Nicolaou S, et al. Clinical utility of ultra high pitch dual source thoracic CT imaging of acute pulmonary embolism in the emergency department: are we one step closer towards a non-gated triple rule out? Eur J Radiol. 2013 Oct;82(10):1793-8.

452. Howarth DM, Booker JA, Voutnis DD. Diagnosis of pulmonary embolus using ventilation/perfusion lung scintigraphy: more than 0.5 segment of ventilation/perfusion mismatch is sufficient. Intern Med J. 2006 May;36(5):281-8.

453. Hsiao SH, Lee CY, Chang SM, Yang SH, Lin SK, Chiou KR. Usefulness of pulmonary arterial flow discordance to identify pulmonary embolism. Am J Cardiol. 2007 Feb 15;99(4):579-83.

454. Hunsaker AR, Zou KH, Poh AC, Trotman-Dickenson B, Jacobson FL, Gill RR, et al. Routine pelvic and lower extremity CT venography in patients undergoing pulmonary CT angiography. AJR Am J Roentgenol [Internet]. 2008 Feb [cited 2016 Oct 7];190(2):322-6. Available from: http://www.ajronline.org/doi/pdf/10.2214/AJR.07.2568

455. Hussein W, Dalouk KA, O'Brien A. Negative predictive value of CTPA in pulmonary embolism in an Irish population. Ir Med J. 2008 Mar;101(3):92-3.

456. Ingrisch M, Maxien D, Meinel FG, Reiser MF, Nikolaou K, Dietrich O. Detection of pulmonary embolism with free-breathing dynamic contrast-enhanced MRI. Journal of Magnetic Resonance Imaging. 2016;43(4):887-93.

457. Inonu H, Acu B, Pazarli AC, Doruk S, Erkorkmaz U, Altunkas A. The value of the computed tomographic obstruction index in the identification of massive pulmonary thromboembolism. Diagn Interv Radiol [Internet]. 2012 May [cited 2016 Oct 4];18(3):255-60. Available from: http://www.dirjournal.org/sayilar/43/buyuk/pdf_DIR_433.pdf

458. Jia CF, Li YX, Yang ZQ, Zhang ZH, Sun XX, Wang ZQ. Prospective evaluation of unsuspected pulmonary embolism on coronary computed tomographic angiography. J Comput Assist Tomogr. 2012 Mar;36(2):187-90.

459. Jögi J, Jonson B, Ekberg M, Bajc M. Ventilation-perfusion SPECT with 99mTc-DTPA versus Technegas: a head-to-head study in obstructive and nonobstructive disease. J Nucl Med [Internet]. 2010 May [cited 2016 Oct 7];51(5):735-41. Available from: http://jnm.snmjournals.org/content/51/5/735.full.pdf+html

460. Jogi J, Markstad H, Tufvesson E, Bjermer L, Bajc M. The added value of hybrid ventilation/perfusion SPECT/CT in patients with stable COPD or apparently healthy smokers. Cancer-suspected CT findings in the lungs are common when hybrid imaging is used. Int J Chron Obstruct Pulmon Dis [Internet]. 2015 [cited 2016 Oct 4];10:25-30. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4279608

461. Jones C, Teixeira PG, Inaba K, Keesara SR, Rhee P, Brown C, et al. Combined CT venography and CT pulmonary angiography for the detection of deep venous thrombosis in injured patients. Am Surg. 2008 Oct;74(10):935-8.

462. Jordan EJ, Godelman A, Levsky JM, Zalta B, Haramati LB. CT pulmonary angiography in pregnant and postpartum women: low yield, high dose. Clin Imaging. 2015 Mar;39(2):251-3.

463. Junger M, Diehm C, Storiko H, Hach-Wunderle V, Heidrich H, Karasch T, et al. Mobilization versus immobilization in the treatment of acute proximal deep venous thrombosis: a prospective, randomized, open, multicentre trial. Curr Med Res Opin. 2006 Mar;22(3):593-602.

464. Kado R, Siegwald E, Lewis E, Goodsitt MM, Christodoulou E, Kazerooni E, et al. Utility and associated risk of pulmonary embolism computed tomography scans in the Michigan lupus cohort. Arthritis Care Res (Hoboken). 2016 Mar;68(3):406-11.

465. Kamel EM, Schmidt S, Doenz F, Adler-Etechami G, Schnyder P, Qanadli SD. Computed tomographic angiography in acute pulmonary embolism: do we need multiplanar reconstructions to evaluate the right ventricular dysfunction? J Comput Assist Tomogr. 2008 May;32(3):438-43.

466. Kaul D, Grupp U, Kahn J, Ghadjar P, Wiener E, Hamm B, et al. Reducing radiation dose in the diagnosis of pulmonary embolism using adaptive statistical iterative reconstruction and lower tube potential in computed tomography. Eur Radiol. 2014 Nov;24(11):2685-91.

467. Kiley CA, Lowry KJ, Mysliwiec V. Examination of hospital referral practices for CT pulmonary angiography. J Hosp Med. 2007 Jul;2(4):253-7.

468. Kim HJ, Walcott-Sapp S, Leggett K, Bass A, Adler RS, Pavlov H, et al. The Use of spiral computed tomography scans for the detection of pulmonary embolism. J Arthroplasty. 2008;23(6 Suppl):31-5.

469. Kindermann DR, McCarthy ML, Ding R, Frohna WJ, Hansen J, Maloy K, et al. Emergency department variation in utilization and diagnostic yield of advanced radiography in diagnosis of pulmonary embolus. J Emerg Med. 2014 Jun;46(6):791-9.

470. King-Im JM, Freeman SJ, Boylan T, Cheow HK. Quality of CT pulmonary angiography for suspected pulmonary embolus in pregnancy. Eur Radiol. 2008 Dec;18(12):2709-15.

471. Kligerman S, Lahiji K, Weihe E, Lin CT, Terpenning S, Jeudy J, et al. Detection of pulmonary embolism on computed tomography: improvement using a model-based iterative reconstruction algorithm compared with filtered back projection and iterative reconstruction algorithms. J Thorac Imaging. 2015 Jan;30(1):60-8.

472. Kline JA, Webb WB, Jones AE, Hernandez-Nino J. Impact of a rapid rule-out protocol for pulmonary embolism on the rate of screening, missed cases, and pulmonary vascular imaging in an urban US emergency department. Ann Emerg Med. 2004 Nov;44(5):490-502.

473. Kluge A, Muller C, Hansel J, Gerriets T, Bachmann G. Real-time MR with TrueFISP for the detection of acute pulmonary embolism: initial clinical experience. Eur Radiol. 2004 Apr;14(4):709-18.

474. Koch C, Schramm R, Roller FC, Hecker A, Henrich M, Schneck E, et al. Impact of unsuspected subsegmental pulmonary embolism in ICU patients. Anaesthesist. 2016 Feb;65(2):122-8.

475. Konstantinides SV, Torbicki A. Management of pulmonary embolism: recent evidence and the new European guidelines. Eur Respir J [Internet]. 2014 Dec [cited 2016 Aug 16];44(6):1385-90. Available from: http://erj.ersjournals.com/content/erj/44/6/1385.full.pdf

476. Kooiman J, Klok FA, Mos IC, van der MA, DE RA, Sijpkens YW, et al. Incidence and predictors of contrast-induced nephropathy following CT-angiography for clinically suspected acute pulmonary embolism. J Thromb Haemost [Internet]. 2010 Feb [cited 2016 Oct 7];8(2):409-11. Available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1538-7836.2009.03698.x/epdf

477. Korkeila PJ, Saraste MK, Nyman KM, Koistinen J, Lund J, Juhani Airaksinen KE. Transesophageal echocardiography in the diagnosis of thrombosis associated with permanent transvenous pacemaker electrodes. Pacing Clin Electrophysiol. 2006 Nov;29(11):1245-50.

478. Krestan CR, Klein N, Fleischmann D, Kaneider A, Novotny C, Kreuzer S, et al. Value of negative spiral CT angiography in patients with suspected acute PE: analysis of PE occurrence and outcome. Eur Radiol. 2004 Jan;14(1):93-8.

479. Krishan S, Panditaratne N, Verma R, Robertson R. Incremental value of CT venography combined with pulmonary CT angiography for the detection of thromboembolic disease: systematic review and meta-analysis. AJR Am J Roentgenol. 2011 May;196(5):1065-72.

480. Kroschel U, Seitz K, Reuss J, Rettenmaier G. [Sonographic imaging of lung emboli. Results of a prospective study]. Ultraschall Med. 1991 Dec;12(6):263-8. German.

481. Kwon WJ, Jeong YJ, Kim KI, Lee IS, Jeon UB, Lee SH, et al. Computed tomographic features of pulmonary septic emboli: comparison of causative microorganisms. J Comput Assist Tomogr. 2007 May;31(3):390-4.

482. Lang O, Balon HR, Píichová R, Krizova H, Kuníková I. Lung tissue density measured by low-dose CT during pulmonary perfusion SPECT/CT as a tool for differentiation pulmonary embolism from chronic obstructive pulmonary disease - A pilot study. Cor et Vasa. 2013 [cited 2016 Oct 12];55(6):e492-e496.

483. Lapergue B, Decroix JP, Evrard S, Wang A, Bendetowicz D, Offroy MA, et al. Diagnostic yield of venous thrombosis and pulmonary embolism by combined CT venography and pulmonary angiography in patients with cryptogenic stroke and patent foramen ovale. Eur Neurol. 2015;74(1-2):69-72.

484. Le Roux P-Y, Delluc A, Abgral R, Reffad A, Cornily JC, Querellou S, et al. Positron emission tomography with ^{18}F-fluorodeoxyglucose of venous thromboembolism. Medecine Nucleaire. 2011;35(4):179-85. French.

485. Le Roux PY, Abgral R, Jaffrelot M, Delluc A, Gut-Gobert C, Querellou S, et al. Diagnosis of pulmonary embolism: planar images generated from V/Q SPECT are not a reliable substitute for traditional planar V/Q scan. Nucl Med Commun. 2012 Jul;33(7):695-700.

486. Le Roux PY, Robin P, Delluc A, Tardy B, Abgral R, Couturaud F, et al. Performance of 18F fluoro-2-desoxy-D-glucose positron emission tomography/computed tomography for the diagnosis of venous thromboembolism. Thromb Res. 2015 Jan;135(1):31-5.

487. Lee EY, Khong PL. The value of ^{18}F-FDG PET/contrast-enhanced CT in detection of tumor thrombus. Clin Nucl Med. 2013 Feb;38(2):e60-e65.

488. Lemb M, Pohlabeln H. Pulmonary thromboembolism: a retrospective study on the examination of 991 patients by ventilation/perfusion SPECT using Technegas. NuklearMedizin. 2001 Dec;40(6):179-86.

489. Lessler AL, Isserman JA, Agarwal R, Palevsky HI, Pines JM. Testing low-risk patients for suspected pulmonary embolism: a decision analysis. Ann Emerg Med. 2010 Apr;55(4):316-26.

490. Lim KY, Kligerman SJ, Lin CT, White CS. Missed pulmonary embolism on abdominal CT. Am J Roentgenol [Internet]. 2014 [cited 2016 Oct 7];202(4):738-43. Available from: http://www.ajronline.org/doi/pdf/10.2214/AJR.13.11436

491. Lombard J, Bhatia R, Sala E. Spiral computed tomographic pulmonary angiography for investigating suspected pulmonary embolism: clinical outcomes. Can Assoc Radiol J. 2003 Jun;54(3):147-51.

492. Lomis NN, Yoon HC, Moran AG, Miller FJ. Clinical outcomes of patients after a negative spiral CT pulmonary arteriogram in the evaluation of acute pulmonary embolism. J Vasc Interv Radiol. 1999 Jun;10(6):707-12.

493. Macdonald WB, Patrikeos AP, Thompson RI, Adler BD, van der Schaaf AA. Diagnosis of pulmonary embolism: ventilation perfusion scintigraphy versus helical computed tomography pulmonary angiography. Australas Radiol. 2005 Feb;49(1):32-8.

494. Mao X, Wang S, Jiang X, Zhang L, Xu W. Diagnostic value of dual-source computerized tomography combined with perfusion imaging for peripheral pulmonary embolism. Iranian Journal of Radiology. 2016;13(2).

495. Mathis G, Metzler J, Feurstein M, Fussenegger D, Sutterlutti G. [Lung infarcts detected with ultrasonography]. Ultraschall Med. 1990 Dec;11(6):281-3. German.

496. Mathis G, Bitschnau R, Gehmacher O, Scheier M, Kopf A, Schwarzler B, et al. Chest ultrasound in diagnosis of pulmonary embolism in comparison to helical CT. Ultraschall Med. 1999 Apr;20(2):54-9.

497. Mathis G, Blank W, Reissig A, Lechleitner P, Reuss J, Schuler A, et al. Thoracic ultrasound for diagnosing pulmonary embolism: a prospective multicenter study of 352 patients. Chest. 2005 Sep;128(3):1531-8.

498. Meinel FG, Nance JW, Schoepf UJ, Hoffmann VS, Thierfelder KM, Costello P, et al. Predictive Value of Computed Tomography in Acute Pulmonary Embolism: Systematic Review and Meta-analysis. Am J Med. 2015 Jul;128(7):747-59.

499. Meysman M, Everaert H, Buls N, Nieboer K, de MJ. Comparison of ventilation-perfusion single-photon emission computed tomography (V/Q SPECT) versus dual-energy CT perfusion and angiography (DECT) after 6 months of pulmonary embolism (PE) treatment. Eur J Radiol. 2015 Sep;84(9):1816-9.

500. Miniati M, Monti S, Pratali L, Di RG, Marini C, Formichi B, et al. Value of transthoracic echocardiography in the diagnosis of pulmonary embolism: results of a prospective study in unselected patients. Am J Med. 2001 May;110(7):528-35.

501. Minshall CT, Doben AR, Leon SM, Fakhry SM, Eriksson EA. Computed tomography pulmonary angiography: more than a screening tool for pulmonary embolus. J Crit Care. 2015 Feb;30(1):196-200.

502. Moon KT. SPECT V/Q scintigraphy is an option for diagnosing pulmonary embolism. Am Fam Physician. 2010;82(5):531-2.

503. Morales-Borrero WJ, Maldonado-Vargas JA. Diagnostic yield of pulmonary CT angiography in the evaluation of pulmonary embolisms treated at the Puerto Rico Medical Center from 2008 to 2012. P R Health Sci J. 2016 Mar;35(1):16-9.

504. Morris TA, Gerometta M, Smart RC, Eisenberg P, Roach PJ, Tsui WW, et al. Pulmonary Emboli Imaging with ^{99m}Tc-labelled Anti-D-dimer (DI-80B3) Fab' Followed by SPECT. Heart Lung and Circulation. 2011;20(8):503-11.

505. Morris TA, Gerometta M, Yusen RD, White RH, Douketis JD, Kaatz S, et al. Detection of pulmonary emboli with ^{99m}Tc-labeled anti-D-dimer (DI-80B3)Fab' fragments (ThromboView). Am J Respir Crit Care Med. 2011 Sep 15;184(6):708-14.

506. Mortensen J, Gutte H. SPECT/CT and pulmonary embolism. European Journal of Nuclear Medicine and Molecular Imaging. 2014;41(Suppl 1):S81-S90.

507. Muangman N, Totanarungroj K. Cost effectiveness of combined CT pulmonary angiography (CTPA) and indirect CTV in patient with intermediate to high probability for pulmonary embolism. J Med Assoc Thai. 2012 Oct;95(10):1321-6.

508. Musset D, Parent F, Meyer G, Maitre S, Girard P, Leroyer C, et al. Diagnostic strategy for patients with suspected pulmonary embolism: a prospective multicentre outcome study. Lancet. 2002 Dec 14;360(9349):1914-20.

509. Nazaroglu H, Ozmen CA, Akay HO, Kilinc I, Bilici A. 64-MDCT pulmonary angiography and CT venography in the diagnosis of thromboembolic disease. AJR Am J Roentgenol. 2009 Mar;192(3):654-61.

510. Nobre C, Thomas B. Ultrasound in suspected pulmonary embolism. Chest. 2014;146(3):e109.

511. Palla A, Marconi L, Bigazzi F, Pistolesi M. Lung scintigraphy in the diagnosis of pulmonary embolism: pathophysiological and practical evidence. Clinical and Translational Imaging. 2014;2(5):363-7.

512. Perrier A, Desmarais S, Miron MJ, de MP, Lepage R, Slosman D, et al. Non-invasive diagnosis of venous thromboembolism in outpatients. Lancet. 1999 Jan 16;353(9148):190-5.

513. Perrier A, Roy PM, Aujesky D, Chagnon I, Howarth N, Gourdier AL, et al. Diagnosing pulmonary embolism in outpatients with clinical assessment, D-dimer measurement, venous ultrasound, and helical computed tomography: a multicenter management study. Am J Med. 2004 Mar 1;116(5):291-9.

514. Precious BJ, Raju R, Leipsic J. Recent advances in thoracic x-ray computed tomography for pulmonary imaging. Can Respir J [Internet]. 2014 [cited 2016 Oct 7];21(5):307-9. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4198234/pdf/crj-21-307.pdf

515. Prevedello LM, Raja AS, Ip IK, Sodickson A, Khorasani R. Does clinical decision support reduce unwarranted variation in yield of CT pulmonary angiogram? Am J Med [Internet]. 2013 Nov [cited 2017 Jan 16];126(11):975-81. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4438082/pdf/nihms-526508.pdf

516. Quinn RJ, Nour R, Butler SP, Glenn DW, Travers PL, Wellings G, et al. Pulmonary embolism in patients with intermediate probability lung scans: diagnosis with Doppler venous US and D-dimer measurement. Radiology. 1994 Feb;190(2):509-11.

517. Quiroz R, Kucher N, Zou KH, Kipfmueller F, Costello P, Goldhaber SZ, et al. Clinical validity of a negative computed tomography scan in patients with suspected pulmonary embolism: a systematic review. JAMA. 2005 Apr 27;293(16):2012-7.

518. Raja AS, Ip IK, Prevedello LM, Sodickson AD, Farkas C, Zane RD, et al. Effect of computerized clinical decision support on the use and yield of CT pulmonary angiography in the emergency department. Radiology [Internet]. 2012 [cited 2016 Nov 16];262(2):468-74. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3267081/pdf/110951.pdf

519. Ranji SR, Shojania KG, Trowbridge RL, Auerbach AD. Impact of reliance on CT pulmonary angiography on diagnosis of pulmonary embolism: a Bayesian analysis. J Hosp Med. 2006 Mar;1(2):81-7.

520. Reagle Z, Tringali S, Gill N, Peterson MW. Diagnostic yield and renal complications after computed tomography pulmonary angiograms performed in a community-based academic hospital. J Community Hosp Intern Med Perspect [Internet]. 2012 [cited 2016 Oct 4];2. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3714054

521. Reichelt A, Hoeper MM, Galanski M, Keberle M. Chronic thromboembolic pulmonary hypertension: evaluation with 64-detector row CT versus digital substraction angiography. Eur J Radiol. 2009 Jul;71(1):49-54.

522. Remy-Jardin M, Remy J, Wattinne L, Giraud F. Central pulmonary thromboembolism: diagnosis with spiral volumetric CT with the single-breath-hold technique--comparison with pulmonary angiography. Radiology. 1992 Nov;185(2):381-7.

523. Remy-Jardin M, Tillie-Leblond I, Szapiro D, Ghaye B, Cotte L, Mastora I, et al. CT angiography of pulmonary embolism in patients with underlying respiratory disease: impact of multislice CT on image quality and negative predictive value. Eur Radiol. 2002 Aug;12(8):1971-8.

524. Richard MC, Lambert R, Rey E, Turpin S. Is perfusion scintigraphy sufficient in pregnant or post-partum women? Medecine Nucleaire. 2015;39(6):479-85. French.

525. Ritchie G, McGurk S, McCreath C, Graham C, Murchison JT. Prospective evaluation of unsuspected pulmonary embolism on contrast enhanced multidetector CT (MDCT) scanning. Thorax [Internet]. 2007 Jun [cited 2016 Oct 6];62(6):536-40. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2117210

526. Rodger MA, Bredeson CN, Jones G, Rasuli P, Raymond F, Clement AM, et al. The bedside investigation of pulmonary embolism diagnosis study: a double-blind randomized controlled trial comparing combinations of 3 bedside tests vs ventilation-perfusion scan for the initial investigation of suspected pulmonary embolism. Arch Intern Med. 2006 Jan 23;166(2):181-7.

527. Rubins JB. The current approach to the diagnosis of pulmonary embolism: lessons from PIOPED II. Postgrad Med. 2008 Apr;120(1):1-7.

528. Ruiz Y, Caballero P, Caniego JL, Friera A, Olivera MJ, Tagarro D, et al. Prospective comparison of helical CT with angiography in pulmonary embolism: global and selective vascular territory analysis. Interobserver agreement. Eur Radiol. 2003 Apr;13(4):823-9.

529. Sakuma M, Nakamura M, Nakanishi N, Miyahara Y, Tanabe N, Yamada N, et al. Diagnostic and therapeutic strategy for acute pulmonary thromboembolism. Intern Med [Internet]. 2006 [cited 2016 Oct 13];45(12):749-58. Available from: https://www.jstage.jst.go.jp/article/internalmedicine/45/12/45_12_749/_pdf

530. Salaun PY, Le Duc-Pennec A, Le Gal G, Couturaud F, Guillo P, Mottier D, et al. Management of suspected pulmonary embolism patients with low clinical and low V/Q probability. Thromb Res. 2008;122(4):450-4.

531. Sampson FC, Goodacre SW, Thomas SM, van Beek EJ. The accuracy of MRI in diagnosis of suspected deep vein thrombosis: systematic review and meta-analysis. Eur Radiol. 2007 Jan;17(1):175-81.

532. Sangwaiya MJ, Kalra MK, Sharma A, Halpern EF, Shepard JA, Digumarthy SR. Dual-energy computed tomographic pulmonary angiography: a pilot study to assess the effect on image quality and diagnostic confidence. J Comput Assist Tomogr. 2010 Jan;34(1):46-51.

533. Sasbou T, Tachinante R, Tazi Saoud A, Ksayr R, Ben Rais Aouad N. Place of scintigraphy in the diagnosis of pulmonary embolism in pregnant women-About 17 cases. Medecine Nucleaire. 2013;37(10-11):439-45. French.

534. Sawyer KN, Shah P, Qu L, Kurz MC, Clark CL, Swor RA. Triple rule ot versus CT angiogram plus stress test for evaluation of chest pain in the emergency department. West J Emerg Med [Internet]. 2015 Sep [cited 2016 Oct 4];16(5):677-82. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4644034

535. Schiebler ML, Ahuja J, Repplinger MD, Francois CJ, Vigen KK, Grist TM, et al. Incidence of actionable findings on contrast enhanced magnetic resonance angiography ordered for pulmonary embolism evaluation. Eur J Radiol. 2016 Aug;85(8):1383-9.

536. Schonfeld C, Cebotari S, Voskrebenzev A, Gutberlet M, Hinrichs J, Renne J, et al. Performance of perfusion-weighted Fourier decomposition MRI for detection of chronic pulmonary emboli. J Magn Reson Imaging. 2015 Jul;42(1):72-9.

537. Scialpi M, Rebonato A, Cagini L, Brunese L, Piscioli I, Pierotti L, et al. Split-bolus single-pass multidetector-row CT protocol for diagnosis of acute pulmonary embolism. Iranian Journal of Radiology [Internet]. 2016 [cited 2016 Oct 7];13(1):e19844. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4837285/pdf/iranjradiol-13-01-19844.pdf

538. Scott K, Rutherford N, Fagermo N, Lust K. Use of imaging for investigation of suspected pulmonary embolism during pregnancy and the postpartum period. Obstet Med [Internet]. 2011 Mar [cited 2016 Oct 6];4(1):20-3. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4989656

539. Sellem A, Elajmi W, Mahjoub Y, Hammami H. Diagnosis pulmonary embolism in pregnancy: contribution of lung scintigraphy. Retrospective study about 116cases. Medecine Nucleaire. 2013;37(10-11):432-8. French.

540. Serra W, Crisafulli E, Sverzellati N, Ugolotti PT, Tzani P, Marangio E, et al. Transthoracic echocardiography and chest computed tomography arteriography in patients with acute pulmonary embolism: a two-year follow-up study. Respiration. 2016;92(4):235-240.

541. Shahir K, Goodman LR, Lam CA, Midia EC. Dose reduction of 69% for computed tomography pulmonary angiography: reduced z-axis computed tomography pulmonary angiography retains accuracy in those younger than 40 years. J Comput Assist Tomogr. 2013 Sep;37(5):765-9.

542. Shao W, Zhang F, Zuo S, Wang X, Song J. Lower limb deep vein thrombosis in patients with suspected pulmonary embolism detected with ^{99m}Tc-MAA simultaneously with lung perfusion scan. Hell J Nucl Med. 2012;15(3):220-3+270.

543. Shapiro MD, Dodd JD, Kalva S, Wittram C, Hsu J, Nasir K, et al. A comprehensive electrocardiogram-gated 64-slice multidetector computed tomography imaging protocol to visualize the coronary arteries, thoracic aorta, and pulmonary vasculature in a single breath hold. J Comput Assist Tomogr. 2009 Mar;33(2):225-32.

544. Silva S, Biendel C, Ruiz J, Olivier M, Bataille B, Geeraerts T, et al. Usefulness of cardiothoracic chest ultrasound in the management of acute respiratory failure in critical care practice. Chest. 2013 Sep;144(3):859-65.

545. Sinzinger H, Berent R, Kummer F. Value of ventilation/perfusion SPECT for diagnosis of pulmonary embolism. European Journal of Nuclear Medicine and Molecular Imaging. 2015;42(6):977-8.

546. Slater S, Oswal D, Bhartia B. A retrospective study of the value of indirect CT venography: a British perspective. Br J Radiol [Internet]. 2012 Jul [cited 2016 Oct 4];85(1015):917-20. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3474055

547. Hoo GW, Wu CC, Vazirani S, Li Z, Barack BM. Does a clinical decision rule using D-dimer level improve the yield of pulmonary CT angiography? AJR Am J Roentgenol [Internet]. 2011 May [cited 2017 Jan 16];196(5):1059-64. Available from: http://www.ajronline.org/doi/pdf/10.2214/AJR.10.4200

548. Sostman HD, Layish DT, Tapson VF, Spritzer CE, DeLong DM, Trotter P, et al. Prospective comparison of helical CT and MR imaging in clinically suspected acute pulmonary embolism. J Magn Reson Imaging. 1996 Mar;6(2):275-81.

549. Stein PD, Woodard PK, Weg JG, Wakefield TW, Tapson VF, Sostman HD, et al. Diagnostic pathways in acute pulmonary embolism: recommendations of the PIOPED II investigators. Am J Med. 2006 Dec;119(12):1048-55.

550. Stein PD, Gottschalk A, Sostman HD, Chenevert TL, Fowler SE, Goodman LR, et al. Methods of prospective investigation of pulmonary embolism diagnosis III (PIOPED III). Semin Nucl Med [Internet]. 2008 Nov [cited 2016 Oct 7];38(6):462-70. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2605689

551. Steiner P, Phillips F, Wesner D, Lund GK, Kreymann G, Nicolas V, et al. [Primary diagnosis and follow-up in acute pulmonary embolism: comparison of digital subtraction angiography and spiral CT]. Rofo. 1994 Oct;161(4):285-91. German.

552. Stone E, Roach P, Bernard E, Briggs G, Havryk A, Faulder K, et al. Use of computed tomography pulmonary angiography in the diagnosis of pulmonary embolismin patients with an intermediate probability ventilation/perfusion scan. Intern Med J. 2003 Mar;33(3):74-8.

553. Su J, Zhai RY, Jiang T, Ma ZH, Liu M. Suspected pulmonary thromboembolism and deep venous thrombosis: a comprehensive 64-slice multidetector computed tomography diagnosis in gynecologic patients. Chin Med J [Internet]. 2015 Jun 5 [cited 2016 Oct 4];128(11):1549-51. Available from: http://www.cmj.org/temp/ChinMedJ128111549-4431971_121839.pdf

554. Subedi D, Bell D, Lewinski MJB, Aslam S, Murchison JT. Use of SimpliRED D-dimer assay and computerised tomography in the diagnosis of acute pulmonary embolism. Acute Med. 2009;8(2):84-6.

555. Subramaniam RM, Chou T, Swarbrick M, Karalus N. Pulmonary embolism: accuracy and safety of a negative CT pulmonary angiogram and value of a negative D-dimer assay to exclude CT pulmonary angiogram-detectable pulmonary embolism. Australas Radiol. 2006 Oct;50(5):424-8.

556. Sun S, Semionov A, Xie X, Kosiuk J, Mesurolle B. Detection of central pulmonary embolism on non-contrast computed tomography: a case control study. Int J Cardiovasc Imaging. 2014 Mar;30(3):639-46.

557. Swensen SJ, Sheedy PF, Ryu JH, Pickett DD, Schleck CD, Ilstrup DM, et al. Outcomes after withholding anticoagulation from patients with suspected acute pulmonary embolism and negative computed tomographic findings: a cohort study. Mayo Clin Proc. 2002 Feb;77(2):130-8.

558. Szucs-Farkas Z, Schaller C, Bensler S, Patak MA, Vock P, Schindera ST. Detection of pulmonary emboli with CT angiography at reduced radiation exposure and contrast material volume: comparison of 80 kVp and 120 kVp protocols in a matched cohort. Invest Radiol. 2009 Dec;44(12):793-9.

559. Szucs-Farkas Z, Christe A, Megyeri B, Rohacek M, Vock P, Nagy EV, et al. Diagnostic accuracy of computed tomography pulmonary angiography with reduced radiation and contrast material dose: a prospective randomized clinical trial. Invest Radiol. 2014 Apr;49(4):201-8.

560. Takagi H, Umemoto T. An algorithm for managing suspected pulmonary embolism. JAMA. 2006;295(22):2603-4.

561. Takahashi EA, Yoon HC. Four-year cumulative radiation exposure in patients undergoing computed tomography angiography for suspected pulmonary embolism. Radiology Research and Practice [Internet]. 2013 [cited 2016 Oct 7];482403. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3745975/pdf/RRP2013-482403.pdf

562. Tarr GP, Modahl L, Jones P. Wells score, D-dimer testing and computer tomographic pulmonary angiography appropriateness in the Auckland Hospital Adult Emergency Department. N Z Med J [Internet]. 2015 [cited 2016 Oct 14];128(1413):81-3. Available from: https://www.nzma.org.nz/__data/assets/pdf_file/0015/42171/Tarr.pdf

563. Thomeer MG, Pattynama PM, Hartmann IJ, Kieft GJ, Van Strijen MJ. High incidence of isolated subsegmental pulmonary emboli on multi-slice spiral CT: a comparative clinical study. Thromb Haemost. 2006 May;95(5):914-5.

564. Tiseo M, Bersanelli M, Pesenti BM, Bartolotti M, De LG, Gelsomino F, et al. Asymptomatic pulmonary embolism in lung cancer: prevalence and analysis of clinical and radiological characteristics in 141 outpatients. Tumori. 2012 Sep;98(5):594-600.

565. Tresoldi S, Kim YH, Baker SP, Kandarpa K. MDCT of 220 consecutive patients with suspected acute pulmonary embolism: incidence of pulmonary embolism and of other acute or non-acute thoracic findings. Radiol Med (Torino). 2008 Apr;113(3):373-84.

566. Tunariu N, Gibbs SJ, Win Z, Gin-Sing W, Graham A, Gishen P, et al. Ventilation-perfusion scintigraphy is more sensitive than multidetector CTPA in detecting chronic thromboembolic pulmonary disease as a treatable cause of pulmonary hypertension. J Nucl Med [Internet]. 2007 May [cited 2016 Oct 6];48(5):680-4. Available from: http://jnm.snmjournals.org/content/48/5/680.full.pdf+html

567. Turkstra F, Kuijer PM, van Beek EJ, Brandjes DP, ten Cate JW, Buller HR. Diagnostic utility of ultrasonography of leg veins in patients suspected of having pulmonary embolism. Ann Intern Med. 1997 May 15;126(10):775-81.

568. van Belle A., Buller HR, Huisman MV, Huisman PM, Kaasjager K, Kamphuisen PW, et al. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. JAMA. 2006 Jan 11;295(2):172-9.

569. Perrier A, Miron MJ, Desmarais S, de MP, Slosman D, Didier D, et al. Using clinical evaluation and lung scan to rule out suspected pulmonary embolism: is it a valid option in patients with normal results of lower-limb venous compression ultrasonography? Arch Intern Med. 2000 Feb 28;160(4):512-6.

570. van Rossum AB, Treurniet FE, Kieft GJ, Smith SJ, Schepers-Bok R. Role of spiral volumetric computed tomographic scanning in the assessment of patients with clinical suspicion of pulmonary embolism and an abnormal ventilation/perfusion lung scan. Thorax [Internet]. 1996 Jan [cited 2017 Jan 16];51(1):23-8. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC472794/pdf/thorax00320-0031.pdf

571. Viau P, Franken P, Padovani B, Koulibaly PM, Benoliel J, Razzouk M, et al. Hybrid imaging for the diagnosis of acute pulmonary embolism: contribution of CT combined to V/P SPECT. Med Nucl. 2011;35(3):117-25. French.

572. Vongchaiudomchoke T, Boonyasirinant T. Positive Pulmonary Computed Tomography Angiography in Patients with Suspected Acute Pulmonary Embolism: Clinical Prediction Rules, Thromboembolic Risk Factors, and Implications for Appropriate Use. J Med Assoc Thai. 2016 Jan;99(1):25-33.

573. Wu L, Yao Y, Chen G, Fan X, Zheng L, Ding L, et al. Intracardiac thrombosis in patients with arrhythmogenic right ventricular cardiomyopathy. J Cardiovasc Electrophysiol. 2014 Dec;25(12):1359-62.

574. Wu HW, Cheng JJ, Li JY, Yin Y, Hua J, Xu JR. Pulmonary embolism detection and characterization through quantitative iodine-based material decomposition images with spectral computed tomography imaging. Invest Radiol. 2012;47(1):85-91.

575. Yasui T, Tanabe N, Terada J, Yanagawa N, Shimizu H, Matsubara H, et al. Multidetector-row computed tomography management of acute pulmonary embolism. Circ J [Internet]. 2007 Dec [cited 2016 Oct 7];71(12):1948-54. Available from: https://www.jstage.jst.go.jp/article/circj/71/12/71_12_1948/_pdf

576. Zhu L, Wang C, Yang Y, Wu Y, Zhai Z, Dai H, et al. Value of transthoracic echocardiography in therapy regimens evaluation in pulmonary embolism. J Thromb Thrombolysis. 2008 Dec;26(3):251-6.

577. Doyle NM, Ramirez MM, Mastrobattista JM, Monga M, Wagner LK, Gardner MO. Diagnosis of pulmonary embolism: a cost-effectiveness analysis. Am J Obstet Gynecol. 2004 Sep;191(3):1019-23.

578. Larcos G, Chi KK, Shiell A, Berry G. Suspected acute pulmonary emboli: cost-effectiveness of chest helical computed tomography versus a standard diagnostic algorithm incorporating ventilation-perfusion scintigraphy. Aust N Z J Med. 2000 Apr;30(2):195-201.

579. Ward MJ, Sodickson A, Diercks DB, Raja AS. Cost-effectiveness of lower extremity compression ultrasound in emergency department patients with a high risk of hemodynamically stable pulmonary embolism. Acad Emerg Med. 2011;18(1):22-31.

580. Nijkeuter M, Ginsberg JS, Huisman MV. Diagnosis of deep vein thrombosis and pulmonary embolism in pregnancy: a systematic review. J Thromb Haemost. 2006 Mar;4(3):496-500.

CADTH

Appendix 1: Literature Search Strategy

Clinical Database Search

OVERVIEW	
Interface:	Ovid
Databases:	Embase MEDLINE Daily and MEDLINE MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	September 13, 2016
Alerts:	Monthly search updates until project completion
Study Types:	**Risk Stratification search**: Health technology assessments; systematic reviews; meta-analyses; network meta-analyses. **Diagnostic Imaging search**: randomized controlled trials; non-randomized studies
Limits:	Date limit: **Risk Stratification search:** 2011-present Date limit: **Dignostic Imaging search:** 2006-present Language limit: English- and French-language Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY

#	Risk Stratification Search
1	exp pulmonary embolism/
2	((pulmonary or lung) adj4 (embolism* or embolus or emboli* or emboly or thromboemboli* or thrombo-emboli* or microemboli* or microembolus or blood clot*)).ti,ab,kf.
3	Venous Thromboembolism/
4	((venous or vein) adj4 (thromboemboli* or thrombo-emboli*)).ti,ab,kf.
5	VTE.ti,ab,kf.
6	or/1-5
7	Fibrin Fibrinogen Degradation Products/
8	(d-dimer or fibrin or fibrinogen or fibrinolytic).ti,ab,kf.
9	Decision Support Techniques/
10	(wells or geneva or PERC or rule out criteria or gestalt or risk stratification).ti,ab,kf.
11	(decision adj4 (rule* or model* or analys?s or support or aid*)).ti,ab,kf.
12	(prediction adj4 (rule* or model* or analys?s or support or aid*)).ti,ab,kf.
13	(rule out or decision or prediction).ti.
14	or/7-13
15	6 and 14
16	15 use pmez
17	lung embolism/
18	pulmonary embolism/
19	((pulmonary or lung) adj4 (embolism* or embolus or emboli* or emboly or thromboemboli* or thrombo-emboli* or microemboli* or microembolus or blood clot*)).ti,ab,kw.
20	Venous Thromboembolism/
21	((venous or vein) adj4 (thromboemboli* or thrombo-emboli*)).ti,ab,kw.
22	VTE.ti,ab,kw.
23	or/17-22
24	fibrin degradation product/ or D dimer/
25	(d-dimer or fibrin or fibrinogen or fibrinolytic).ti,ab,kw.
26	decision support system/
27	(wells or geneva or PERC or rule out criteria or gestalt or risk stratification).ti,ab,kw.
28	(decision adj4 (rule* or model* or analys?s or support or aid*)).ti,ab,kw.
29	(prediction adj4 (rule* or model* or analys?s or support or aid*)).ti,ab,kw.
30	(rule out or decision or prediction).ti.
31	or/24-30
32	23 and 31
33	32 use oemezd
34	33 not conference abstract.pt.
35	16 or 34
36	meta-analysis.pt.

37	meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/
38	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf,kw.
39	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf,kw.
40	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf,kw.
41	(data synthes* or data extraction* or data abstraction*).ti,ab,kf,kw.
42	(handsearch* or hand search*).ti,ab,kf,kw.
43	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf,kw.
44	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf,kw.
45	(meta regression* or metaregression*).ti,ab,kf,kw.
46	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
47	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
48	(cochrane or (health adj2 technology assessment) or evidence report).jw.
49	(meta-analysis or systematic review).md.
50	(comparative adj3 (efficacy or effectiveness)).ti,ab,kf,kw.
51	(outcomes research or relative effectiveness).ti,ab,kf,kw.
52	((indirect or indirect treatment or mixed treatment or bayesian) adj3 comparison*).ti,ab,kf,kw.
53	(network* adj3 (meta-analys* or metaanalys*)).ti,ab,kf,kw.
54	(multi* adj3 treatment adj3 comparison*).ti,ab,kf,kw.
55	umbrella review*.ti,ab,kf,kw.
56	nma.ti,ab,kf,kw.
57	(Multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.
58	(Multiparamet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.
59	(multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.
60	MPES.ti,ab,kw,kf.
61	or/36-60
62	35 and 61
63	limit 62 to (english or french)
64	limit 63 to yr="2011 -Current"
65	remove duplicates from 64
#	**Diagnostic Imaging Search**
1	exp pulmonary embolism/
2	((pulmonary or lung) adj4 (embolism* or embolus or emboli* or emboly or thromboemboli* or thrombo-emboli* or microemboli* or microembolus or blood clot*)).ti,ab,kf.
3	Venous Thromboembolism/
4	((venous or vein) adj4 (thromboemboli* or thrombo-emboli*)).ti,ab,kf.
5	VTE.ti,ab,kf.

6	or/1-5
7	exp Tomography, X-Ray Computed/ or Tomography Scanners, X-Ray Computed/
8	((computed or computer* or electron beam) adj3 (tomograph* or angiograph*)).ti,ab,kf.
9	(CT scan* or X-ray CT or CT X Ray? or CAT scan* or multi-detector CT or tomodensitometry or cine CT or Helical CT or spiral CT or Four Dimensional CT).ti,ab,kf.
10	(CTPA or CT pulmonary angiography or CT angiography).ti,ab,kf.
11	or/7-10
12	exp Magnetic Resonance Imaging/
13	(magnetic resonance imag* or MR imag* or MRI* or fMRI* or magnetic resonance tomograph* or MR tomograph* or magnetization transfer contrast imag* or magnetisation transfer imag* or magnetization transfer imag* or magnetisation transfer imag* or chemical shift imag* or NMR imag* or zeugmatography or NMR tomography or proton spin tomography or magnetic resonance scan* or MR scan*).ti,ab,kf.
14	12 or 13
15	Perfusion Imaging/ or Tomography, Emission-Computed, Single-Photon/ or Radionuclide Imaging/
16	(radionuclide imag* or gamma camera imag* or perfusion imaging or lung perfusion or scintigraph* or scintigram* or scintiphotograph* or laminoscintigraph* or scintillation or scintillograph* or scintiscan).ti,ab,kf.
17	(ventilation-perfusion adj5 (imag* or scan* or SPECT)).ti,ab,kf.
18	("ventilation/perfusion" adj5 (imag* or scan* or SPECT)).ti,ab,kf.
19	((ventilation and perfusion) adj5 (imag* or scan* or SPECT)).ti,ab,kf.
20	((VQ or V-Q or "v/q" or "V/P" or VP or V-P) adj5 (imag* or scan* or SPECT)).ti,ab,kf.
21	or/15-20
22	Positron-Emission Tomography/
23	(PET adj3 (scan* or imag*)).ti,ab,kf.
24	(FDGPET or FDG PET or PETCT or PET CT or positron).ti,ab,kf.
25	or/22-24
26	exp Lung/us
27	exp Ultrasonography/
28	(ultrasound or sonogra* or ultrasonic or ultrasonogra* or echotomogra* or echogra* or doppler).ti,ab,kf.
29	or/27-28
30	exp lung/
31	(lung or lungs or thoracic or thorax or chest).ti,ab,kf.
32	or/30-31
33	29 and 32
34	exp Echocardiography/
35	(cardiac echo* or heart echo* or echocardiogra* or echo-cardiogra* or cardiac echogra* or cardiac scan* or cardial echography or cardioechography or heart echography or heart scanning or myocardium scanning or ultrasound cardiography).ti,ab,kf.
36	or/26,33-35
37	11 or 14 or 21 or 25 or 36

38	6 and 37
39	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial).pt.
40	Randomized Controlled Trial/
41	exp Randomized Controlled Trials as Topic/
42	"Randomized Controlled Trial (topic)"/
43	Controlled Clinical Trial/
44	exp Controlled Clinical Trials as Topic/
45	"Controlled Clinical Trial (topic)"/
46	Randomization/
47	Random Allocation/
48	Double-Blind Method/
49	Double Blind Procedure/
50	Double-Blind Studies/
51	Single-Blind Method/
52	Single Blind Procedure/
53	Single-Blind Studies/
54	Placebos/
55	Placebo/
56	Control Groups/
57	Control Group/
58	(random* or sham or placebo*).ti,ab,hw,kf,kw.
59	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
60	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
61	(control* adj3 (study or studies or trial*)).ti,ab,kf,kw.
62	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.
63	allocated.ti,ab,hw.
64	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.
65	or/39-64
66	Epidemiologic Methods/
67	exp Epidemiologic Studies/
68	Observational Studies as Topic/
69	Clinical Studies as Topic/
70	(Observational Study or Validation Studies or Clinical Study).pt.
71	(observational adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.
72	cohort*.ti,ab,kf.
73	(prospective adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.
74	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.
75	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data)).ti,ab,kf.
76	(retrospective adj7 (study or studies or design or analysis or analyses or data or

	review)).ti,ab,kf.
77	((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab,kf.
78	(case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.
79	(population adj3 (study or studies or analysis or analyses)).ti,ab,kf.
80	(descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.
81	((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.
82	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab,kf.
83	((natural adj experiment) or (natural adj experiments)).ti,ab,kf.
84	(quasi adj (experiment or experiments or experimental)).ti,ab,kf.
85	((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.
86	(prevalence adj3 (study or studies or analysis or analyses)).ti,ab,kf.
87	case series.ti,ab,kf.
88	or/66-87
89	65 or 88
90	38 and 89
91	90 use pmez
92	lung embolism/
93	pulmonary embolism/
94	((pulmonary or lung) adj4 (embolism* or embolus or emboli* or emboly or thromboemboli* or thrombo-emboli* or microemboli* or microembolus or blood clot*)).ti,ab,kw.
95	Venous Thromboembolism/
96	((venous or vein) adj4 (thromboemboli* or thrombo-emboli*)).ti,ab,kw.
97	VTE.ti,ab,kw.
98	or/92-97
99	exp computer assisted tomography/
100	((computed or computer* or electron beam) adj3 (tomograph* or angiograph*)).ti,ab,kw.
101	(CT scan* or X-ray CT or CT X Ray? or CAT scan* or multi-detector CT or tomodensitometry or cine CT or Helical CT or spiral CT or Four Dimensional CT).ti,ab,kw.
102	(CTPA or CT pulmonary angiograph* or CT angiograph*).ti,ab,kw.
103	or/99-102
104	exp nuclear magnetic resonance imaging/
105	(magnetic resonance imag* or MR imag* or MRI* or fMRI* or magnetic resonance tomograph* or MR tomograph* or magnetization transfer contrast imag* or magnetisation transfer imag* or magnetization transfer imag* or magnetisation transfer imag* or chemical shift imag* or NMR imag* or zeugmatography or NMR tomography or proton spin tomography or magnetic resonance scan* or MR scan*).ti,ab,kw.
106	104 or 105
107	exp scintigraphy/ or single photon emission computer tomography/ or exp scintiscanning/ or lung scintiscanning/
108	(radionuclide imag* or gamma camera imag* or perfusion imaging or lung perfusion or

	scintigraph* or scintigram* or scintiphotograph* or laminoscintigraph* or scintillation or scintillograph* or scintiscan).ti,ab,kw.
109	(ventilation-perfusion adj5 (imag* or scan* or SPECT)).ti,ab,kw.
110	("ventilation/perfusion" adj5 (imag* or scan* or SPECT)).ti,ab,kw.
111	((ventilation and perfusion) adj5 (imag* or scan* or SPECT)).ti,ab,kw.
112	((VQ or V-Q or "v/q" or "V/P" or VP or V-P) adj5 (imag* or scan* or SPECT)).ti,ab,kw.
113	or/107-112
114	positron emission tomography/
115	(PET adj3 (scan* or imag*)).ti,ab,kw.
116	(FDGPET or FDG PET or PETCT or PET CT or positron).ti,ab,kw.
117	or/114-116
118	exp echography/
119	(ultrasound or sonogra* or ultrasonic or ultrasonogra* or echotomogra* or echogra* or doppler).ti,ab,kw.
120	or/118-119
121	exp lung/
122	(lung or lungs or thoracic or thorax or chest).ti,ab,kw.
123	or/121-122
124	120 and 123
125	(cardiac echo* or heart echo* or echocardiogra* or echo-cardiogra* or cardiac echogra* or cardiac scan* or cardial echography or cardioechography or heart echography or heart scanning or myocardium scanning or ultrasound cardiography).ti,ab,kw.
126	exp echocardiography/
127	or/124-126
128	103 or 106 or 113 or 117 or 127
129	98 and 128
130	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial).pt.
131	Randomized Controlled Trial/
132	exp Randomized Controlled Trials as Topic/
133	"Randomized Controlled Trial (topic)"/
134	Controlled Clinical Trial/
135	exp Controlled Clinical Trials as Topic/
136	"Controlled Clinical Trial (topic)"/
137	Randomization/
138	Random Allocation/
139	Double-Blind Method/
140	Double Blind Procedure/
141	Double-Blind Studies/
142	Single-Blind Method/
143	Single Blind Procedure/
144	Single-Blind Studies/

145	Placebos/
146	Placebo/
147	Control Groups/
148	Control Group/
149	(random* or sham or placebo*).ti,ab,hw,kf,kw.
150	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
151	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
152	(control* adj3 (study or studies or trial*)).ti,ab,kf,kw.
153	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.
154	allocated.ti,ab,hw.
155	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.
156	or/130-155
157	observational study/
158	cohort analysis/
159	longitudinal study/
160	follow up/
161	retrospective study/
162	exp case control study/
163	cross-sectional study/
164	quasi experimental study/
165	prospective study/
166	(observational adj3 (study or studies or design or analysis or analyses)).ti,ab,kw.
167	cohort*.ti,ab,kw.
168	(prospective adj7 (study or studies or design or analysis or analyses)).ti,ab,kw.
169	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,kw.
170	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data)).ti,ab,kw.
171	(retrospective adj7 (study or studies or design or analysis or analyses or data or review)).ti,ab,kw.
172	((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab,kw.
173	(case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,kw.
174	(population adj3 (study or studies or analysis or analyses)).ti,ab,kw.
175	(descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kw.
176	((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kw.
177	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab,kw.
178	((natural adj experiment) or (natural adj experiments)).ti,ab,kw.
179	(quasi adj (experiment or experiments or experimental)).ti,ab,kw.
180	((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab,kw.

181	(prevalence adj3 (study or studies or analysis or analyses)).ti,ab,kw.
182	case series.ti,ab,kw.
183	or/157-182
184	156 or 183
185	129 and 184
186	185 use oemezd
187	186 not conference abstract.pt.
188	91 or 187
189	limit 188 to (english or french)
190	limit 189 to yr="2006 -Current"
191	limit 190 to yr="2006 - 2010"
192	remove duplicates from 191
193	limit 190 to yr="2011 -Current"
194	remove duplicates from 193
195	192 or 194

OTHER DATABASES	
PubMed	Searched to capture records not indexed in MEDLINE. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used.
Cochrane Database of Systematic Reviews (CDSR) Database of Abstracts of Reviews of Effects (DARE) Cochrane Central Register of Controlled Trials	Searched to capture records not indexed in MEDLINE. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used.
CINAHL	Searched to capture records not indexed in MEDLINE. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used, including the addition of CINAHL headings.

Patient Experiences and Preferences Database Search

OVERVIEW	
Interface:	Ovid
Databases:	Embase MEDLINE Daily and MEDLINE MEDLINE In-Process & Other Non-Indexed Citations PsycINFO **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	September 29, 2016
Alerts:	Monthly search updates until project completion
Study Types:	Qualitative studies
Limits:	Date limit: 2006-present Language limit: English- and French-language Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj	Requires words are adjacent to each other (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.kw	Author keyword (Embase); Keyword (CDSR and DARE)
.kf	Author keyword heading word (MEDLINE)
.mp	Mapped term
.yr	Year
.jw	Journal title word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily
freq=2	Frequency (must appear at least two times)

MULTI-SEARCH STRATEGY	
#	**Searches**
1	exp Tomography, X-Ray Computed/ or Tomography Scanners, X-Ray Computed/
2	((computed or computer* or electron beam) adj4 (tomograph* or angiograph*)).ti,ab,kf.
3	(CT scan* or X-ray CT or CT X Ray? or CAT scan* or multi-detector CT or tomodensitometry or cine CT or Helical CT or spiral CT or Four Dimensional CT).ti,ab,kf.
4	(CTPA or CT pulmonary angiography or CT angiography).ti,ab,kf.
5	or/1-4
6	exp Magnetic Resonance Imaging/
7	(magnetic resonance imag* or MR imag* or MRI* or fMRI* or magnetic resonance tomograph* or MR tomograph* or magnetization transfer contrast imag* or magnetisation transfer imag* or magnetization transfer imag* or magnetisation transfer imag* or chemical shift imag* or NMR imag* or zeugmatography or NMR tomography or proton spin tomography or magnetic resonance scan* or MR scan*).ti,ab,kf.
8	6 or 7
9	Perfusion Imaging/ or Tomography, Emission-Computed, Single-Photon/ or Radionuclide Imaging/
10	(radionuclide imag* or gamma camera imag* or perfusion imaging or lung perfusion or scintigraph* or scintigram* or scintiphotograph* or laminoscintigraph* or scintillation or scintillograph* or scintiscan).ti,ab,kf.
11	(ventilation-perfusion adj4 (imag* or scan* or SPECT)).ti,ab,kf.
12	("ventilation/perfusion" adj4 (imag* or scan* or SPECT)).ti,ab,kf.
13	((ventilation and perfusion) adj4 (imag* or scan* or SPECT)).ti,ab,kf.
14	((VQ or V-Q or "v/q" or "V/P" or VP or V-P) adj4 (imag* or scan* or SPECT)).ti,ab,kf.
15	or/9-14
16	Positron-Emission Tomography/
17	(PET adj4 (scan* or imag*)).ti,ab,kf.
18	(FDGPET or FDG PET or PETCT or PET CT or positron).ti,ab,kf.
19	or/16-18
20	exp Lung/us
21	exp Ultrasonography/
22	(ultrasound or sonogra* or ultrasonic or ultrasonogra* or echotomogra* or echogra* or doppler).ti,ab,kf.
23	or/21-22
24	exp lung/
25	(lung or lungs or thoracic or thorax or chest).ti,ab,kf.
26	or/24-25
27	23 and 26
28	exp Echocardiography/
29	(cardiac echo* or heart echo* or echocardiogra* or echo-cardiogra* or cardiac echogra* or cardiac scan* or cardial echography or cardioechography or heart echography or heart scan* or myocardi* scan* or ultrasound cardiography).ti,ab,kf.
30	or/20,27-29
31	5 or 8 or 15 or 19 or 30
32	exp computer assisted tomography/
33	((computed or computer* or electron beam) adj4 (tomograph* or angiograph*)).ti,ab,kw.
34	(CT scan* or X-ray CT or CT X Ray? or CAT scan* or multi-detector CT or tomodensitometry or cine CT or Helical CT or spiral CT or Four Dimensional CT).ti,ab,kw.
35	(CTPA or CT pulmonary angiograph* or CT angiograph*).ti,ab,kw.

MULTI-SEARCH STRATEGY	
#	**Searches**
36	or/32-35
37	exp nuclear magnetic resonance imaging/
38	(magnetic resonance imag* or MR imag* or MRI* or fMRI* or magnetic resonance tomograph* or MR tomograph* or magnetization transfer contrast imag* or magnetisation transfer imag* or magnetization transfer imag* or magnetisation transfer imag* or chemical shift imag* or NMR imag* or zeugmatography or NMR tomography or proton spin tomography or magnetic resonance scan* or MR scan*).ti,ab,kw.
39	37 or 38
40	exp scintigraphy/ or single photon emission computer tomography/ or exp scintiscanning/ or lung scintiscanning/
41	(radionuclide imag* or gamma camera imag* or perfusion imaging or lung perfusion or scintigraph* or scintigram* or scintiphotograph* or laminoscintigraph* or scintillation or scintillograph* or scintiscan).ti,ab,kw.
42	(ventilation-perfusion adj4 (imag* or scan* or SPECT)).ti,ab,kw.
43	("ventilation/perfusion" adj4 (imag* or scan* or SPECT)).ti,ab,kw.
44	((ventilation and perfusion) adj4 (imag* or scan* or SPECT)).ti,ab,kw.
45	((VQ or V-Q or "v/q" or "V/P" or VP or V-P) adj4 (imag* or scan* or SPECT)).ti,ab,kw.
46	or/40-45
47	positron emission tomography/
48	(PET adj4 (scan* or imag*)).ti,ab,kw.
49	(FDGPET or FDG PET or PETCT or PET CT or positron).ti,ab,kw.
50	or/47-49
51	exp echography/
52	(ultrasound or sonogra* or ultrasonic or ultrasonogra* or echotomogra* or echogra* or doppler).ti,ab,kw.
53	or/51-52
54	exp lung/
55	(lung or lungs or thoracic or thorax or chest).ti,ab,kw.
56	or/54-55
57	53 and 56
58	(cardiac echo* or heart echo* or echocardiogra* or echo-cardiogra* or cardiac echogra* or cardiac scan* or cardial echography or cardioechography or heart echography or heart scan* or myocardi* scan* or ultrasound cardiography).ti,ab,kw.
59	exp echocardiography/
60	or/57-59
61	36 or 39 or 46 or 50 or 60
62	exp Empirical Research/
63	Nursing Methodology Research/
64	Interviews as Topic/
65	Focus Groups/
66	(ethnon* or emic or etic or ethnograph* or hermeneutic* or heidegger* or husserl* or colaizzi* or fiorgi* or van kaam* or van manen or participant observ* or constant compar* or focus group* or grounded theory or narrative analysis or lived experience* or life experience* or theoretical samp* or in-depth interview* or purposive sampl* or action research or indepth interview*).ti,ab,kf.
67	qualitative.ti,kf.
68	(merleau* or ricoeur* or spiegelberg*).ti,ab,kf.
69	(glaser adj2 strauss).ti,ab,kf.
70	or/62-69

MULTI-SEARCH STRATEGY	
#	**Searches**
71	exp qualitative research/
72	exp interview/
73	(ethnon* or emic or etic or ethnograph* or hermeneutic* or heidegger* or husserl* or colaizzi* or fiorgi* or van kaam* or van manen or participant observ* or constant compar* or focus group* or grounded theory or narrative analysis or lived experience* or life experience* or theoretical samp* or in-depth interview* or purposive sampl* or action research or indepth interview*).ti,ab,kw.
74	qualitative.ti,kw.
75	(merleau* or ricoeur* or spiegelberg*).ti,ab,kw.
76	(glaser adj2 strauss).ti,ab,kw.
77	or/71-76
78	31 and 70
79	78 use pmez
80	61 and 77
81	80 use oemezd
82	exp patient acceptance of health care/ or caregivers/
83	((patient or patients or proband* or individuals or survivor* or family or families or familial or kindred* or relative or relatives or care giver* or caregiver* or carer or carers or personal or spous* or partner or partners or couples or users or participant* or people or child* or teenager* or adolescent* or youth or girls or boys or adults or elderly or females or males or women* or men or men's or mother* or father* or parents or parent or parental or maternal or paternal) and (preference* or preferred or input or experience or experiences or value or values or perspective* or perception* or perceive or perceived or expectation* or choice* or choose* or choosing or "day-to-day" or lives or participat* or acceptance or acceptability or acceptable or accept or accepted or adheren* or adhere or nonadheren* or complian* or noncomplian* or willingness or convenience or convenient or challenges or concerns or limitations or quality of life or satisfaction or satisfied or dissatisfaction or dissatisfied or burden or attitude* or knowledge or belief* or opinion* or understanding or lessons or reaction* or motivation* or motivated or intention* or involvement or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding or empower* or survey* or focus group* or interview* or questionnaire* or Likert or qualitative or theme* or thematic or barrier* or facilitator*)).ti.
84	((patient or patients or proband* or individuals or survivor* or family or families or familial or kindred* or relative or relatives or care giver* or caregiver* or carer or carers) adj2 (preference* or preferred or input or experience or experiences or value or values or perspective* or perception* or perceive or perceived or expectation* or choice* or choose* or choosing or "day-to-day" or lives or participat* or acceptance or acceptability or acceptable or accept or accepted or adheren* or adhere or nonadheren* or complian* or noncomplian* or willingness or convenience or convenient or challenges or concerns or limitations or quality of life or satisfaction or satisfied or dissatisfaction or dissatisfied or burden or attitude* or knowledge or belief* or opinion* or understanding or lessons or reaction* or motivation* or motivated or intention* or involvement or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding or empower* or survey* or focus group* or interview* or questionnaire* or Likert or qualitative or theme* or thematic or barrier* or facilitator*)).ab,kf.
85	((patient or patients or proband* or individuals or survivor* or family or families or familial or kindred* or relative or relatives or care giver* or caregiver* or carer or carers) adj7 (preference* or preferred or input or experience or experiences or value or values or perspective* or perception* or perceive or perceived or expectation* or choice* or choose* or choosing or "day-to-day" or lives or participat* or acceptance or acceptability or acceptable or accept or accepted or adheren* or adhere or nonadheren* or complian* or noncomplian* or willingness or convenience or convenient or challenges or concern or limitations or quality of life or satisfaction or satisfied or dissatisfaction or dissatisfied or burden or attitude* or knowledge or belief* or opinion* or understanding or lessons or reaction* or motivation* or motivated or intention* or involvement or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding or empower* or survey* or focus group* or interview* or questionnaire* or Likert or qualitative or theme* or thematic or barrier* or facilitator*)).ab. /freq=2
86	((personal or spous* or partner or partners or couples or users or participant* or people or child* or teenager* or adolescent* or youth or girls or boys or adults or elderly or females or males or women* or men or men's or mother* or father* or parents or parent or parental or maternal or paternal) adj2 (preference* or preferred or input or experience or experiences or value or values or perspective* or perception* or perceive or perceived or expectation* or choice* or choose* or choosing or "day-to-

MULTI-SEARCH STRATEGY	
#	**Searches**
	day" or lives or participat* or acceptance or acceptability or acceptable or accept or accepted or adheren* or adhere or nonadheren* or complian* or noncomplian* or willingness or convenience or convenient or challenges or concerns or limitations or quality of life or satisfaction or satisfied or dissatisfaction or dissatisfied or burden or attitude* or knowledge or belief* or opinion* or understanding or lessons or reaction* or motivation* or motivated or intention* or involvement or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding or empower* or survey* or focus group* or interview* or questionnaire* or Likert or qualitative or theme* or thematic or barrier* or facilitator*)).ab. /freq=2
87	(patient adj (reported or centered* or centred* or focused)).ti,ab,kf.
88	(treatment* adj2 (satisf* or refus*)).ti,ab,kf.
89	(lived experience* or shared decision making).ti,ab,kf.
90	or/82-89
91	90 use pmez
92	79 and 91
93	exp patient attitude/ or patient preference/ or patient participation/ or patient satisfaction/ or patient decision making/ or caregiver/ or relative/ or caregiver burden/ or caregiver support/
94	((patient or patients or proband* or individuals or survivor* or family or families or familial or kindred* or relative or relatives or care giver* or caregiver* or carer or carers or personal or spous* or partner or partners or couples or users or participant* or people or child* or teenager* or adolescent* or youth or girls or boys or adults or elderly or females or males or women* or men or men's or mother* or father* or parents or parent or parental or maternal or paternal) and (preference* or preferred or input or experience or experiences or value or values or perspective* or perception* or perceive or perceived or expectation* or choice* or choose* or choosing or "day-to-day" or lives or participat* or acceptance or acceptability or acceptable or accept or accepted or adheren* or adhere or nonadheren* or complian* or noncomplian* or willingness or convenience or convenient or challenges or concerns or limitations or quality of life or satisfaction or satisfied or dissatisfaction or dissatisfied or burden or attitude* or knowledge or belief* or opinion* or understanding or lessons or reaction* or motivation* or motivated or intention* or involvement or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding or empower* or survey* or focus group* or interview* or questionnaire* or Likert or qualitative or theme* or thematic or barrier* or facilitator*)).ti.
95	((patient or patients or proband* or individuals or survivor* or family or families or familial or kindred* or relative or relatives or care giver* or caregiver* or carer or carers) adj2 (preference* or preferred or input or experience or experiences or value or values or perspective* or perception* or perceive or perceived or expectation* or choice* or choose* or choosing or "day-to-day" or lives or participat* or acceptance or acceptability or acceptable or accept or accepted or adheren* or adhere or nonadheren* or complian* or noncomplian* or willingness or convenience or convenient or challenges or concerns or limitations or quality of life or satisfaction or satisfied or dissatisfaction or dissatisfied or burden or attitude* or knowledge or belief* or opinion* or understanding or lessons or reaction* or motivation* or motivated or intention* or involvement or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding or empower* or survey* or focus group* or interview* or questionnaire* or Likert or qualitative or theme* or thematic or barrier* or facilitator*)).ab,kw.
96	((patient or patients or proband* or individuals or survivor* or family or families or familial or kindred* or relative or relatives or care giver* or caregiver* or carer or carers) adj7 (preference* or preferred or input or experience or experiences or value or values or perspective* or perception* or perceive or perceived or expectation* or choice* or choose* or choosing or "day-to-day" or lives or participat* or acceptance or acceptability or acceptable or accept or accepted or adheren* or adhere or nonadheren* or complian* or noncomplian* or willingness or convenience or convenient or challenges or concern or limitations or quality of life or satisfaction or satisfied or dissatisfaction or dissatisfied or burden or attitude* or knowledge or belief* or opinion* or understanding or lessons or reaction* or motivation* or motivated or intention* or involvement or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding or empower* or survey* or focus group* or interview* or questionnaire* or Likert or qualitative or theme* or thematic or barrier* or facilitator*)).ab. /freq=2
97	((personal or spous* or partner or partners or couples or users or participant* or people or child* or teenager* or adolescent* or youth or girls or boys or adults or elderly or females or males or women* or men or men's or mother* or father* or parents or parent or parental or maternal or paternal) adj2 (preference* or preferred or input or experience or experiences or value or values or perspective* or perception* or perceive or perceived or expectation* or choice* or choose* or choosing or "day-to-day" or lives or participat* or acceptance or acceptability or acceptable or accept or accepted or adheren* or adhere or nonadheren* or complian* or noncomplian* or willingness or convenience or convenient or challenges or concerns or

MULTI-SEARCH STRATEGY	
#	**Searches**
	limitations or quality of life or satisfaction or satisfied or dissatisfaction or dissatisfied or burden or attitude* or knowledge or belief* or opinion* or understanding or lessons or reaction* or motivation* or motivated or intention* or involvement or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding or empower* or survey* or focus group* or interview* or questionnaire* or Likert or qualitative or theme* or thematic or barrier* or facilitator*)).ab. /freq=2
98	(patient adj (reported or centered* or centred* or focused)).ti,ab,kw.
99	(treatment* adj2 (satisf* or refus*)).ti,ab,kw.
100	(lived experience* or shared decision making).ti,ab,kw.
101	or/93-100
102	101 use oemezd
103	81 and 102
104	92 or 103
105	limit 104 to yr="2006 -Current"
106	limit 105 to (english or french)
107	106 not conference abstract.pt.
108	remove duplicates from 107

OTHER DATABASES	
PubMed	Searched to capture records not indexed in MEDLINE. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used.
CINAHL	Searched to capture records not indexed in MEDLINE. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used, including the addition of CINAHL headings.
Scopus (Social Science & Humanities)	Searched to capture records not indexed in MEDLINE. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used.

Ethics Implications Database Search

OVERVIEW	
Interface:	Ovid
Databases:	Embase MEDLINE Daily and MEDLINE MEDLINE In-Process & Other Non-Indexed Citations PsycINFO **Note:** Duplicates between databases were removed in Ovid.
Date of Search:	October 12, 2016
Alerts:	Monthly search updates until project completion
Study Types:	Ethics/legal/social studies
Limits:	Date limit: 2006-present Language limit: English- and French-language Conference abstract excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj	Requires words are adjacent to each other (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word
.fs	Floating subheading
psyb	Ovid database code; PsycINFO 1967 to present
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-SEARCH STRATEGY	
#	**Searches**
1	exp pulmonary embolism/
2	((pulmonary or lung) adj4 (embolism* or embolus or emboli* or emboly or thromboemboli* or thrombo-emboli* or microemboli* or microembolus or micro-emboli* or micro-embolus or blood clot*)).ti,ab,kf.
3	Venous Thromboembolism/
4	((venous or vein) adj4 (thromboemboli* or thrombo-emboli*)).ti,ab,kf.
5	VTE.ti,ab,kf.
6	or/1-5
7	exp Tomography, X-Ray Computed/ or Tomography Scanners, X-Ray Computed/

MULTI-SEARCH STRATEGY	
#	**Searches**
8	((computed or computer* or electron beam) adj4 (tomograph* or angiograph*)).ti,ab,kf.
9	(CT scan* or X-ray CT or CT X Ray? or CAT scan* or multi-detector CT or tomodensitometry or cine CT or Helical CT or spiral CT or Four Dimensional CT).ti,ab,kf.
10	(CTPA or CT pulmonary angiography or CT angiography).ti,ab,kf.
11	or/7-10
12	exp Magnetic Resonance Imaging/
13	(magnetic resonance imag* or MR imag* or MRI* or fMRI* or magnetic resonance tomograph* or MR tomograph* or magnetization transfer contrast imag* or magnetisation transfer imag* or magnetization transfer imag* or magnetisation transfer imag* or chemical shift imag* or NMR imag* or zeugmatography or NMR tomography or proton spin tomography or magnetic resonance scan* or MR scan*).ti,ab,kf.
14	12 or 13
15	Perfusion Imaging/ or Tomography, Emission-Computed, Single-Photon/ or Radionuclide Imaging/
16	(radionuclide imag* or gamma camera imag* or perfusion imaging or lung perfusion or scintigraph* or scintigram* or scintiphotograph* or laminoscintigraph* or scintillation or scintillograph* or scintiscan).ti,ab,kf.
17	(ventilation-perfusion adj4 (imag* or scan* or SPECT)).ti,ab,kf.
18	("ventilation/perfusion" adj4 (imag* or scan* or SPECT)).ti,ab,kf.
19	((ventilation and perfusion) adj4 (imag* or scan* or SPECT)).ti,ab,kf.
20	((VQ or V-Q or "v/q" or "V/P" or VP or V-P) adj4 (imag* or scan* or SPECT)).ti,ab,kf.
21	or/15-20
22	Positron-Emission Tomography/
23	(PET adj4 (scan* or imag*)).ti,ab,kf.
24	(FDGPET or FDG PET or PETCT or PET CT or positron).ti,ab,kf.
25	or/22-24
26	exp Lung/us
27	exp Ultrasonography/
28	(ultrasound or sonogra* or ultrasonic or ultrasonogra* or echotomogra* or echogra* or doppler).ti,ab,kf.
29	or/27-28
30	exp lung/
31	(lung or lungs or thoracic or thorax or chest).ti,ab,kf.
32	or/30-31
33	29 and 32
34	exp Echocardiography/
35	(cardiac echo* or heart echo* or echocardiogra* or echo-cardiogra* or cardiac echogra* or cardiac scan* or cardial echography or cardioechography or heart echography or heart scan* or myocardi* scan* or ultrasound cardiography).ti,ab,kf.
36	or/26,33-35
37	11 or 14 or 21 or 25 or 36
38	6 and 37
39	38 use pmez
40	lung embolism/
41	pulmonary embolism/
42	((pulmonary or lung) adj4 (embolism* or embolus or emboli* or emboly or thromboemboli* or thrombo-emboli* or microemboli* or microembolus or micro-emboli* or micro-embolus or blood clot*)).ti,ab,kw.

MULTI-SEARCH STRATEGY	
#	**Searches**
43	Venous Thromboembolism/
44	((venous or vein) adj4 (thromboemboli* or thrombo-emboli*)).ti,ab,kw.
45	VTE.ti,ab,kw.
46	or/40-45
47	exp computer assisted tomography/
48	((computed or computer* or electron beam) adj4 (tomograph* or angiograph*)).ti,ab,kw.
49	(CT scan* or X-ray CT or CT X Ray? or CAT scan* or multi-detector CT or tomodensitometry or cine CT or Helical CT or spiral CT or Four Dimensional CT).ti,ab,kw.
50	(CTPA or CT pulmonary angiograph* or CT angiograph*).ti,ab,kw.
51	or/47-50
52	exp nuclear magnetic resonance imaging/
53	(magnetic resonance imag* or MR imag* or MRI* or fMRI* or magnetic resonance tomograph* or MR tomograph* or magnetization transfer contrast imag* or magnetisation transfer imag* or magnetization transfer imag* or magnetisation transfer imag* or chemical shift imag* or NMR imag* or zeugmatography or NMR tomography or proton spin tomography or magnetic resonance scan* or MR scan*).ti,ab,kw.
54	52 or 53
55	exp scintigraphy/ or single photon emission computer tomography/ or exp scintiscanning/ or lung scintiscanning/
56	(radionuclide imag* or gamma camera imag* or perfusion imaging or lung perfusion or scintigraph* or scintigram* or scintiphotograph* or laminoscintigraph* or scintillation or scintillograph* or scintiscan).ti,ab,kw.
57	(ventilation-perfusion adj4 (imag* or scan* or SPECT)).ti,ab,kw.
58	("ventilation/perfusion" adj4 (imag* or scan* or SPECT)).ti,ab,kw.
59	((ventilation and perfusion) adj4 (imag* or scan* or SPECT)).ti,ab,kw.
60	((VQ or V-Q or "v/q" or "V/P" or VP or V-P) adj4 (imag* or scan* or SPECT)).ti,ab,kw.
61	or/55-60
62	positron emission tomography/
63	(PET adj4 (scan* or imag*)).ti,ab,kw.
64	(FDGPET or FDG PET or PETCT or PET CT or positron).ti,ab,kw.
65	or/62-64
66	exp echography/
67	(ultrasound or sonogra* or ultrasonic or ultrasonogra* or echotomogra* or echogra* or doppler).ti,ab,kw.
68	or/66-67
69	exp lung/
70	(lung or lungs or thoracic or thorax or chest).ti,ab,kw.
71	or/69-70
72	68 and 71
73	(cardiac echo* or heart echo* or echocardiogra* or echo-cardiogra* or cardiac echogra* or cardiac scan* or cardial echography or cardioechography or heart echography or heart scan* or myocardi* scan* or ultrasound cardiography).ti,ab,kw.
74	exp echocardiography/
75	or/72-74
76	51 or 54 or 61 or 65 or 75
77	46 and 76
78	77 use oemezd

MULTI-SEARCH STRATEGY	
#	**Searches**
79	78 not conference abstract.pt.
80	exp pulmonary embolism/
81	((pulmonary or lung) adj4 (embolism* or embolus or emboli* or emboly or thromboemboli* or thrombo-emboli* or microemboli* or microembolus or micro-emboli* or micro-embolus or blood clot*)).ti,ab,kf.
82	Venous Thromboembolism/
83	((venous or vein) adj4 (thromboemboli* or thrombo-emboli*)).ti,ab,kf.
84	VTE.ti,ab,kf.
85	or/80-84
86	Fibrin Fibrinogen Degradation Products/
87	(d-dimer or fibrin or fibrinogen or fibrinolytic).ti,ab,kf.
88	Decision Support Techniques/
89	(wells or geneva or PERC or rule out criteria or gestalt or risk stratification).ti,ab,kf.
90	(decision adj4 (rule* or model* or analys?s or support or aid*)).ti,ab,kf.
91	(prediction adj4 (rule* or model* or analys?s or support or aid*)).ti,ab,kf.
92	(rule out or decision or prediction).ti.
93	or/86-92
94	85 and 93
95	94 use pmez
96	lung embolism/
97	pulmonary embolism/
98	((pulmonary or lung) adj4 (embolism* or embolus or emboli* or emboly or thromboemboli* or thrombo-emboli* or microemboli* or microembolus or micro-emboli* or micro embolus or blood clot*)).ti,ab,kw.
99	Venous Thromboembolism/
100	((venous or vein) adj4 (thromboemboli* or thrombo-emboli*)).ti,ab,kw.
101	VTE.ti,ab,kw.
102	or/96-101
103	fibrin degradation product/ or D dimer/
104	(d-dimer or fibrin or fibrinogen or fibrinolytic).ti,ab,kw.
105	decision support system/
106	(wells or geneva or PERC or rule out criteria or gestalt or risk stratification).ti,ab,kw.
107	(decision adj4 (rule* or model* or analys?s or support or aid*)).ti,ab,kw.
108	(prediction adj4 (rule* or model* or analys?s or support or aid*)).ti,ab,kw.
109	(rule out or decision or prediction).ti.
110	or/103-109
111	102 and 110
112	111 use oemezd
113	112 not conference abstract.pt.
114	39 or 79 or 95 or 113
115	exp Ethics/
116	exp Privacy/
117	exp Sociology/

MULTI-SEARCH STRATEGY	
#	**Searches**
118	exp Jurisprudence/
119	Morale/
120	exp Morals/
121	Paternalism/
122	exp Prejudice/
123	Social Values/
124	Social Norms/
125	"Legislation & Jurisprudence".fs.
126	ethics.fs.
127	exp Geography, Medical/
128	Medically Underserved Area/
129	((Healthcare or Health Care or nonclinical or Community Based) adj (Deliver* or Distribution* or System*)).ti,ab,kf.
130	(geographic adj (region* or area*)).ti,ab,kf.
131	(remote or urban or rural).ti,ab,kf.
132	(ethic or ethics or ethical or moral* or bioethic*).ti,ab,hw,kf.
133	(legal* or liabilit* or litigation* or constitutional or justice or law or laws or jurisprudence or complicit*).ti,ab,hw,kf.
134	(lawsuit* or lawyer* or lawmaker*).ti,ab,kf.
135	human right*.ti,ab,kf.
136	civil right*.ti,ab,kf.
137	(prejudice* or stigma or stigmas or stigmatization or stigmatize or stigmatise or stigmatisation or inequalit* or fairness).ti,ab,kf.
138	((care or treatment) adj2 (duty or obligat*)).ti,ab,kf.
139	(social* adj (responsibl* or obligat*)).ti,ab,kf.
140	(communitarian* or beneficence or nonmaleficence or maleficence or accountability).ti,ab,kf.
141	harm.ti,ab,kf.
142	(privacy or private or confidential*).ti,ab,hw,kf.
143	((informed or presumed) adj2 (consent or choice or decision making)).ti,ab,kf.
144	autonomy.ti,ab,hw,kf.
145	transparency.ti,ab,kf.
146	or/115-145
147	114 and 146
148	limit 147 to yr="2006 -Current"
149	embolisms/
150	((pulmonary or lung) adj4 (embolism* or embolus or emboli* or emboly or thromboemboli* or thrombo-emboli* or microemboli* or microembolus or micro-emboli* or micro-embolus or blood clot*)).ti,ab.
151	((venous or vein) adj4 (thromboemboli* or thrombo-emboli*)).ti,ab.
152	VTE.ti,ab.
153	or/149-152
154	exp ethics/
155	exp "law (government)"/
156	privacy/
157	exp social influences/

MULTI-SEARCH STRATEGY	
#	**Searches**
158	morality/
159	((Healthcare or Health Care or nonclinical or Community Based) adj (Deliver* or Distribution* or System*)).ti,ab,id.
160	(geographic adj (region* or area*)).ti,ab,id.
161	(remote or urban or rural).ti,ab,id.
162	(ethic or ethics or ethical or moral* or bioethic*).ti,ab,id.
163	(legal* or liabilit* or litigation* or constitutional or justice or law or laws or jurisprudence or complicit*).ti,ab,id.
164	(lawsuit* or lawyer* or lawmaker*).ti,ab,id.
165	human right*.ti,ab,id.
166	civil right*.ti,ab,id.
167	(prejudice* or stigma or stigmas or stigmatization or stigmatize or stigmatise or stigmatisation or inequalit* or fairness).ti,ab,id.
168	((care or treatment) adj2 (duty or obligat*)).ti,ab,id.
169	(social* adj (responsibl* or obligat*)).ti,ab,id.
170	(communitarian* or beneficence or nonmaleficence or maleficence or accountability).ti,ab,id.
171	harm.ti,ab,id.
172	(privacy or private or confidential*).ti,ab,id.
173	(distributive justice or precautionary principle or solidarity or equity).ti,ab,id.
174	((informed or presumed or shared) adj2 (consent or choice or decision making)).ti,ab,id.
175	autonomy.ti,ab,hw,id.
176	transparency.ti,ab,id.
177	or/154-176
178	153 and 177
179	limit 178 to yr="2006 -Current"
180	179 use psyb
181	148 or 180
182	limit 181 to (english or french)
183	remove duplicates from 182
178	153 and 177
179	limit 178 to yr="2006 -Current"
180	179 use psyb
181	148 or 180
182	limit 181 to (english or french)
183	remove duplicates from 182

OTHER DATABASES	
PubMed	Searched to capture records not indexed in MEDLINE. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used.
CINAHL	Searched to capture records not indexed in MEDLINE. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used, including the addition of CINAHL headings.

Implementation Issues Database Search

OVERVIEW	
Interface:	Ovid
Databases:	Embase MEDLINE Daily and MEDLINE MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	October 7, 2016
Alerts:	Monthly search updates until project completion
Study Types:	Limited to Canadian articles
Limits:	Date limit: 2006-present Language limit: English- and French-language Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj	Requires words are adjacent to each other (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.kw	Author keyword (Embase)
.kf	Author keyword heading word (MEDLINE)
.mp	Mapped term
.yr	Year
.jw	Journal title word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-SEARCH STRATEGY	
#	**Searches**
1	exp pulmonary embolism/
2	((pulmonary or lung) adj4 (embolism* or embolus or emboli* or emboly or thromboemboli* or thrombo-emboli* or microemboli* or microembolus or micro-emboli* or micro-embolus or blood clot*)).ti,ab,kf.
3	Venous Thromboembolism/
4	((venous or vein) adj4 (thromboemboli* or thrombo-emboli*)).ti,ab,kf.
5	VTE.ti,ab,kf.
6	or/1-5
7	exp Tomography, X-Ray Computed/ or Tomography Scanners, X-Ray Computed/
8	((computed or computer* or electron beam) adj4 (tomograph* or angiograph*)).ti,ab,kf.
9	(CT scan* or X-ray CT or CT X Ray? or CAT scan* or multi-detector CT or tomodensitometry or cine CT or Helical CT or spiral CT or Four Dimensional CT).ti,ab,kf.
10	(CTPA or CT pulmonary angiography or CT angiography).ti,ab,kf.
11	or/7-10
12	exp Magnetic Resonance Imaging/
13	(magnetic resonance imag* or MR imag* or MRI* or fMRI* or magnetic resonance tomograph* or MR tomograph* or magnetization transfer contrast imag* or magnetisation transfer imag* or magnetization transfer imag* or magnetisation transfer imag* or chemical shift imag* or NMR imag* or zeugmatography or NMR tomography or proton spin tomography or magnetic resonance scan* or MR scan*).ti,ab,kf.
14	12 or 13
15	Perfusion Imaging/ or Tomography, Emission-Computed, Single-Photon/ or Radionuclide Imaging/
16	(radionuclide imag* or gamma camera imag* or perfusion imaging or lung perfusion or scintigraph* or scintigram* or scintiphotograph* or laminoscintigraph* or scintillation or scintillograph* or scintiscan).ti,ab,kf.
17	(ventilation-perfusion adj4 (imag* or scan* or SPECT)).ti,ab,kf.
18	("ventilation/perfusion" adj4 (imag* or scan* or SPECT)).ti,ab,kf.
19	((ventilation and perfusion) adj4 (imag* or scan* or SPECT)).ti,ab,kf.
20	((VQ or V-Q or "v/q" or "V/P" or VP or V-P) adj4 (imag* or scan* or SPECT)).ti,ab,kf.
21	or/15-20
22	Positron-Emission Tomography/
23	(PET adj4 (scan* or imag*)).ti,ab,kf.
24	(FDGPET or FDG PET or PETCT or PET CT or positron).ti,ab,kf.
25	or/22-24
26	exp Lung/us
27	exp Ultrasonography/
28	(ultrasound or sonogra* or ultrasonic or ultrasonogra* or echotomogra* or echogra* or doppler).ti,ab,kf.
29	or/27-28
30	exp lung/
31	(lung or lungs or thoracic or thorax or chest).ti,ab,kf.
32	or/30-31
33	29 and 32
34	exp Echocardiography/
35	(cardiac echo* or heart echo* or echocardiogra* or echo-cardiogra* or cardiac echogra* or cardiac scan* or cardial echography or cardioechography or heart echography or heart scan* or myocardi* scan* or ultrasound cardiography).ti,ab,kf.

MULTI-SEARCH STRATEGY	
#	**Searches**
36	or/26,33-35
37	11 or 14 or 21 or 25 or 36
38	6 and 37
39	38 use pmez
40	lung embolism/
41	pulmonary embolism/
42	((pulmonary or lung) adj4 (embolism* or embolus or emboli* or emboly or thromboemboli* or thrombo-emboli* or microemboli* or microembolus or micro-emboli* or micro-embolus or blood clot*)).ti,ab,kw.
43	Venous Thromboembolism/
44	((venous or vein) adj4 (thromboemboli* or thrombo-emboli*)).ti,ab,kw.
45	VTE.ti,ab,kw.
46	or/40-45
47	exp computer assisted tomography/
48	((computed or computer* or electron beam) adj4 (tomograph* or angiograph*)).ti,ab,kw.
49	(CT scan* or X-ray CT or CT X Ray? or CAT scan* or multi-detector CT or tomodensitometry or cine CT or Helical CT or spiral CT or Four Dimensional CT).ti,ab,kw.
50	(CTPA or CT pulmonary angiograph* or CT angiograph*).ti,ab,kw.
51	or/47-50
52	exp nuclear magnetic resonance imaging/
53	(magnetic resonance imag* or MR imag* or MRI* or fMRI* or magnetic resonance tomograph* or MR tomograph* or magnetization transfer contrast imag* or magnetisation transfer imag* or magnetization transfer imag* or magnetisation transfer imag* or chemical shift imag* or NMR imag* or zeugmatography or NMR tomography or proton spin tomography or magnetic resonance scan* or MR scan*).ti,ab,kw.
54	52 or 53
55	exp scintigraphy/ or single photon emission computer tomography/ or exp scintiscanning/ or lung scintiscanning/
56	(radionuclide imag* or gamma camera imag* or perfusion imaging or lung perfusion or scintigraph* or scintigram* or scintiphotograph* or laminoscintigraph* or scintillation or scintillograph* or scintiscan).ti,ab,kw.
57	(ventilation-perfusion adj4 (imag* or scan* or SPECT)).ti,ab,kw.
58	("ventilation/perfusion" adj4 (imag* or scan* or SPECT)).ti,ab,kw.
59	((ventilation and perfusion) adj4 (imag* or scan* or SPECT)).ti,ab,kw.
60	((VQ or V-Q or "v/q" or "V/P" or VP or V-P) adj4 (imag* or scan* or SPECT)).ti,ab,kw.
61	or/55-60
62	positron emission tomography/
63	(PET adj4 (scan* or imag*)).ti,ab,kw.
64	(FDGPET or FDG PET or PETCT or PET CT or positron).ti,ab,kw.
65	or/62-64
66	exp echography/
67	(ultrasound or sonogra* or ultrasonic or ultrasonogra* or echotomogra* or echogra* or doppler).ti,ab,kw.
68	or/66-67
69	exp lung/
70	(lung or lungs or thoracic or thorax or chest).ti,ab,kw.
71	or/69-70

MULTI-SEARCH STRATEGY	
#	**Searches**
72	68 and 71
73	(cardiac echo* or heart echo* or echocardiogra* or echo-cardiogra* or cardiac echogra* or cardiac scan* or cardial echography or cardioechography or heart echography or heart scan* or myocardi* scan* or ultrasound cardiography).ti,ab,kw.
74	exp echocardiography/
75	or/72-74
76	51 or 54 or 61 or 65 or 75
77	46 and 76
78	77 use oemezd
79	78 not conference abstract.pt.
80	exp pulmonary embolism/
81	((pulmonary or lung) adj4 (embolism* or embolus or emboli* or emboly or thromboemboli* or thrombo-emboli* or microemboli* or microembolus or micro-emboli* or micro-embolus or blood clot*)).ti,ab,kf.
82	Venous Thromboembolism/
83	((venous or vein) adj4 (thromboemboli* or thrombo-emboli*)).ti,ab,kf.
84	VTE.ti,ab,kf.
85	or/80-84
86	Fibrin Fibrinogen Degradation Products/
87	(d-dimer or fibrin or fibrinogen or fibrinolytic).ti,ab,kf.
88	Decision Support Techniques/
89	(wells or geneva or PERC or rule out criteria or gestalt or risk stratification).ti,ab,kf.
90	(decision adj4 (rule* or model* or analys?s or support or aid*)).ti,ab,kf.
91	(prediction adj4 (rule* or model* or analys?s or support or aid*)).ti,ab,kf.
92	(rule out or decision or prediction).ti.
93	or/86-92
94	85 and 93
95	94 use pmez
96	lung embolism/
97	pulmonary embolism/
98	((pulmonary or lung) adj4 (embolism* or embolus or emboli* or emboly or thromboemboli* or thrombo-emboli* or microemboli* or microembolus or micro-emboli* or micro embolus or blood clot*)).ti,ab,kw.
99	Venous Thromboembolism/
100	((venous or vein) adj4 (thromboemboli* or thrombo-emboli*)).ti,ab,kw.
101	VTE.ti,ab,kw.
102	or/96-101
103	fibrin degradation product/ or D dimer/
104	(d-dimer or fibrin or fibrinogen or fibrinolytic).ti,ab,kw.
105	decision support system/
106	(wells or geneva or PERC or rule out criteria or gestalt or risk stratification).ti,ab,kw.
107	(decision adj4 (rule* or model* or analys?s or support or aid*)).ti,ab,kw.
108	(prediction adj4 (rule* or model* or analys?s or support or aid*)).ti,ab,kw.
109	(rule out or decision or prediction).ti.

MULTI-SEARCH STRATEGY	
#	**Searches**
110	or/103-109
111	102 and 110
112	111 use oemezd
113	112 not conference abstract.pt.
114	39 or 78 or 95 or 112
115	policy/ or delivery of health care/ or health policy/ or Health Services Accessibility/
116	(implementation or implementer* or barrier* or facilitator* or enabler*).ti,ab,kf.
117	implementation science.jn.
118	(adopt* or sustainability or acceptability or appropriateness or feasibility or uptake).ti,kf.
119	(training or trained or train or travel* or cultur* or socio* or social* or society or supply or supplies or education* or access or economic* or availab*).ti,ab,kf.
120	(geography or geographic or renovation* or transportation or staff or electricity or reimbursement or equipment or technical support or rural or remote or urban or waiting time* or allergy or allergies or radiation or renal failure or kidney failure or metal implant* or know-do gap or weight or height).ti,ab,kf.
121	(physician* adj2 knowledge).ti,ab,kf.
122	or/115-121
123	122 use pmez
124	health care policy/ or policy/ or health care delivery/
125	(implementation or implementer* or barrier* or facilitator* or enabler*).ti,ab,kw.
126	(adopt* or sustainability or acceptability or appropriateness or feasibility or uptake).ti,kw.
127	(training or trained or train or travel* or cultur* or socio* or social* or society or supply or supplies or education* or access or economic* or availab*).ti,ab,kw.
128	(geography or geographic or renovation* or transportation or staff or electricity or reimbursement or equipment or technical support or rural or remote or urban or waiting time* or allergy or allergies or radiation or renal failure or kidney failure or metal implant* or know-do gap or weight or height).ti,ab,kw.
129	(physician* adj2 knowledge).ti,ab,kw.
130	or/124-129
131	130 use oemezd
132	123 or 131
133	114 and 132
134	exp Canada/
135	(canadian* or canada* or british columbia* or alberta* or saskatchewan* or manitoba* or ontario* or quebec* or new brunswick* or prince edward island* or nova scotia* or labrador* or newfoundland* or nunavut* or northwest territor* or yukon* or toronto* or montreal* or vancouver* or ottawa* or calgary* or edmonton* or winnipeg* or first nation* or metis).ti,ab,hw,kf,kw.
136	(canadian* or canada* or british columbia* or alberta* or saskatchewan* or manitoba* or ontario* or quebec* or new brunswick* or prince edward island* or nova scotia* or labrador* or newfoundland* or nunavut* or northwest territor* or yukon* or toronto* or montreal* or vancouver* or ottawa* or calgary* or edmonton* or winnipeg* or first nation* or metis).jw,jx.
137	canada.lo.
138	(canadian* or canada* or british columbia* or alberta* or saskatchewan* or manitoba* or ontario* or quebec* or new brunswick* or prince edward island* or nova scotia* or labrador* or newfoundland* or nunavut* or northwest territor* or yukon* or toronto* or montreal* or vancouver* or ottawa* or calgary* or edmonton* or winnipeg* or first nation* or metis).sd,ss,if,cr.
139	or/134-138
140	133 and 139

MULTI-SEARCH STRATEGY	
#	**Searches**
141	limit 140 to yr="2006 -Current"
142	limit 141 to (english or french)
143	remove duplicates from 142

OTHER DATABASES		
PubMed	Searched to capture records not indexed in MEDLINE. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used.	
CINAHL	Searched to capture records not indexed in MEDLINE. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used, including the addition of CINAHL headings.	
Scopus (Social Science & Humanities)	Searched to capture records not indexed in MEDLINE. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used.	

Environmental Impact Database Search

OVERVIEW	
Interface:	Ovid
Databases:	Embase MEDLINE Daily and MEDLINE MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	April 7, 2017
Alerts:	Monthly search updates until project completion
Study Types:	No filters used
Limits:	Date limit: 2007-present Language limit: English- and French-language

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj	Requires words are adjacent to each other (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.kw	Author keyword (Embase)
.kf	Author keyword heading word (MEDLINE)
.mp	Mapped term
.yr	Year

.jw	Journal title word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-SEARCH STRATEGY

#	Searches
1	exp environmental pollution/
2	ecotoxicology/
3	exp environmental pollutants/
4	exp hazardous substances/ and environment*.ti,ab,kf.
5	(waste* or pollution* or polluting or pollutant* or contamination* or contaminated).ti,ab,kf.
6	((hazardous or toxic or toxicity) and environmental*).ti,ab,kf.
7	or/1-6
8	7 use ppez
9	exp pollution/ or exp pollutant/ or environmental exposure/ or exp environmental impact/ or ecotoxicology/
10	(waste* or pollution* or polluting or pollutant* or contamination* or contaminated).ti,ab,kw.
11	((hazardous or toxic or toxicity) and environmental*).ti,ab,kw.
12	or/9-11
13	12 use oemezd
14	8 or 13
15	exp Tomography, X-Ray Computed/ or Tomography Scanners, X-Ray Computed/
16	((computed or computer* or electron beam) adj4 (tomograph* or angiograph*)).ti,ab,kf.
17	(CT scan* or X-ray CT or CT X Ray? or CAT scan* or multi-detector CT or tomodensitometry or cine CT or Helical CT or spiral CT or Four Dimensional CT).ti,ab,kf.
18	(CTPA or CT pulmonary angiography or CT angiography).ti,ab,kf.
19	or/15-18
20	exp Magnetic Resonance Imaging/
21	(magnetic resonance imag* or MR imag* or MRI or MRIs or fMRI or fMRIs or magnetic resonance tomograph* or MR tomograph* or magnetization transfer contrast imag* or magnetisation transfer imag* or magnetization transfer imag* or magnetisation transfer imag* or chemical shift imag* or NMR imag* or zeugmatography or NMR tomography or proton spin tomography or magnetic resonance scan* or MR scan*).ti,ab,kf.
22	20 or 21
23	Perfusion Imaging/ or Tomography, Emission-Computed, Single-Photon/ or Radionuclide Imaging/
24	(radionuclide imag* or gamma camera imag* or perfusion imaging or lung perfusion or scintigraph* or scintigram* or scintiphotograph* or laminoscintigraph* or scintillation or scintillograph* or scintiscan).ti,ab,kf.
25	(ventilation-perfusion adj4 (imag* or scan* or SPECT)).ti,ab,kf.
26	("ventilation/perfusion" adj4 (imag* or scan* or SPECT)).ti,ab,kf.
27	((ventilation and perfusion) adj4 (imag* or scan* or SPECT)).ti,ab,kf.
28	((VQ or V-Q or "v/q" or "V/P" or VP or V-P) adj4 (imag* or scan* or SPECT)).ti,ab,kf.
29	or/23-28
30	Positron-Emission Tomography/
31	(PET adj4 (scan* or imag*)).ti,ab,kf.
32	(FDGPET or FDG PET or PETCT or PET CT or positron).ti,ab,kf.

MULTI-SEARCH STRATEGY	
#	**Searches**
33	or/30-32
34	exp Lung/us
35	exp Ultrasonography/
36	(ultrasound or sonogra* or ultrasonic or ultrasonogra* or echotomogra* or echogra* or doppler).ti,ab,kf.
37	or/35-36
38	exp lung/
39	(lung or lungs or thoracic or thorax or chest).ti,ab,kf.
40	or/38-39
41	37 and 40
42	exp Echocardiography/
43	(cardiac echo* or heart echo* or echocardiogra* or echo-cardiogra* or cardiac echogra* or cardiac scan* or cardial echography or cardioechography or heart echography or heart scan* or myocardi* scan* or ultrasound cardiography).ti,ab,kf.
44	or/34,41-43
45	19 or 22 or 29 or 33 or 44
46	exp computer assisted tomography/
47	((computed or computer* or electron beam) adj4 (tomograph* or angiograph*)).ti,ab,kw.
48	(CT scan* or X-ray CT or CT X Ray? or CAT scan* or multi-detector CT or tomodensitometry or cine CT or Helical CT or spiral CT or Four Dimensional CT).ti,ab,kw.
49	(CTPA or CT pulmonary angiograph* or CT angiograph*).ti,ab,kw.
50	or/46-49
51	exp nuclear magnetic resonance imaging/
52	(magnetic resonance imag* or MR imag* or MRI or MRIs or fMRI or fMRIs or magnetic resonance tomograph* or MR tomograph* or magnetization transfer contrast imag* or magnetisation transfer imag* or magnetization transfer imag* or magnetisation transfer imag* or chemical shift imag* or NMR imag* or zeugmatography or NMR tomography or proton spin tomography or magnetic resonance scan* or MR scan*).ti,ab,kw.
53	51 or 52
54	exp scintigraphy/ or single photon emission computer tomography/ or exp scintiscanning/ or lung scintiscanning/
55	(radionuclide imag* or gamma camera imag* or perfusion imaging or lung perfusion or scintigraph* or scintigram* or scintiphotograph* or laminoscintigraph* or scintillation or scintillograph* or scintiscan).ti,ab,kw.
56	(ventilation-perfusion adj4 (imag* or scan* or SPECT)).ti,ab,kw.
57	("ventilation/perfusion" adj4 (imag* or scan* or SPECT)).ti,ab,kw.
58	((ventilation and perfusion) adj4 (imag* or scan* or SPECT)).ti,ab,kw.
59	((VQ or V-Q or "v/q" or "V/P" or VP or V-P) adj4 (imag* or scan* or SPECT)).ti,ab,kw.
60	or/54-59
61	positron emission tomography/
62	(PET adj4 (scan* or imag*)).ti,ab,kw.
63	(FDGPET or FDG PET or PETCT or PET CT or positron).ti,ab,kw.
64	or/61-63
65	exp echography/
66	(ultrasound or sonogra* or ultrasonic or ultrasonogra* or echotomogra* or echogra* or doppler).ti,ab,kw.
67	or/65-66
68	exp lung/

MULTI-SEARCH STRATEGY	
#	**Searches**
69	(lung or lungs or thoracic or thorax or chest).ti,ab,kw.
70	or/68-69
71	67 and 70
72	(cardiac echo* or heart echo* or echocardiogra* or echo-cardiogra* or cardiac echogra* or cardiac scan* or cardial echography or cardioechography or heart echography or heart scan* or myocardi* scan* or ultrasound cardiography).ti,ab,kw.
73	exp echocardiography/
74	or/71-73
75	50 or 53 or 60 or 64 or 74
76	45 or 75
77	14 and 76
78	Radiation/
79	carbon footprint/
80	Electromagnetic radiation/
81	(radiation or carbon or radioactive or hard copy or film or energy consumption).ti,ab,kf,kw.
82	((medical adj4 isotope*) or radioisotope).ti,ab,kf,kw.
83	(environmental cost* or environmental impact*).ti,ab,kf,kw.
84	or/78-83
85	77 and 84
86	limit 85 to yr="2007 -Current"
87	remove duplicates from 86

Grey Literature

Dates for Search:	Sept 2016
Keywords:	Pulmonary embolism, venous thromboembolism
Limits:	Publication years Jan 2006 – Sept 2016

Relevant websites from the following sections of the CADTH grey literature checklist, “Grey matters: a practical tool for searching health-related grey literature” (https://www.cadth.ca/grey-matters) will be searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Databases (free)
- Internet Search
- Open Access Journals

Appendix 2: Supplemental Search Strategy

This protocol amendment was written a priori, executed before final study selection and data extraction, and followed throughout the review process.

Preamble and Rationale

The initial study design, as laid out in the original health technology assessment (HTA) protocol,[100,355] indicated that we would be conducting a systematic review (SR) based on a search and selection process with a ten-year timeframe (2006 to 2016 with search alerts until date of publication). Upon reflection on the needs of our jurisdictional stakeholders, and in the interest of maximizing the utility of this review, we chose to make provisions to ensure that as much of the relevant literature on currently used technologies as possible was captured.

This decision was guided by a review of included studies lists of SRs identified during a pre-protocol scoping review, feedback from our panel of clinical experts, and feedback from the Health Technology Expert Review Panel. The combined input indicated that our original search timeframe likely did not fully capture all the relevant literature for some of the modalities of interest. In particular, these concerns were relevant to modalities that had comparable technology in operation prior to 2006, for which older literature may still be relevant. The protocol amendments reflected the goal of extending the eligible timeframe to ensure maximum sensitivity of our search and optimal representation of the relevant literature base.

Study Design

To address the decision to expand the eligible search timeframe, the SR of primary studies conducted for research questions 2 and 3 outlined in the main HTA protocol was augmented by a systematic search for SRs published between 2011 and 2016 on the diagnostic test accuracy, clinical utility, and safety of diagnostic imaging modalities and pathways for the diagnosis of acute pulmonary embolism (PE). This supplemental search focussed on addressing research questions 2 and 3 with the intention of identifying additional primary studies (i.e. those not identified in our original searches) meeting our inclusion criteria that were published prior to 2006 through review of included studies lists of existing SRs that had wider or non-restricted search timeframes. Primary studies identified were considered for inclusion in the final analyses.

Research Questions

Research Question 2
What are the A) diagnostic test accuracy, B) comparative clinical utility, and C) safety of diagnostic pathways including imaging studies for the diagnosis of PE in adult patients in urban, rural, and remote settings?
Research Question 3
What are the A) diagnostic test accuracy, B) comparative clinical utility, and C) safety of imaging studies for the diagnosis of PE in adult patients in urban, rural, and remote settings?

The rationale for only reviewing SRs published between 2011 and 2016 is that the search timeframes of these reports will likely have captured primary studies published earlier than 2006 (i.e., from database inception until the end search date of each respective SR). We were confident in this approach based on the preliminary scan of SRs identified from the scoping review conducted during project development. Due to resources and timeline constraints, a supplemental literature search of primary studies was not feasible.

Literature Search

The literature search will be performed by an information specialist, using a peer-reviewed search strategy.

Published literature will be identified by searching the following bibliographic databases: MEDLINE (1946-), with in-process records and daily updates, via Ovid; Embase (1974-) via Ovid; the Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews of Effects (DARE) via Ovid; Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCO; and PubMed.

The clinical search strategy will comprise both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts will be PE/VTE and CT technologies, MRI technologies, V/Q-based technologies, PET-CT and thoracic ultrasound (plus echocardiography).

Methodological filters will be applied to limit retrieval to HTAs, SRs, meta-analyses (MAs), network meta-analyses, and overviews of reviews. Retrieval will be limited to documents published since January 1, 2011. The search will also be limited to English- or French-language publications. Conference abstracts will be excluded from the search results.

Relevant websites from the CADTH grey literature checklist, "Grey matters: a practical tool for searching health-related grey literature" (https://www.cadth.ca/grey-matters), were previously searched, using the methods described in the main HTA protocol.[100,355] As well, clinical trial registries were already searched to retrieve study data from completed trials. The complete search strategy is presented as follows.

OVERVIEW	
Interface:	Ovid
Databases:	Embase MEDLINE Daily and MEDLINE MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	Nov 23, 2016
Study Types:	Health technology assessments; systematic reviews; meta-analyses; network meta-analyses; overviews of reviews.
Limits:	Date limit: 2011-2016 Language limit: English- and French-language Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-SEARCH STRATEGY	
#	**Searches**
1	exp pulmonary embolism/
2	((pulmonary or lung) adj4 (embolism* or embolus or emboli* or emboly or thromboemboli* or thrombo-emboli* or microemboli* or microembolus or micro-emboli* or micro-embolus or blood clot*)).ti,ab,kf.
3	Venous Thromboembolism/
4	((venous or vein) adj4 (thromboemboli* or thrombo-emboli*)).ti,ab,kf.
5	VTE.ti,ab,kf.
6	or/1-5
7	exp Tomography, X-Ray Computed/ or Tomography Scanners, X-Ray Computed/
8	((computed or computer* or electron beam) adj4 (tomograph* or angiograph*)).ti,ab,kf.
9	(CT scan* or X-ray CT or CT X Ray? or CAT scan* or multi-detector CT or tomodensitometry or cine CT or Helical CT or spiral CT or Four Dimensional CT).ti,ab,kf.
10	(CTPA or CT pulmonary angiography or CT angiography).ti,ab,kf.
11	or/7-10
12	exp Magnetic Resonance Imaging/
13	(magnetic resonance imag* or MR imag* or MRI* or fMRI* or magnetic resonance tomograph* or MR tomograph* or magnetization transfer contrast imag* or magnetisation transfer imag* or magnetization transfer imag* or magnetisation transfer imag* or chemical shift imag* or NMR imag* or zeugmatography or NMR tomography or proton spin tomography or magnetic resonance scan* or MR scan*).ti,ab,kf.
14	12 or 13
15	Perfusion Imaging/ or Tomography, Emission-Computed, Single-Photon/ or Radionuclide Imaging/
16	(radionuclide imag* or gamma camera imag* or perfusion imaging or lung perfusion or scintigraph* or scintigram* or scintiphotograph* or laminoscintigraph* or scintillation or scintillograph* or scintiscan).ti,ab,kf.
17	(ventilation-perfusion adj4 (imag* or scan* or SPECT)).ti,ab,kf.
18	("ventilation/perfusion" adj4 (imag* or scan* or SPECT)).ti,ab,kf.
19	((ventilation and perfusion) adj4 (imag* or scan* or SPECT)).ti,ab,kf.
20	((VQ or V-Q or "v/q" or "V/P" or VP or V-P) adj4 (imag* or scan* or SPECT)).ti,ab,kf.
21	or/15-20
22	Positron-Emission Tomography/
23	(PET adj4 (scan* or imag*)).ti,ab,kf.
24	(FDGPET or FDG PET or PETCT or PET CT or positron).ti,ab,kf.
25	or/22-24
26	exp Lung/us
27	exp Ultrasonography/
28	(ultrasound or sonogra* or ultrasonic or ultrasonogra* or echotomogra* or echogra* or doppler).ti,ab,kf.
29	or/27-28
30	exp lung/
31	(lung or lungs or thoracic or thorax or chest).ti,ab,kf.
32	or/30-31
33	29 and 32
34	exp Echocardiography/
35	(cardiac echo* or heart echo* or echocardiogra* or echo-cardiogra* or cardiac echogra* or cardiac scan* or cardial echography or cardioechography or heart echography or heart scan* or myocardi* scan* or ultrasound cardiography).ti,ab,kf.

MULTI-SEARCH STRATEGY	
#	**Searches**
36	or/26,33-35
37	11 or 14 or 21 or 25 or 36
38	6 and 37
39	38 use pmez
40	lung embolism/
41	pulmonary embolism/
42	((pulmonary or lung) adj4 (embolism* or embolus or emboli* or emboly or thromboemboli* or thrombo-emboli* or microemboli* or microembolus or micro-emboli* or micro-embolus or blood clot*)).ti,ab,kw.
43	Venous Thromboembolism/
44	((venous or vein) adj4 (thromboemboli* or thrombo-emboli*)).ti,ab,kw.
45	VTE.ti,ab,kw.
46	or/40-45
47	exp computer assisted tomography/
48	((computed or computer* or electron beam) adj4 (tomograph* or angiograph*)).ti,ab,kw.
49	(CT scan* or X-ray CT or CT X Ray? or CAT scan* or multi-detector CT or tomodensitometry or cine CT or Helical CT or spiral CT or Four Dimensional CT).ti,ab,kw.
50	(CTPA or CT pulmonary angiograph* or CT angiograph*).ti,ab,kw.
51	or/47-50
52	exp nuclear magnetic resonance imaging/
53	(magnetic resonance imag* or MR imag* or MRI* or fMRI* or magnetic resonance tomograph* or MR tomograph* or magnetization transfer contrast imag* or magnetisation transfer imag* or magnetization transfer imag* or magnetisation transfer imag* or chemical shift imag* or NMR imag* or zeugmatography or NMR tomography or proton spin tomography or magnetic resonance scan* or MR scan*).ti,ab,kw.
54	52 or 53
55	exp scintigraphy/ or single photon emission computer tomography/ or exp scintiscanning/ or lung scintiscanning/
56	(radionuclide imag* or gamma camera imag* or perfusion imaging or lung perfusion or scintigraph* or scintigram* or scintiphotograph* or laminoscintigraph* or scintillation or scintillograph* or scintiscan).ti,ab,kw.
57	(ventilation-perfusion adj4 (imag* or scan* or SPECT)).ti,ab,kw.
58	("ventilation/perfusion" adj4 (imag* or scan* or SPECT)).ti,ab,kw.
59	((ventilation and perfusion) adj4 (imag* or scan* or SPECT)).ti,ab,kw.
60	((VQ or V-Q or "v/q" or "V/P" or VP or V-P) adj4 (imag* or scan* or SPECT)).ti,ab,kw.
61	or/55-60
62	positron emission tomography/
63	(PET adj4 (scan* or imag*)).ti,ab,kw.
64	(FDGPET or FDG PET or PETCT or PET CT or positron).ti,ab,kw.
65	or/62-64
66	exp echography/
67	(ultrasound or sonogra* or ultrasonic or ultrasonogra* or echotomogra* or echogra* or doppler).ti,ab,kw.
68	or/66-67
69	exp lung/
70	(lung or lungs or thoracic or thorax or chest).ti,ab,kw.
71	or/69-70

MULTI-SEARCH STRATEGY	
#	**Searches**
72	68 and 71
73	(cardiac echo* or heart echo* or echocardiogra* or echo-cardiogra* or cardiac echogra* or cardiac scan* or cardial echography or cardioechography or heart echography or heart scan* or myocardi* scan* or ultrasound cardiography).ti,ab,kw.
74	exp echocardiography/
75	or/72-74
76	51 or 54 or 61 or 65 or 75
77	46 and 76
78	77 use oemezd
79	78 not conference abstract.pt.
80	39 or 79
81	meta-analysis.pt.
82	meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/
83	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf,kw.
84	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf,kw.
85	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf,kw.
86	(data synthes* or data extraction* or data abstraction*).ti,ab,kf,kw.
87	(handsearch* or hand search*).ti,ab,kf,kw.
88	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf,kw.
89	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf,kw.
90	(meta regression* or metaregression*).ti,ab,kf,kw.
91	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
92	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
93	(cochrane or (health adj2 technology assessment) or evidence report).jw.
94	(meta-analysis or systematic review).md.
95	(comparative adj3 (efficacy or effectiveness)).ti,ab,kf,kw.
96	(outcomes research or relative effectiveness).ti,ab,kf,kw.
97	((indirect or indirect treatment or mixed treatment or bayesian) adj3 comparison*).ti,ab,kf,kw.
98	(network* adj3 (meta-analy* or metaanaly*)).ti,ab,kf,kw.
99	(multi* adj3 treatment adj3 comparison*).ti,ab,kf,kw.
100	umbrella review*.ti,ab,kf,kw.
101	nma.ti,ab,kf,kw.
102	(Multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.
103	(Multiparamet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.
104	(multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.
105	MPES.ti,ab,kw,kf.
106	((overview* or review or synthesis or summary or cochrane or analysis) and (reviews or meta-analyses or articles or umbrella)).ti,kf,kw. or umbrella review.ab. or (meta-review or metareview).ti,ab,kf,kw.
107	((overview* or reviews) and (systematic or cochrane)).ti,kf,kw.
108	(reviews adj2 meta).ab.

MULTI-SEARCH STRATEGY	
#	**Searches**
109	(reviews adj2 (published or quality or included or summar*)).ab.
109	(reviews adj2 (published or quality or included or summar*)).ab.
110	cochrane reviews.ab.
111	(evidence and (reviews or meta-analyses)).ti,kf,kw.
112	or/81-111
113	80 and 112
114	limit 113 to (english or french)
115	limit 114 to yr="2011 -Current"
116	remove duplicates from 115

OTHER DATABASES		
PubMed	Searched to capture records not indexed in MEDLINE. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used.	
Cochrane Database of Systematic Reviews (CDSR) Database of Abstracts of Reviews of Effects (DARE)	Searched to capture records not indexed in MEDLINE. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used.	
CINAHL	Searched to capture records not indexed in MEDLINE. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used, including the addition of CINAHL headings.	

Selection Criteria

Selection criteria used for this SR search are outlined in the table below and were mainly consistent with the selection criteria relevant to research questions 2 and 3 outlined in the main HTA protocol.[100,355] As this review is designed to identify existing evidence syntheses, only specific study types were of interest as noted in in the table below.

From the selected SRs, included studies lists were reviewed for eligible primary studies which were evaluated for inclusion using the selection criteria stated in the original HTA protocol.[100,355] The only deviation from this original inclusion criteria was an expanded non-truncated eligible publication timeframe.

Selection Criteria for Systematic Reviews Addressing Clinical Research Questions 2 and 3

Population
Q2 to 3: Adult patients ≥ 18 years undergoing testing for acute PE[a] **Subgroups of interest:** • Pregnant women • Patients presenting for assessment at centres with access to imaging versus without access to imaging • Emergency room patients versus in-patients (secondary or tertiary care) • Patients who present with symptoms in the primary care setting • Geographical subgroups (urban, rural, and remote) • Patients with high versus low pretest probability

Interventions	Comparators (or Reference Standards)
Q2 and 3: Diagnostic Imaging	
Q2: Any of the below interventions, including at least 1 of any clinical decision rule, and/or biochemical or imaging-based risk stratification strategy)[b] **Q3:** Any of the following imaging studies • CT technologies[c] • MRI technologies • V/Q-based technologies[d] • Thoracic ultrasound (+ echocardiography)	Q2 and 3A: • Composite reference standard (must include advanced diagnostic imaging tests [e.g., multidetector CT]) Q2 and 3 A, B, and C: • Any alternative diagnostic imaging exam (± clinical decision rule ± biochemical or imaging-based risk stratification strategies)

Outcomes[f]
Q2 and 3: A) Diagnostic test accuracy (i.e., sensitivity, specificity, PPV, NPV, PLR, NLR, DOR, AUROC, Youden's Index B) **Primary:** • Clinical utility (failure rate [i.e., morbidity and mortality due to misdiagnosis at 30 days' follow-up])[e] **Secondary:** • Clinical utility (e.g., efficiency,[f] identification of patients with different diagnoses, change in referring physician's diagnostic thinking, change in patient management, change in patient outcomes) C) Harms (safety outcomes of imaging procedures [e.g., radiation exposure, CT-attributed malignancy, contrast nephropathy, patient discomfort, allergic reactions])

Study design
Q2 and 3: SRs with or without an MA, HTAs

Timeframe
Q2 and 3: Publications within the last 5 years (i.e., between January 2011 and December 2016)

± = with or without; AUROC = area under the receiver operating curve; CT = computed tomography; DOR = diagnostic odds ratio; HTA = health technology assessment; MA = meta-analysis; MRI = magnetic resonance imaging; NLR = negative likelihood ratio; NPV = negative predictive value; PE = pulmonary embolism; PLR = positive likelihood ratio; PPV = positive predictive value; RCT = randomized controlled trial; SPECT = single-photon emission computed tomography; SR = systematic review; V/Q = ventilation-perfusion.

[a] Excluding pediatric patients, patients with recurrent VTE, and patients with suspected DVT.

[b] Leg compression ultrasound, capnography, electrocardiography, echocardiography, chest radiograph.

[c] Excluding single-detector, including CTA/CTV and triple-rule-out CT.

[d] Including planar V/Q scan, V/Q SPECT, V/Q SPECT-CT.

[e] Morbidity and mortality due to misdiagnosis such as A) morbidity and mortality in false-negative patients (the proportion of patients classified as having low risk of PE who receive an ultimate diagnosis of PE based on the reference standard [false-negatives/true-negatives + false-negatives], and B) risk of bleeding in false-positive patients who receive anticoagulation treatment.

[f] The proportion of patients in the study cohort stratified to the group with low predicted probability of PEs (sum of true- and false-negatives/total cohort).

Exclusion Criteria

Systematic Reviews

To be included, SRs must have included a detailed description of comprehensive selection criteria and search methods (i.e., as described in Assessment of Multiple Systematic Reviews [AMSTAR] checklist item 3, searched at least two electronic sources, adequately reported years searched and databases used, key words and/or MeSH terms, and where feasible, provided the search strategy); assessed the quality (or risk of bias) of included studies; and synthesized the findings quantitatively and/or qualitatively.

Systematic reviews were excluded if they did not meet the selection criteria outlined in the selection criteria, if they were duplicate publications, or if they were published prior to 2011. Multiple publications of the same SR were excluded unless they provided additional primary studies of interest. Older SRs (based on publication year) identified in the literature search results were excluded if they were superseded by an updated SR, or if all the included studies in the older SRs were included in newer SR(s). The degree of overlap between SRs with overlapping primary studies was judged by building a matrix of included studies in the SRs, which was used to assist in making decisions about which primary studies to consider for inclusion in the main HTA synthesis. If an SR had unique primary studies, but they were limited to case reports, they were excluded consistent with the selection criteria established in the original HTA protocol.[100,355] A list of excluded SRs, with reasons for exclusion after full-text review, will be recorded and is available upon request.

Primary Studies Identified from Systematic Reviews

Exclusion criteria for the primary studies identified from the included studies lists of the selected SRs was consistent with the original HTA protocol.[100,355] Outcomes of this selection process will be combined with the outcomes of the main search and the included and excluded studies list will be reported accordingly.

Screening and Selecting Studies for Inclusion

Systematic Review Screening

Two reviewers independently screened titles and abstracts of all SRs retrieved from the literature search, reference lists of identified eligible SRs, and any additional SRs identified by content experts. This was followed by an independent review of all full-text SRs selected by at least one reviewer based on the pre-determined selection criteria outlined in the selection criteria using the following screening checklist. The two reviewers compared their selections from the full-text review and resolved disagreements through discussion until consensus was reached, consulting a third reviewer if necessary.

CADTH

Full-Text Screening Checklist for Supplementary Systematic Review Search

Reviewer: _____ Date: _____

Ref ID: **Author:** **Publication Year:**			
Did the study include:	Yes (Include)	Unclear (Include or exclude)[a]	No (Exclude)
1) Adults (i.e., aged ≥ 18 years), being tested for PE (as per Table 2)	☐	☐	☐
2) The interventions of interest: **Imaging** • CT-based studies • MRI-based studies • V/Q-based studies • PET-based studies • Thoracic ultrasound	☐	☐	☐
3) The comparators of interest: **Imaging** • Composite reference standard • CT-based studies • MRI-based studies • V/Q-based studies • PET-based studies • Thoracic ultrasound	☐	☐	☐
4) The outcomes of interest: • DTA • Clinical utility • Direct patient harms	☐	☐	☐
5) The study designs of interest: • SR • MA • HTA	☐	☐	☐
Decision to include the study:[b]	Yes ☐		No ☐
Reason(s) for exclusion:	☐ Inappropriate study population ☐ No intervention of interest ☐ No or inappropriate comparator ☐ No relevant outcomes ☐ Irrelevant study design ☐ Study description only ☐ Other:		

CT = computed tomography; DTA = diagnostic test accuracy; HTA = health technology assessment; MA = meta-analysis; MRI = magnetic resonance imaging; PE = pulmonary embolism; PET = positron emission tomography; SR = systematic review; V/Q = ventilation-perfusion.

[a] This will be discussed with a second reviewer.

[b] If all items above are answered "yes" or "unclear," then the study will be included.

Did the study report any data relevant to another research question? ☐ Yes: RQ# _____ ☐ No

Identification and Screening of Primary Studies from Selected Systematic Reviews

Once SRs were selected, the included studies lists of these publications were reviewed and primary studies were selected for further review by two reviewers based on the information in the citation titles and primary study characteristics disclosed in the SR. An independent review of the full-texts of all primary studies selected by either reviewer (excluding studies already identified during the original search [both included and excluded]) based on the established selection criteria and screening form presented in the main HTA protocol was conducted.[100,355]. Selections were compared and disagreements resolved through discussion until consensus was reached.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart[356] was amended to reflect this additional search (Appendix 8).

Data Extraction

No formal data extraction was conducted for the SRs identified from the supplemental search. Data extraction of the additional primary studies identified during this process was consistent with the items and forms included in main HTA protocol.[100,355]

Risk of Bias Assessments

The primary studies included from the SRs we selected were critically appraised consistent with the approach for primary studies outlined in the main HTA protocol.[100,355]

Summary of Evidence

Primary studies identified from the original search and this update were described and synthesized consistent with the methods outlined in the main HTA protocol.[100,355]

CADTH

Appendix 3: Clinical Full-Text Screening Checklist

Reviewer: _____ Date: _____

Ref ID: **Author:** **Publication Year:**			
Did the study include:	**Yes (Include)**	**Unclear (Include or exclude)[a]**	**No (Exclude)**
6) Adults (i.e., aged ≥ 18 years), being tested for PE (as per Table 2)	☐	☐	☐
7) The interventions of interest: **Risk Stratification Strategies** • Wells or Geneva rules • PERC • D-Dimer • Biochemical or imaging studies **Imaging** • CT-based studies • MRI-based studies • VQ-based studies • PET-based studies • Thoracic ultrasound	☐	☐	☐
8) The comparators of interest: **Risk Stratification Strategies** • Composite reference standard • Any alternative clinical decision rule or modified/tailored tool ± PERC ± D-dimer ± biochemical or imaging-based risk stratification • No clinical rule (Gestalt) **Imaging** • Composite reference standard • CT-based studies • MRI-based studies • VQ-based studies • PET-based studies • Thoracic ultrasound	☐	☐	☐
9) The outcomes of interest: • DTA • Clinical utility • Direct patient harms	☐	☐	☐
10) The study designs of interest: • SR • MA • HTA • RCT • NRS • CS	☐	☐	☐
Decision to include the study:[b]	Yes ☐		No ☐

Ref ID: **Author:** **Publication Year:**	
Reason(s) for exclusion:	☐ Inappropriate study population ☐ No intervention of interest ☐ No or inappropriate comparator ☐ No relevant outcomes ☐ Irrelevant study design ☐ Study description only ☐ Other:

CS = case series; CT = computed tomography; DTA = diagnostic test accuracy; HTA = health technology assessment; MA = meta-analysis; MRI = magnetic resonance imaging; NRS = non-randomized study; PE = pulmonary embolism; PERC = Pulmonary Embolism Rule-Out Criteria; PET = positron emission tomography; RCT = randomized controlled trial; SR = systematic review; VQ = ventilation-perfusion.

[a] This will be discussed with a second reviewer.

[b] If all items above are answered "yes" or "unclear," then the study will be included.

Did the study report any data relevant to another research question (RQ)? □ Yes: RQ# _____ □ No

CADTH

Appendix 4: Clinical Data Extraction Form for Primary Studies

Reviewer: _____ Date: _____

STUDY CHARACTERISTICS	
Ref ID:	
Author(s):	
Publication title	
Publication year:	
Country (where the study was conducted):	
Funding:	

METHODOLOGY	
Study design:	☐ RCT ☐ NRS ☐ CS
Details of study design	
Number of included participants:	
Study eligibility criteria:	
Period of conduct:	
Setting of conduct:	☐ Emergency room ☐ Secondary or tertiary in-patient care ☐ Primary care ☐ Rural ☐ Remote ☐ Urban
Subgroup analyses	
Multivariate analyses	

CS = case series; NRS = non-randomized study; RCT = randomized controlled trial.

POPULATION	
Age	
Clinical condition or subgroup	☐ Trauma or ICU ☐ Pregnancy ☐ Cancer ☐ Hemodynamically unstable ☐ Oral contraceptive or HRT ☐ Obesity ☐ Renal insufficiency ☐ Allergy to contrast dye ☐ Patients with COPD or pneumonia ☐ Elderly patients ☐ Patients with inherited or acquired thrombophilias
Sex	

COPD = chronic obstructive pulmonary disease; HRT = hormone replacement therapy; ICU = intensive care unit.

COMPARISON	
Intervention (specify disease threshold and cut-off values,[a] manufacturer, technological specifications):	
Comparator (specify disease threshold and cut-off values,[a] manufacturer, technological specifications):	
Duration between index and reference test:	
Occupation or expertise of practitioner administering and interpreting test	

[a] Including any information about age-specific cut-offs (e.g., for D-dimer)

REPORTED OUTCOMES	
Primary (including definition):	
Secondary (including definition):	
Length of follow-up:	

RESULTS (TO BE COMPLETED FOR EACH COMPARISON AND OUTCOME)	
Comparison	
Intervention:	
Comparator:	
Outcome	
Subgroup analysis	
Variable 1	
Variable 2	
(Add variables as needed)	
Multivariate analysis	
Variable1	
Variable 2	
(Add variables as needed)	
Main conclusions:	

Did the study report any data relevant to another research question (RQ)? □ Yes: RQ# _____ □ No

CADTH

Appendix 5: Clinical Data Extraction Form for Systematic Reviews

Reviewer: _____ Date: _____

STUDY CHARACTERISTICS	
Ref ID:	
Author(s):	
Publication title	
Publication year:	
Country (where the study was conducted):	
Funding:	

METHODOLOGY	
Study design:	☐ SR ☐ MA ☐ HTA
Number of included studies:	
Total number of participants within studies included in the review:	
Study eligibility criteria:	
Type of included studies:	
Range of publication years of included studies:	
Databases searched:	
Search period:	
Quality assessment tool:	
Subgroup analyses and/or meta-regression:	

HTA = health technology assessment; MA = meta-analysis; SR = systematic review.

COMPARISON	
Intervention (specify disease threshold and cut-off values, manufacturer, technological specifications):	
Comparator (specify disease threshold and cut-off values, manufacturer, technological specifications):	
Duration between index and reference test:	

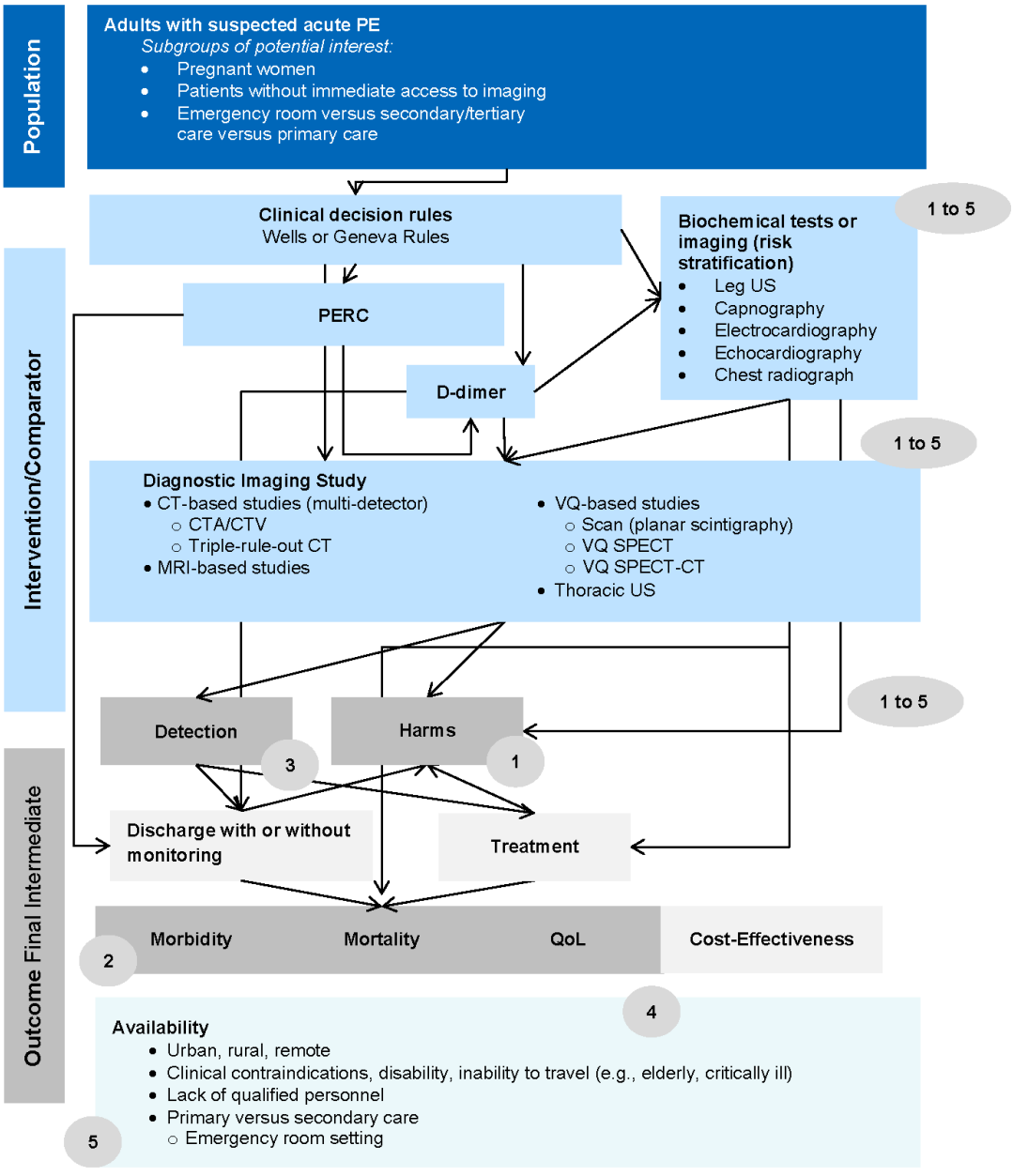
REPORTED OUTCOMES	
Primary (including definition):	
Secondary (including definition):	
Length of follow-up:	

RESULTS (TO BE COMPLETED FOR EACH COMPARISON AND OUTCOME)	
Comparison	
Intervention:	
Comparator:	
Outcome	
Study (1st author) [REF ID]	
Number of included studies:	
Range of publication years of included studies:	
Study population (nuances)	
Pairwise MA	
Pooled DTA or effect estimate (95% CI)	
P value for effect	
I^2 statistics	
NMA	
DTA (95% CI)	
P value for effect	
Subgroups	
Subgroup 1:	
Number of included studies	
DTA or effect estimate (95% CI)	
P value for effect	
I^2 statistics	
Subgroup 2:	
Number of included studies	
DTA or effect estimate (95% CI)	
P value for effect	
I^2 statistics	
(Add subgroups as needed)	
Meta-regression	
Variables	
Variable 1:	
Variable 2:	
(Add variables as needed)	
Main conclusions:	

CI = confidence interval; DTA = diagnostic test accuracy; MA = meta-analysis; NMA = network meta-analysis.

Did the systematic review report any data relevant to another research question (RQ)? □ Yes: RQ# _____ □ No

Appendix 6: Pulmonary Embolism Diagnosis and Management Strategies and Subsequent Outcomes



1	Clinical Effectiveness (Safety)	4	Cost-Effectiveness
2	Clinical Utility	5	Factors Influencing Modality Implementation and Use
3	Diagnostic Accuracy		

CT = computed tomography; CTA/CTV = computed tomographic angiography in combination with venous-phase imaging; MRI = magnetic resonance imaging; PE = pulmonary embolism; PERC = Pulmonary Embolism Rule-Out Criteria; PET = positron emission tomography; QoL = quality of life; SPECT = single-photon emission computed tomography; US = ultrasound; VQ = ventilation-perfusion.

Appendix 7: Selection Criteria for Network Meta-Analysis

Table A1: Selection Criteria for Network Meta-Analysis

Population	
Q2 and 3: Adult patients undergoing testing for acute PE[a] **Patient subgroups of interest:** • Pregnant women • Patients presenting for treatment at centres with access to imaging versus without access to imaging • Emergency room patients versus in-patients (secondary or tertiary care)	
Interventions	**Comparators**
Any of the following imaging studies (± clinical decision rule ± biochemical or imaging-based risk stratification strategies[b]) • CT technologies[c] • MRI technologies • VQ-based technologies[d] • Thoracic ultrasound (+ echocardiography)	Q2 and 3A: • Composite reference standard (must include advanced diagnostic imaging tests [e.g., multidetector CT]) Q2 and 3 A, B, and C: Any alternative diagnostic imaging exam (± clinical decision rule ± biochemical or imaging-based risk stratification strategies)
Outcomes[e]	
Q2 and 3: A) Diagnostic test accuracy (i.e., sensitivity, specificity, PPV, NPV, PLR, NLR, DOR, AUROC, Youden's Index B) Clinical utility (failure rate [i.e., morbidity and mortality due to misdiagnosis at 30 days' follow-up],[f] efficiency,[g] yield,[h] identification of patients with different diagnoses, change in referring physician's diagnostic thinking, change in patient management, change in patient outcomes) C) Harms (safety outcomes of imaging procedures [e.g., radiation exposure, CT-attributed malignancy, contrast nephropathy, patient discomfort, allergic reactions])	
Study Design	
A) Diagnostic test accuracy outcomes: RCTs and non-randomized studies (i.e., controlled clinical trials, cohort studies, and cross-sectional studies) B) Clinical utility outcomes: RCTs and non-randomized studies (i.e., controlled clinical trials, cohort studies, controlled before-and-after studies, and case-control studies) C) Safety outcomes: in addition to the above study designs, non-randomized studies without a control group (excluding non-sequential case series and case reports) will also be included	
Time Frame	
Publications within the last 10 years (i.e., between January 2006 and September 2016)	

± = with or without; AUROC = area under the receiver operating curve; CT = computed tomography; CTV/CTA = computed tomographic angiography in combination with venous-phase imaging; DOR = diagnostic odds ratio; DVT = deep vein thrombosis; MRI = magnetic resonance imaging; NLR = negative likelihood ratio; NPV = negative predictive value; PE = pulmonary embolism; PLR = positive likelihood ratio; PPV = positive predictive value; RCT = randomized controlled trial; SPECT = single-photon emission computed tomography; VQ = ventilation-perfusion; VTE = venous thromboembolism.

[a] Excluding pediatric patients, patients with recurrent VTE, and patients with suspected DVT.

[b] Leg compression US, capnography, electrocardiography, echocardiography, chest radiograph.

[c] Excluding single-detector, including CTA/CTV and triple-rule-out CT.

[d] Including planar VQ scan, VQ SPECT, VQ SPECT-CT.

[e] No restriction on length of follow-up.

[f] The failure rate of a risk stratification strategy is the proportion of suspected PE patients confirmed to have venous thromboembolism or sudden unexplained death during the follow-up period although they were initially classified as having a low risk of PE by the strategy and excluded from imaging or anticoagulation as a result (false-negatives/true-negatives + false-negatives).

[g] The efficiency of a risk stratification strategy is the proportion of suspected PE patients classified by the strategy to have a low predicted probability of PE (sum of true and false-negatives/total cohort).

[h] The yield of an imaging modality referred to the proportion of studies with positive results for PE among all studies

Appendix 8: Study Selection Flowchart (PRISMA) for Clinical Review

Figure A1: PRISMA Flowchart for Study Selection for the Overview of Systematic Reviews of Risk Stratification Strategies

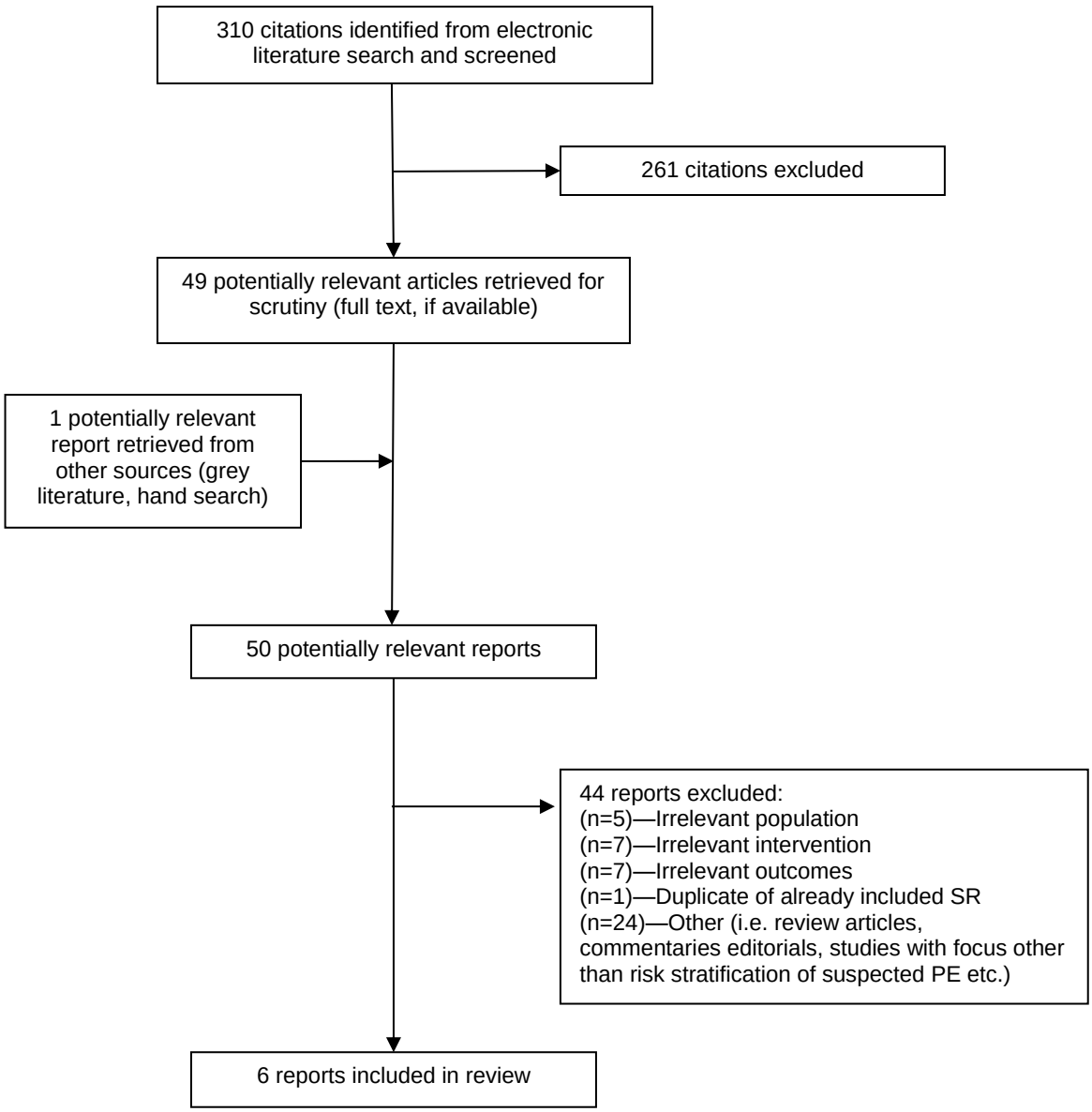
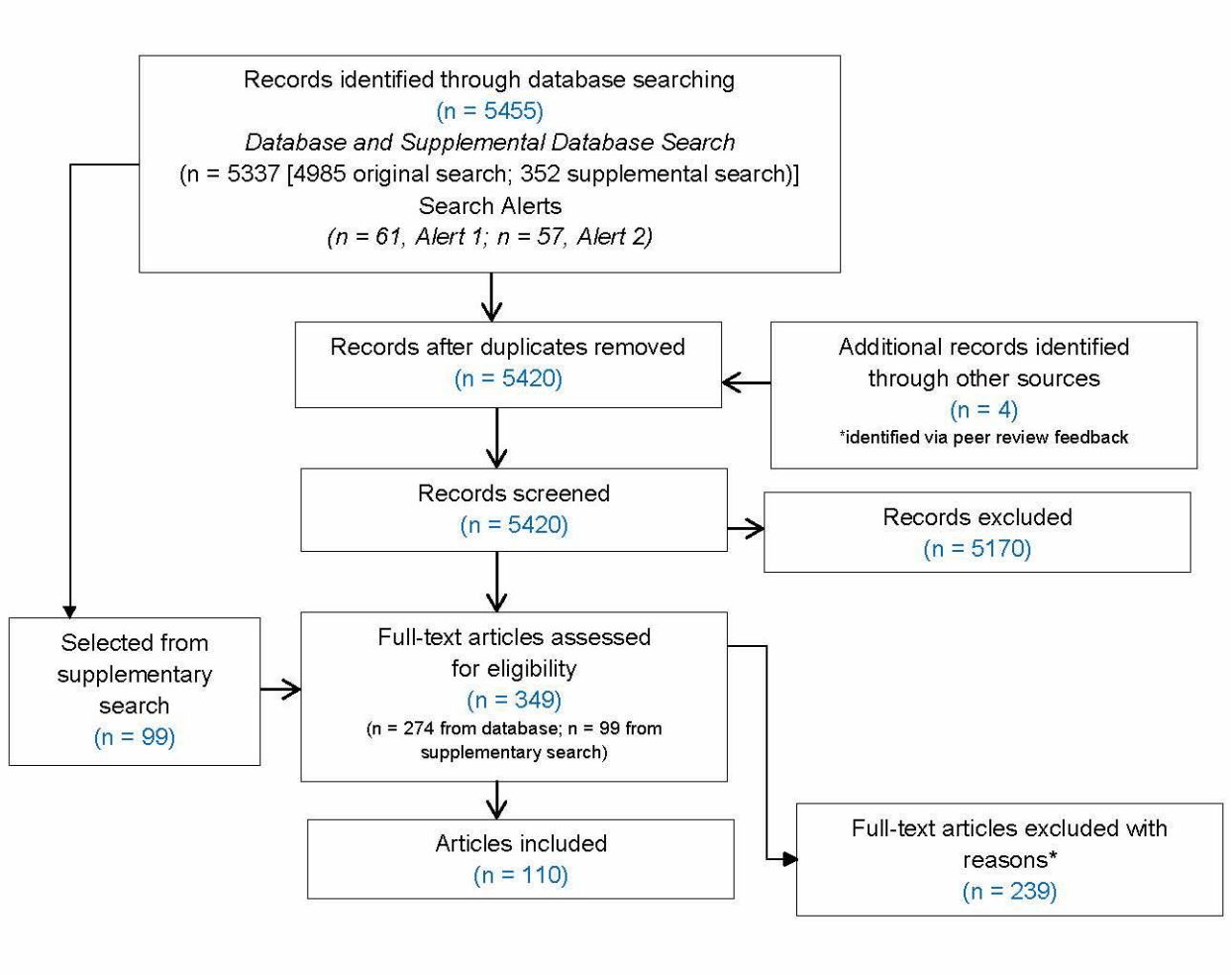


Figure A2: PRISMA Flowchart for Diagnostic Imaging and Pathway Studies (Research Questions 2 and 3)



Appendix 9: Overlap Among Primary Studies from Included Systematic Reviews

	First Author, Publication Year	Lucassen, 2011[26]	Shen, 2016[24]	Siccama, 2011[103]	Van Es, 2016[104,357]	Sanders, 2015[105]	Wang, 2016[25]
1	ADJUST-PE, 2014				•		
2	Aguilar, 2005			•			
3	Albrizio, 2007						•
4	Anderson, 2005	•					
5	Aujesky, 2003	•					
6	Barghouth, 2000	•					
7	Calisir, 2009	•					
8	Carrier, 2006					•	
9	Carrier, 2008			•			
10	Chagnon, 2002	•	•			•	
11	Correia, 2012		•				
12	Cross, 1998	•					
13	Douma, 2009	•					
14	Douma, 2011	•			•		
15	Dresher, 2011						•
16	Elias, 2005	•					
17	Galipienzo, 2012				•		
18	Goekoop, 2007	•			•		
19	Guo, 2009		•				
20	Guo, 2015		•				
21	Hugli, 2011	•					
22	Janes, 2001			•			
23	Kabrhel, 2005	•				•	
24	Kabrhel, 2009	•				•	
25	Kearon, 2006	•					
26	Kline and Hogg, 2006	•					
27	Kline, 2002	•					
28	Kline, 2004						•
29	Kline, 2006	•					
30	Kline, 2008	•				•	
31	Kline, 2014						•
32	Klok, 2008	•	•				

	First Author, Publication Year	Lucassen, 2011[26]	Shen, 2016[24]	Siccama, 2011[103]	Van Es, 2016[104,357]	Sanders, 2015[105]	Wang, 2016[25]
33	Klok, 2008 a	•					
34	Le Gal, 2006	•					
35	Legnani, 2010	•					
36	Luo, 2014		•				
37	Miniati, 1996	•					
38	Miniati, 2003	•					
39	Miniati, 2003 a	•					
40	Miniati, 2005	•	•				
41	Miniati, 2008	•					
42	Miron, 1999	•					
43	Musset, 2002	•					
44	Nilsson, 2001	•					
45	Ong, 2013						•
46	Parent, 2007	•					
47	Penaloza, 2011	•	•				
48	Penaloza, 2012					•	
49	Penaloza, 2013		•			•	
50	Perrier, 2000	•					
51	Perrier, 2004	•					
52	Perrier, 2005	•					
53	PIOPED Investigators, 1990	•					
54	Prevedello, 2013						•
55	Raja, 2012						•
56	REPEAD, 2014				•		
57	Righini, 2004			•			
58	Righini, 2005						
59	Righini, 2007			•			
60	Righini, 2008	•					
61	Runyon, 2005	•				•	
62	Runyon, 2008	•					
63	Sanson, 2000	•				•	
64	Schutgens, 2005			•			
65	Siragusa, 2007	•					
66	Sohne, 2005			•			

	First Author, Publication Year	Lucassen, 2011[26]	Shen, 2016[24]	Siccama, 2011[103]	Van Es, 2016[104,357]	Sanders, 2015[105]	Wang, 2016[25]
67	Sohne, 2006			•			
68	Soo Hoo, 2011						•
69	Steeghs, 2005	•					
70	Stein, 2006	•					
71	Ten Wolde, 2004	•					
72	Toll, 2007			•			
73	Tsimogianni, 2011		•				
74	Turedi, 2008		•				
75	Van Belle, 2006	•			•		
76	Wells, 2000	•					
77	Wells, 2001	•					
78	Wicki, 2001	•					
79	Wolf, 2004	•					
80	Wolf, 2008	•					
81	Yap, 2007	•					
82	Ye, 2012		•				
Total Number of primary studies		52	12	9	6	31	8

Appendix 10: List of Excluded Studies for Clinical Review (Questions 1, 2, and 3)

Question 1: Overview of Systematic Reviews

	Author, Year	Reasons for Exclusion
1	Adams, 2014[358]	Other—Summary of an article without a specified CPR
2	Akgul 2013[359]	Other—Narrative article
3	Ayaram, 2013[360]	Other—Insufficient numbers of patients with PE
4	Barnes, 2016[361]	Irrelevant Outcome—No diagnostic accuracy or comparative utility outcome
5	Becattini, 2012[362]	Other—Association between D-dimer levels and mortality and/or markers of PE severity
6	Ceriani, 2010[363]	Irrelevant Outcome—Prevalence
7	Carrier, 2010[364]	Irrelevant outcomes—Single vs. multi-slice CTPA
8	Challen, 2011[365]	Irrelevant study—Scoping Review
9	Crawford, 2016[366]	Irrelevant Outcome—reported on primary study (n=4) basis. D-dimer cut-offs were unconventional and varied from study to study
10	Da Costa Rodrigues, 2016[33]	Irrelevant Intervention—Data on CUS alone
11	Douketis, 2011[367]	Irrelevant population—Patients with recurrent PE
12	Emerg Med J 2011[368]	Other—Abstract with insufficient information
13	Geersing, 2009[29]	Other—Out of study selection date range
14	Graham, 2013[369]	Other—Prognosis of PE in HIV
15	Hallifax 2015[370]	Irrelevant population—Not suspected PE patients
16	Hendriksen, 2015[371]	Other—Validation study of all diagnostic prediction models
17	J of Thromb 2013[372]	Other—A corrigendum to an excluded study
18	Klok, 2008[373]	Irrelevant intervention—BNP
19	Kohn, 2015[374]	Irrelevant Outcome—All-cause mortality in early post-acute PE
20	Manara, 2013[375]	Irrelevant intervention—Data on capnography alone
21	Mos, 2009[376]	Irrelevant outcome—Not specifically associated with CPRs
22	Mos, 2014[377]	Irrelevant population—Suspected recurrent PE patients
23	Pasha, 2010[19]	Other—Out of study selection date range
24	Ouatu, 2014[378]	Other—Narrative review
25	Pulivarthi, 2014[379]	Other—Narrative review
26	Raymakers, 2014[227]	Irrelevant outcome—Cost-effectiveness
27	Rehnberg, 2014[380]	Other—Insufficient information for appraisal
28	Schouten, 2013[381]	Other—Findings are not adequately specific to CPRs. Study is not specifically for PE
29	Self, 2012[382]	Other—Editor's note and discussion points on study/insufficient info
30	Self, 2012[383]	Other—Summary of finding of meta-analysis of PERC alone
31	Sharma, 2012[384]	Irrelevant intervention—Thromboprophylaxis
32	Singh, 2012[385]	Irrelevant intervention—Sole focus on PERC
33	Singh, 2014[249]	Irrelevant intervention—Sole focus on PERC
34	Squizzato 2012[386]	Irrelevant population—Not suspected PE patients
35	Stevens, 2012[387]	Other—Summary of findings of and commentary on already included study
36	Tafur 2014[388]	Irrelevant population—Not suspected PE patients
37	Van der Pol, 2016[35]	Other—Only one primary studies with some relevant outcomes
38	van Es 2016[389]	Other—Abstract with insufficient information
39	van Es 2016[104]	Duplicate of already included study

	Author, Year	Reasons for Exclusion
40	Van Es, 2017[390]	Other—Post-hoc analysis of data from already included study.
41	van Leent, 2015[391]	Other—Cost effectiveness of Dabigatran vs. Vit K
42	Wessler, 2015[392]	Other—Non-specific intervention and PE outcomes
43	Witt 2011[393]	Other—Commentary
44	Zhou, 2012 [394]	Irrelevant intervention—PESI to evaluate prognosis of PE

Questions 2 and 3: Primary studies

	Author, Year	Reasons for Exclusion
1.	Abujideh, 2009[395]	Other—Evaluation of CTPA reporting
2.	Adams, 2014[358]	Other—Summary of another article by unnamed authors, and without a specified PTP
3.	Akgul 2013[359]	Other—Narrative article
4.	Albrizio, 2007[396]	Irrelevant interventions—CDST, pre-test probability
5.	Alhadad 2012[397]	Not suspected PE patients/irrelevant outcomes
6.	Alhassan, 2016[331]	Irrelevant outcomes
7.	Ann Int Med 2015[398]	Other—Guideline summary
8.	Ann-In med, 2010[399]	Other—Summary for patients
9.	Arnason 2007[400]	Irrelevant intervention—Non SR study for CDR
10.	Astani, 2014[401]	The focus is on radiation doses not diagnostic ability
11.	Ayaram, 2013[360]	Insufficient numbers of patients with PE
12.	Bajc, 2012[402]	Other—Narrative review
13.	Baliga 2008[403]	Other—Insufficient data for analysis
14.	Bannas 2014[404]	Identification of signal drops that were due to truncation artifacts, not PE
15.	Barnes, 2016[361]	Other—Not focused on diagnostic strategy
16.	Bates 2016[405]	Irrelevant study
17.	Becattini, 2012[362]	Other—Focused on D-dimer levels and mortality
18.	Bejic, 2015[406]	Post-diagnosis imaging
19.	Blackmore, 2012[407]	Irrelevant outcomes
20.	Blum, 1994[408]	Irrelevant intervention—Single detector CT
21.	Boldt, 2013[409]	Irrelevant outcomes
22.	Bova, 2003[410]	Irrelevant intervention—Ancillary tests for PE
23.	Brader, 2008[411]	Irrelevant intervention—Paddlewheel reformations
24.	Branch, 2013[412]	CT sensitivity to detect obstructive CAD in ACS patients
25.	Carrier, 2010[364]	Irrelevant interventions—Single detector CT Single vs. multi-slice CTPA
26.	Cereser, 2011[413]	Irrelevant Comparator—None
27.	Challen, 2011[365]	Other—Scoping Review
28.	Christiansen, 1997[414]	Other—Thesis with unclear comparators
29.	Callejas, 2014[415]	Not suspected PE patients, unclear outcome (VTE) reporting
30.	Corrigan, 2015[361]	Other—Narrative review
31.	Cueto, 2002[416]	Inappropriate study design (SR)
32.	Da Costa Rodrigues, 2016[33]	Irrelevant Intervention—CUS as standalone strategy
33.	Darze, 2012[417]	NPV of re-current VTE
34.	Douketis, 2011[367]	Recurrent PE
35.	Douma, 2010[418]	Comparison of 4-slices and 64-slices MCTA devices
36.	Douma, 2010[419]	Inappropriate study design (Comparison of different modalities within the same diagnostic strategy I.e. 4-slice vs. 64-slice)

	Author, Year	Reasons for Exclusion
37.	Drucker, 1998[420]	Irrelevant intervention—Single detector CT
38.	Duralde, 2012[421]	Arthroscopic Transtendinous Repair
39.	Easther, 2016[422]	Other—Guideline
40.	Elias, 2005[423]	Irrelevant comparator
41.	Emerg Med J 2011[368]	Other—Abstract with insufficient data
42.	Emet, 2007[424]	Irrelevant Comparator—None
43.	Engelke 2006[425]	Patients with unsuspected PE
44.	Ersoy, 2007[426]	Image quality of MRA scans. Incomplete comparison of MRA to CTA
45.	Fabia Vallis, 2015[427]	Study in patients with a history of VTE, thus recurrence DVT/PE
46.	Fabia Vallis, 2015[427] suppl	Other—Supplemental with not additional relevant data or information
47.	Feragalli 2012[428]	Research question was not about technology/device but scanning of additional body parts
48.	Ferreira, 2016[429]	Study in patients already diagnosed as not having PE
49.	Ferretti, 1997[430]	Irrelevant intervention—Single detector CT
50.	Flaveli, 2014[431]	Incidental diagnoses of PE
51.	Friera, 2004[432]	Irrelevant intervention—Single detector CT
52.	Garg 2008[433]	Unsure of suspected PE; irrelevant outcome; and insufficient details
53.	Garg, 1998[434]	Irrelevant intervention—Single detector CT
54.	Garg, 1999[435]	Irrelevant intervention—Single detector CT
55.	Ghazvinian, 2016[436]	Study in patients already diagnosed with small PE
56.	Glaser, 2011[437]	Interpretation and reporting strategy for V/Q lung scan
57.	Gleeson, 2006[438]	Irrelevant study design—Comparison of V/Q to Q alone in selected patients
58.	Goldhaber, 2010[65]	Other—Abstract and commentary
59.	Goodman, 1995[439]	Irrelevant intervention—Single detector CT
60.	Goodman, 1995[440]	Irrelevant intervention—Single detector CT
61.	Graham, 2013[369]	Prognosis in HIV
62.	Grimm, 2013[441]	Utility of the ventilation phase when the perfusion phase is defective
63.	Gruettner, 2013[442]	Irrelevant P and I
64.	Gruettner, 2013[443]	Irrelevant intervention—An in-house algorithm for diagnosis of PE
65.	Gupta, 2014[134]	Study of integrity of data entry
66.	Hallifax 2015[370]	Not suspected PE patients
67.	Hansch, 2011[444]	A feasibility study in patients with no clinical signs of PE (i.e. unsuspected PE)
68.	Hata 2006N[445]	Uncertain if patients were suspected of PE
69.	Hayes, 2014[446]	Irrelevant design—Evaluation of the clinical outcome and management of oncology patients who had a limited CTPA
70.	Hendriksen, 2015[371]	Irrelevant study design—Validation study of CDRs
71.	Hirsch 2006[447]	Other—Abstract with insufficient data
72.	Hochuli, 2007[448]	Irrelevant outcome—Clot burden
73.	Hofman, 2011[449]	Irrelevant Intervention—^{68}GaPET/CT V/Q
74.	Holmquist, 2009[450]	Irrelevant Outcome—Contrast medium dose
75.	Hou, 2013[451]	Irrelevant Outcome—Image quality and radiation dose
76.	Howarth 2006[452]	Irrelevant design—Determination of optimal diagnostic cut-off point
77.	Hsiao, 2007[453]	Irrelevant intervention
78.	Hunsaker, 2008[454]	Irrelevant Outcome—The incremental value of CT-Venography
79.	Hussein 2008[455]	Other—Letter
80.	Ingrisch, 2016[456]	Already confirmed PE patients and healthy control
81.	Inonu, 2012[457]	Irrelevant Outcome—CT obstructive index ratio
82.	Ishiyama, 2011[170]	Irrelevant intervention—3-D T2-weighted imaging using the dark blood method

	Author, Year	Reasons for Exclusion
83.	J of Thromb 2013[372]	Other—Corrigendum to an already excluded study
84.	Jia, 2012[458]	Patients without or unsuspected of having PE
85.	Jogi, 2010[459]	Irrelevant intervention—Radio-aerosols in V/Q
86.	Jogi, 2015[460]	In appropriate population—COPD
87.	Jones, 2008[461]	In appropriate population—Diagnosis of DVT in patients without PE
88.	Jordan, 2015[462]	In appropriate population—Unclear if patients had suspected PE.
89.	Junger 2006[463]	Irrelevant outcome— Not specific to suspected PE patients. I
90.	Kado, 2016[464]	Irrelevant Outcome- Incidence of PE in Lupus patients
91.	Kamel 2008[465]	Not suspected PE patients. Irrelevant outcomes – ventricular dysfunction
92.	Kaul 2014[466]	Irrelevant intervention/Outcome—Software assisted imaging/Image quality
93.	Kiley 2007[467]	Information not specific to suspected PE patients. Irrelevant outcome
94.	Kim, 2008[468]	Not suspected PE patients
95.	Kim, 2016[159]	Irrelevant PICO
96.	Kindermann, 2014[469]	Irrelevant Outcome—Evaluation of the variation in utilization and diagnostic yield of imaging in hospitals
97.	King-Im, 2008[470]	Irrelevant outcome—Subjectively determined test quality
98.	Kligerman, 2015[471]	Irrelevant Design—A retrospective reconstruction study
99.	Kline, 2004[472]	Irrelevant Intervention—Non-SR CDR
100.	Kline, 2014[193]	Inappropriate intervention—CDST, CDR
101.	Klok, 2008[373]	Irrelevant intervention—BNP
102.	Kluge, 2004[473]	Irrelevant design—Comparative MRI
103.	Koch, 2016[474]	Irrelevant Design—Impact study
104.	Kohn, 2015[374]	Inappropriate population—Early post-acute PE all-cause mortality
105.	Konstantinides 2014[475]	Other—Guideline summary
106.	Kooiman, 2010[476]	Irrelevant Outcome—Incidence of contrast-induced AEs
107.	Korkeila, 2006[477]	Inappropriate population—Not suspected PE patient
108.	Krestan, 2004[478]	Irrelevant intervention—Single detector CT
109.	Krishan, 2011[479]	Not suspected PE patients at baseline
110.	Kroschel, 1991[480]	Other—Language, German
111.	Kumamaru 2016[171]	Inappropriate population—Uncertain if suspected of PE patients
112.	Kwon, 2007[481]	Irrelevant study
113.	Lang, 2013[482]	Irrelevant outcome
114.	Lapergue 2015[483]	Inappropriate population—Not suspected PE patients.
115.	Le Roux 2011[484]	Other—Language, French
116.	Le Roux, 2012[485]	Duplicate patient data
117.	Le Roux, 2013[55]	Criteria for interpretations of outcomes
118.	Le Roux, 2015[174]	Irrelevant Outcome—Software aided outcomes
119.	Le Roux, 2015[486]	Inappropriate population—Confirm idiopathic VTE patients
120.	Le Roux, 2012[485]	Duplicate patients
121.	Lee, 2013[487]	Irrelevant outcome—Tumor thrombus
122.	Lemb, 2001[488]	Inappropriate study design—A single cohort, with part reassessed with the same V/P-SPECT test 22 months later
123.	Lessler, 2010[489]	Irrelevant outcome
124.	Lim, 2014[490]	Inappropriate population—Not suspected PE
125.	Lombard, 2003[491]	Irrelevant intervention—Single detector CT
126.	Lomis, 1999[492]	Irrelevant intervention—Single detector CT
127.	Lu, 2014[119]	Comparison of contrast dose and radiation intensity in CT
128.	Lucassen, 2013[71]	Comparison of diagnosis made by local radiologist versus experts

	Author, Year	Reasons for Exclusion
129.	Macdonald, 2005[493]	Irrelevant intervention—Single detector CT
130.	Manara, 2013[375]	Irrelevant intervention—Capnography as standalone strategy
131.	Mao, 2016[494]	Irrelevant Intervention—PED software of dual-source CT combined with perfusion imaging
132.	Mathis, 1990[495]	Other—Language, Germany
133.	Mathis, 1999[496]	Irrelevant comparator—Single detector CT
134.	Mathis, 2005[497]	Irrelevant intervention—Single detector CT, TUS_DTA
135.	Meinel, 2015[498]	Irrelevant Outcome—Predictive value of CT in prognosis of PE
136.	Meysman, 2015[499]	Inappropriate Population—Not suspected PE patients
137.	Miniati, 2001[500]	Inappropriate intervention—Echocardiography
138.	Minshall, 2015[501]	Inappropriate Population—Not suspected PE patients
139.	Moon 2010[502]	Other—Abstract with insufficient data
140.	Morales-Borrero, 2016[503]	Irrelevant Outcome—None
141.	Morris 2011[504]	Not suspected PE patients
142.	Morris, 2011[505]	Irrelevant intervention
143.	Mortensen, 2014[506]	Other—A narrative review
144.	Mos, 2014[377]	Inappropriate Population—Recurrent PE patients
145.	Muangman, 2012[507]	Irrelevant Outcome—Cost-effectiveness study
146.	Musset, 2002[508]	Irrelevant Design—Pathway_CT_LUS_CPR_failure rate
147.	Nazaroglu, 2009[509]	Irrelevant outcome—Diagnostic quality
148.	Nobre, 2014[510]	Other—Letter
149.	Ouatu, 2014[378]	Other—Narrative review
150.	Palla, 2014[511]	Other—Narrative review
151.	Perrier, 1999[512]	Inappropriate population—VTE, not suspected PE Patients
152.	Perrier, 2004[513]	Irrelevant intervention—Single and multi-detector CT mix)
153.	Precious, 2014[514]	Other—Narrative review
154.	Prevedello, 2013[515]	Irrelevant Intervention—CDST
155.	Pulivarthi, 2014[379]	Other—Narrative review
156.	Quinn, 1994[516]	Irrelevant intervention—D-dimer testing
157.	Quiroz, 2005[517]	Irrelevant Design—SR
158.	Raja, 2012[518]	Irrelevant intervention—CDST
159.	Ranji, 2006[519]	Irrelevant Outcome—None
160.	Raymakers, 2014[227]	Irrelevant Outcome—Cost effectiveness
161.	Reagle, 2012[520]	Inappropriate population—Unspecified if suspected PE patients
162.	Rehnberg, 2014[380]	Other—Abstract with insufficient data
163.	Reichelt, 2009[521]	Inappropriate Population—CTEPH patients
164.	Reinartz, 2006[186]	Irrelevant intervention—Automation of detection of mismatch defects
165.	Remy-jardin, 1992[522]	Irrelevant intervention—Single detector CT
166.	Remy-jardin, 1996[440]	Irrelevant intervention—Single detector CT
167.	Remy-jardin, 2002[523]	Irrelevant intervention—Single detector CT
168.	Rhavar 2012[59]	Irrelevant study
169.	Rhee, 2007[212]	Irrelevant Outcome—Non-specific VTE outcomes
170.	Richard 2015[524]	Other—Language, French
171.	Ritchie, 2007[525]	Inappropriate Population—Not suspected PE patients
172.	Rodger 2006[526]	Irrelevant Intervention—Non-ELISA test, and alveolar dead-space fraction
173.	Rubins, 2008[527]	Other—Narrative review
174.	Ruiz, 2003[528]	Irrelevant Intervention—Single detector CT

	Author, Year	Reasons for Exclusion
175.	Sakuma 2006[529]	Irrelevant study
176.	Salaun, 2008[530]	Irrelevant objective
177.	Sampson, 2007[531]	Irrelevant Outcomes—DVT outcomes only
178.	Sangwaiya, 2010[532]	Irrelevant outcome—Image quality and diagnostic confidence
179.	Sasbou 2013[533]	Other—Language, French
180.	Sawyer, 2015[534]	Other—Nonspecific
181.	Schiebler, 2016[535]	Irrelevant Outcomes—Actionable, non-actionable, and normal outcomes
182.	Schonfeld, 2015[536]	Inappropriate Population—Chronic PE patients
183.	Schouten, 2013[381]	Irrelevant Outcome—Unclear contribution of interventions to reported findings
184.	Scialpi, 2016[537]	Irrelevant outcome—Image quality and occurrence and severity of artifact
185.	Scott, 2011[538]	Irrelevant Outcome—Utilization of imaging in one institution
186.	Self, 2012[382]	Other—Editor's note and discussion points
187.	Self, 2012[383]	Other—Summary of finding of meta-analysis of PERC alone
188.	Sellem 2013[539]	Other—Language, French
189.	Serra 2016[540]	Inappropriate Population—Not suspected PE patients
190.	Shahir 2013[541]	Inappropriate Population—Not suspected PE patients
191.	Shao, 2012[542]	Inappropriate Population—Already confirmed PE patients
192.	Shapiro, 2009[543]	Irrelevant Outcome—Image quality
193.	Sharma, 2012[384]	Irrelevant Intervention—Thromboprophylaxis
194.	Shen, 2012[56]	Irrelevant outcomes
195.	Silva, 2013[544]	Inappropriate Population—Not suspected PE
196.	Sinzinger 2015[545]	Other—Letter
197.	Slater, 2012[546]	Irrelevant outcome—Not PE specific
198.	Soo hoo, 2011[547]	Irrelevant intervention—Non-SR CDR plus D-Dimer test
199.	Sostman, 2008[180]	Duplicate patient data
200.	Sostman, 1996[548]	Irrelevant intervention—Single detector CT
201.	Squizzato 2012[386]	Inappropriate Population—Not suspected PE patients
202.	Stawicki 2008[411]	Inappropriate Population—Not suspected PE patients
203.	Stein, 1992[181]	Duplicate patient data
204.	Stein, 2006[549]	Irrelevant outcome—Recommendations for diagnostic approach
205.	Stein, 2008[550]	Other—Protocol
206.	Steiner, 1994[551]	Other—Language, German
207.	Stevens, 2012[387]	Other—Commentary on already included study
208.	Stone, 2003[552]	Irrelevant Intervention—Single detector CT
209.	Su, 2015[553]	Irrelevant outcomes
210.	Subedi, 2009[554]	Other—Insufficient information for appraisal
211.	Subramaniam, 2006[555]	Irrelevant intervention—Single detector CT
212.	Sun, 2014[556]	Inappropriate design—A case study
213.	Swensen, 2002[557]	Irrelevant intervention—Single detector CT
214.	Szucs-Farkas, 2009[558]	Irrelevant Outcome—Lower radiation intensity and contrast dose
215.	Szucs-Farkas, 2014[559]	Irrelevant Outcome—Lower radiation intensity and contrast dose
216.	Tafur 2014[388]	Inappropriate Population—Not suspected PE patients
217.	Takagi, 2006[560]	Other—Letter
218.	Takahashi, 2013[561]	Irrelevant outcomes
219.	Tarr 2015[562]	Other—Letter
220.	Thomeer, 2006[563]	Other—Letter
221.	Tiseo, 2012[564]	Irrelevant study

	Author, Year	Reasons for Exclusion
222.	Tresoldi, 2008[565]	Irrelevant Outcome—The incidence of PE and other thoracic findings
223.	Tunariu, 2007[566]	Inappropriate Population—Chronic PE patients
224.	Turkstra, 1997[567]	Irrelevant intervention—Ultrasonography of leg veins
225.	Van Belle, 2006[568]	Other—Identical to Perrier 2000[569]
226.	van Es 2016[389]	Other—Abstract with insufficient data
227.	van Es 2016[104]	Other—Duplicate of Ref id [104]
228.	van Leent, 2015[391]	Irrelevant Intervention/Outcome—Pharmacotherapy/ Cost-effectiveness
229.	van Rossum, 1996[570]	Irrelevant intervention—Single detector CT
230.	Viau 2011[571]	Other—language, French
231.	Vongchaiudomchoke 2016[572]	Irrelevant outcome—Prevalence of PE by pulmonary CTA
232.	Watanabe, 2015[160]	Irrelevant study—Assessment of PISAPED Criteria
233.	Wessler, 2015[392]	Irrelevant Intervention/Outcome—No specific relevant intervention; no specific PE outcomes
234.	Witt 2011[393]	Other—Commentary
235.	Wu, 2014[573]	Inappropriate Population—Not suspected PE patients
236.	Wu, 2012[574]	Irrelevant study—Correlation of the distribution of iodine-based material in the lung parenchyma to CTPA findings
237.	Yasui 2007[575]	Irrelevant outcome—Diagnostic accuracy/utility outcomes are different from what has been defined for this OU review
238.	Zhou, 2012 [394]	Irrelevant Intervention—PESI
239.	Zhu, 2008[576]	Irrelevant intervention and outcome

Appendix 11: Quality Assessment Questions for Clinical Review

Quality Assessment of Diagnostic Accuracy Studies (QUADAS) II

DOMAIN 1	PATIENT SELECTION (Could the selection of patients have introduced bias)
Signalling Q1	Was a consecutive or random sample of patients enrolled?
Signalling Q2	Was a case-control design avoided?
Signalling Q3	Did the study avoid inappropriate exclusions?
Applicability	Are there concerns that the included patients and setting do not match the review question?
DOMAIN 2	INDEX TEST (could the conduct or interpretation of the index test have introduced bias)
Signalling Q1	Were the index test results interpreted without knowledge of the results of the reference standard?
Signalling Q2	If a threshold was used, was it prespecified?
Applicability	Are there concerns that the index test, its conduct, or its interpretation differ from the review question?
DOMAIN 3	REFERENCE STANDARD (could the reference standard, its conduct, or interpretation have introduced bias)
Signalling Q1	Is the reference standard likely to correctly classify the target condition?
Signalling Q2	Were the reference standard results interpreted without knowledge of the results of the index test?
Applicability	Are there concerns that the target condition as defined by the reference standard does not match the question?
DOMAIN 4	FLOW AND TIMING (could the patient flow have introduced bias)
Signalling Q1	Was there an appropriate interval between the index test and reference standard?
Signalling Q2	Did all patients receive the same reference standard?
Signalling Q3	Were all patients included in the analysis

ROBIS

1. Domain 1: study eligibility criteria
   - 1.1 Did the review adhere to pre-defined objectives eligibility criteria?
   - 1.2 Were the eligibility criteria appropriate for the review questions?
   - 1.3 Were eligibility criteria unambiguous?
   - 1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g.. date, study design, sample size, study quality, outcomes measured)?
   - 1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g., publication status or format, language, availability of data)?
2. Domain 2: identification and selection of studies
   - 2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?
   - 2.2 Were methods additional to database searching used to identify relevant methods?
   - 2.3 Were the terms and structure of the search strategy likely to retreive as many eligibility studies as possible?
   - 2.4 Were restrictions based on date, publication format, or language appropriate?
   - 2.5 Were efforts made to minimise error in selection of studies?
3. Domain 3: data collection and study appraisal
   - 3.1 Were efforts made to minimise error in data collection?
   - 3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?

3.3 Were all relevant study results collected for use in the synthesis?

3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?

3.5 Were efforts made to minimise error in risk of bias assessment?

Domain 4: synthesis and findings

4.1 Did the synthesis include all studies that it should?

4.2 Were all pre-defined analyses reported or departures explained?

4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?

4.4 Was between-study variation (heterogeneity) minimal or addressed in the synthesis?

4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?

4.6 Were biases in primary studies minimal or addressed in the synsthesis?

Cochrane Risk of Bias

1. Sequence generation: was the allocation sequence adequately generated?
2. Allocation concealment: was the sequence generation adequately concealed before group assignments?
3. Blinding of participants and personnel: was knowledge of the allocated interventions adequately hidden from the participants and personnel after participants were assigned to respective groups?
4. Blinding of outcome assessment: was knowledge of the allocated interventions adequately hidden from the outcome assessors after participants were assigned to respective groups?
5. Incomplete outcome data: were incomplete outcome data adequately addressed?
6. Selective outcome reporting: are reports of the study free of suggestion of selective outcome reporting?
7. Other potential threats to validity: was the study apparently free of other problems that could put it at a risk of bias?

ROBINS-I

BIAS DUE TO CONFOUNDING

1.1 Is there potential for confounding of the effect of intervention in this study

1.2 Was the analysis based on splitting participants' follow up time according to the intervention received?

1.3 Did the study avoid inappropriate exclusions?

Questions related to baseline confounding only

1.4 Did the authors use an appropriate analysis method that controlled for all of the important confounding domains

1.5 If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?

1.6 Did the authors control for any post- intervention variables that could have been affected by the intervention?

Questions related to baseline and time-varying confounding

1.7 Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?

1.8 If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?

Risk of bias judgement;

Answer: (low/moderate/serious/critical/NI);

Favours experimental, favours comparator, unpredictable

What is the predicted direction of bias due to confounding?

BIAS in SELECTION OF PARTICIPANTS INTO THE STUDY (or analysis)

2.1 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?

2.2 If Y/PY to 2.1: Were the post- intervention variables that influenced selection likely to be associated with intervention?
2.3 If Y/PY to 2.2: Were the postintervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?
2.4 Do start of follow-up and start of intervention coincide for most participants?
2.5 If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?

Risk of bias judgement;
Answer: (low/moderate/serious/critical/NI);
Favours experimental, favours comparator, unpredictable
Optional: What is the predicted direction of bias due to selection of participants into the study?

BIAS in CLASSIFICATION OF INTERVENTIONS

3.1 Were intervention groups clearly defined?
3.2 Was the information used to define intervention groups recorded at the start of the intervention?
3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?

Risk of bias judgement;
Answer: (low/moderate/serious/critical/NI);
Favours experimental, favours comparator, unpredictable
Optional: What is the predicted direction of bias due to measurement of outcomes or interventions?

BIAS DUE TO DEVIATIONS FROM INTENDED INTERVENTIONS

If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2

4.1 Were there deviations from the intended intervention beyond what would be expected in usual practice?
4.2 If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?

If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6

4.3 Were important co-interventions balanced across intervention groups?
4.4 Was the intervention implemented successfully for most participants?
4.5 Did study participants adhere to the assigned intervention regimen?
4.6 If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?

Risk of bias judgement;
Answer: (low/moderate/serious/critical/NI);
Favours experimental, favours comparator, unpredictable
Optional: What is the predicted direction of bias due to measurement of outcomes or interventions?

BIAS DUE TO MISSING DATA

5.1 Were outcome data available for all, or nearly all, participants?
5.2 Were participants excluded due to missing data on intervention status?
5.3 Were participants excluded due to missing data on other variables needed for the analysis?
5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?
5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?

Risk of bias judgement;
Answer: (low/moderate/serious/critical/NI);
Favours experimental, favours comparator, unpredictable
Optional: What is the predicted direction of bias due to measurement of outcomes or interventions?

BIAS in MEASUREMENT OF OUTCOMES

6.1 Could the outcome measure have been influenced by knowledge of the intervention received?
6.2 Were outcome assessors aware of the intervention received by study participants?
6.3 Were the methods of outcome assessment comparable across intervention groups?

6.4 Were any systematic errors in measurement of the outcome related to intervention received?
Risk of bias judgement;
Answer: (low/moderate/serious/critical/NI);
Favours experimental, favours comparator, unpredictable
Optional: What is the predicted direction of bias due to measurement of outcomes or interventions?

BIAS in SELECTION OF THE REPORTED RESULT

Is the reported effect estimate likely to be selected on the basis of the results from…

7.1 multiple outcome measurements within the outcome domain?
7.2 multiple analyses of the intervention-outcome relationship?
7.3 different subgroups?
Risk of bias judgement;
Answer: (low/moderate/serious/critical/NI);
Favours experimental, favours comparator, unpredictable
Optional: What is the predicted direction of bias due to measurement of outcomes or interventions?

OVERALL BIAS

Risk of bias judgement;
Answer: (low/moderate/serious/critical/NI);
Favours experimental, favours comparator, towards null, away from null, unpredictable
What is the OVERALL predicted direction of bias for this outcome?

Appendix 12: Characteristics of Included Systematic Reviews for Clinical Review of Risk Stratification (Question 1)

First Author, Publication year, Country	Study Design	Number and types of Primary Studies	Search strategy	Publication Date range of Primary Studies	Quality measure	Participants	Intervention	Reference standard	Outcome
Wang, 2016[25] USA	Systematic review and meta-analysis	One RCT and 7 prospective cohort studies	MEDLINE, EMBASE, and the Cochrane Library. Bibliographies of identified studies were reviewed. Topic experts were consulted to identify additional studies	2004 to 2014	The Cochrane Group Effective Practice and Organization of Care instrument	6,677 patients with suspected PE. The ages of included patients were not specified. Five primary studies were conducted in EDs, while three included outpatients and inpatients from multiple departments at a single institution	CPR–based diagnostic strategies for pulmonary (CT + Wells/Charlotte/PERC ± D-Dimer)	For the RCT, the control was usual care. The remaining were before-and-after studies	CT use and yield, and failure rate of risk stratification strategy
Shen, 2016[24] China	Systematic review and meta-analysis	12 prospective and retrospective cohorts studies	PubMed, Web of Science, and a search of reference lists, and conference proceedings	2002 to 2015	QUADAS	3,613 Patients with suspected PE. The mean age of included patients ranged from 47 to 76.1 years. The settings of the primary studies were not reported	3-Level Wells and 3-Level Geneva Scores	CTPA; composite of angiography CT and VQ; VQ; DSPA; VQ or PA	Sensitivity, Specificity, and Prevalence.
van Es, 2016[104] The Netherlands	Systematic review and meta-analysis	6 prospective cohort studies	MEDLINE, EMBASE	2006 to 2014	QUADAS-II	7,268 patients with suspected acute PE The mean age of included patients was 56 years; 42% were men. They were inpatient or ED	Wells Rule + Subsequent D-Dimer Testing (500 µg/L threshold, quantitative latex-based assay or enzyme-linked immunosorbent assay); D-dimer alone (secondary analysis) Simplified or original	N/A. Patients were re-evaluated for PE 3 months after the initial tests	Diagnostic efficiency; failure rate, and risk factor assessment

First Author, Publication year, Country	Study Design	Number and types of Primary Studies	Search strategy	Publication Date range of Primary Studies	Quality measure	Participants	Intervention	Reference standard	Outcome
						patients at secondary care settings.	Wells + age-adjusted D-dimer		
Lucassen, 2011[26] The Netherlands	Systematic review and meta-analysis	52 prospective cohort studies	MEDLINE, EMBASE, and search of the reference lists of selected articles	1996 to 2011	QUADAS	55,268 patients with suspected acute PE. The mean age of included patients ranged from 45 to 72 years. All of the primary studies were performed in a hospital setting and included ED patients, referred patients, or inpatients.	CPR (Wells, Geneva, and Gestalt) ± D-dimer	VQ, CT, PA, or autopsy, diagnosis of DVT as surrogate for diagnosis of PE	Sensitivity, specificity, failure rate, and efficiency
Siccama, 2011[103] The Netherlands	Systematic review	9 studies, four of which involved suspected PE patients. Details of the designs of primary studies were not specified	MEDLINE, EMBASE, a search of the reference lists of selected articles, and hand searching of all key journals. Experts were consulted for additional relevant publications	2004 to 2007 (PE studies only)	QUADAS	6.739 patients with suspected PE, who were inpatients or outpatients. The mean age of included patients was not clearly specified.	CPR (Wells, Geneva, Revised Geneva)	PA, VQ scanning (50% had either inadequate or unclear reference standards)	Sensitivity, specificity, failure rate,[a] and efficiency.
Sanders, 2015[105] Australia	Systematic review	31 studies in all, with 9 in suspected PE patients. Details of study design were not specified	MEDLINE, EMBASE, and CINAHL. Also searched for systematic reviews of diagnostic CPRs using PubMed	2000 to 2013	QUADAS-2	22,366 patients with suspected acute PE. The ages of included patients were not reported. The primary studies on PE were	CPR (Wells rule, or Geneva score) clinical judgment (gestalt)	CPR alone or in combination with gestalt	Sensitivity, specificity, proportion of TR, TF, FP, FN

First Author, Publication year, Country	Study Design	Number and types of Primary Studies	Search strategy	Publication Date range of Primary Studies	Quality measure	Participants	Intervention	Reference standard	Outcome
			Clinical Queries			performed in a hospital setting and included ED patients, outpatients, or inpatients.			

AUC = area under the receiver operating characteristic (ROC) curve, CI = confidence interval; CPR= clinical prediction rule, CT = computed tomography, DVT = deep vein thrombosis, ED emergency department, FN = false negative, FP = false positive, ISTH = International Society on Thrombosis and Haemostasis, MOOSE = Meta-analysis Of Observational Studies in Epidemiology, PA = pulmonary angiography, PE = pulmonary embolism, RCT = randomized controlled trial, TN = true negative, TP = true positive, VQ = ventilation perfusion scintigraphy.

Appendix 13: Diagnostic Accuracy Outcomes Reported by Included Systematic Review (Question 1)

Author	Diagnostic Strategy	Interpretation Criteria	Sensitivity, % (95% CI)	Specificity % (95% CI)	AUC (95% CI; p-value)
Shen, 2016[24 a]	3-level Wells rule	(Low – Score <2 Medium–score 2–6 High–score >6	63.8 to 79.3	48.8 to 90.0	**0.778 (0.740–0.818; <0.001)**
	3-level R-Geneva score	Low – Score <4 Medium–score 4–10 High–score >10	55.3 to 73.6	51.2 to 89	**0.693 (0.653–0.736; <0.001**
Sanders, 2015[105]	Dichotomized CPRs (Wells rule, Geneva score, and R-Geneva score) and Gestalt (with or without SDC),	**Wells <2** vs. **Geneva ≤4 vs.** Gestalt + **Geneva**	**73 (61–83)** vs. **72 (60–82) vs.** 89 (79–95)	**69 (63–76)** vs **64 (57–71) vs.** 67 (60–73)	NR
		Wells <2 vs. R-Geneva <4 vs. Gestalt + SDC	**82 (77–85)** vs. 89 (85–92) vs. 90 (86–93)	**60 (56–63) vs**. 33 (30–37) vs. 58 (54–61)	
		Wells <2 vs. Wells ≤4 vs. Gestalt + SDC [b]	**66 (57–75) to 95 (87–99)** vs. 83 (73–91) to 83 (73–91) vs. 54 (41–67) to 91 (85–96)	**57 (53–61) to 19 (15–24)** vs. 41 (35–46) to 78 (74–81) vs. 76 (73–80) to 16 (12–21)	
		Wells<2 vs. Gestalt + SDC vs. Charlotte	**62 (54–70)** vs. 69 (61–76) vs. 36 (28–45)	**75 (73–77)** vs. 72 (70–74) vs. 89 (88–91)	
		Wells <2 vs. Gestalt	**68 (64–72) vs.** 69 (65–73)	**72 (71–73)** 70 (69–71)	
		R-Geneva ≤4 + PERC vs. PERC alone vs Gestalt + SDC	99 (97–99.6) vs. 99 (97–99.6) vs 91 (87–94)	9 (7–12) vs. 10 (8–13) vs. 55 (52–59)	
Lucassen, 2011[26]	Dichotomized CPRs (Wells rule, Geneva score, and R-Geneva score).	**Wells <2**	**84 (78–89)**	**58 (52–65)**	
		Wells ≤4	60 (49–69)	80 (75–84)	
		Geneva (cut-off not clear)	**84 (81–87)**	**50 (29–72)**	
		R-Geneva <4	91 (73–98)	37 (22–55)	

Author	Diagnostic Strategy	Interpretation Criteria	Sensitivity, % (95% CI)	Specificity % (95% CI)	AUC (95% CI; p-value)
Siccama, 2011[103]	Wells rule [c]	<65 years	100 (NR)	50 (NR)	
		65 to 75 years	100 (NR)	31 (NR)	
		>75 years	100 (NR)	22 (NR)	

AUC = area under the receiver operating characteristic (ROC) curve, CI = confidence interval, CPR= clinical prediction rule, NR = not reported, SDC = structured data collection, vs. = versus

Appendix 14: Utility Outcomes Reported by Included Systematic Reviews (Question 1)

Summary of findings for utility of CPRs

Author	Diagnostic Strategy	Population Subgroups	Failure rate, % (95% CI)	Efficiency, % (95% CI)	Yield, % (95% CI)
Van Es, 2016[104]	Wells ≤4 plus fixed quantitative D-dimer cut-off (500 µg/L)	Overall	0.65 (0.38–1.11)	28.0 (20.5–37.0)	NR
		≥ 75 years	NE	8.4 (6.3–11.0)	
		51–74 years		22.4 (17.5–28.2)	
		≤ 50years		45.1 (34.9–55.7)	
	Wells ≤4 plus age-adjusted quantitative D-dimer	Overall	0.94 (0.58–1.5)	32.6 (24.6–41.7)	
		≥ 75 years	2.1 (0.71–5.9)	20.3 (15.9–25.5)	
		51–74 years	0.83 (0.15–4.3)	28.0 (20.7–36.5)	
		≤ 50years	0.59 (0.22–1.6)	45.1 (34.7–55.8)	
Wang, 2016[25]	Imaging after CPR (Wells)	NA	0.4 (NR) to 1.2 (NR) [c, d]	NR	12 (11–14)
	Imaging without CPR				9 (6–12)
	Increase in Yield due to Wells				**3.1 (1.4–4.9)**
Sanders, 2015[105]	**Wells <2**		**3.0 (2.3–3.9) to 27.9 (21.3–35.6)**	**17 (13–21) to 73 (70–74)**	NR
	Wells ≤4		5.5 (3.8–8.1) to 8.7 (5.1–14.3)	36 (32–41) to 74 (70–77)	
	Geneva score ≤4		**13.2 (8.7–19.5)**	**55 (49–61)**	
	R-Geneva score <4		13.0 (9.5–17.5)	26 (23–29)	
	R-Geneva score <4 + PERC		6.2 (2.4–14.8)	7 (5–9)	
	Gestalt + Geneva score ≤4		5.5 (2.8–10.4)	53 (47–59)	
	Gestalt +SDC [b]		3.0 (2.6–3.5) to 19.0 (10.9–30.9)	14 (11–18) to 73 (70–77)	
	Gestalt alone		3.1 (2.7– 3.6)	68 (67–69)	
Lucassen, 2011[26]	Wells ≤4 + quantitative D-dimer		0.5 (0.2–0.9)	39 (31–47)	
	Geneva score [c] + quantitative D-dimer		0.0 (0.0–1.3)	21 (14–31)	
	S-Geneva score [c] + quantitative D-dimer		0.3 (0.0–1.7)	23 (15–33)	
	Wells <2 + qualitative D-dimer		0.9 (0.6–1.5)	40 (33–48)	
	Wells ≤4 + qualitative D-dimer		1.7 (1.0–2.8)	42 (32–52)	
	Gestalt (cut-off <15%)		0.7 (0.4–1.2)	52 (40–64)	

CI = confidence interval, CPR = clinical prediction rule, NA = not applicable, NE = not estimated, NR = not reported, R-Geneva = revised Geneva rule, SDC = structured data collection, S-Geneva = simplified Geneva rule

[a] The authors reported outcomes for the overall Wells rule or Geneva scores, not the different probability levels of these CpRs.

[b] The threshold for the gestalt + SDC strategy was different for different comparisons and described variously as "low," "Alternate diagnosis not less likely," <15%; and "<20%".

[c] Neither the probability levels nor cut-off value were specified clearly

[d] Failure rate data were available for one RCT (0.4%) and one before-after study (1.2%), and there was no difference between intervention and control cohorts in either study

Appendix 15: Summary of Quality or Risk of Bias Assessments Conducted by Included Systematic Reviews for Clinical Review (Question 1)

Assessment of the methodological quality of included studies using the ROBIS criteria							
First author, Publication Year		Wang, 2016[25]	Shen, 2016[24]	van Es, 2016[104]	Lucassen, 2011[26]	Siccama, 2011[103]	Sanders, 2015[105]
DOMAIN 1: STUDY ELIGIBILITY CRITERIA							
1.1	Did the review adhere to pre-defined objectives eligibility criteria?	Y	Y	Y	Y	Y	Y
1.2	Were the eligibility criteria appropriate for the review questions?	Y	Y	Y	Y	Y	Y
1.3	Were eligibility criteria unambiguous?	Y	Y	Y	Y	Y	Y
1.4	Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g.. date, study design, sample size, study quality, outcomes measured)?	PY	Y	PY	PY	Y	PY
1.5	Were any restrictions in eligibility criteria based on sources of information appropriate (e.g., publication status or format, language, availability of data)?	Y	Y	PY	PY	PY	PY
DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES							
2.1	Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Y	Y	PY	PY	PY	Y
2.2	Were methods additional to database searching used to identify relevant studies?	Y	Y	PN	Y	Y	Y
2.3	Were the terms and structure of the search strategy likely to retrieve as many eligibility studies as possible?	Y	Y	Y	Y	NI	PY
2.4	Were restrictions based on date, publication format, or language appropriate?	Y	Y	Y	PY	PY	Y
2.5	Were efforts made to minimize error in the selection of studies?	Y	U	Y	Y	NI	PY
DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL							
3.1	Were efforts made to minimize error in data collection?	Y	Y	Y	Y	Y	Y
3.2	Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Y	PY	Y	Y	N	PY
3.3	Were all relevant study results collected for use in the synthesis?	Y	PY	Y	Y	Y	PY

Assessment of the methodological quality of included studies using the ROBIS criteria							
First author, Publication Year		Wang, 2016[25]	Shen, 2016[24]	van Es, 2016[104]	Lucassen, 2011[26]	Siccama, 2011[103]	Sanders, 2015[105]
3.4	Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Y	PY	Y	Y	PY	Y
3.5	Were efforts made to minimize error in risk of bias assessment?	Y	Y	Y	Y	Y	Y
DOMAIN 4: SYNTHESIS AND FINDINGS							
4.1	Did the synthesis include all studies that it should?	Y	Y	Y	PY	PY	PY
4.2	Were all pre-defined analyses reported or departures explained?	PY	PN	PY	Y	Y	y
4.3	Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Y	PN	Y	PY	NA	PY
4.4	Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	Y	PN	Y	Y	NA	PN
4.5	Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Y	PN	PY	Y	N	PY
4.6	Were biases in primary studies minimal or addressed in the synthesis?	PY	PN	PY	PY	N	Y
DOMAIN 5: SELECTED CRITERIA FROM AMSTAR							
5.1	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	N	N	N	N	N	N
5.2	Was a list of included studies provided?	Y	Y	Y	Y	Y	Y
5.3	Was a list of excluded studies provided?	N	N	Y	N	N	N
5.4	Was the conflict of interest included?	Y	Y	Y	Y	N	Y

N = no, NA = not applicable, NI = no information, PN = probably no, PY = probably yes, Y = yes

CADTH

Appendix 16: Characteristics of Included Primary Studies for Clinical Review (Questions 2 and 3)

Studies reporting diagnostic test accuracy, utility, and/or safety are included in these tables. The table is ordered alphabetically by the name of the first author.

Study information	Patients	Index test	Reference test	Outcomes
Abootalebi 2016 [150] **Location:** Iran. Dates: September 2011 to September 2012 **No. centres:** Single; **Type of setting:** Secondary / ER	**No. patients:** 77. Non-Pregnant **Inclusion criteria:** Clinical signs, symptoms and risk factors for PE with moderate to high PE probability (including dyspnea pleuritic, chest pain, hemoptysis, tachypnea, and vertigo or syncope) Wells scoring system (>6 points: High risk; 26 points: Moderate risk; **Exclusion criteria:** Overweight, pregnant.	**Index test class:** US **Interpretation:** PE present: typical triangular or round hypoechoic pleural-based lesion, often wedge-shaped, move with respiration. Pleural effusion (as an indirect sign).	**Reference standard class:** CT. **Reference standard details:** MSCT **Interpretation:** NA	**Primary:** Number of lesions, shape, size and location of lesions **Secondary:** sensitivity, specificity, PPV, NPV and accuracy of ultrasonography **Follow-up:** NA
Anderson 2007 [57] **Location:** Canada; US. Dates: May 2001 to April 2005 **No. centres:** Multi-International; **Type of setting:** Secondary / Tertiary / ER	**No. patients:** 1417. Non-Pregnant **Inclusion criteria:** Symptoms or signs suspicious of acute PE (acute onset of new or worsening shortness of breath, chest pain, hemoptysis, presyncope, or syncope) with or without signs of DVT. **Exclusion criteria:** DVT or PE diagnosed within the previous 3 months, no change in severity of pulmonary symptoms within the previous 2 weeks, use of therapeutic doses of parenteral anticoagulants for >48 hours, comorbid condition making life expectancy	**Index test class:** CT **CT slices:** Single or multi. **Contrast:** Omnipaque 240 contrast (Nykomed Ingenor, Paris, France). For single-detector scans, 150 mL injected of 5 mL/s. For multidectector scans, 100mL at 5 mL/s. **Interpretation:** PE present: intraluminal filling dedefect within a pulmonary arterial vessel. PE absent: no filling defect observed.	**Reference standard class:** VQ. **Reference standard details:** VQ **Interpretation:** VQ: High probability if 1 or more segmental perfusion defect(s) with normal ventilation or 2 or more large subsegmental perfusion defects (75% or more of a segment) with normal ventilation. Normal: no perfusion defects. Nondiagnostic: All other combinations of VQ scan results.	**Primary:** subsequent development of symptomatic PE or proximal DVT in patients in whom PE had initially been excluded **Secondary:** NA **Follow-up:** 3 months
Bajc 2013 [173] **Location:** Sweden. Dates: 1.5 years	**No. patients:** 152. Non-Pregnant **Inclusion criteria:** Clinically suspected PE based on clinical	**Index test class:** Q-SPECT. **Isotope:** V: Inhaled aerosolized 99m-Tc-pertechnetate (Technegas)	**Reference standard class:** CC. **Reference standard details:** Combination of clinical findings,	**Primary:** Failure rate; rate of non-diagnostic tests; specificity; diagnostic accuracy; positive and negative

Study information	Patients	Index test	Reference test	Outcomes
(dates not specified) **No. centres:** Single; **Type of setting:** Secondary	symptoms and ancillary tests. **Exclusion criteria:** NA	or 99m-Tc-DTPA until 30 MBq reached the lung. Q: 120 MBq 99m-Tq-MAA given by IV **VQ Interpretation:** EANM. **Interpretation:** PE present: single or multiple wedge-shaped perfusion defects (EANM criteria); PE absent: No perfusion defects, perfusion defects other than "wedge shaped"	VQ SPECT, 16-detecor CT; multidetector CT, and compression ultrasonography **Interpretation:** VQ SPECT: in accodance with European guidelines (EANM see Definitions); CT: PE present: embolus obstructing a vessel or the outline of an embolus within a vessel	predictive values **Secondary:** NA **Follow-up:** 3 months
Bajc 2008 [184] **Location:** Sweden. Dates: January 2004 to December 2005 **No. centres:** Single; **Type of setting:** Secondary / Tertiary	**No. patients:** 1785. Non-Pregnant **Inclusion criteria:** NA **Exclusion criteria:** NA	**Index test class:** VQ-SPECT. **Isotope:** V; 99mTechnegas or 99mTcDTPA Q: 99mTc-MAA 120 MBq **VQ Interpretation:** Unclear. **Interpretation:** Recognition of patterns typical for PE based upon segmental charts, recognition of patterns of other diseases than PE	**Reference standard class:** FU. **Reference standard details:** Follow up of 6 months **Interpretation:** NA	**Primary:** Sensitivity, specificity **Secondary:** NA **Follow-up:** 6 months
Bajc 2004 [189] **Location:** Sweden. Dates: NA **No. centres:** Single; **Type of setting:** Secondary / Tertiary	**No. patients:** 53. Non-Pregnant **Inclusion criteria:** Suspected PE, gamma camera available for imaging **Exclusion criteria:** NA	**Index test class:** VQ-SPECT. **Isotope:** V: 99mTc-DTPA 30 MBq aerosolized Q: 99mTc-MAA 100 MBq IV **VQ Interpretation:** Unclear. **Interpretation:** PE present: >1 segmental or subsegmental defect of mismatch (at least 2 points); PE absent: absence of unmatched perfusion defects; Other pathology: matched defects with typical patterns for other lung diseases; Nondiagnostic.	**Reference standard class:** VQ. **Reference standard details:** VQ Planar **Interpretation:** A segmental reduction or a subsegmental total deficiency was attributed 1 point; a segmental total deficiency was attributed 2 points.	**Primary:** NA **Secondary:** NA **Follow-up:** 6 months
Bhatia 2016 [192] **Location:** Australia. Dates: May 2012 to November 2013 **No. centres:** Single; **Type of**	**No. patients:** 102. Non-Pregnant **Inclusion criteria:** Underwent SPECT-CT/VQ scanning, CTPA during the same admission with **Exclusion criteria:** NA	**Index test class:** VQ-SPECT-CT. **Isotope:** Q: 200 MBq of 99m-Technetium-MAA **VQ Interpretation:** Unclear. **Interpretation:** NA	**Reference standard class:** CT. **Reference standard details:** CTPA **Interpretation:** NA	**Primary:** Sensitivity, specificity **Secondary:** NA **Follow-up:** NA

Study information	Patients	Index test	Reference test	Outcomes
setting: Secondary / Tertiary				
Blachere 2000 [132] **Location:** France. Dates: 18-month period (dates not specified) **No. centres:** Single; **Type of setting:** Secondary	**No. patients:** 179. Non-Pregnant **Inclusion criteria:** Clinically suspected of acute PE **Exclusion criteria:** Contraindication for the use of iodine contrast material (renal failure, history of allergy), unstable hemodynamic status, and pregnancy.	**Index test class:** CT **CT slices:** 4. **Contrast:** Iohexol 240 (Omnipaque 240; Nycomed Ingenor, Paris, France), 120-150 ml at 4-5 ml/sec. **Interpretation:** PE present: normal-sized or enlarged pulmonary obstructed completely by nonenhancing thrombus, or central nonocclusive filling defects. Main, lobar, segmental, and sub-segmental arteries recorded. PE absent: no clot observed. Indeterminate if poor examination, in-adequate enhancement, or motion artifacts precluded confident interpretation of the study.	**Reference standard class:** CC. **Reference standard details:** Composite (PA positive, CT, VQ, and US concordant, event during clinical follow-up) **Interpretation:** Original and revised PIOPED	**Primary:** Negative diagnosis of PE were followed up to determine whether a recurrence of PE or of a VTE had occurred. **Secondary:** NA **Follow-up:** 3-months
Bosson 2007 [107] **Location:** France. Dates: February 1999 to November 1999 **No. centres:** Single; **Type of setting:** Secondary	**No. patients:** 1134. Non-Pregnant **Inclusion criteria:** Clinically suspected of acute non-severe PE **Exclusion criteria:** Severe life threatening PE or interval of >72 hours between clinical suspicion for PE and entry to the algorithm.	**Index test class:** PW **Interpretation:** Unclear. "Previous published criteria."	**Reference standard class:** FU. **Reference standard details:** 3 month follow-up **Interpretation:** NA	**Primary:** Incidence of DVT or PE **Secondary:** NA **Follow-up:** 3 months
Bourriot 2003 [193] **Location:** France. Dates: June 1996 to December 1998 **No. centres:** Single; **Type of setting:** Secondary	**No. patients:** 117. Non-Pregnant **Inclusion criteria:** Suspicion of acute PE (PE) in a population of inpatients with cardiac and/or respiratory disease, with negative spiral CT (SCT) angiographic finding. **Exclusion criteria:** NA	**Index test class:** CT **CT slices:** 4. **Contrast:** 120 to 150 mL of nonionic contrast material (Omnipaque 240; Nycomed Ingenor; Paris, France) at 4-5 mL/s **Interpretation:** CT characterized: (1) PE present if clot observed, (2) PE absent no clot observed, or (3) indeterminate if poor examination, inadequate enhancement, or motion artifacts precluded confident	**Reference standard class:** FU. **Reference standard details:** Follow up of mean 21 months **Interpretation:** NA	**Primary:** recurrent thromboembolism, mortality, and cause of death **Secondary:** NA **Follow-up:** 6-months

Study information	Patients	Index test	Reference test	Outcomes
		interpretation of the study. PE present if normal-sized or enlarged pulmonary artery obstructed completely by an enhancing thrombus, or if nonocclusive filling defects centrally in the vessel. Doppler leg US: DVT intraluminal thrombus or incomplete compressibility of the veins, or both. D-dimer: considered positive at > 500 ng/mL.		
Coche 2003 [126] **Location:** Belgium. Dates: 21 months (dates not reported) **No. centres:** Single; **Type of setting:** Secondary / ER	**No. patients:** 94. Non-Pregnant **Inclusion criteria:** Clinical suspicion of PE, age >18 years, absence of clinically suspected deep venous thrombosis, and plasma D-dimer levels >500 ng/mL. **Exclusion criteria:** D-dimer test that was negative, clinical signs of deep venous thrombosis, D-dimer values that were positive with an obvious alternative diagnosis, incomplete study protocols, contraindications to spiral CT, patient transfer, death, and patient refusal or inability to participate.	**Index test class:** CT **CT slices:** 4. **Contrast:** 70100 mL of iobitridol (Xenetix 350; Guerbet, Aulnaysousbois, France), diluted with 2030 mL of saline IV at 3 mL/sec **Interpretation:** PE absent: either complete or partial filling defects within the main, lobar, segmental, or subsegmental arteries were identified	**Reference standard class:** SC. **Reference standard details:** Ventilation-perfusion (VQ) scintigraphy, pulmonary digital subtraction angiography when indicated, and chest radiography **Interpretation:** VQ: PE excluded if perfusion defects of any kind. PE unlikely (low probability): perfusion defects of any size matched by equal or larger ventilation defects and smaller or equal insize and shape to CXR abnormalities. PE present (high probability): single or multiple large, wedge-shaped perfusion defects, coexisted with a normal distribution of ventilation. Pulmonary angiography: partially occlusive filling defect within an arterial branch or a completely occlusive filling defect indicated by a meniscus of contrast material outlining the trailing edge of the PE.	**Primary:** Episodes of recurrent or new deep venous thrombosis or PE were recorded **Secondary:** Baseline creatinine levels were measured in all patients before the spiral CT examination, and the creatinine level was monitored in hospitalized patients **Follow-up:** 6 months

Study information	Patients	Index test	Reference test	Outcomes
Collart 2002 [169] **Location:** Belgium. Dates: November 1997 to September 1998 **No. centres:** Single; **Type of setting:** Secondary / Tertiary	**No. patients:** 70. Non-Pregnant **Inclusion criteria:** Clinical suspicion of PE on the basis of history, clinical examination, chest X-ray, electrocardiogram and blood gas values **Exclusion criteria:** NA		**Reference standard class:** CC. **Reference standard details:** Positive CT, high probability VQ + abnormal D-dimer + positive LUS, high porbability VQ + abnormal D-dimer + positive CT **Interpretation:** PE present: positive chest spiral CT in a central pulmonary region (lobar arteries included), whatever the results of the other investigations.	**Primary:** NA **Secondary:** NA **Follow-up:** 2 months
Comert 2013 [152] **Location:** Turkey. Dates: January 2010 to July 2011 **No. centres:** Single; **Type of setting:** Secondary / Tertiary	**No. patients:** 50. Non-Pregnant **Inclusion criteria:** Clinical suspicion of PE under consideration of risk factors (malignancy, lower extremity fracture, obesity, congestive heart failure, postpartum period, and history of venous thromboembolism, operation, and PE) **Exclusion criteria:** NA	**Index test class:** US **Interpretation:** PE suggested: at least one typical pleural-based/subpleural wedge-shaped or round hypoechoic lesion with or without pleural effusion was reported by TUS. PE absent: Presence of pure pleural effusion or normal sonographic findings.	**Reference standard class:** CT. **Reference standard details:** CTPA **Interpretation:** PE present: one filling defect in the pulmonary artery.	**Primary:** Number of lesions / sensitivity, specificity, NPV, PPV **Secondary:** NA **Follow-up:** NA
Donato 2003 [194] **Location:** US. Dates: NA **No. centres:** Single; **Type of setting:** Secondary / Tertiary	**No. patients:** 243. Non-Pregnant **Inclusion criteria:** Reports using words "PE" and "clot" for the 2 years before the initiation of the study **Exclusion criteria:** NA	**Index test class:** CT **CT slices:** NA. **Contrast:** 15 mL iohexol at 3-4 mL/s **Interpretation:** NA	**Reference standard class:** FU. **Reference standard details:** Follow up of three months **Interpretation:** NA	**Primary:** NA **Secondary:** NA **Follow-up:** 3 months
Erdman 1994 [148] **Location:** US. Dates: December 1986 to June 1990 **No. centres:** Single; **Type of setting:** Secondary / Tertiary	**No. patients:** 86. Non-Pregnant **Inclusion criteria:** Referral to department for scintigraphic or angiographic evaluation of possible PE **Exclusion criteria:** NA	**Index test class:** MRI **MRI Field strength:** 0.35. **Contrast:** None **Interpretation:** NA	**Reference standard class:** PA. **Reference standard details:** Angiography **Interpretation:** NA	**Primary:** NA **Secondary:** NA **Follow-up:** NA

Study information	Patients	Index test	Reference test	Outcomes
Galipienzo 2012 [108] **Location:** Spain. Dates: May 2007 to December 2008 **No. centres:** Single; **Type of setting:** NA	**No. patients:** 241. Non-Pregnant **Inclusion criteria:** Clinically suspected PE, defined as a sudden onset of dyspnea, acute deterioration of existing dyspnea, or onset of pleuritic chest pain without another apparent cause **Exclusion criteria:** Age 24 hours, logistic reasons (eg, unavailability of CT, patient too ill to undergo CT scanning), or hemodynamic instability.	**Index test class:** PW **Interpretation:** PE present: contrast material outlined a central intraluminal defect or if a vessel was totally occluded in at least two different projections.	**Reference standard class:** FU. **Reference standard details:** 3 month follow-up **Interpretation:** NA	**Primary:** incidence of symptomatic VTE events during 3 months of follow-up, defined as fatal PE, nonfatal PE, or DVT (DVT) **Secondary:** As secondary objectives, we determined D-dimer levels in patients with likely probability of VTE to confirm the importance of assessing the clinical probability before D-dimer result is known. We also determined the utility of high quantitative D-dimer levels in the diagnosis of PE calculating the prevalence of this disease in different intervals of D-dimer levels and for each level of clinical probability. We also evaluated the effectiveness of the diagnostic strategy according to the age of patients. **Follow-up:** 3 months
Galipienzo 2010 [118] **Location:** Spain. Dates: January 2007 to July 2008 **No. centres:** Single; **Type of setting:** Secondary / ER	**No. patients:** 242. Non-Pregnant **Inclusion criteria:** Clinically suspected PE and negative MCTPA **Exclusion criteria:** Exclusion criteria included age 24 h, logistic reasons (eg, unavailability of CT and patient too ill to undergo CT scanning), or hemodynamic instability.	**Index test class:** CT **CT slices:** 16. **Contrast:** total volume of 100 to 120 mL of nonionic contrast material injected with a power injector at 3 to 5 mL/s; imaging 9 to 20 s after initiation of the contrast material injection **Interpretation:** PE present: contrast material outlined central intraluminal defect or if a vessel was totally occluded in at least two different projections. Recurrent thromboembolic events: positive Doppler ultrasound findings for deep-vein thrombosis, ventilationperfusion scintigram showing high probability of PE following the PIOPED	**Reference standard class:** FU. **Reference standard details:** Follow up of 3 months **Interpretation:** NA	**Primary:** percentage of patients in whom venous thromboembolic events or death related to this condition within three months after the negative CT **Secondary:** NA **Follow-up:** 3 months

Study information	Patients	Index test	Reference test	Outcomes
		recommendations for high and intermediate clinical probability patients, positive multidetector CT showing repletion defects as above mentioned, or death attributed to PE by 3 researchers.		
Ghanima 2005 [109] **Location:** Norway. Dates: February 2002, and December 2003 **No. centres:** Single; **Type of setting:** ER	**No. patients:** 329. Non-Pregnant **Inclusion criteria:** Clinical suspicion of PE defined as acute onset of dyspnea, chest pain, palpitation, or syncope, >= 18 years of age. **Exclusion criteria:** Clinical probability not assessed in patients normal D-dimer, CT not performed, anticoabulation, iodinated contrast medium, pregnancy, expected survival	**Index test class:** PW **Interpretation:** PE present: filling defect or complete occlusion in proximal, segmental or subsegmental arteries. PE absent: pulmonary vasculature, including subsegmental branches, visualized and was free of filling defects. Iinconclusive, poor opacification or major motion artefact observed or due to the ambiguity of findings as irregular arterial walls or the presence of an adjacent pulmonary abnormality. Ultrasonography: DVT present: lack of vein compressibility.	**Reference standard class:** FU. **Reference standard details:** Follow up of 3 months **Interpretation:** NA	**Primary:** 3-month thromboembolic risk, which was de?ned as an objectively veri?ed VTE or death from PE in those patients who initially were diagnosed not to have a PE and had not received anticoagulation for >48 h during the follow-up period **Secondary:** The ef?cacy of the diagnostic strategy was assessed in terms of the proportion of patients in whom a de?nite diagnosis was made according to the diagnostic algorithm. Deaths were adjudicated by an independent committee on the basis of autopsy reports, death certi?cates and hospital charts as de?nitely caused by PE, de?nitely unrelated to PE, or possibly related to PE if the cause of death could not be clearly established. **Follow-up:** 3-months
Gimber 2009 [195] **Location:** US. Dates: February 2005 to January 2006 **No. centres:** Single; **Type of setting:** Tertiary / ER	**No. patients:** 347. Non-Pregnant **Inclusion criteria:** Suspected PE, underwent pulmonary CTA and had a D-dimer level of ?1.0 mg/dL. **Exclusion criteria:** NA	**Index test class:** CT **CT slices:** Single or multi. **Contrast:** 120 mL Omnipaque 300 at a rate of 3mL/s **Interpretation:** PE present: filling defect in one or more pulmonary arteries. PE absent: no filling defect and normal enhancement of pulmonary arteries. Indeterminate: pulmonary study findings could not be classified as positive or negative.	**Reference standard class:** FU. **Reference standard details:** Follow up of 3 months **Interpretation:** NA	**Primary:** NA **Secondary:** NA **Follow-up:** 3 months

Study information	Patients	Index test	Reference test	Outcomes
Gray 1990 [178] **Location:** Scotland. Dates: 1979 and 1984 **No. centres:** Single; **Type of setting:** Secondary	**No. patients:** 101. Non-Pregnant **Inclusion criteria:** Underwent angiography or were to undergo angiography and were referred for lung scanning **Exclusion criteria:** NA	**Index test class:** VQ. **Isotope:** V: 133Xe (dose not specified). Q: 99m-Tc-macroaggregates. **VQ Interpretation:** Study-specific. **Interpretation:** Highly specific criteria (normal, low probability, indeterminate probability, significant probability, high probability); Equivalent areas of abnormality in VF/Q were matched; areas of abnormal perfusion with normal ventilation were mismatched; Nondiagnostic: abnormality on chest X-ray and corresponding matched ventiation and perfusion abnorlaity	**Reference standard class:** PA. **Reference standard details:** Pulmonary angiography **Interpretation:** PE present: intraluminal filling defects or multiple cut-off vessels; PE absent: normal angiography or minor perfusion abnormalities; Indeterminate: other abnormalities (e.g., oligaemia or flow asymmetry)	**Primary:** Diagnostic accuracy; failure rate **Secondary:** NA **Follow-up:** NA
Grist 1993 [142] **Location:** US. Dates: NA **No. centres:** Single; **Type of setting:** Secondary / Tertiary	**No. patients:** 14. Non-Pregnant **Inclusion criteria:** NA **Exclusion criteria:** NA	**Index test class:** MRI **MRI Field strength:** 1.5. **Contrast:** NA **Interpretation:** PE present: Intraluminal filling defects, occluded pulmonary artery branches and the presence of hypovascularity manifested by poor blood-flow related enhangements in the pulmonary arteries.	**Reference standard class:** CT. **Reference standard details:** CPA **Interpretation:** NA	**Primary:** NA **Secondary:** NA **Follow-up:** NA
Gupta 1999 [144] **Location:** Australia. Dates: 8 months (dates not specified) **No. centres:** Single; **Type of setting:** Secondary / Tertiary	**No. patients:** 36. Non-Pregnant **Inclusion criteria:** Intermediate-probability VQ scan or a low-probability VQ scan, with a high clinical suspicion for acute PE **Exclusion criteria:** NA	**Index test class:** MRI **MRI Field strength:** 1.5. **Contrast:** Gadodiamide **Interpretation:** PE present: Intravascular filling defect or an abrupt vessel cutoff. Other abnormalities, such as vascular irregularity and zones of hypovascularity, were ignored.	**Reference standard class:** PA. **Reference standard details:** DSA **Interpretation:** PE present: intravascular filling defect or an abrupt vessel cutoff. Other abnormalities, such as vascular irregularity and zones of hypovascularity, ignored.	**Primary:** Sensitivity and specificity **Secondary:** NA **Follow-up:** NA
Gutte 2010 [176] **Location:** Denmark. Dates: June 2006 to	**No. patients:** 36. Non-Pregnant **Inclusion criteria:** Suspected acute PE defined as an acute onset of new or worsening of shortness of	**Index test class:** VQ-SPECT. **Isotope:** Q: 199mTc-MAA 150 MBq V: 81mKr **VQ Interpretation:** Unclear.	**Reference standard class:** VQ. **Reference standard details:** Planar Lung Scintigraphy **Interpretation:** NA	**Primary:** sens, spec **Secondary:** NA **Follow-up:** 6 months

Study information	Patients	Index test	Reference test	Outcomes
February 2008 **No. centres:** Single; **Type of setting:** Secondary / Tertiary	breath, chestpain without any cause, combined with positive D-dimer results (>0.5 mmol/mL) or Wells score >2 **Exclusion criteria:** Contraindication to CT incluing allergy to contrast agents, impaired renal function (P-creatinine level >0.120 mmol/L), women	**Interpretation:** PE present: if one or more perfusion defects (> 0.5 segment) with normal ventilation (mismatch)		
Gutte 2009 [128] **Location:** Denmark. Dates: June 2006 to February 2008 **No. centres:** Multi-National or Regional; **Type of setting:** Secondary / Tertiary	**No. patients:** 81. Non-Pregnant **Inclusion criteria:** Suspected acute PE defined as an acute onset of new or worsening of shortness of breath, chestpain without any cause, combined with positive D-dimer results (>0.5 mmol/mL) or Wells score >2 **Exclusion criteria:** Contraindication to CT incluing allergy to contrast agents, impaired renal function (P-creatinine level >0.120 mmol/L), women	**Index test class:** VQ-SPECT. **Isotope:** Q: 81mKr **VQ Interpretation:** Unclear. **Interpretation:** PE present: one or more mismatched perfusion defects with normal ventilation	**Reference standard class:** CC. **Reference standard details:** Composite: Side-by-side consensus based on MDCT, VQ SPECT and all available information (ECG, echo, LUS, D-dimer, clinical data and follow-up of 6 months) **Interpretation:** NA	**Primary:** Diagnostic accuracy (sens/spec) **Secondary:** NA **Follow-up:** 6 months
Hantous-Zannad 2010 [196] **Location:** Tunisie. Dates: June 2006 to March 2007 **No. centres:** Single; **Type of setting:** Secondary	**No. patients:** 184. Non-Pregnant **Inclusion criteria:** Suspected PE based on empiric clinical probability assessment **Exclusion criteria:** NA	**Index test class:** CT **CT slices:** 16. **Contrast:** A mechanical injector was used for intravenous injection of iodinated contrast material at a rate of 5 ml/sec and an amount of 80 - 90 ml. **Interpretation:** PE present: large filling defect, a partial filling defect surrounded by contrast material, peripheral incraluminal filling defect that forms acute angles with the pulmonary arterial wall. PE inconclusive: important artefacts making segmental pulmonary arteries poorly analyzed, high image noise, poor enhancement of	**Reference standard class:** FU. **Reference standard details:** Follow up of 6 months **Interpretation:** NA	**Primary:** reccurent VTE events, prevalance of acute PE, calculate sensitivity and specificity of multidetector CT **Secondary:** NA **Follow-up:** 6 months

Study information	Patients	Index test	Reference test	Outcomes
		pulmonary arteries and pulmonary infarction images without embolus in the corresponding pulmonary artery.		
Harris 2007 [185] **Location:** Australia. Dates: NA **No. centres:** Single; **Type of setting:** Secondary / Tertiary	**No. patients:** 50. Non-Pregnant **Inclusion criteria:** Suspected PE **Exclusion criteria:** Past medical history of PE, renal disfunction, significant contrast hypersensitivity, unable to comply with study protocol, if imaging was unable to be completed within 24 hours of presentation, patients	**Index test class:** VQ-SPECT. **Isotope:** Q: 99mTc MAA (Pulmolite) 160 to 220 MBq **VQ Interpretation:** Modified PIOPED. **Interpretation:** Modified PIOPED criteria (see Definition)	**Reference standard class:** CC. **Reference standard details:** Composite: Consensus panel of 3 physicians with access to all clinical details, including VQ, CTPA, and CTV **Interpretation:** NA	**Primary:** AUROC **Secondary:** NA **Follow-up:** 3 month
He 2012 [131] **Location:** China. Dates: June 2007 to January 2011 **No. centres:** Multi-National or Regional; **Type of setting:** Secondary	**No. patients:** 544. Non-Pregnant **Inclusion criteria:** Suspected PE (based on signs and symptoms, laboratory findings, medical history and predisposing factors - assessed formally by Wells) **Exclusion criteria:** Abnormal serum creatinine, unwilling to investigations, pregnancy, circulatory shock, hypotension, renal failure, hemodynamically unstable, ventilatory support, anticoagulation, history of allergy to contrast media, received thrombolytic therapy before examinations excluded.	**Index test class:** VQ. **Isotope:** CT: 75 to 85 mL contrast medium at 5 mL/s with double power injector. Q: 99mTc MAA 185-370 MBq (5-10 mCi) V: 99mTc-Technegas 10 mCi inhaled over 5-8 cycles. **VQ Interpretation:** Multiple. **Interpretation:** PISAPED and PIOPED II criteria (See Definition) VQ: PE present, PE absent, or non-diagnostic; Q only: PE present or PE absent CT: PE present, PE absent, or non-diagnostic	**Reference standard class:** CC. **Reference standard details:** Composite Reference Test (clinical data, laboratory recorders (D-dimer and Doppler US available), imaging information (e.g., echocardiography), CTPA, VQ, right heart cardiac catheterization, and PA (performed in patients with indeterminate tests by other modalities) as well as physician opinions and 6-month clinical follow-up (see reference 5); Pulmonary contrast angiography (Allura Xper FD10/10 angiographic unit) peformed in patients in whom PE not conclusively diagnosed or ruled out by non-invasive tests **Interpretation:** Final diagnosis made at consensus meeting	**Primary:** Sensitivity, specificity, PPV, NPV, proportion of non-diagnostic tests **Secondary:** NA **Follow-up:** 6 months
Hogg 2006 [110] **Location:** UK. Dates: February 2002 to May 2003 **No. centres:** Single; **Type of**	**No. patients:** 425. Non-Pregnant **Inclusion criteria:** Pleuritic chest pain **Exclusion criteria:** Trauma, pregnancy, pneumothorax, myocardial infarction, cardiac	**Index test class:** PW **Interpretation:** PIOPED criteria (See Definitions)	**Reference standard class:** FU. **Reference standard details:** Folllow up of three months **Interpretation:** NA	**Primary:** Safety **Secondary:** NA **Follow-up:** 3 months

Study information	Patients	Index test	Reference test	Outcomes
setting: Secondary / Tertiary	ischemia, pericarditis, hypoxia with Pao2140 kg			
Huisman 2006 [197] **Location:** Netherlands. Dates: November 2002 to December 2004 **No. centres:** Multi-National or Regional; **Type of setting:** Secondary / ER	**No. patients:** 3306. Non-Pregnant **Inclusion criteria:** Suspected PE (sudden onset of dyspnea, sudden deterioration of existing dyspnea or onset of pleuritic chest pain) **Exclusion criteria:** Treatment with therapeutic doses of unfractionated or low-molecular-weight heparin for more than 24 hours, life expectancy less than 3 months, pregnancy, geographic inaccessibility precluding follow-up, age	**Index test class:** CT **CT slices:** Single or multi. **Contrast:** Single row: 120-140 nonionic contrast material containing 350 mg of iodine per mL. Multidetector: 80-100mL nonionic contrast material containing 350mg of iodine per mL **Interpretation:** PE present: Contrast material outlined an intraluminal defect or vessal totally occluded by low-attenuation material on at least 2 adjacent slices	**Reference standard class:** FU. **Reference standard details:** Follow up of three months **Interpretation:** NA	**Primary:** incidence of symptomatic VTE events during 3 month follow-up (fatal PE, DVT) **Secondary:** NA **Follow-up:** 3 months
Ibanez-Bravo 2016 [188] **Location:** Spain. Dates: November 2011 to October 2014 **No. centres:** Single; **Type of setting:** ER	**No. patients:** 53. Non-Pregnant **Inclusion criteria:** NA **Exclusion criteria:** NA	**Index test class:** VQ-SPECT. **Isotope:** V: 99mTc-Technegas over 3-5 respiratory cycles Q: 99mTc-MAA 150 MBq **VQ Interpretation:** EANM. **Interpretation:** EANMMI guidelines. PE positive: VQ mismatch in at least one segment or two subsegments. PE negative: perfusion normal or maximum of one sub-segmental mismatch. PE non-diagnostic if the VQ abnormalities did not allow a positive or negative diagnosis.	**Reference standard class:** CT. **Reference standard details:** CTPA **Interpretation:** PE positive: occlusive or no occlusive. PE negative: normal enhancement of pulmonary vasculature. Indeterminate: attributed to patient or technical factors.	**Primary:** Diagnosis of PE by CTPA or VQ SPECT **Secondary:** NA **Follow-up:** 6 months
Jouveshomme 2007 [111] **Location:** France. Dates: December 2002 and February 2005 **No. centres:** Single; **Type of setting:** Secondary	**No. patients:** 400. Pregnant **Inclusion criteria:** Inpatients referred for diagnostic imaging with clinically suspected PE **Exclusion criteria:** Not hospitalised for >24 hours; patients without 3 month follow-up data	**Index test class:** PW **Interpretation:** Read on high-quality workstations (CT); Lack of compressibility (CUS); PIOPED criteria (VQ; see Definitions)	**Reference standard class:** FU. **Reference standard details:** No comparator **Interpretation:** NA	**Primary:** Failure Rate **Secondary:** Incidental findings (alternative diagnoses) **Follow-up:** 3 months

Study information	Patients	Index test	Reference test	Outcomes
Kluge 2006 [209] **Location:** Germany. Dates: June 2002 and February 2005 **No. centres:** Single; **Type of setting:** Secondary	**No. patients:** 221. Non-Pregnant **Inclusion criteria:** Suspected acute PE (based on clinical symptoms + ECG and echocardiography + D-dimer in a subet) in cardiology and cardiac surgery departments before and after surgery **Exclusion criteria:** Cardiogenic shock; prolonged low cardiac output; implanted device	**Index test class:** MRI **MRI Field strength:** NA. **Contrast:** Applied through peripheral veous access with powr injector; Pulmonary Perfusion MRI Gadopentetate dimeglumine 0.125 mmol/kg body weight at 4 mL/seconds - 25 repeated measurements covered the first and second passes of the contrast medium bolus in 45 seconds; MR angiography: second injection of 0.125 mmol/kg of body weight of gadopentetate dimeglumine at 4 mL/sec after bolus timing sequence **Interpretation:** Interpreted in fixed order of sequence types: Criteria: direct thrombus visualization or vessel cutoff (real-time - oncordant results from two planes; perfusion - sharply delineated perfusion defects defined as PE if contours consistent with segmental or subsegmental; the most central embolus location determined extent of PE; final onsensus interpretation on all thoracic techniques if discrepancy between techniques evident	**Reference standard class:** MRI. **Reference standard details:** Alternative MRI modalities **Interpretation:** NA	**Primary:** Diagnostic quality; reasons for non-compliance or insufficient image quality **Secondary:** Safety; Technical quality; comparison of combined and standalone examinations (MRI+MRV versus MRI or MRV alone); Intertechnique agreeement with duplex sonography **Follow-up:** NA
Kluge 2006 [141] **Location:** Germany. Dates: NA **No. centres:** Single; **Type of setting:** Secondary	**No. patients:** 65. Non-Pregnant **Inclusion criteria:** Symptoms of acute PE (symptoms, ECG, echo, pulse oximetry, arterial blood gas, D-dimer) **Exclusion criteria:** History of adverse reaction to contasts; elevated serum creatinine (CT); cardiogenic shock; prolonged low varidac output; implanted cardiac	**Index test class:** MRI **MRI Field strength:** 1.5. **Contrast:** (3) MR angiograpy. Gadopentetate dimeglumine injected at 0.125 mmol/kg of body weight at 4 mL/s and followed by 20-mL saline flush **Interpretation:** PE present: (1) Real-time MRI. Thrombotic material directly visualized on >one image in each of two planes, or if vessel	**Reference standard class:** CT. **Reference standard details:** 16-MDCT (CT-CTA) **Interpretation:** PE positive: embolic material directly visualized or vessel truncation implies the presence of occlusion (categorized as central, lobar, segmental, subsegmental, or isolated subsegmental)	**Primary:** DTA **Secondary:** Incidental diagnoses **Follow-up:** Median = 4.6 days (range 1 to 121 days)

Study information	Patients	Index test	Reference test	Outcomes
	pacemaker or cardioverter; other implants	truncation implied an occlusion (central, lobar, or segmental) - non-diagnostic if vessel not identified or blurred vessel representation - if 3+ lobar or 10+ segmental arteries not assessed also non-diagnostic. (2) MR angiography: As real-time except subsegmental embolism differentiated from segmental PE. (3) MR perfusion: Single or multiple sharply delineated perfusion defects in accordance with subsegmental, segmental, or lobar anatomic features.		
Kumar 2015 [175] **Location:** US. Dates: December 2011 to June 2013 **No. centres:** Single; **Type of setting:** NA	**No. patients:** 49. Non-Pregnant **Inclusion criteria:** Group I: Scintigraphic perfusion imaging within 7 days of nondiagnostic CTPA study. Group II: Perfusion imaging due to contraindication to CTPA or clinician preference **Exclusion criteria:** NA	**Index test class:** Q-SPECT-CT. **Isotope:** 3.0 mCi Tc- 99 m MAA **VQ Interpretation:** MSKCC-Q-SPECT-CT. **Interpretation:** PE present: >=1 wedge-shaped peripheral defect estimated as ?50 % of a pulmonary segment without corresponding CT image abnormality, clearly seen in all three orthogonal planes. PE absent: Perfusion defects corresponding to CT abnormalities (such as radiation fibrosis, pleural effusion, emphysematous bullae, pneumonia, or solid tumor mass, etc.).	**Reference standard class:** CC. **Reference standard details:** final diagnosis of PE was determined by consensus of the pulmonologist (RM) and all imaging physicians using a composite of all clinical information, including clinical symptoms and presentation, physical examination, ECG, D-dimer levels, and all available initial and at least 6-month follow-up imaging tests such as lower-extremity Doppler ultrasound, planar Q and VQ, Q-SPECT-CT and CTPA **Interpretation:** Interpreted in accordance with the modified PIOPED II criteria	**Primary:** NA **Secondary:** NA **Follow-up:** 6 months
Kyrtatos 2013 [210] **Location:** UK. Dates: May to August 2012 **No. centres:** Single; **Type of**	**No. patients:** 81. Non-Pregnant **Inclusion criteria:** Underwent VQ SPECT for suspected PE **Exclusion criteria:** Did not undergo both ventilation and perfusion scans; did not undergo both SPECT and	**Index test class:** VQ-SPECT. **Isotope:** Perfusion: 200 MBq of technetium-99m MAA Ventilation: Krypton-81m **VQ Interpretation:** Unclear. **Interpretation:** PE present : at least	**Reference standard class:** VQ. **Reference standard details:** traditional Planar VQ **Interpretation:** PE present: at least one segmental mismatched perfusion defect or at least two	**Primary:** number of defects **Secondary:** NA **Follow-up:** NA

Study information	Patients	Index test	Reference test	Outcomes
setting: NA	planar study	one segmental mismatched perfusion defect or at least 2 two subsegmental mismatched perfusion defects. PE indeterminate: only one subsegmental mismatch, one or more nonsegmental mismatches, perfusion image of inadequate quality, or ventilation image of inadequate quality (when perfusion was abnormal). PE absent: any other condition.	subsegmental mismatched perfusion defects. Indeterminate: only one subsegmental mismatch, one or more nonsegmental mismatches, perfusion image of inadequate quality, or ventilation image of inadequate quality (when perfusion was abnormal). PE negative: any other scenario.	
Le Duc-Pennec 2012 [190] **Location:** France. Dates: April 2004 to September 2006 **No. centres:** Single; **Type of setting:** Secondary / Tertiary	**No. patients:** 321. Non-Pregnant **Inclusion criteria:** Over 18 years old, high clinical probabily of PE, or non-high clinical probabiliy but abnormal plasma enzyme-linked immunosorbent assay D-dimer concentration (>500 ug/mL) **Exclusion criteria:** Pregnancy, breastfeeding, life expectancy 48 h at the time of screening, and a previously confirmed PE	**Index test class:** VQ-SPECT. **Isotope:** Q: 99m Tc MAA 200 MBq V: 81m Kr **VQ Interpretation:** Modified PIOPED. **Interpretation:** Modified PIOPED (see Definitions)	**Reference standard class:** VQ. **Reference standard details:** Planar VQ scan **Interpretation:** NA	**Primary:** Prevalence of PE in each SPECT VQ scan probability group **Secondary:** NA **Follow-up:** 3 month
Le Roux 2015 [174] **Location:** France. Dates: April 2011 to March 2013 **No. centres:** Single; **Type of setting:** Secondary / Tertiary	**No. patients:** 393. Non-Pregnant **Inclusion criteria:** ?18 years, symptoms suggestive of PE, high clinical probability of PE or nonhigh clinical probability but abnormal plasma ELISA D-dimer concentration (>500ug/ml). **Exclusion criteria:** NA	**Index test class:** VQ-SPECT-CT. **Isotope:** Perfusion: 200 MBq of 99m Tc MAA Ventilation: 81m Kr gas obtained **VQ Interpretation:** Unclear. **Interpretation:** PE present: one segmental or rwo subsegmental mismatched defects	**Reference standard class:** CC. **Reference standard details:** Composite: Final diagnostic conclusion was established by the physician in charge of patient care on the basis of clinical symptoms, laboratory tests, VQ SPECT and other imaging procedures performed. **Interpretation:** NA	**Primary:** NA **Secondary:** NA **Follow-up:** 3 months
Leblanc 2007 [211] **Location:** Canada. Dates: October 2004 to July 2005 **No. centres:** Single; **Type of**	**No. patients:** 584. Non-Pregnant **Inclusion criteria:** NA **Exclusion criteria:** NA	**Index test class:** VQ-SPECT. **Isotope:** Ventilation: inhalation of 99mTc-Technegas Perfusion: 210300MBq of 99mTc labelled MAA **VQ Interpretation:** Unclear. **Interpretation:** Normal CXR: PE	**Reference standard class:** FU. **Reference standard details:** 3 month follow-up **Interpretation:** NA	**Primary:** NA **Secondary:** NA **Follow-up:** 3 months

Study information	Patients	Index test	Reference test	Outcomes
setting: Secondary / Tertiary		absent: no mismatched defect. PE present: any clear-cut perfusion vascular-type defect, regardless of size, with normal ventilation (mismatched). Abnormal chest X-ray only. Indeterminate: matching vascular-type defects of the same size (triple match). PE negative: Perfusion defect no vascular configuration as defined above (no evidence of PTE).		
Lechleitner 2002 [117] **Location:** Austria. Dates: NA **No. centres:** Single; **Type of setting:** Secondary	**No. patients:** 55. Non-Pregnant **Inclusion criteria:** Suspected PE **Exclusion criteria:** Haemodynamically unstable patients, those receiving mechanical ventilation, patients with contraindications to MRI, pregnant women		**Reference standard class:** MRI. **Reference standard details:** MRI angiography (reference method) **Interpretation:** NA	**Primary:** categorize sonographic lesions (specific lesions, unspecific lesions, no lesion) **Secondary:** sensitivity, specificity **Follow-up:** NA
Lechleitner 1998 [158] **Location:** Austria. Dates: 15-month period (1995-1996) **No. centres:** NA; **Type of setting:** NA	**No. patients:** 119. Non-Pregnant **Inclusion criteria:** Clinical signs of PE **Exclusion criteria:** NA	**Index test class:** US **Interpretation:** Thoracic US: Suggestive of PE: Echo poor and homogenous. rounded and less sharply bordered to the ventilated lung wedge shaped, or well demarcated lesions with a hyperechoic reflexion at the center. Possibly corresponding to the bronchioles. Echogenicity influenced by the presence of a pleural effusion which was present in 10% of patients. Unspecific lesions: All lesions of other shapes. never been described in connection with PE. No lesion; Normal pleural reflex.	**Reference standard class:** VQ. **Reference standard details:** since pulmonary angiography was performed only in some selected cases, perfusion/ventilation scintigraphy was the reference method **Interpretation:** Categorized as high probability, intermediate probability, low/very low probability and normal according to the PIOPED criteria.	**Primary:** categorize sonographic lesions (specific lesions, unspecific lesions, no lesion) **Secondary:** sensitivity, specificity **Follow-up:** NA
Li 2017 [135] **Location:** China. Dates: NA	**No. patients:** 32. Non-Pregnant **Inclusion criteria:** Suspected acute PE based on clinical symptoms and	**Index test class:** MRI **MRI Field strength:** 3. **Contrast:** Gadobenate dimeglumine (20 mL)	**Reference standard class:** CT. **Reference standard details:** CTPA	**Primary:** Sensitivity, specificity, PPV, NPV **Secondary:** NA

Study information	Patients	Index test	Reference test	Outcomes
No. centres: Single; **Type of setting:** Secondary	D-dimer **Exclusion criteria:** 30, dependency on connection to external electrical device or pump	IV injection **Interpretation:** PE present: Complete arterial occlusion, failure to opacify the entire lumen on >one image in each of two places with or without an artery enlarged compared with the pulmonary arteries of the same order of branching; a central arterial filling defect surrounded by IV contrast material; peripheral intra-luminal filling defect making an acute angle with the arterial wall; non-diagnostic if vessel could not be identified or if blurred vessel representation precluded analysis or if >three lobar arteries or >10 segmental arteries were not assessed within the sequence	**Interpretation:** Same as index	**Follow-up:** NA
Ling 2012 [191] **Location:** Australia. Dates: 2009 **No. centres:** Single; **Type of setting:** Secondary / Tertiary	**No. patients:** 106. Non-Pregnant **Inclusion criteria:** NA **Exclusion criteria:** NA	**Index test class:** VQ-SPECT. **Isotope:** NA **VQ Interpretation:** Unclear. **Interpretation:** PE present: >50% perfusion mismatch in an anatomical segment or 2 regions of perfusion mismatch regardless of size	**Reference standard class:** CC. **Reference standard details:** Composite: The reference diagnosis was PE if the final physician diagnosis was PE and there were no alternative diagnoses at 6 months; and not PE if the final physician diagnosis was not PE and there was no occurrence of venous thromboembolism (VTE) at 6 months **Interpretation:** NA	**Primary:** Sensitivity, specificity **Secondary:** NA **Follow-up:** 6 months
Lu 2014 [163] **Location:** US. Dates: 2006 to 2010 **No. centres:** Single; **Type of**	**No. patients:** 106. Non-Pregnant **Inclusion criteria:** Cancer patients who underwent both planar / and -SPECT-CT imaging on the same day, with at least 3 months of clinical follow-up.	**Index test class:** Q-SPECT-CT. **Isotope:** None for Q SPECT-CT **VQ Interpretation:** Unclear. **Interpretation:** PE present: at least one wedge-shaped peripheral defect estimated as at least 50% of	**Reference standard class:** CC. **Reference standard details:** Planar VQ scan was comparator, final diagnosis was made by by consensus of the pulmonologist and the imaging arbiter who used	**Primary:** NA **Secondary:** NA **Follow-up:** 3 months

Study information	Patients	Index test	Reference test	Outcomes
setting: Secondary / Tertiary	**Exclusion criteria:** NA	a pulmonary segment 27 without corresponding CT image abnormality and clearly seen in all three orthogonal planes	a composite of all clinical information, including ECG, D-dimer levels, physical examination, lower-extremity doppler US, echocardiography studies, and other imaging studies as well as a clinical follow-up of at least 3 months **Interpretation:** Modified PIOPED II and PISAPED criteria	
Lu 2014 [119] **Location:** China. Dates: May 2013 to December 2013 **No. centres:** Single; **Type of setting:** Secondary	**No. patients:** 100. Non-Pregnant **Inclusion criteria:** Suspected PE **Exclusion criteria:** History of allergy to iodinated contrast agent, age 80 kg.	**Index test class:** CT **CT slices:** 64. **Contrast:** Group A received 60 ml of iodinated contrast material (iopromide 300 mg I/ml, Bayer Schering, Berlin, Germany) at 4 ml/s. Group B received 20 ml iodinated contrast material (iopromide 300 mg I/ml, Bayer Schering, Berlin, Germany) at 4 ml/s, both followed by a 30-ml saline flush at 4 ml/s. **Interpretation:** PE present: luminal filling defects or non-visualisation of segmental pulmonary and subsegmental arteries compared to the contralateral side.	**Reference standard class:** CC. **Reference standard details:** Consensus reading including patient history, clinical data and supplementary imaging modalities **Interpretation:** Unblinded consensus reading (patient histories, clinical data and results from supplementary imaging modalities),	**Primary:** Image quality, diagnostic accuracy and radiation dose were evaluated and compared **Secondary:** NA **Follow-up:** NA
Mahdavi 2013 [127] **Location:** US. Dates: January 2007 to December 2008 **No. centres:** Single; **Type of setting:** Secondary / Tertiary	**No. patients:** 100. Non-Pregnant **Inclusion criteria:** Admitted and underwent both VQ and CTA within a 3 day period **Exclusion criteria:** NA	**Index test class:** VQ-SPECT. **Isotope:** 35 mCi of Tc-99 m labeled DTPA followed by 4 mCi of Tc-99 m labeled MAA **VQ Interpretation:** Unclear. **Interpretation:** NA	**Reference standard class:** CT. **Reference standard details:** CTPA **Interpretation:** NA	**Primary:** degree of agreement between the two tests **Secondary:** NA **Follow-up:** None
Mathis 1993 [157] **Location:** Austria. Dates: October	**No. patients:** 58. Non-Pregnant **Inclusion criteria:** Clinical signs of PE / infarction	**Index test class:** US **Interpretation:** NA	**Reference standard class:** SC. **Reference standard details:** Ventilation-perfusion scintigraphy	**Primary:** diagnostic accuracy of chest sonography **Secondary:** NA

Study information	Patients	Index test	Reference test	Outcomes
1989 to August 1991 **No. centres:** Single; **Type of setting:** NA	**Exclusion criteria:** NA		pulmonary angiography **Interpretation:** NA	**Follow-up:** NA
Mazurek 2015 [166] **Location:** Poland. Dates: 2010 to 2011 **No. centres:** Single; **Type of setting:** Secondary / Tertiary	**No. patients:** 84. Non-Pregnant **Inclusion criteria:** Perfusion scintigraphy preformed using planar scintigraphy, SPECT, or SPECT-CT **Exclusion criteria:** Images could not be recorded or absence of obervational data 6 months after the examination	**Index test class:** Q-SPECT-CT. **Isotope:** Q: 185 MBq (5mCi) 99m-Tc-MAA by IV. **VQ Interpretation:** Unclear. **Interpretation:** PE present: At least 1 segmental or 2 subsegmental perfusion defects without abnormalities in the lung parenchyma. PE negative: Normal perfusion pattern, perfusion defects that were not arranged in accordance with the pulmonary vasculature and perfusion defects caused by abnormalities in the lung parenchyma	**Reference standard class:** CC. **Reference standard details:** Composite reference standard - side-by-side consensus based on clinical presentation, lab test results, other imaging test results, and follow-up data **Interpretation:** Clinical presentation (dyspnea, chest pain, hemoptysis, syncope, jugular vein distention and DVT symptoms), lab test (arterial blood gas analysis, troponin and NT-proBNP levels, other imaging test results (check x-ray, echocardiography and lower extremity ultrasound), and follow-up data.	**Primary:** Sensitivity and specificiaty of planar, SPECT-CT, SPECT **Secondary:** NA **Follow-up:** 6 months
Meaney 1997 [145] **Location:** US. Dates: Eight month period (dates not reported) **No. centres:** Single; **Type of setting:** Secondary / Tertiary	**No. patients:** 30. Non-Pregnant **Inclusion criteria:** Referred to centre for investigation. **Exclusion criteria:** Contraindication to MRI, mechanical ventilation.	**Index test class:** MRI **MRI Field strength:** 1.5. **Contrast:** 40 to 60 ml of gadopentetate dimeglumine (approximately 0.3 mmol per kil- ogram of body weight) was injected over a 20-second period, fol- lowed by a 20-ml saline flush to ensure maximal enhancement of the pulmonary arteries. **Interpretation:** PE present: Presence of an intravascular filling defect. Insufficient evidence: Nonvisualization of a vessel.	**Reference standard class:** PA. **Reference standard details:** Conventional angiography **Interpretation:** NA	**Primary:** sensitivity, specificity, and positive and negative predictive values of magnetic resonance angiography in detecting pulmo- nary embolism, along with exact two-sided 95 percent confidence intervals for binomial proportions, were calculated for each re- viewers reading and for the final consensus of opinion. **Secondary:** NA **Follow-up:** NA

Study information	Patients	Index test	Reference test	Outcomes
Megyeri 2014 [130] **Location:** Switzerland. Dates: September 2007 to April 2011 **No. centres:** Single; **Type of setting:** Tertiary / ER	**No. patients:** 123 (BW > 100kg): 114 (BW **Inclusion criteria:** ?100 kg BW, requiring CTPA to exclude PE; **Exclusion criteria:** None.	**Index test class:** CT **CT slices:** 16. **Contrast:** One hundred milliliters of standard contrast medium (CM) with 300 mg/mL iodine concentration (iobitridol, Xenetix 300, Guerbet, Aulnay-sous-Bois, France) was injected intravenously using an injector (CT Expres, Swiss Medical Care, Lausanne, Switzerland). **Interpretation:** PE present: complete or partial filling defect in the pulmonary arteries on at least three contiguous transverse images of 1 mm thickness with no major movement artifacts.	**Reference standard class:** CC. **Reference standard details:** Composite reference standard (clinical probability, reference CTPA result, additional imaging (US, VQ) when performed, and 90-day follow-up) **Interpretation:** NA	**Primary:** Diagnistic accuarcy of CTPA in two patient groups **Secondary:** NA **Follow-up:** 3 - 12 months
Meier 2016 [198] **Location:** France. Dates: Screened May to October 2015 **No. centres:** Single; **Type of setting:** Secondary	**No. patients:** 101 (65 after exclusions and indeterminate tests). Non-Pregnant **Inclusion criteria:** Clinically suspected PE **Exclusion criteria:** Severely impaired renal function (eGFR	**Index test class:** CT **CT slices:** 384. **Contrast:** Injected with power injector in antecubital vesin - vessel patency tested prior to injection with saline flush; injection was followed by saline flush; low-CM flow rate 0.6 g iodine/second injection time 10 seconds increased iodine concentration and 15 mL injected (iodine load 6 g) at 1.5 mL/second; standard-CM = 80 mL iodine load, Imerson at 4mL/s **Interpretation:** Not specified for PE. Primary outcome image quality.	**Reference standard class:** CT. **Reference standard details:** CTPA standard protocol **Interpretation:** NA	**Primary:** Objective and subjetive image quality **Secondary:** Subsequent PE or PE-related deaths within 3 months after CTPA examination (based on hospital follow-up or referring physician contact) **Follow-up:** Three-month clinical follow-up
Miles 2009 [183] **Location:** Australia. Dates: March 2004 to May 2006 **No. centres:** Multi-National or	**No. patients:** 79. Non-Pregnant **Inclusion criteria:** NA **Exclusion criteria:** Patients	**Index test class:** VQ-SPECT. **Isotope:** V: 99mTc Technegas Q: 99mTc MAA 185 MBq (5 mCi) **VQ Interpretation:** Unclear. **Interpretation:** PE present: at least one mismatched defect of > 0.5 of a lung segment was present.	**Reference standard class:** CC. **Reference standard details:** Final diagnosis made by respiratory physicians who were provided with the planar scintigraphy and CTPA reports and with extensive clinical	**Primary:** NA **Secondary:** NA **Follow-up:** 3 months

Study information	Patients	Index test	Reference test	Outcomes
Regional; **Type of setting:** Secondary / Tertiary			information, including D-dimer levels, modified Wells score, and patient status at the 3-month follow-up **Interpretation:** NA	
Miniati 2003 [112] **Location:** Italy. Dates: April 2000 to September 2001 **No. centres:** Single; **Type of setting:** Secondary	**No. patients:** 425 patients referred, 390 entered study. Pregnant **Inclusion criteria:** Referred for selected PE **Exclusion criteria:** Contraindication to pulmonary angiography, >3 days antiocoagulant therapy	**Index test class:** PW **Interpretation:** PISAPED (see Definitions)	**Reference standard class:** FU. **Reference standard details:** Clinical follow-up **Interpretation:** NA	**Primary:** Proportion of patients diagnosted by pathway **Secondary:** Failure rate **Follow-up:** 1 year
Miniati 1996 [168] **Location:** Italy. Dates: November 1991 to April 1995 **No. centres:** Single; **Type of setting:** NA	**No. patients:** 890. Non-Pregnant **Inclusion criteria:** Suspected PE **Exclusion criteria:** NA	**Index test class:** Q. **Isotope:** 180 MBq of MAA with 99mTc **VQ Interpretation:** PISAPED. **Interpretation:** PISAPED (see Definitions)	**Reference standard class:** PA. **Reference standard details:** Pulmonary angiography **Interpretation:** PE present: embolus obstructing the vessel or the outline of an ambolus within a vessel	**Primary:** Sensitivity; specificity (adjusted using Bayes theorem) **Secondary:** NA **Follow-up:** Clinical, reoentgenographic and scintigraphic follow-up at 1 week, 1 month, and 1 year after anrollment (in positive patients); Follow-up duration for perfusion abnormalities not typical of PE PE was unclear but some indication that it was undertaken; patients with near-normal scans were followed-up until discharge
Miron 1999 [113] **Location:** Switzerland. Dates: June 1995 to June 1997 **No. centres:** Single; **Type of setting:** Secondary	**No. patients:** 114. Non-Pregnant **Inclusion criteria:** ?16 years, admitted for medical or surgical procedure, with PE suspected during their stay **Exclusion criteria:**	**Index test class:** PW **Interpretation:** VQ scans by PIOPED (see Definitions): normal, near-normal/very low, low, intermediate, high probability; US positive: common femoral or popliteal vein noncompressible	**Reference standard class:** FU. **Reference standard details:** FU **Interpretation:** NA	**Primary:** Proportion of patients who could be diagnosed by a non-invasive workup (excluding pulmonary angiography) **Secondary:** NA **Follow-up:** 3 months
Mitchell 2007 [206] **Location:** US. Dates: April 2003 and October 2005 **No. centres:**	**No. patients:** 1224. Non-Pregnant **Inclusion criteria:** Adult (> 17 years) patients undergoing CTA to evaluate for suspected PE who had high pretest probability or positive D-	**Index test class:** CT **CT slices:** NA. **Contrast:** 120 mL of Iopamidol via power injector through antecubital peripheral venous catheter over 30 seconds	**Reference standard class:** None. **Reference standard details:** NA **Interpretation:** NA	**Primary:** Severe acute renal failure or laboratory defined contrast nephropathy **Secondary:** Increase in creatinine from

Study information	Patients	Index test	Reference test	Outcomes
Single; **Type of setting:** NA	dimer **Exclusion criteria:** severe allergy to iodinated contrast material, unable or unwilling to provide informed consent, patients receiving chronic hemodialysis	**Interpretation:** NA		**Follow-up:** 45 days post-enrollment
Mohn 2003 [155] **Location:** France. Dates: November 2000 to May 2001 **No. centres:** Single; **Type of setting:** Secondary	**No. patients:** 74. Non-Pregnant **Inclusion criteria:** Suspicion of PE. Recent clinical symptoms of PE had to be present (e.g., pleuritic chest pain, unexplained dyspnea, or hemoptysis). **Exclusion criteria:** Symptoms reported >7 days previously, clinical indication of acute massive PE in the Emergency Department (e.g., hemodynamic failure), unavailability of a 3-month follow-up.	**Index test class:** US **Interpretation:** PE suggestive: (1) wedge-shaped, hypoechoic, homogeneous pleural-based lesions or (2) sharply outlined pleural-based lesions, triangular or rounded to the hilus, with a hyperechoic reflection at the center, possibly corresponding to the bronchioles. PE nonsuggestive: unspecific lesions of other shapes not described in connection with PE, or no lesions detected; isolated pleural effusion, nonsuggestive.	**Reference standard class:** CC. **Reference standard details:** Composite including VQ, LUS, CT, PA, and clinical follow-up (not all patients received the same tests) **Interpretation:** NA	**Primary:** DTA values **Secondary:** Other sonographic findings (describe transthoracic abnormalities) **Follow-up:** 3 months
Moores 2015 [199] **Location:** Spain. Dates: January 2008 to December 2013 **No. centres:** Single; **Type of setting:** Secondary / ER	**No. patients:** 134. Non-Pregnant **Inclusion criteria:** High pretest probability of PE (based on Wells criteria ? 7) **Exclusion criteria:** Non-high cjinical probability of PE (Wells), treatment with therapeutic doses of anticoagulants >24 hours, life expectancy of	**Index test class:** CT **CT slices:** 64. **Contrast:** 80-100 mL of non-ionic contrast material containing 250 mg of iodine per milliliter, injection speed of 4.0 mL/s **Interpretation:** PE present: contrast material outlined an intraluminal defect or if a vessel was totally occluded by low-attenuation material on at least two adjacent slices; Inconclusive: images uniterpretable because motion arefacts or insufficient contrast enhancement of the pulmonary arteries	**Reference standard class:** CC. **Reference standard details:** Confirmation of PE by VQ perfusion scan showing high probability, abnormal findings on venous ultrasonography in patients without history of DVT, occurrence of symptomatic (fatal and non-fatal) venous thromboembolism (VTE) at 3 month-follow-up (scheduled outpatient visit or telephone interview, patient self-reporting, hospital records and autopsies) after anticoagulation withheld (fatal PE, definitely present if PE confirmed by autopsy or if death followed clincially severe PE; possibly present in	**Primary:** Failure rate **Secondary:** Incidental findings **Follow-up:** 3 months

Study information	Patients	Index test	Reference test	Outcomes
			patients who died suddenly or unexpectedly) **Interpretation:** NA	
Nazerian 2014 [151] **Location:** Italy. Dates: June 2012 to November 2012 **No. centres:** Multi-National or Regional; **Type of setting:** Secondary / ER	**No. patients:** 357. Non-Pregnant **Inclusion criteria:** Aged >=18 years suspected of having a PE; Wells score > 4 or D-dimer value >=500 ng/mL (positive D-dimer); Underwent MCTPA. **Exclusion criteria:** Wells score	**Index test class:** US **Interpretation:** PE present: lung US, at least one pulmonary subpleural infarct, or heart US, right ventricular dilatation or thrombi in the right cavities; leg US, DVT. PE absent: multiorgan sonography, Investigator asked to specify if alternative ultrasonography diagnosis among pneumonia, pleural effusion, diffuse interstitial syndrome, pericardial effusion, or aortic dissection could justify the symptoms of presentation.	**Reference standard class:** CT. **Reference standard details:** MCTPA **Interpretation:** NA	**Primary:** Number of pulmonary subpleural infarcts **Secondary:** DTA values **Follow-up:** NA
Niemann 2013 [208] **Location:** Switzerland. Dates: NA **No. centres:** Single; **Type of setting:** NA	**No. patients:** 691. Non-Pregnant **Inclusion criteria:** Admitted for suspected PE **Exclusion criteria:** NA	**Index test class:** CT **CT slices:** 64. **Contrast:** NA **Interpretation:** NA	**Reference standard class:** None. **Reference standard details:** None **Interpretation:** NA	**Primary:** lifetime attributable risk (LAR) of cancer incidence/mortality; Estimations of the radiation doses received by individual organs in the course of diagnostic radiology and the resulting whole-body effective dose **Secondary:** NA **Follow-up:** 1-year
Nilsson 2002 [124] **Location:** Sweden. Dates: March 1999 and May 2001 **No. centres:** Multi-National or Regional; **Type of setting:** NA	**No. patients:** 90. Non-Pregnant **Inclusion criteria:** emodynamically stable outpatients with symptoms of acute PE presenting during the daytime **Exclusion criteria:** Pregnancy, previous adverse reactions to contrast media, renal insufciency (serum-creatinin >150 mmol/l), treatment with metformine, ongoing anticoagulation therapy, two or more previous VTE events, severe malnutrition or cachexia, expected	**Index test class:** CT **CT slices:** NA. **Contrast:** A standard dose of 120 to 150 ml Omnipaque, 240 or 300 mg I/ml (Amersham Health AB, Lidingo, Sweden) was delivered in an antecubital vein at 4 ml/s, 15 to 20 seconds before the start of scanning **Interpretation:** PE present: Low-attenuation area that completely or partially filled the lumen of an opacified vessel.	**Reference standard class:** PA. **Reference standard details:** PA **Interpretation:** PE present: Intraluminal filling defect or an occlusion with a concave border at the end of the contrast medium column, indicating a trailing edge of an embolus.	**Primary:** Sensitivity, specificity, PPV and NPV **Secondary:** NA **Follow-up:** 3 months

Study information	Patients	Index test	Reference test	Outcomes
	survival			
Nyren 2016 [137] **Location:** Sweden. Dates: February 2012 to January 2014 **No. centres:** Single; **Type of setting:** Secondary	**No. patients:** 33. Non-Pregnant **Inclusion criteria:** Clinically suspected PE, underwent diagnostic CTA, examined by the same two clinicians (primarily patients admitted to hospital) **Exclusion criteria:** Contraindications to MRI, >48 hrs between exams	**Index test class:** MRI **MRI Field strength:** NA. **Contrast:** None used **Interpretation:** PE present: filling defect, partial filling defect, and or railway track sign; if embolus detected distal vasculature was not studied further	**Reference standard class:** CT. **Reference standard details:** CTA **Interpretation:** NA	**Primary:** DTA (sensitivity, specificity, PPV, NPV) **Secondary:** Inter-reader agreement **Follow-up:** NR/no follow-up?
Ohno 2004 [147] **Location:** US. Dates: NA **No. centres:** Single; **Type of setting:** NA	**No. patients:** 48. Non-Pregnant **Inclusion criteria:** Suspicion of PE due to risk factors, symptoms, signs, or laboratory findings. **Exclusion criteria:**	**Index test class:** MRI **MRI Field strength:** 1.5. **Contrast:** 5 mL of gadodiamide hydrate (Omniscan, Daiichi Pharmaceutical) at 5 mL/sec via an antecubital vein with an automatic infusion system (Sonic Shot, Nemoto) followed by 20 mL of saline solution at same rate **Interpretation:** PE present: Vascular signs of PE reported in the literature; decreased area of perfusion within the lung parenchyma with or without filling defect in the corresponding pulmonary artery	**Reference standard class:** CC. **Reference standard details:** Composite: Pulmonary angiography + one yar of follow-up, and low/normal VQ + uneventful follow-up and no anticoagulation in those without PA **Interpretation:** VQ: Revised PIOPED.	**Primary:** Sensitivity, specificity, positive and negative predictive values, and accuracy of data sets per vascular zone **Secondary:** NA **Follow-up:** 1 year
Okada 2015 [129] **Location:** Japan. Dates: April 2012 and March 2013 **No. centres:** Single; **Type of setting:** NA	**No. patients:** 83. Non-Pregnant **Inclusion criteria:** All initial weighted average CTPA using the dual-energy technique. **Exclusion criteria:** Motion artifact caused by insufficient breath-holding or previous history of PE.	**Index test class:** CT **CT slices:** 64. **Contrast:** Low-osmolar nonionic iodinated contrast material (body weight **Interpretation:** Qanadli scoring used. The pulmonary arterial tree of each lung regarded to have 10 segmental pulmonary arteries. Embolus segmental PA scored 1 point, and emboli at the most proximal arterial level were scored a value equal to the number of	**Reference standard class:** CC. **Reference standard details:** CTPA / LPBV + clinical and physical findings **Interpretation:** PE present: complete filling defect without enhancement of lumen, or partial filling defect surrounded by areas of contrast enhancement or a peripheral filling defect that forming acute angle with the pulmonary arterial wall.	**Primary:** Number and locations of intra-pulmonary clots (IPCs) **Secondary:** DTA values **Follow-up:** 1-month

Study information	Patients	Index test	Reference test	Outcomes
		segmental arteries arising distally. Weighting factor 0 = no defect, 1 = partial occlusion, and 2 = complete occlusion). An isolated subsegmental embolus was considered to be a partially occluded segmental PA, and was assigned a value of 1, and the maximum CTOI was 40.		
Ost 2001 [200] **Location:** US. Dates: 18-month period (dates not specified) **No. centres:** Single; **Type of setting:** NA	**No. patients:** 103. Non-Pregnant **Inclusion criteria:** High clinical suspicion of PE, and non-diagnostic ventilation-perfusion scan, defined as an intermediate- or low-probability scan that was discordant with the clinical suspicion. **Exclusion criteria:** No spiral CT due to weight, prior high probability of PE or a normal ventilation-perfusion scan, prior positive lower extremity duplex studies, a serum creatinine > 2.0 mg/dL, were	**Index test class:** CT **CT slices:** NA. **Contrast:** 130 to 160 mL of Omnipaque 240 at 3.5 to 4.5 mL/sec. **Interpretation:** PE present: intraluminal filling defect in pulmonary artery. Results were recorded as positive, negative, or indeterminate for PE. If both radiologists did not agree on the reading, it was classified as indeterminate.	**Reference standard class:** CC. **Reference standard details:** Conventional PA and clinical FU of 6 months **Interpretation:** All studies were read as positive, negative, or indeterminate.	**Primary:** angiographic evidence of PE recurrent thromboembolism events **Secondary:** NA **Follow-up:** 6 months
Oudkerk 2002 [143] **Location:** Netherlands. Dates: NA **No. centres:** Single; **Type of setting:** NA	**No. patients:** 118. Non-Pregnant **Inclusion criteria:** NA **Exclusion criteria:** NA	**Index test class:** MRI **MRI Field strength:** 1.5. **Contrast:** Gadoteric acid (Dotarem, Guerbet; Paris, France) 2 mL/s, 10 s injection time for each lung. **Interpretation:** NA	**Reference standard class:** PA. **Reference standard details:** Pulmonary angiography **Interpretation:** PE present: filling defect or a persistent cut-off of a large artery in spite of highly selective injection.	**Primary:** Sensitivity, specificity, and positive and negative predictive values were assessed and 95% CI calculated **Secondary:** NA **Follow-up:** NA
Pasin 2017 [136] **Location:** Brazil. Dates: NA **No. centres:** Single; **Type of setting:** Secondary	**No. patients:** 93. Non-Pregnant **Inclusion criteria:** Referred with clinical suspicion of acute PE **Exclusion criteria:** Contraindications to MRI examinations (e.g., claustrophobia or iodinated contrast media)	**Index test class:** MRI **MRI Field strength:** 1.5. **Contrast:** None. **Interpretation:** PE present: Concordant results from two planes and one of the following criterion: direct visualization of the thrombus; cutoff of pulmonary vessel, any sudden changes in the signal	**Reference standard class:** CT. **Reference standard details:** Multidetector CT **Interpretation:** PE present: Direct visualization of the thrombus; cutoff of pulmonary vessel; or any sudden changes in the signal intensity during the course of the pulmonary artery (graded as	**Primary:** Sensitivity, specificity, PPV, NPV, Accuracy, NPV **Secondary:** NA **Follow-up:** 1 year

Study information	Patients	Index test	Reference test	Outcomes
		intensity during the course of the pulmonary artery (graded as central, lobar, segmental, or subsegmental)	central, lobar, segmental, subsegmental)	
Perez de Llano 2006 [201] **Location:** Spain. Dates: January 2001 to December 2002 **No. centres:** Single; **Type of setting:** Secondary / ER	**No. patients:** 87. Non-Pregnant **Inclusion criteria:** Clinically suspected PE, a negative helical CT, and no symptoms or signs of DVT were eligible. **Exclusion criteria:** Contraindications to CT positive helical CT	**Index test class:** CT **CT slices:** 1. **Contrast:** One hundred milliliters of nonionic contrast was administered intravenously at an injection rate of 2.5 ml/s for 40 s. **Interpretation:** PE present: direct visualization of an endoluminal nonocclusive thrombus (a central filling defect completely or partially outlined with contrast material) or complete occlusion by a thrombus in a vessel. Inconclusive: segmental arterial anatomy of all lobes, inadequate to exclude thrombus based on motion artifacts, poor contrast opacification, or inadequate anatomic visualization on axial reconstructions. Indirect signs like wedgeshaped pleural based consolidation, linear bands, and dilated central or segmental pulmonary arteries were not considered, by themselves, sufficient for a diagnosis of PE.	**Reference standard class:** FU. **Reference standard details:** Follow up of three months **Interpretation:** NA	**Primary:** To determine the safety of withholding anticoagulants in patients with clinically suspected PE (PE) and negative CT results when ultrasonography (US) was performed only in patients with clinical suspicion of DVT (DVT) **Secondary:** to evaluate the effect of CT findings on the final clinical diagnosis **Follow-up:** 3 months
Perrier 2005 [114] **Location:** Switzerland; France. Dates: August 2002, to November 2003 **No. centres:** Multi-International; **Type of setting:** Secondary / ER	**No. patients:** 756. Pregnant **Inclusion criteria:** Suspicion of PE, defined as acute onset of new or worsening shortness of breath or chest pain without another obvious cause. **Exclusion criteria:** Contraindication to CT (i.e., known allergy to contrast agents or risk of allergic reaction), impaired renal function, pregnancy,	**Index test class:** PW **Interpretation:** PE present: contrast material outlined an intraluminal defect or a vessel was totally occluded by low-attenuation material. PE absent: either a low or intermediate probability), and D-dimer negative (g per liter or above to proximal leg US or CT. High clinical probability of PE, no D-dimer	**Reference standard class:** FU. **Reference standard details:** Follow up of three months **Interpretation:** NA	**Primary:** proportion of patients with proximal deep venous thrombosis and negative findings on CT **Secondary:** estimate of the three-month risk of thromboembolism if lower-limb ultrasonography had not been performed **Follow-up:** 3-months

Study information	Patients	Index test	Reference test	Outcomes
	ongoing anticoagulant therapy for a reason other than venous thromboembolism, a life expectancy of 24 hours before admission, hemodynamic instability,' transfer to another facility	measurement, direct to CT and/or leg US. Either test was positive, treated. High clinical probability and negative findings on both CT and ultrasonography had PA.		
Pesavento 2011 [202] **Location:** Italy. Dates: June 2007 to September 2009 **No. centres:** Single; **Type of setting:** Secondary / ER	**No. patients:** 545. Non-Pregnant **Inclusion criteria:** Suspected PE, **Exclusion criteria:** Previous PE, VTE of the upper or lower extremities, other indications for anticoagulant drugs, contraindications to contrast medium (allergy or severe renal insufficiency, creatinine clearance	**Index test class:** CT **CT slices:** 64. **Contrast:** 4060 ml of non-ionic, low osmolarity contrast medium was injected with a flow of 35 ml/second (s) **Interpretation:** PE present: intraluminal filling defect outlined by contrast medium or total vessel occlusion by low-attenuation material in at least two adjacent layers. Inconclusive: artifacts from either the heart or movement of the patient, inadequate contrast enhancement of the pulmonary arteries, poor visualisation of sub-segmental arteries or unclear findings in them.	**Reference standard class:** FU. **Reference standard details:** 3 month follow-up **Interpretation:** NA	**Primary:** prevalence of PE; incidence of VTE after three months of follow-up in those with negative findings **Secondary:** NA **Follow-up:** 3 months
Pfeil 2010 [153] **Location:** Germany. Dates: NA **No. centres:** Single; **Type of setting:** NA	**No. patients:** 33. Non-Pregnant **Inclusion criteria:** Symptoms of suspected PE were enrolled in the study (including dyspnea, pleuritic chest pain, hemoptysis, vertigo or syncope, and/or tachypnea). **Exclusion criteria:** NA	**Index test class:** US **Interpretation:** NA	**Reference standard class:** CT. **Reference standard details:** MSCT **Interpretation:** PE present: intraluminal filling defects within the central and segmental/subsegmental pulmonary arteries, dilatation of main pulmonary arteries, decrease in the size of small branches, and vessel irregularities.	**Primary:** presence of intraluminal filling defects within the central and segmental/subsegmental pulmonary arteries, the dilatation of main pulmonary arteries, a decrease in the size of small branches, and vessel irregularities **Secondary:** DTA values **Follow-up:** NA
PIOPED Investigators 1990 [177] **Location:** US.	**No. patients:** 931 (755 with DTA data). Non-Pregnant **Inclusion criteria:** >= 18 years, with symptoms of PE within 24 hours of	**Index test class:** VQ. **Isotope:** V: 113Xe 5.6 to 11.1 x 10^8 Bq inhaled Q: 99mTc MAA 150 MBq IV **VQ Interpretation:** PIOPED.	**Reference standard class:** PA. **Reference standard details:** Pulmonary angiography **Interpretation:** PE present:	**Primary:** Sensitivity, specificity of VQ scans at various strata (high, intermediate, low, etc) or thresholds (high, high/intermediate,

Study information	Patients	Index test	Reference test	Outcomes
Dates: January 1985 to September 1986 **No. centres:** Multi-National or Regional; **Type of setting:** Secondary / ER	study entry, and request for VQ scan or pulmonary angiogram **Exclusion criteria:** Contraindications to CTA, pregnancy, creatinine >260 umol/L, hypersensitivity to contrast medium	**Interpretation:** High probability, intermediate probability (indeterminate), low probability, very low probability, normal, per PIOPED criteria (see Descriptions)	identification of embolus obstructing a vessel, or outline of an embolus (filling defect) in a vessel.	high/intermediate/low) **Secondary:** NA **Follow-up:** 12 months
Pleszewski 2006 [149] **Location:** Canada. Dates: NA **No. centres:** Single; **Type of setting:** Secondary / ER	**No. patients:** 48. Non-Pregnant **Inclusion criteria:** Clinical suspicion of PE referred form emergency unit, medical unit, or surgical unit **Exclusion criteria:** NA	**Index test class:** MRI **MRI Field strength:** 1.5. **Contrast:** IV 30 to 50 mL (2 mmol/kg) of gadopentetate dimeglumine (2 ml/s); 20 mL saline flush **Interpretation:** PE present: Luminal filling defect.	**Reference standard class:** Sequential. **Reference standard details:** Catheter angiography, CTA, VQ **Interpretation:** PE present: Luminal filling defect	**Primary:** Sensitivity, specificity **Secondary:** NA **Follow-up:** 6 to 12 months
Qanadli 2000 [125] **Location:** France. Dates: September 1996 to August 1998 **No. centres:** Single; **Type of setting:** Secondary	**No. patients:** 158. Non-Pregnant **Inclusion criteria:** Age of 1875 years, a clinical suspicion of acute PE (dyspnea, chest pain, hemoptysis, syncope, risk factors for thromboembolic disease, abnormal findings at chest radiography or electrocardiography, or abnormal arterial blood gas test results). **Exclusion criteria:** Clinical signs of lifethreatening PE, renal failure, history of allergy to iodinated contrast media, refused CT.	**Index test class:** CT **CT slices:** 2. **Contrast:** Contrast material was administered through an 1821-gauge catheter by using a monophasic bolus injection technique and an automated injector (MCT FLS; Medrad, Rungis, France). Two hundred fifty milligrams of iodine per liter of iodinated contrast agent (iobitridol, Xenetix 250; Guerbet, Aulnay-sous-Bois, France) was used in all patients. A total of 120150 mL (iodine dose, 30.037.5 g) was injected at 4 mL/sec, and the patient was carefully monitored by a nurse. A 10-second injection delay was selected for patients in whom an antecubital venous approach was used. **Interpretation:** Pulmonary vascular bed, divided into five anatomic	**Reference standard class:** PA. **Reference standard details:** Pulmonary Arteriography (PA) **Interpretation:** PE present: intraluminal filling defect or a vessel cutoff at least 2 mm in diameter was seen. PE negative: two projections (posteroanterior and oblique) did not show PE.	**Primary:** Presence of PE, CT Sensitivity, CT Specificity **Secondary:** NA **Follow-up:** NA

Study information	Patients	Index test	Reference test	Outcomes
		arterial levels: first-order (main pulmonary artery), second-order (right and left pulmonary arteries), third-order (lobar and interlobar arteries), fourth-order (segmental arteries), and fifth order (subsegmental arteries), using a slightly modified Boyden classification. Anatomic segments were graded as positive, negative, or inconclusive. PE present: at least one anatomic segment graded as positive. PE negative: all anatomic segments were graded as negative. Inconclusive if at least one segment was graded as inconclusive, without associated positive segments.		
Quirce 2014 [182] **Location:** Spain. Dates: November 2011 to February 2013 **No. centres:** Single; **Type of setting:** Secondary / Tertiary	**No. patients:** 102. Non-Pregnant **Inclusion criteria:** Elevated serum D-dimer and a Wells score of higher than 2 (85 intermediate risk/Wells score 36 and 17 high risk/Wells score > 6). **Exclusion criteria:** NA	**Index test class:** VQ-SPECT. **Isotope:** V: 99mTc Technegas 3-5 respiratory cycles Q: 150 MBq of 99mTc-MAA **VQ Interpretation:** EANM. **Interpretation:** VQ analyzed by modified PIOPED criteria; VQ SPECT by EANMMI guideline	**Reference standard class:** CT. **Reference standard details:** CTPA **Interpretation:** NA	**Primary:** NA **Secondary:** NA **Follow-up:** NA
Reinartz 2006 [186] **Location:** Germany. Dates: July 2003 to July 2005 **No. centres:** Single; **Type of setting:** NA	**No. patients:** 53. Non-Pregnant **Inclusion criteria:** Had VQ lung scintigraphy using the SPECT technique and multidetector-row spiral CT (MDCT) within an interval of 48 h **Exclusion criteria:** NA	**Index test class:** VQ-SPECT. **Isotope:** V: 99mTc-technegas (Vita Medical Ltd.) 50 MBq **VQ Interpretation:** Unclear. **Interpretation:** PE present: mismatch defects of at least half-segment size	**Reference standard class:** CT. **Reference standard details:** MDCT **Interpretation:** NA	**Primary:** Sensitivity, specificity, and accuracy of the conventional visual assessment **Secondary:** NA **Follow-up:** 6 months
Reinartz 2004 [122] **Location:** Germany. Dates: January 2001 to	**No. patients:** 83. Non-Pregnant **Inclusion criteria:** Had VQ lung scintigraphy in SPECT technique as well as multislice spiral CT within an	**Index test class:** VQ. **Isotope:** V: Inhaled 485 +/- 72 MBq 99mTc-technegas over 35 respiratory cycles. Q: 99mTc MAA 206+/- 22	**Reference standard class:** CT. **Reference standard details:** Multislice CT **Interpretation:** PE present: one or	**Primary:** NA **Secondary:** NA **Follow-up:** at least 5 months (max 10 months)

Study information	Patients	Index test	Reference test	Outcomes
April 2003 **No. centres:** Single; **Type of setting:** NA	interval of 3 d **Exclusion criteria:** NA	MBq MAA IV **VQ Interpretation:** PIOPED. **Interpretation:** PIOPED criteria (See Definitions)	more embolic clots were detected in the pulmonary arteries	
Reissig 2004 [154] **Location:** Germany. Dates: NA **No. centres:** Single; **Type of setting:** NA	**No. patients:** 62. Non-Pregnant **Inclusion criteria:** US as well as spiral CT performed within 24 h after the onset of symptoms **Exclusion criteria:** NA	**Index test class:** US **Interpretation:** PE present: Intraluminal filling defects within central and segmental/ subsegmental pulmonary arteries, dilatation of main pulmonary arteries, decrease in size of small branches as well as vessel irregularities.	**Reference standard class:** CT. **Reference standard details:** Spiral CT **Interpretation:** NA	**Primary:** Sensitivity, specificity, and positive and negative predictive values **Secondary:** NA **Follow-up:** NA
Reissig 2001 [156] **Location:** Germany. Dates: February 1998 to March 2000 **No. centres:** Single; **Type of setting:** NA	**No. patients:** 69. Non-Pregnant **Inclusion criteria:** NA **Exclusion criteria:** NA	**Index test class:** US **Interpretation:** PE present: Intraluminal filling defects, defects within the central pulmonary srteries, dilatation of the main pulmonary arteries and decreases in the size of the small branches of the lung as well as irregularites of the blood vessels	**Reference standard class:** CT. **Reference standard details:** Spiral CT **Interpretation:** NA	**Primary:** Sensitivity, specificity, and positive and negative predictive values **Secondary:** NA **Follow-up:** NA
Revel 2013 [139] **Location:** France. Dates: June 2007 to June 2009 **No. centres:** Single; **Type of setting:** Secondary	**No. patients:** 300 (277 completed MRI). Non-Pregnant **Inclusion criteria:** High clinical probability of PE or D-dimer >500 ug/L **Exclusion criteria:** Signs of severe PE (hypotension), curative anticoagulation >=48h, 3 month follow-up not possible, MRI contraindicated (claustrophobia, metallic occular implant, pacemaker, allergy to gadolinium-based contrast agents, obesity (weight >130 kg, postero-anterior abdominal diameter >60 cm), contraindications to CTA (GFR	**Index test class:** MRI **MRI Field strength:** 1.5. **Contrast:** Perfusion sequences: 0.1 ml/kg DOTA-Gd at 5 ml/s. Contrast-enhanced 0.15 mg/kg body weight DOTA-Gd at 3 ml/s, per acquistion. **Interpretation:** Unenhanced: PE present: signal void within pulmonary artery branch, whatever its division order; PE absent: no signal void up to subsegmental level, artefact-free; Inconclusive due artefacts or partial acquisition. Perfusion sequences: PE perfusion defect: defect with sharp borders fitting sub-segmental, segmental, or	**Reference standard class:** CT. **Reference standard details:** CTPA **Interpretation:** No details. All results considered as confirming CTA.	**Primary:** Diagnostic accuracy, comparing 3 MRI sequences **Secondary:** NA **Follow-up:** NA

Study information	Patients	Index test	Reference test	Outcomes
		lobar distribution. PE negative: homogenous enhancement of lung parenchyma.PE inclusive: artefacts or partial aquisition or poor enhancement, poorly circumscribed defect not fitting sub-segmental, segmental or lobar distribution. Contrast-enhanced sequence: PE positive: Signal void within pulmoary artery branch, whatever its division order. PE negative: No signal void on well-enhanced artefact-free pulmonary arteries. Inconclusive due artefacts or partial aquisition or poor enhancement, and no PE detected otherwise.		
Revel 2012 [140] **Location:** France. Dates: June 2007 to June 2009 **No. centres:** Single; **Type of setting:** Secondary / Tertiary / ER	**No. patients:** 300 (275 completed MRI). Non-Pregnant **Inclusion criteria:** Suspected PE, >18 years, high clinical probability (based on Geneva) or D-dimer > 500 ug/L on ELISA based test, provided written informed consent (first patient per day identified included as only one MRI scan could be completed per day) **Exclusion criteria:** Unstable hemodynamics; on therapeutic anticoagulation for >48 hours; contraindication to MRI (claustrophobia, metallic ocular implant, pacemaker, reported allergy to gadolinium based contrast, glomerular filtration rate 130 kg or postero anterior abdonimal diameter > 60 cm were additional exclusions; patients with inconclusive CT 9unless normal VQ or uneventful	**Index test class:** MRI **MRI Field strength:** 1.5. **Contrast:** NA **Interpretation:** Positive; negative; or inconclusive (if technically inadequate). Criteria not described.	**Reference standard class:** CT. **Reference standard details:** CTA (64 detector) including all subsegmental results; Seconadry reference standard where all single-subsegmental emboli were considered negative (considering unclear clinical significance) **Interpretation:** See reference 7 for interpretation criteria	**Primary:** Sensitivity, specificity **Secondary:** NA **Follow-up:** 3 months

Study information	Patients	Index test	Reference test	Outcomes
	follow-up were excluded); patients who presented out of hours (882/1796 ineligible on this basis)			
Revel 2005 [203] **Location:** France. Dates: January 2001 to June 2001 **No. centres:** Single; **Type of setting:** NA	**No. patients:** 220. Non-Pregnant **Inclusion criteria:** Referred to undergo thoracic CT angiography for suspicion of PE **Exclusion criteria:** Contrast contraindicated, previous PE and prior ventilation-perfusion scanning, young patients free of prior cardiopulmonary disease, low clinical suspicion of PE and normal chest radiographs		**Reference standard class:** FU. **Reference standard details:** Follow up of 3 months **Interpretation:** NA	**Primary:** Recurrent VTE events **Secondary:** NA **Follow-up:** 3 months
Righini 2008 [116] **Location:** Switzerland; France; Brussells. Dates: January 2005 to August 2006 **No. centres:** Multi-International; **Type of setting:** Secondary / Tertiary / ER	**No. patients:** 1819 (1812 who entered testing (intention-to-diagnose), 1693 completed testing per protocol (Primary analysis group). Non-Pregnant **Inclusion criteria:** >18 years with clinical suspicion of PE (acute onset of new or worsening SOB or chest pain without another obvious cause). **Exclusion criteria:** Contraindication to CT (allergy/at risk of allergic reaction to contrast) or impaired renal function, pregnancy, age	**Index test class:** PW **Interpretation:** PE present on CT: Positive if contrast material outlined intraluminal defect or vessel totally occluded by low attenuation. DVT positive: Incomplete compressibility of proximal deep vein.	**Reference standard class:** APW. **Reference standard details:** Pathway (Clinical probability assessment, D-dimer, and CT): Calculated clinical probability of PE (revised Geneva score) Randomized D-dimer test for patients with low or intermediate probability If D-dimer concentration = r/o PE, no further testing If D-dimer concentration > 500 ng/mL or if high clinical probability --> MSCT If MSCT showed PE --> anticoagulate If MSCT negative + high clinical probability --> VQ scan or pulmonary angiography If MSCT non-conclusive or isolated subsegmental PE, any clinical probability --> VQ scan or pulmonary angiography If VQ scan high probability --> anticoagulate If VQ scan normal --> no PE, no further testing If VQ scan intermediate --> pulmonary	**Primary:** 3-month thromboembolic risk in patients left untreated because PE was excluded **Secondary:** Adverse events. Clinical outcomes of treatment. **Follow-up:** 3 months

Study information	Patients	Index test	Reference test	Outcomes
			angiography **Interpretation:** See interpretation of index test	
Rubini 2007 [165] **Location:** Italy. Dates: May 2002 to June 2004 **No. centres:** NA; **Type of setting:** Secondary / Tertiary	**No. patients:** 107. Non-Pregnant **Inclusion criteria:** PLS and MSCT examination obtained within 7 days of the clinical-laboratory suspicion of PE, no thrombolytic therapy under way, prior chest radiography. **Exclusion criteria:** NA	**Index test class:** Q. **Isotope:** 185 MBq of MAA with 99 mTc **VQ Interpretation:** PISAPED. **Interpretation:** PISAPED (see Definitions)	**Reference standard class:** CT. **Reference standard details:** Multislice CT **Interpretation:** PE present: eccentric filling defects or of complete occlusion of the pulmonary artery lumen, whether associated or not to the presence of areas of parenchymal hypoventilation.	**Primary:** PE **Secondary:** NA **Follow-up:** 7days
Schiebler 2013 [54] **Location:** US. Dates: September 2007 to December 2009 **No. centres:** Single; **Type of setting:** Secondary	**No. patients:** 190 with MRA; 167 with 3+ months follow-up; 148 with 1 year follow-up. Non-Pregnant **Inclusion criteria:** Possible PE in symptomatic patient **Exclusion criteria:** Contraindications to MRI (metal, pacemakers, non-compatible implants). Outside hours of MRA-PE availability	**Index test class:** MRI **MRI Field strength:** 1.5. **Contrast:** 0.1 mmol/kg gadobenate dimeglumine diluted to 30 mL with saline injected at 1.5 mL/s **Interpretation:** Adequate: no significant breathing motion and clear visualization of the segmental pulmonary arteries	**Reference standard class:** FU. **Reference standard details:** NA **Interpretation:** NA	**Primary:** VTE or death at 3 months (for all patients) and 1 year of follow-up (in patients with an initial negative scan) **Secondary:** NA **Follow-up:** 1 year
Skarlovnik 2014 [161] **Location:** Slovenia. Dates: 2010 **No. centres:** Multi-National or Regional; **Type of setting:** Secondary / Tertiary	**No. patients:** 147. Non-Pregnant **Inclusion criteria:** NA **Exclusion criteria:** Technically inadequate scans,	**Index test class:** VQ-SPECT. **Isotope:** Q: 120-200 MBq 99mTc MAA. VQ-SPECT: V: 99mTc-Technegas 20 40 MBq inhalation. Q: 99mTc-MAA 100-125 MBq IV **VQ Interpretation:** EANM. **Interpretation:** EANM guidelines.Using 0.5 segment mismatch criteria and revised PIOPED II. PE present: ?2 segments of VQ mismatch or ?3 VQ mismatch defects >50% of segment.	**Reference standard class:** CC. **Reference standard details:** Composite diagnosis absed on clinical decision and 12 months follow-up where all investigations including CTPA were taken into account **Interpretation:** 0.5 segment mismatch criteria; ?2 segments of VQ mismatch. ?3 VQ mismatch defects >50% of segment	**Primary:** NA **Secondary:** NA **Follow-up:** 12 month
Sodhi 2010 [204] **Location:** India. Dates: 2-year	**No. patients:** 50. Non-Pregnant **Inclusion criteria:** High clinical suspicion of PE: Hemodynamic	**Index test class:** CT **CT slices:** 4. **Contrast:** The contrast protocol was standardized	**Reference standard class:** CC. **Reference standard details:** combination of clinical, imaging,	**Primary:** to evaluate the role of CT pulmonary angiography (CT-PA) in detecting additional information that

Study information	Patients	Index test	Reference test	Outcomes
period (dates not specified) **No. centres:** Single; **Type of setting:** Tertiary	compromise (systolic BP **Exclusion criteria:** NA	in all patients. 100 ml of 30% contrast agent (Ultravist 300, Schering, Berlin, Germany) was injected with a power injector through an 18-20-gauge venous line in antecubital fossa or through central venous catheter, at a flow rate of 4 ml/ s using a timing bolus (smart prep technique). **Interpretation:** Not specified	and laboratory analysis, after adequate imaging, laboratory tests (VQ scintigraphy and Doppler ultrasound for deep venous thrombosis were performed at the clinicians discretion. However chest x-ray, arterial blood gas analysis (ABG), compression sonography, and echocardiography (Echo) were done in all patients) **Interpretation:** All available imaging, laboratory analysis, and clinical information was used by the radiologists to provide a possible alternative diagnosis	may help in making an alternative diagnosis, in patients referred to CT for a suspected acute PE **Secondary:** NA **Follow-up:** 3 months
Sostman 2008 [164] **Location:** US. Dates: September 2001 to July 2004 **No. centres:** Multi-National or Regional; **Type of setting:** Secondary / ER	**No. patients:** 910 usable data, 889 complete data (41 excluded due to incomplete data). Non-Pregnant **Inclusion criteria:** Included in PIOPED II (Stein 2006[67]), had DSA diagnosis or CTA result concordant with Wells score, interpretable perfusion scans. **Exclusion criteria:** As for PIOPED II (Stein 2006[67]), did not undergo CTA, VQ; does not have CTA diagnosis, or CTA discordant with Wells score, intermediate or low probability VQ scan, perfusion scan not available or interpretable	**Index test class:** Q. **Isotope:** NA **VQ Interpretation:** Multiple. **Interpretation:** PIOPED II (see Definitions), modified for absence of V component, and examining perfusion-chest radiograph match: High probability (2 or more segments of perfusion-chest radiograph mismatch); PE absent: Normal, very low probability; Not diagnostic: all other findings. PISAPED; PE persent: one or more wedge-shaped perfusion defects; PE absent: normal perfusion, near-normal, contour defect caused by enlarged heart, mediastinum, or diaphragm, non-wedge shaped perfusion defect; PE nondiagnostic	**Reference standard class:** DSA or CT+Wells. **Reference standard details:** DSA, or if no DSA, CTA results concordant with Wells results (e.g., CTA positive + Wells score >2 or CTA negative + Wells score <6) **Interpretation:** NA	**Primary:** Sensitivity and specificity of Q + CXR in patients categorized as PE present or PE absent **Secondary:** NA **Follow-up:** NA
Sostman 2008 [180] **Location:** US. Dates: September 2001 to July 2003	**No. patients:** 951 enrolled, 910 had DSA or concordant CT/Wells scores (41 excluded). Non-Pregnant **Inclusion criteria:** Included in	**Index test class:** VQ. **Isotope:** NA **VQ Interpretation:** Modified PIOPED II. **Interpretation:** Modified PIOPED II: Includes PE present	**Reference standard class:** DSA or CT+Wells. **Reference standard details:** DSA, or if no DSA, CTA results concordant with Wells	**Primary:** Sensitivity and specificity of VQ studies of patients categorized as PE present or PE absent **Secondary:** NA

Study information	Patients	Index test	Reference test	Outcomes
No. centres: Multi-National or Regional; **Type of setting:** Secondary / ER	PIOPED II (Stein 2006[67]), had DSA diagnosis or CTA result concordant with Wells score **Exclusion criteria:** As for PIOPED II (Stein 2006[67]), did not undergo CTA, VQ, does not have CTA diagnosis, or CTA discordant with Wells score, intermediate or low probability VQ scan	(high probability), PE absent (normal low or vey low), nondiagnostic (all other findings - intermediate probability)	results (e.g., CTA positive + Wells score >2 or CTA negative + Wells score <6) **Interpretation:** NA	**Follow-up:** NA
Stein 2010 [146] **Location:** US. Dates: April 2006 to September 2008 **No. centres:** Multi-National or Regional; **Type of setting:** Secondary / ER	**No. patients:** 818 (371 completed both imaging modalities, 279 with diagnosis on imaging). Non-Pregnant **Inclusion criteria:** 18 years or older, hospitalized or in ER with diagnosed or excluded PE. (Recruitment during nurse-coordinator's working hours). **Exclusion criteria:** Implanted ferromagnetic foreign bodies, dependency on external electrical device, claustrophobia, pregnant or nursing, inability to lie still for 30 minutes, renal exclusions (criteria changed multiple times).	**Index test class:** MRIMRV **Interpretation:** PE Positive: Partially occlusive intraluminal filling defect or complete arterial occlusion with termination of column of contrast material in a meniscus that outlined trailing edge of embolus. Combined MRA+MRV positive if one test was positive. PE negative: Adequate opacification of subsegmental branches; Both MRA and MTV had to be considered technically adequate	**Reference standard class:** CC. **Reference standard details:** Imaging: CT angiogram and venography; VQ lung scan; PE excluded only: Normal D-dimer in patient with low (whole blood or latex D-dimer) or intermediate probability. Clinical assessment **Interpretation:** CT: PE positive: PE in main or lobar pumonary artery or PE in segmental or subsegmental artery + high clinical probability (Wells). PE excluded: Negative + low clinical probability (Wells) or Negative angiogram and venogram / US venogram + intermediate probability (Wells). VQ: High probability VQ + no previous PE + high/intermediate clinical probability (Wells)	**Primary:** Sensitivity, specificity, likelihood ratio **Secondary:** Adverse events **Follow-up:** 3 months. 6 months for patients with reduced renal function.
Stein 2007 [133] **Location:** Canada; US. Dates: September 2001 to July 2003 **No. centres:** Multi-National or Regional; **Type of setting:** Secondary	**No. patients:** 824. Non-Pregnant **Inclusion criteria:** As for PIOPED II (Stein 2006[67]). At least 18 years of age with clinically suspected acute PE, referred for diagnostic imaging for suspected PE, consultation request for suspected PE. **Exclusion criteria:** As for PIOPED II (Stein 2006[67]). Unable to complete		**Reference standard class:** SC. **Reference standard details:** Composite reference standard **Interpretation:** Refer Stein 2006 (Ref ID 221)	**Primary:** DTA values **Secondary:** NA **Follow-up:** NA

Study information	Patients	Index test	Reference test	Outcomes
/ Tertiary	testing within 36 hr, abnormal creatinine levels, receiving long-term renal dialysis, history of long-term anticoagulant use, critically ill receiving ventilatory support, allergic to contrast agents, myocardial infarction within preceding month, possible pregnancy, inferior vena caval filter in situ, no suspected PE, upper-extremity DVT, VF or sustained VT within 24 hr, shock or hypotension, planned thrombolytic therapy within 24 hours,			
Stein 2006 [67] **Location:** Canada; US. Dates: September 2001 to July 2003 **No. centres:** Multi-International; **Type of setting:** Secondary / Tertiary	**No. patients:** 824. Non-Pregnant **Inclusion criteria:** At least 18 years of age with clinically suspected acute PE, referred for diagnostic imaging for suspected PE, consultation request for suspected PE. **Exclusion criteria:** Unable to complete testing within 36 hr, abnormal creatinine levels, receiving long-term renal dialysis, history of long-term anticoagulant use, critically ill, receiving ventilatory support, allergic to contrast agents, myocardial infarction within preceding month, possible pregnancy, inferior vena caval filter in situ, no suspected PE, upper-extremity DVT, previously enrolled in the study, VF or sustained VT within 24 hr, shock or hypotension, planned thrombolytic therapy within the next 24 hr,		**Reference standard class:** SC. **Reference standard details:** Composite reference standard (VQ scan showing high probability, abnormal DSA, abnormal US) **Interpretation:** PE present: ventilationperfusion lung scanning showing a high probability of PE in a patient with no history of PE, abnormal findings on pulmonary DSA, or abnormal findings on venous ultrasonography in a patient without previous deep venous thrombosis at that site and nondiagnostic results on ventilationperfusion scanning (not normal and not high probability without previous PE). Abnormal venous ultrasonography in such a patient was interpreted as a surrogate for the diagnosis of PE. Exclusion of PE according to the composite reference standard required one of the following conditions: normal findings on	**Primary:** diagnosis of PE **Secondary:** addition of Wells score improved ability to detect or rule out PE **Follow-up:** 3- and 6-months

Study information	Patients	Index test	Reference test	Outcomes
			DSA, normal findings on ventilationperfusion scanning, ventilationperfusion scanning showing either a low or very low probability of PE, a clinical Wells score of	
Thieme 2012 [120] **Location:** Germany. Dates: October 2007 and November 2009 **No. centres:** Single; **Type of setting:** NA	**No. patients:** 15. Non-Pregnant **Inclusion criteria:** Suspected PE (9 patients) or suspected pulmonary arterial hypertension (PAH, 10 patients). **Exclusion criteria:** NA	**Index test class:** CT **CT slices:** NA. **Contrast:** 80mL of high-concentration iodine-based contrast material (Iopromide, Ultravist370, BayerScheringPharma, Berlin, Germany) were administered at a flow rate of 4.0mL/s, followed by a 100mL saline chaser bolus at the same injection rate. Bolus tracking with a threshold of 100 HU in the pulmonary trunk and a delay of 7s were applied. **Interpretation:** Embolic clot or an abrupt intravascular stop of contrast opacification.	**Reference standard class:** VQ-SPECT-CT. **Reference standard details:** VQ SPECT-CT **Interpretation:** Comprehensive reading of perfusion SPECT-CT and inhalation scintigram and diagnosis of acute PE on the basis of a characteristic mismatch of the respective patterns	**Primary:** determine the diagnostic accuracy of Dual Energy CT (DECT) in the detection of perfusion defects **Secondary:** evaluate the potential of DECT to improve the sensitivity for PE **Follow-up:** NA
van Es 2015 [167] **Location:** Netherlands; Belgium. Dates: October 2008 and February 2012 **No. centres:** Multi-International; **Type of setting:** Secondary / Tertiary	**No. patients:** 76 (74 with definite diagnosis). Non-Pregnant **Inclusion criteria:** In/out patients **Exclusion criteria:** 50 years, pregnancy, >48 hours use of therapeutic dose LMWH or unfractionated heparin prior to eligibility assessment, thrombolytic therapy and inability to perform a perfusion scan within 24 hrs after CTPA	**Index test class:** Q. **Isotope:** 148-155 MBq 99mTc MAA particles **VQ Interpretation:** PISAPED. **Interpretation:** PISAPED criteria (see Definitions). PE present: Single or multiple wedge-shaped perfusion defects, irrespective of abnormalities on the chest X-ray; PE absent: either no perfusion defects of any kind or defects smaller or equal in size and shape to chest radiograph abnormalities. Or defects not wedge shaped; PE nondiagnostic = all other cases. Chest X-Ray: abnormal if: enlargement of the heart or hilar vessels; elevated diagrapgm;	**Reference standard class:** CT. **Reference standard details:** CPTA **Interpretation:** PE confirmed if constant intraluminal defect in sub-segmental or more proximal branches of pulmonary artery	**Primary:** Sensitivity, specificity, PPV, NPV. Inter-observer agreement. **Secondary:** NA **Follow-up:** No formal follow up. Retrospective assessment of PE in patients with negative scans. (Discrepancy between CTPA and X/Q scan result)

Study information	Patients	Index test	Reference test	Outcomes
		pleural effusion; increased lung desnity; pulmonary edema; consolidation suggestive of infarction; emphysema; or fibrothorax		
Vigo 2006 [115] **Location:** Italy. Dates: April 2001 to November 2005 **No. centres:** Multi-National or Regional; **Type of setting:** Secondary / Tertiary	**No. patients:** 702. Non-Pregnant **Inclusion criteria:** Clinical suspicion of the first episode of PE **Exclusion criteria:** Previous venous thromboembolism (VTE) episodes, hemodynamic instability, proven (symptomatic or asymptomatic) leg vein thrombosis as assessed by bilateral vein ultrasonography, life expectancy shorter than 6 months, other indications for anticoagulation, severe renal insufficiency or other contraindications to contrast agents, poor compliance, ongoing or presumed pregnancy, age	**Index test class:** PW **Interpretation:** PIOPED criteria (see Definitions). PE present: contrast material outlined intraluminal filling defect or if vessel totally occluded by low-attenuation material. With VQ, the Prospective Investigation of PE Diagnosis study criteria were used for its interpretation. high probability of PE were considered to have the thromboembolic complication. negative or very low probability of PE were considered not to have the disease. In all other patients, a pulmonary angiography was attempted, and patients were considered to have or not to have PE according to angiographic findings.	**Reference standard class:** FU. **Reference standard details:** Follow up of 6 months **Interpretation:** NA	**Primary:** VTE events **Secondary:** NPV, safety of withholding anticoagulation from patients with negative CT and negative D-dimer (estimated rate of alternative diagnoses on spiral CT in patients free from PE) **Follow-up:** 6 months
Wang 2009 [121] **Location:** China. Dates: October 2005 to February 2007 **No. centres:** Single; **Type of setting:** NA	**No. patients:** 82. Non-Pregnant **Inclusion criteria:** Normal creatinine level, willing to undergo VQ scan and CTPA. **Exclusion criteria:** Pregnant, currently experiencing circulatory shock or had hypotension or renal failure, hemodynamically unstable, ventilatory support, chronic pulmonary hypertension, receiving anticoagulation, history of allergy to contrast media.		**Reference standard class:** CC. **Reference standard details:** Composite reference standard (all imaging modalities, all available laboratory recorders, clinical data, opinions of physicians responsible for treatment, and outcomes) **Interpretation:** The final diagnosis was made using a composite reference test that was based upon all imaging modalities, all available laboratory recorders, clinical data, the opinions of the	**Primary:** DTA values **Secondary:** NA **Follow-up:** NA

Study information	Patients	Index test	Reference test	Outcomes
			physicians responsible for treatment and outcomes.	
Watanabe 2015 [160] **Location:** Slovenia;Turkey; Czeck Republic; Uruguay; India. Dates: October 2004 and September 2008 **No. centres:** Multi-International; **Type of setting:** Secondary / Tertiary	**No. patients:** 201 (129 with abnormal CXR). Non-Pregnant **Inclusion criteria:** Presenting with suspicion of acute PE within 24 h, No abnormalities on CXR. **Exclusion criteria:** 3 days thrombolytic therapy before event, difficult to follow-up for 24 weeks, renal failure, known allergy to iodine, known pulmonary hypertension, abnormalities on CXR	**Index test class:** VQ. **Isotope:** V: 99mTc aerosol (2 sites), 99mTc ultrafine gas (2 sites), Xe-133 gas (1 site) Q: Not reported. **VQ Interpretation:** Multiple. **Interpretation:** 3 sets of diagnostic criteria applied:: PIOPED (VQ) (PE present, PE absent or non-diagnostic), PISAPED (Q alone) (PE present, PE absent or nondiagnostic), modified PISAPED (VQ) (PE present, PE absent, nondiagnostic). CT: PE present: complete arterial occlusion, failure to opacify, artery possibly enlarged. Central filling defect. Peripheral intraluminar defect that makes acute angle with arterial wall. PE absent: Normal, without perfusion defects. As chronic PE: complete occlusion of vessel smaller than others at same order of branching. Peripheral filling defect making obtuse angle with vessel wall. Vessel wall thickening.	**Reference standard class:** FU. **Reference standard details:** Final clinical assessment at 24 weeks by physician blinded to interpretations of imaging except CXR. Assessment took into account response to anticoagulation. **Interpretation:** NA	**Primary:** Sensitivity and specificity **Secondary:** AUROC **Follow-up:** 24 weeks
Weinmann 2008 [187] **Location:** France. Dates: NA **No. centres:** NA; **Type of setting:** NA	**No. patients:** 142. Non-Pregnant **Inclusion criteria:** Clinical suspicion of acute PE (**Exclusion criteria:** CT already undergone, pregnancy, age	**Index test class:** VQ-SPECT. **Isotope:** V: 99m Tc Technegas 445 to 555 MBq over 3-5 respiratory cycles. Q: 99mTc MAA 300 MBq **VQ Interpretation:** Unclear. **Interpretation:** Updated PIOPED II (see Definitions): normal, very low, low, intermediate, or high probability. PE present: Very high probability (at least one segmental or sub-segmental (>15% of a	**Reference standard class:** CT. **Reference standard details:** Multidetector-Row CT **Interpretation:** PE present: (1) CT showed thrombus in a main or lobar or a segmental branch of a pulmonary artery or at least two thrombus at the subsegmental level and/or (2) US showed thrombus or/and non compressibility of the vein.	**Primary:** NA **Secondary:** NA **Follow-up:** 6 month

Study information	Patients	Index test	Reference test	Outcomes
		segment) perfusion defect with a normal corresponding ventilation (mismatch defect). PE absent: Normal or very low. Non diagnostic: Low and intermediate probability.		
Winer-Muram 2004 [123] **Location:** US. Dates: September 1999 to March 2001 **No. centres:** Single; **Type of setting:** Secondary / Tertiary / ER	**No. patients:** 93. Non-Pregnant **Inclusion criteria:** Suspicion of acute PE on the basis of clinical presentation. **Exclusion criteria:** Age 1.5 mg/dL (132.6 mol/L) within the previous 24 hours (unless the patient was undergoing hemodialysis for chronic renal failure), history of severe allergic reaction to iodinated contrast material, pregnancy or possibility of pregnancy, and recent lower-extremity US study that demonstrated deep venous thrombosis.	**Index test class:** CT **CT slices:** 4. **Contrast:** Contrast material was injected with a 20-gauge catheter into the antecubital vein with a monophasic technique at a rate of 4 mL/sec. The total amount of contrast material injected was 120 mL, with an average scan delay of 20 seconds (range, 1722 seconds) from the start of injection to the start of scanning. **Interpretation:** PE present: low-attenuation filling defect	**Reference standard class:** PA. **Reference standard details:** Pulmonary Arteriography (PA) **Interpretation:** Since the study was directed toward acute PE, patients who had only chronic PE (eg, organizing mural thrombus and/or recanalization of the lumen) were categorized as negative for PE. Findings suggestive of chronic PE were defined as dilatation of the central pulmonary arteries, areas of poor perfusion, and tortuous and pruned peripheral arteries with strictures, webs, or both. Those findings might be seen with pulmonary hypertension resulting from a cause other than emboli as well, but they are highly suggestive of chronic PE in a person with an appropriate history (eg, a history of chronic venous thromboembolic disease).	**Primary:** Presence of PE, CT Sensitivity, CT Specificity **Secondary:** NA **Follow-up:** NA
Woo 2012 [205] **Location:** Canada. Dates: January 2007 to December 2007 **No. centres:** Multi-National or Regional; **Type of setting:** Secondary / Tertiary	**No. patients:** 1424. Non-Pregnant **Inclusion criteria:** NA **Exclusion criteria:** NA	**Index test class:** CT **CT slices:** 8. **Contrast:** The total volume of contrast material ranged from 80 to 150 mL and the injection rate ranged from 2 to 4 mL/s. **Interpretation:** PE present: one or more low-density filling defects within the contrast-enhanced lumen of central, segmental, or subsegmental pulmonary arteries.	**Reference standard class:** None. **Reference standard details:** None **Interpretation:** NA	**Primary:** We estimated mortality benefit of pulmonary CTA by multiplying the rate of positive pulmonary CTA examinations by published estimates of mortality of untreated PE in ambulatory and inpatient settings. We estimated the lifetime attributable risk of cancer mortality due to radiation from pulmonary CTA by calculating the

Study information	Patients	Index test	Reference test	Outcomes
		PE negative: no central or segmental PE but subsegmental PE cannot be excluded. Nondiagnostic: excessive motion artifact or because of inadequate pulmonary arterial contrast density		estimated effective dose and using sex-specific polynomial equations derived from the Biological Effects of Ionizing Radiation VII report. We calculated benefit-torisk ratios by dividing the mortality benefit of preventing a fatal PE by the mortality risk of a radiation-induced cancer. **Secondary:** NA **Follow-up:** one-year
Woods 1989 [179] **Location:** Canada. Dates: February 1985 to September 1987 **No. centres:** NA; **Type of setting:** NA	**No. patients:** 38. Non-Pregnant **Inclusion criteria:** Suspected PE with PA within 48 hours of VQ lung scan, and 24 hours of chest radiograph **Exclusion criteria:** Not specified	**Index test class:** VQ. **Isotope:** V: 1.11 GBq of 99mTC-DTPA radioaerosol inhaled. Q: 185 MBq of 99mTC MAA **VQ Interpretation:** Multiple. **Interpretation:** Modified Biello; PIOPED criteria with ratings of normal, low, indeterminate, or high probability (see Definitions)	**Reference standard class:** PA. **Reference standard details:** PA **Interpretation:** PA PE present: intraluminal filling defect identified	**Primary:** Differences between the Biello and PIOPED criteria of interpreting VQ scans with respect to sensitivity of high probability VQ scans and specificity of low probability VQ scans. Accuracy of the two criteria based on ROC curve analysis **Secondary:** NA **Follow-up:** NA
Yazici 2016 [207] **Location:** Turkey. Dates: 2011 to 2015 **No. centres:** Single; **Type of setting:** Tertiary	**No. patients:** 189. Non-Pregnant **Inclusion criteria:** Diagnosed with PE with CTPA. **Exclusion criteria:** Diagnosed using other methods, renal replacement therapy, cardiogenic shock, only one creatinine measurement during follow-up, taking nephrotoxic drugs,	**Index test class:** CT **CT slices:** 16. **Contrast:** a bolus infusion of 85 ml iodinated contrast agent (350 mg I/ml, OMNIPAQUE, GE Healthcare Ireland, Cork, Ireland) was administered intravenously at 4 ml/s using an automatic injector via an antecubital vein. **Interpretation:** NA	**Reference standard class:** None. **Reference standard details:** None **Interpretation:** NA	**Primary:** contrast induced nephropathy incidence, renal replacement therapy incidence **Secondary:** In-hospital adverse events (death, hemodynamic instability requiring positive inotropic agents, hypoxia requiring mechanical ventilation, major bleeding) were secondary end points **Follow-up:** 4-years
Zhang 2013 [138] **Location:** China. Dates: December 2010 to March 2012 **No. centres:** Single; **Type of setting:** Unclear	**No. patients:** 27 (43 assessed, 16 excluded). Non-Pregnant **Inclusion criteria:** Recruited from department of nephrology, >15 years old, no PE symptoms, diagnosis of nephrotic syndrome (24 hours urine protein >3.5 g; blood plasma albumin 16 d/dl; prothrombin time 400 mg/L; serum total	**Index test class:** MRI **MRI Field strength:** 3. **Contrast:** 20 ml of gadopentetate dimeglumine (Bayer HealthCare Pharmaceuticals) injected through antecubital vein 2 mL/sec; 20 mL aline flush **Interpretation:** PE positive: nonenhancing intraluminal filling	**Reference standard class:** CT. **Reference standard details:** CT, on dual-source CT scanner. Somatom Definition, Siemens Medical Solutions. **Interpretation:** PE present: intraluminal filling defect partially or completely occluding the pulmonary arteries	**Primary:** Diagnostic sensitivity, specificity, PPV, NPV, accuracy for MRPA on per-patient, per-lobe basis, and different pulmonary artery levels. **Secondary:** Inter-reader agreement **Follow-up:** NA

Study information	Patients	Index test	Reference test	Outcomes
	cholesterol ≥10 mmol/L), serum creatinine **Exclusion criteria:** >3 days between CTPA and MPRA	defect within specified pulmonary arterial branch resulting in partially or completely occluding pulmonary arteries.		

Abbreviations: 133Xe = xenon-133; 81mKr = krypton-81; 99mTc = technecium-99m; BW = body weight; CC = complex composite; CM = constrast medium; CT = computed tomography; CTPA = computed tomography pulmonary angiography; CTUS = computed tomography and ultrasound; CXR = chest X-ray; DSA = digital subtraction angiography; DVT = deep vein thrombosis; EANM = European Association of Nuclear Medicine; eGFR = estimated glomerular filtration rate; ER = emergency room; GFR = glomerular filtration rate; MAA = macro-aggregated albumin; MBq = megaBecquerels; MDCT = multidetector computed tomography; MRI = magnetic resonance imaging; MRIMRV = magnetic resonance imaging (of the chest) and magnetic resonance venography; NPV = negative predictive value; NR = not reported; PE = pulmonary embolism; PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis; PISAPED = Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis; PPV = positive predictive value; SC = simple composite; SPECT = single photon emission tomography; VQ = ventilation-perfusion; VTE = venous thromboembolism; NA = not available;

Appendix 17: Quality Assessment of Included Primary Studies for Clinical Review (Questions 2 and 3)

Quality appraisal detailed displays contain all DTA studies, including those that were not included in the meta-analyses due to being a post-hoc analysis, or reporting use of the index test as part of the reference.
Key to abbreviations for individual questions:

QUADAS II: Questions and key

Abbreviation	QUADAS II domain	QUADAS II question
	DOMAIN 1	PATIENT SELECTION (Could the selection of patients have introduced bias)
D1Q1	Signalling Q1	Was a consecutive or random sample of patients enrolled?
D1Q2	Signalling Q2	Was a case-control design avoided?
D1Q3	Signalling Q3	Did the study avoid inappropriate exclusions?
D1A	Applicability	Are there concerns that the included patients and setting do not match the review question?
	DOMAIN 2	INDEX TEST (could the conduct or interpretation of the index test have introduced bias)
D2A1	Signalling Q1	Were the index test results interpreted without knowledge of the results of the reference standard?
D2A2	Signalling Q2	If a threshold was used, was it prespecified?
D2A	Applicability	Are there concerns that the index test, its conduct, or its interpretation differ from the review question?
	DOMAIN 3	REFERENCE STANDARD (could the reference standard, its conduct, or interpretation have introduced bias)
D3Q1	Signalling Q1	Is the reference standard likely to correctly classify the target condition?
D3Q2	Signalling Q2	Were the reference standard results interpreted without knowledge of the results of the index test?
D3A	Applicability	Are there concerns that the target condition as defined by the reference standard does not match the question?
	DOMAIN 4	FLOW AND TIMING (could the patient flow have introduced bias)
D4Q1	Signalling Q1	Was there an appropriate interval between the index test and reference standard?
D4Q2	Signalling Q2	Did all patients receive the same reference standard?
D4Q3	Signalling Q3	Were all patients included in the analysis

ROBINS-I: Questions and key

	BIAS DUE TO CONFOUNDING
1.1	Is there potential for confounding of the effect of intervention in this study
1.2	Was the analysis based on splitting participants' follow up time according to the intervention received?
1.3	Did the study avoid inappropriate exclusions?
	Questions related to baseline confounding only
1.4	Did the authors use an appropriate analysis method that controlled for all of the important confounding domains
1.5	If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?
1.6	Did the authors control for any post- intervention variables that could have been affected by the intervention?

	Questions related to baseline and time-varying confounding
1.7	Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?
1.8	. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?
Confounding	**Risk of bias judgement;** Answer: (low/moderate/serious/critical/NI); Favours experimental, favours comparator, unpredictable
	What is the predicted direction of bias due to confounding?
	BIAS in SELECTION OF PARTICIPANTS INTO THE STUDY (or analysis)
2.1	Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?
2.2	If Y/PY to 2.1: Were the post- intervention variables that influenced selection likely to be associated with intervention?
2.3	If Y/PY to 2.2: Were the postintervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?
2.4	Do start of follow-up and start of intervention coincide for most participants?
2.5	If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?
Selection	**Risk of bias judgement;** Answer: (low/moderate/serious/critical/NI); Favours experimental, favours comparator, unpredictable
	Optional: What is the predicted direction of bias due to selection of participants into the study?
	BIAS in CLASSIFICATION OF INTERVENTIONS
3.1	Were intervention groups clearly defined?
3.2	Was the information used to define intervention groups recorded at the start of the intervention?
3.3	Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?
Intervention	**Risk of bias judgement;** Answer: (low/moderate/serious/critical/NI); Favours experimental, favours comparator, unpredictable
	Optional: What is the predicted direction of bias due to measurement of outcomes or interventions?
	BIAS DUE TO DEVIATIONS FROM INTENDED INTERVENTIONS
	If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2
4.1	Were there deviations from the intended intervention beyond what would be expected in usual practice?
4.2	If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?
	If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6
4.3	Were important co-interventions balanced across intervention groups?
4.4	Was the intervention implemented successfully for most participants?
4.5	Did study participants adhere to the assigned intervention regimen?
4.6	If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?
Deviation	**Risk of bias judgement;** Answer: (low/moderate/serious/critical/NI); Favours experimental, favours comparator, unpredictable
	Optional: What is the predicted direction of bias due to measurement of outcomes or interventions?
	BIAS DUE TO MISSING DATA
5.1	Were outcome data available for all, or nearly all, participants?
5.2	Were participants excluded due to missing data on intervention status?
5.3	Were participants excluded due to missing data on other variables needed for the analysis?

5.4	If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?
5.5	If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?
Missing data	**Risk of bias judgement;** Answer: (low/moderate/serious/critical/NI); Favours experimental, favours comparator, unpredictable
	Optional: What is the predicted direction of bias due to measurement of outcomes or interventions?
	BIAS in MEASUREMENT OF OUTCOMES
6.1	Could the outcome measure have been influenced by knowledge of the intervention received?
6.2	Were outcome assessors aware of the intervention received by study participants?
6.3	Were the methods of outcome assessment comparable across intervention groups?
6.4	Were any systematic errors in measurement of the outcome related to intervention received?
Outcome	**Risk of bias judgement;** Answer: (low/moderate/serious/critical/NI); Favours experimental, favours comparator, unpredictable
	Optional: What is the predicted direction of bias due to measurement of outcomes or interventions?
	BIAS in SELECTION OF THE REPORTED RESULT
	Is the reported effect estimate likely to be selected on the basis of the results from…
7.1	multiple outcome measurements within the outcome domain?
7.2	multiple analyses of the intervention-outcome relationship?
7.3	different subgroups?
Reporting	**Risk of bias judgement;** Answer: (low/moderate/serious/critical/NI); Favours experimental, favours comparator, unpredictable
	Optional: What is the predicted direction of bias due to measurement of outcomes or interventions?
	OVERALL BIAS
Overall	**Risk of bias judgement;** Answer: (low/moderate/serious/critical/NI); Favours experimental, favours comparator, towards null, away from null, unpredictable
	What is the OVERALL predicted direction of bias for this outcome?

Moga checklist: Questions and key

Flow Diagram	Review or create flow diagram to facilitate judgements of risk of bias
	STUDY OBJECTIVE
D1Q1	Is the hypothesis/aim/objective of the study clearly stated in the abstract, introduction, or methods section?
	STUDY POPULATION
D2Q1	Are the characteristics of the participants included in the study described?
D2Q2	Were the cases collected in more than one centre?
D2Q3	Are the eligibility criteria (inclusion and exclusion criteria) to entry the study explicit and appropriate?
D2Q4	Were participants recruited consecutively?
D2Q5	Did participants enter the study at a similar point in the disease?
	INTERVENTION and CO-INTERVENTION
D3Q1	Was the intervention clearly described in the study?
D3Q2	Were additional interventions (co-interventions) clearly reported in the study?
	OUTCOME MEASURES
D4Q1	Are the outcome measures clearly defined in the introduction or methods section?
D4Q2	Were relevant outcomes appropriately measured with objective and/or subjective methods?
D4Q3	Were outcomes measured before and after intervention?
	STATISTICAL ANALYSIS

D5Q1	Were the statistical tests used to assess the relevant outcomes appropriate?
	RESULTS AND CONCLUSIONS
D6Q1	Was the length of follow-up reported?
D6Q2	Was the loss to follow-up reported?
D6Q3	Does the study provide estimates of the random variability in the data analysis of relevant outcomes?
D6Q4	Are adverse events reported?
D6Q5	Are the conclusions of the study supported by results?
	COMPETING INTEREST and SOURCE OF SUPPORT
D7Q1	Are both competing interest and source of support for the study reported?

Table 17-A: QUADAS II risk of bias and applicability assessment for DTA studies of CT

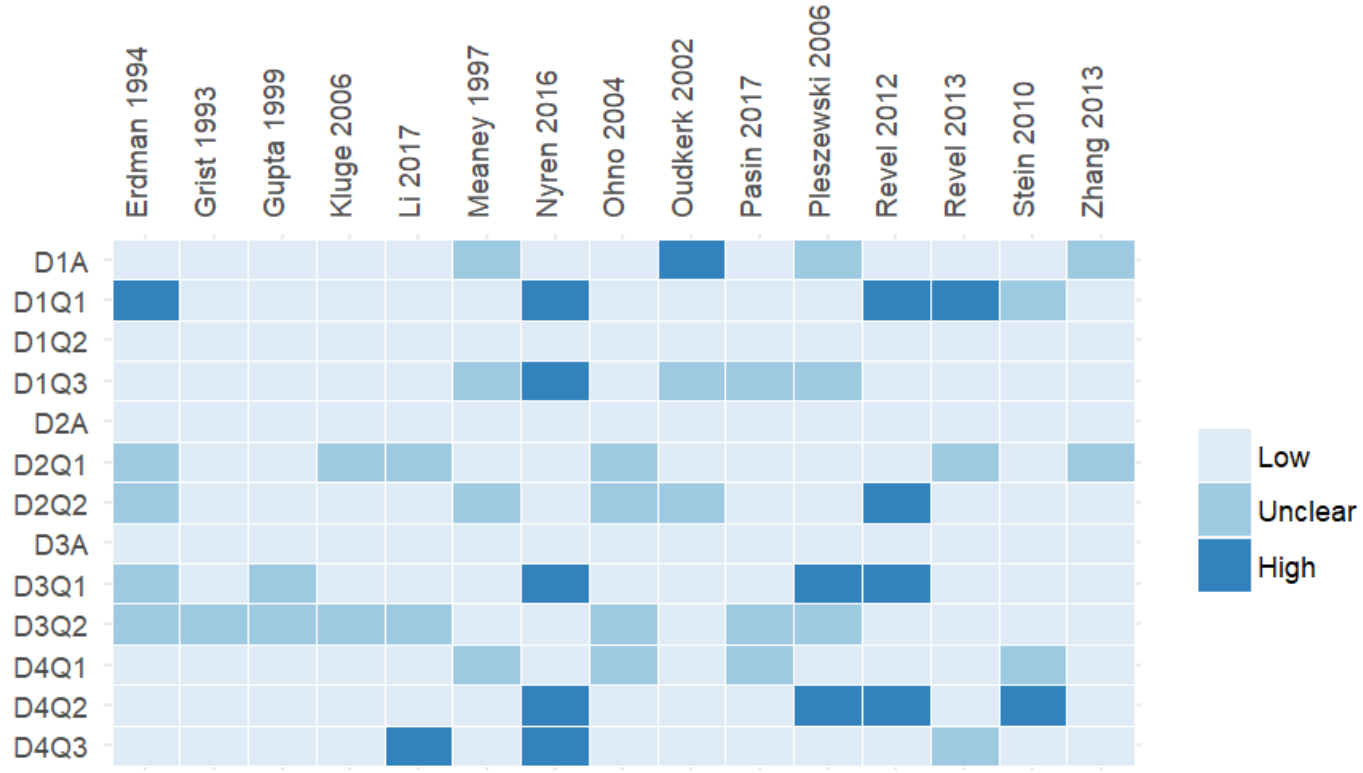


Table 17-B: QUADAS II risk of bias and applicability assessment for DTA studies of MRI

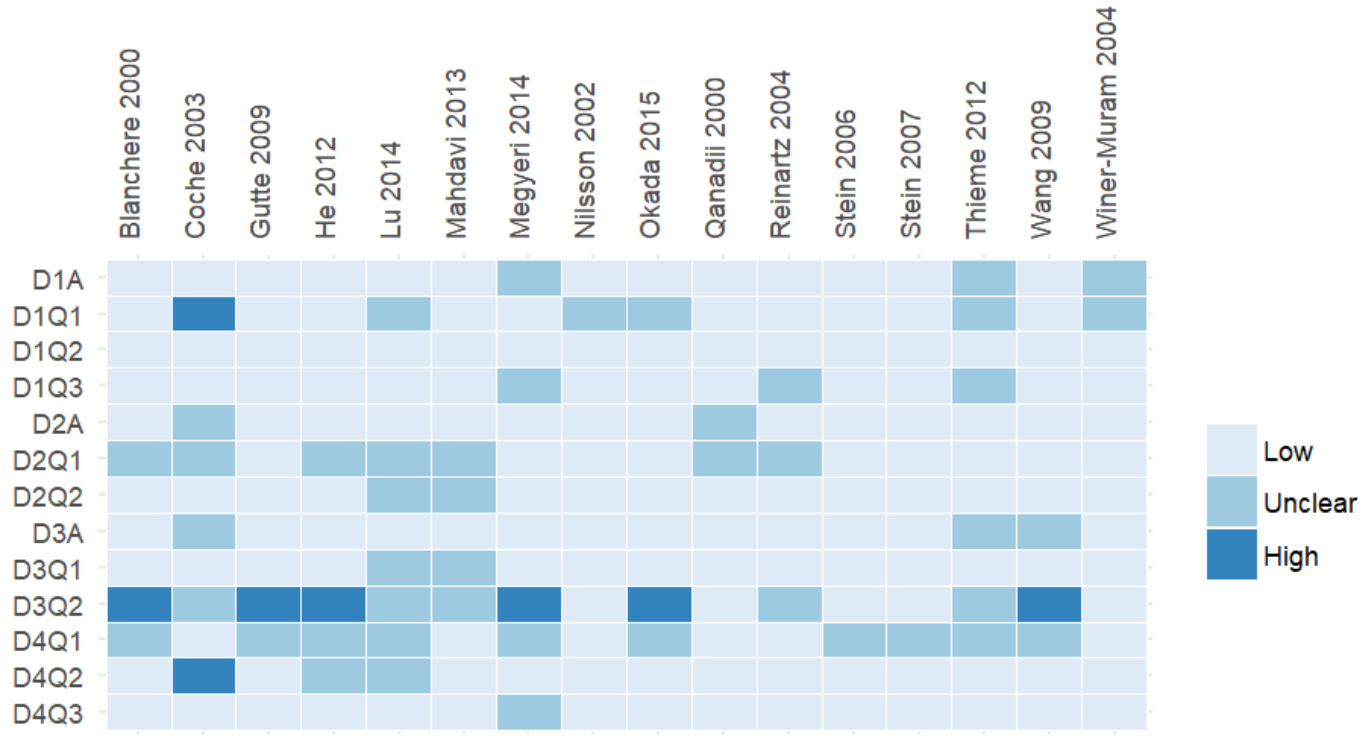


Table 17-C: QUADAS II risk of bias an applicability assessment for DTA studies of US

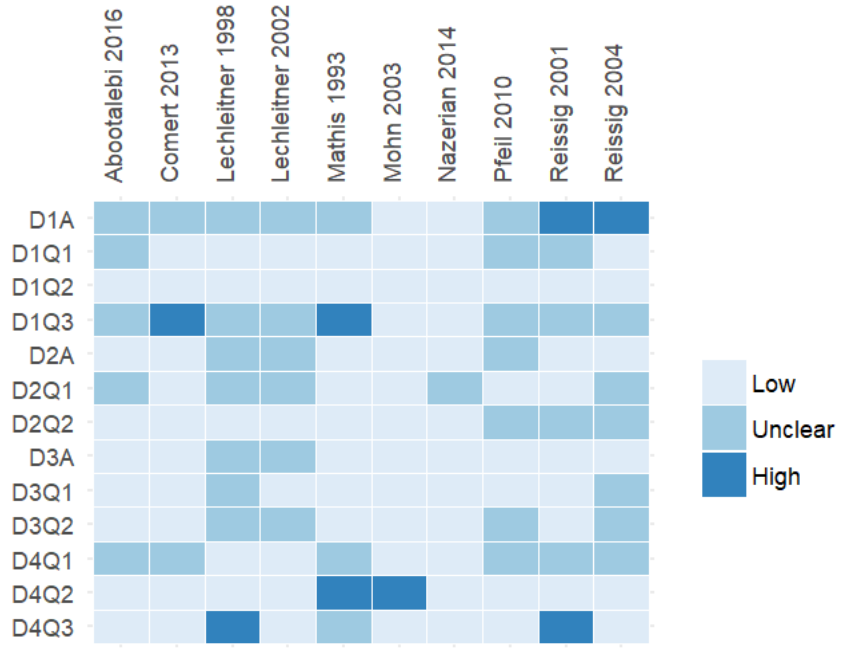


Table 17-D: QUADAS II risk of bias and applicability assessment for DTA studies of perfusion (Q)

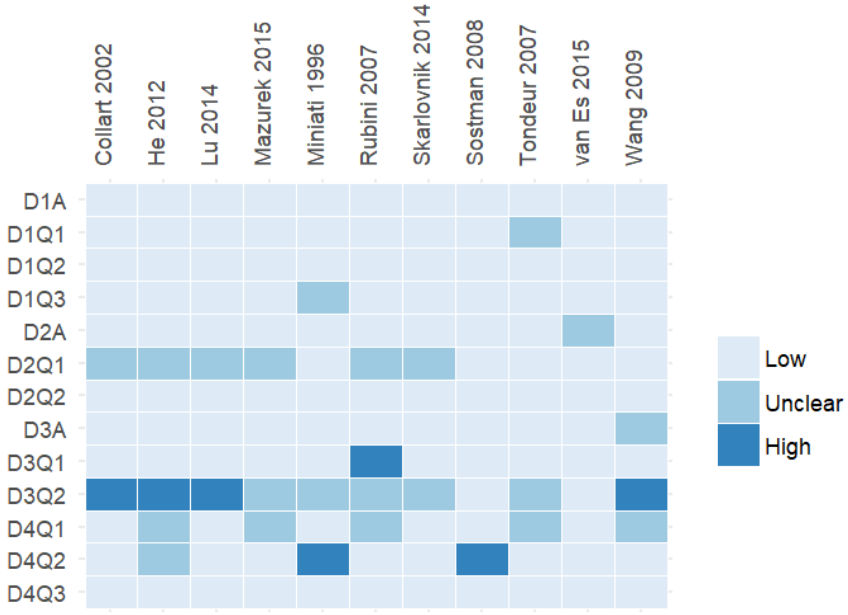


Table 17-E: QUADAS II risk of bias and applicability assessment for DTA studies of Q-SPECT

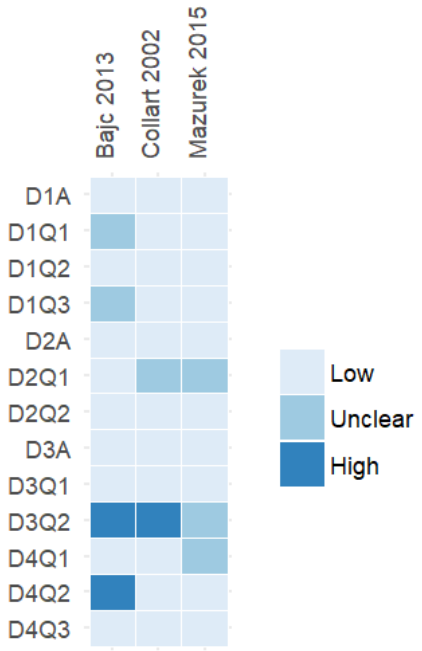


Table 17-F: QUADAS II risk of bias and applicability assessment for DTA studies of Q-SPECT-CT

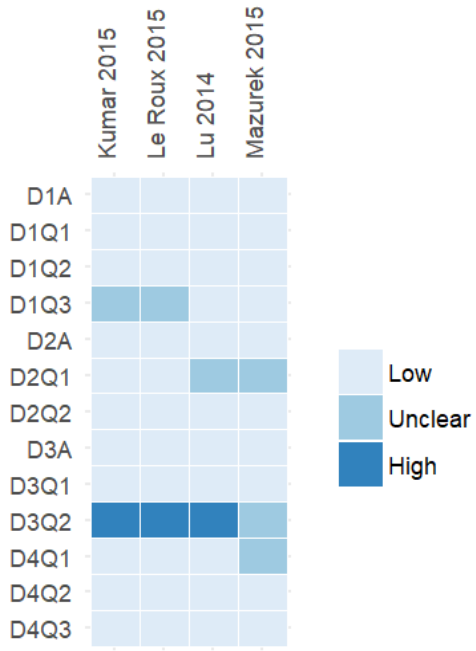


Table 17-G: QUADAS II risk of bias and applicability assessment for DTA studies of VQ

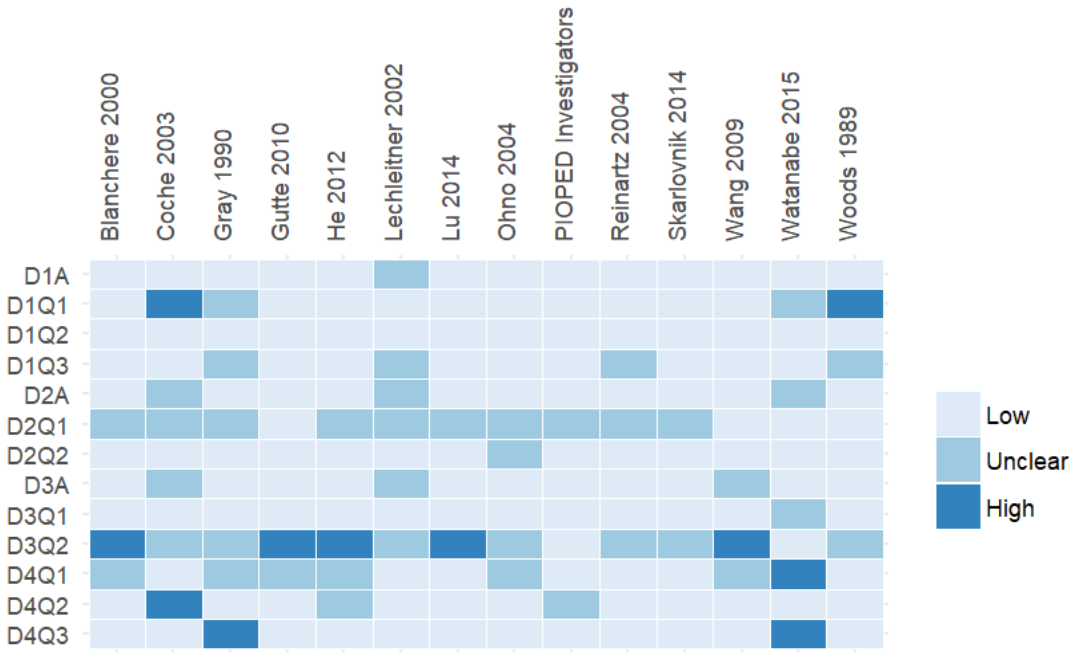


Table 17-H: QUADAS II risk of bias and applicability assessment for DTA studies of VQ-SPECT

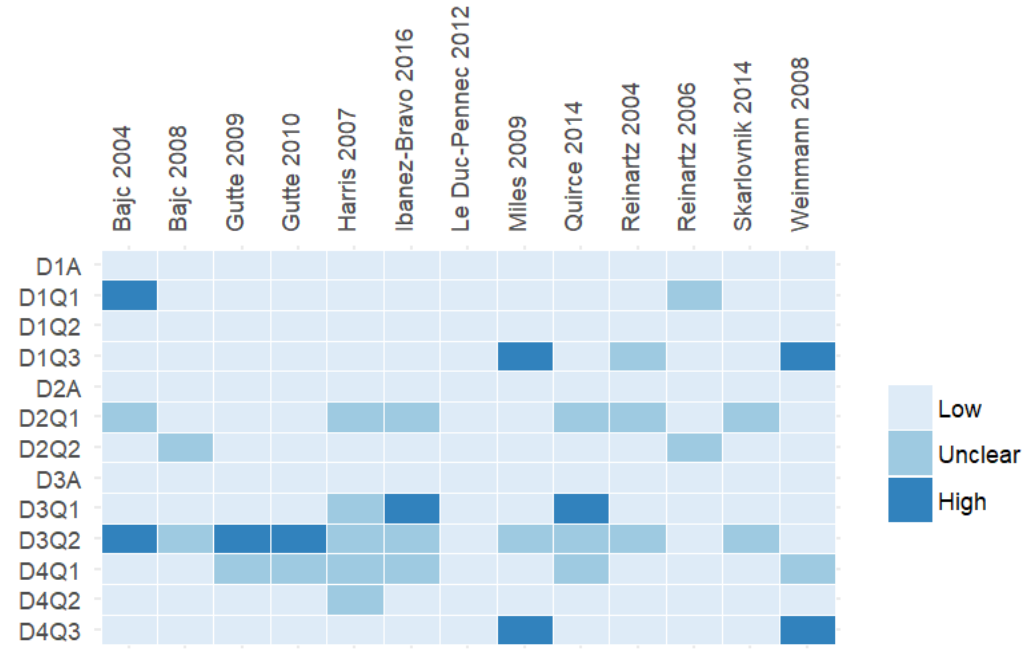


Table 17-J: QUADAS II risk of bias and applicability assessment for DTA studies of VQ-SPECT-CT

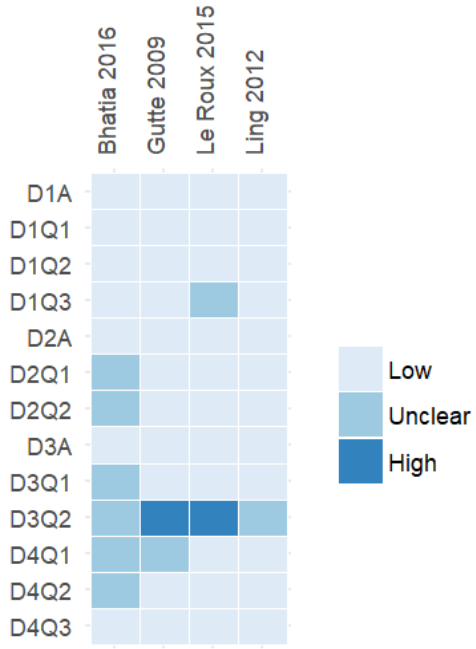


Figure 17-K: ROBINS-I quality assessment of PW utility and safety studies

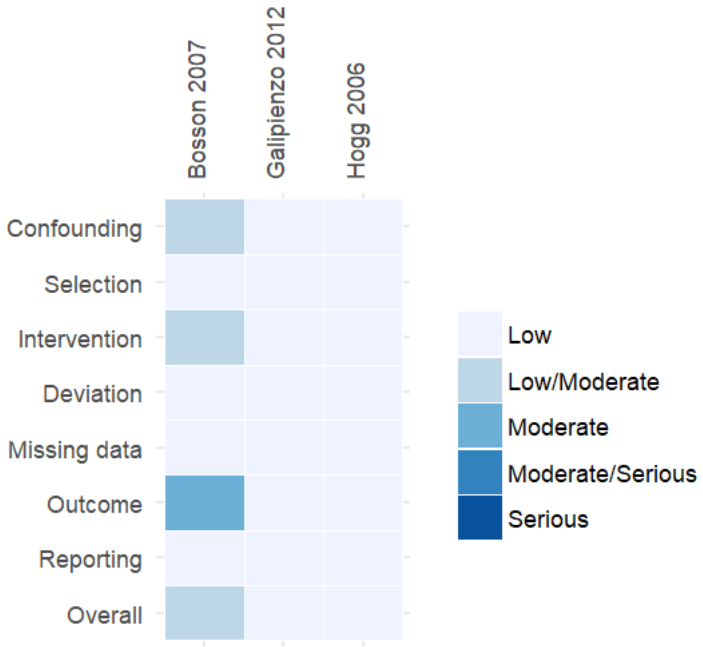


Figure 17-L: ROBINS-I quality assessment of CT utility and safety studies

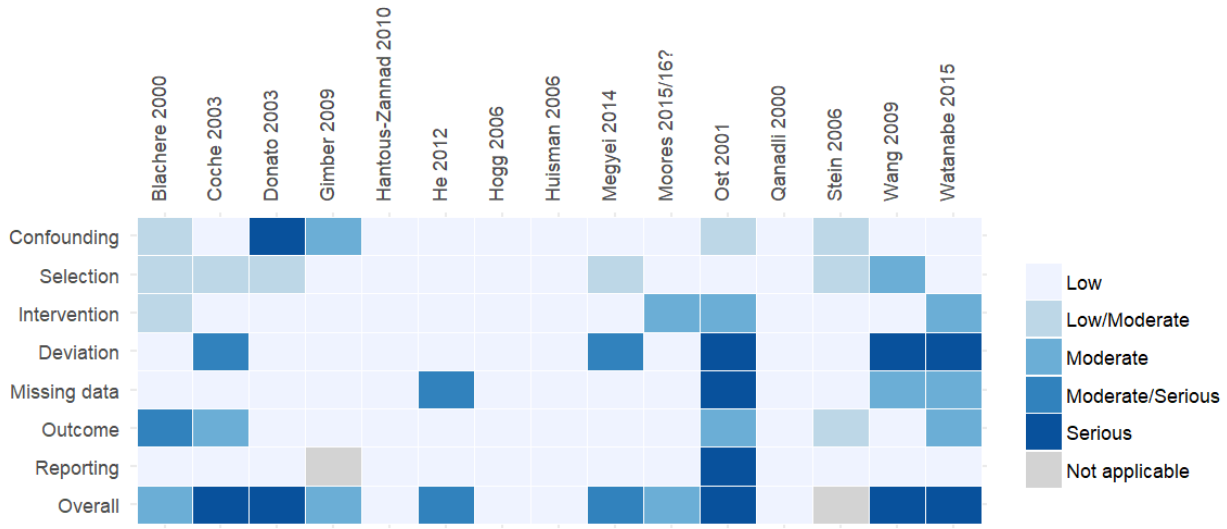


Figure 17-M: ROBINS-I quality assessment of MRI utility and safety studies

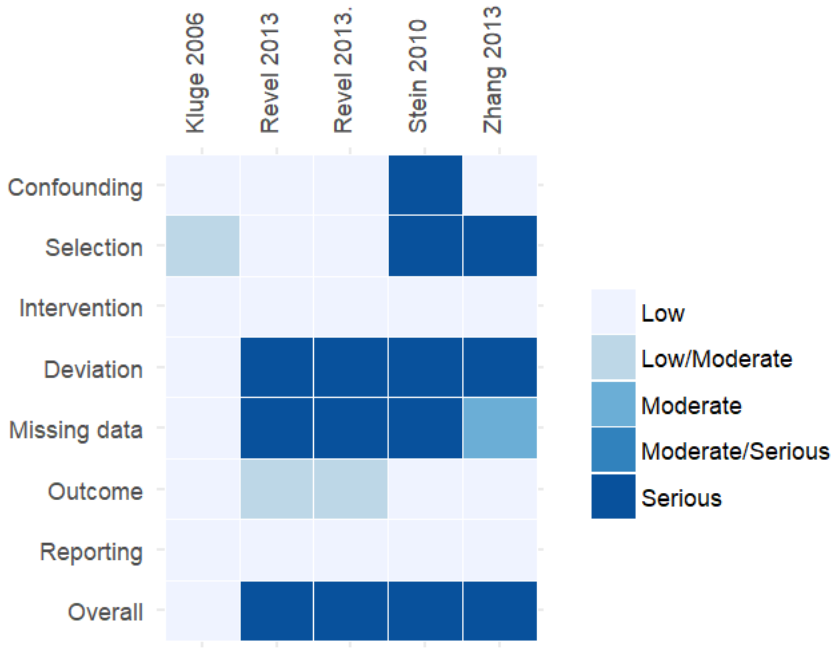


Figure 17-N: ROBINS-I quality assessment of Q utility and safety studies

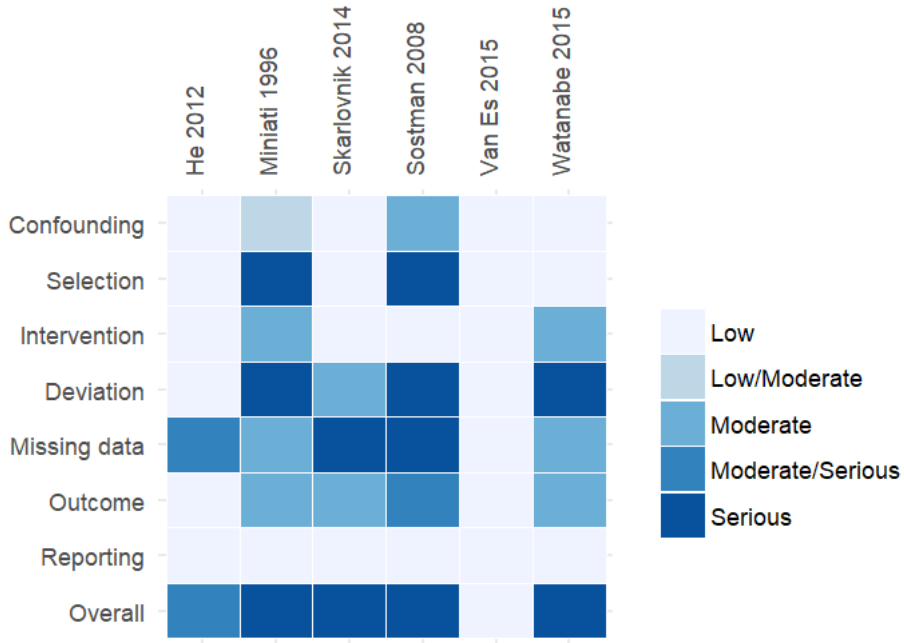


Figure 17-O: ROBINS-I quality assessment of VQ utility and safety studies

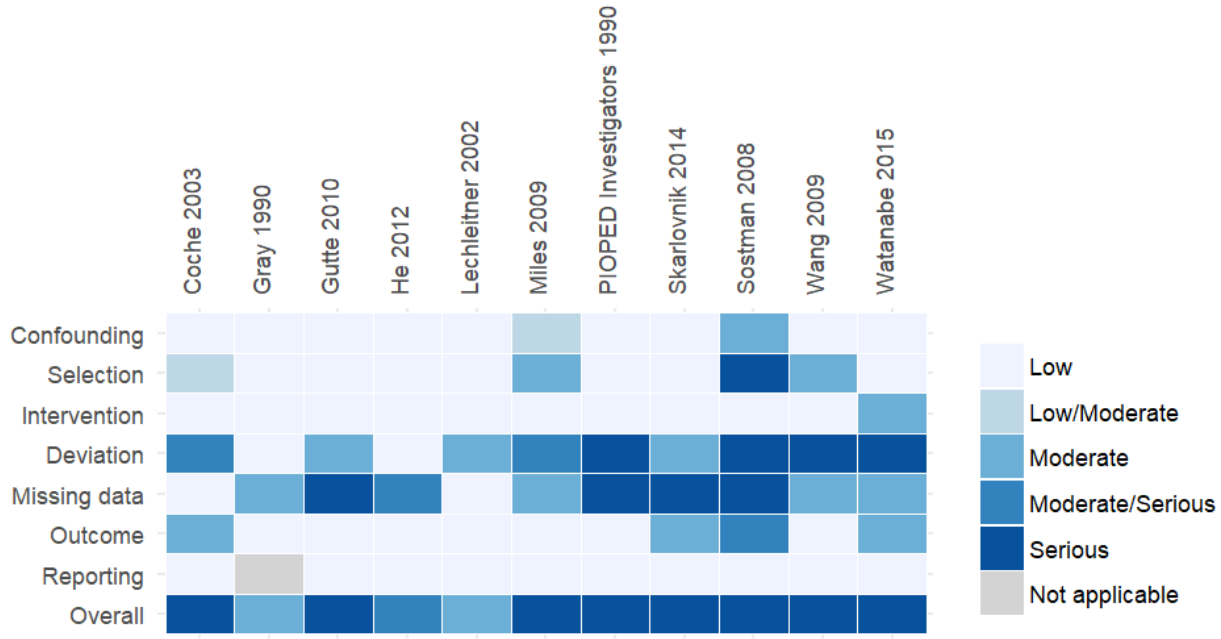


Figure 17-P: ROBINS-I quality assessment of VQ-SPECT utility and safety studies

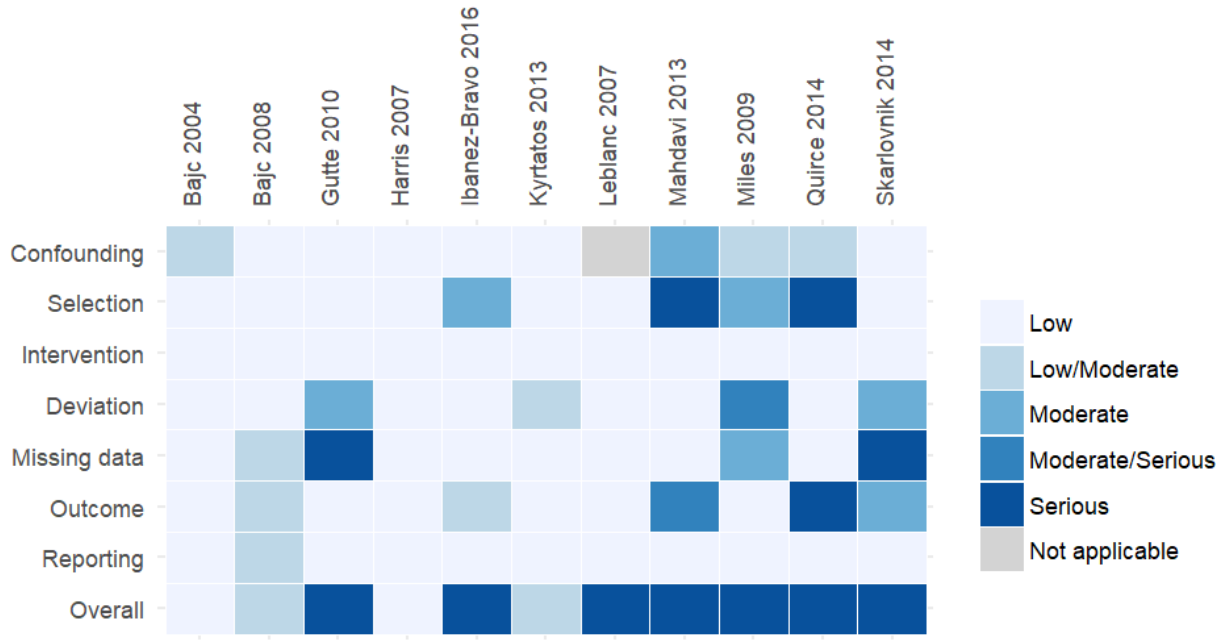


Figure 17-Q: ROBINS-I quality assessment of utility and safety studies in pregnancy

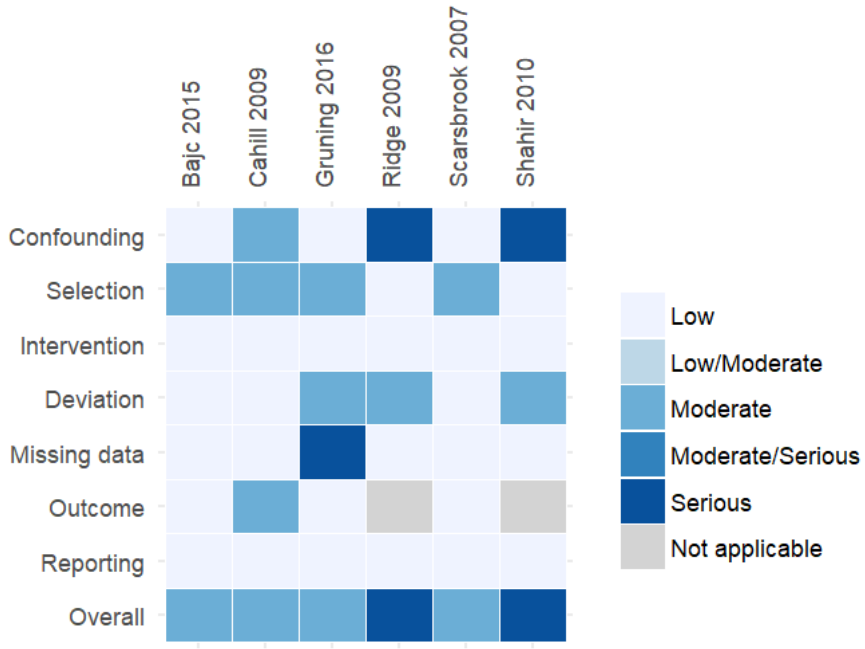


Figure 17-R: Moga checklist for pathway utility and safety studies

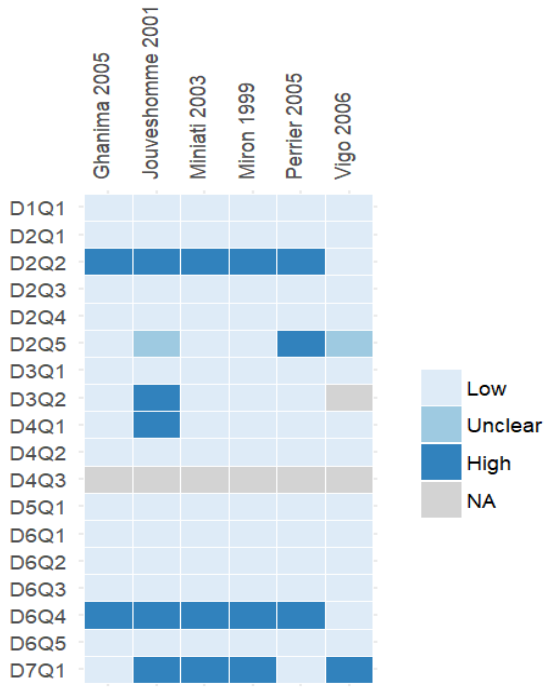


Figure 17-S: Moga checklist for CT utility and safety studies

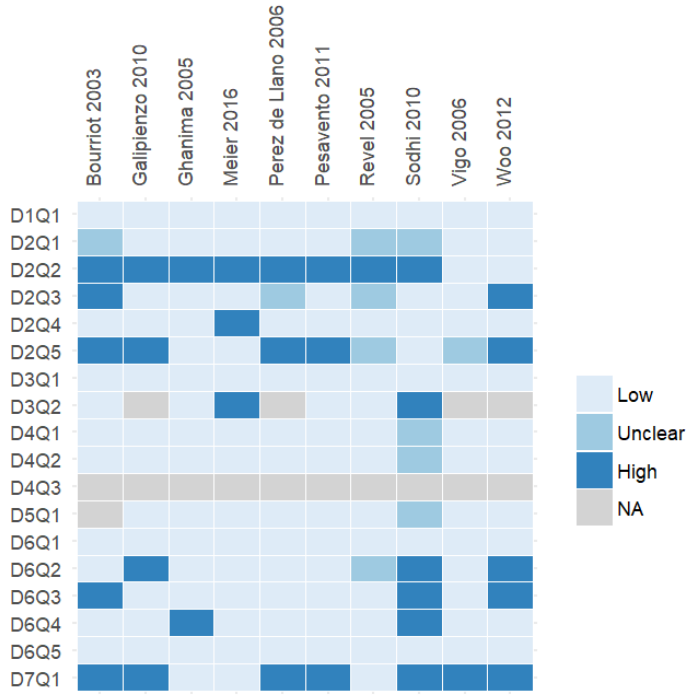


Figure 17-T: Moga checklist for MRI utility and safety studies

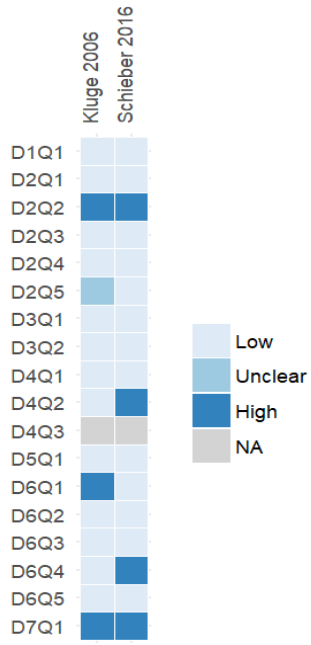
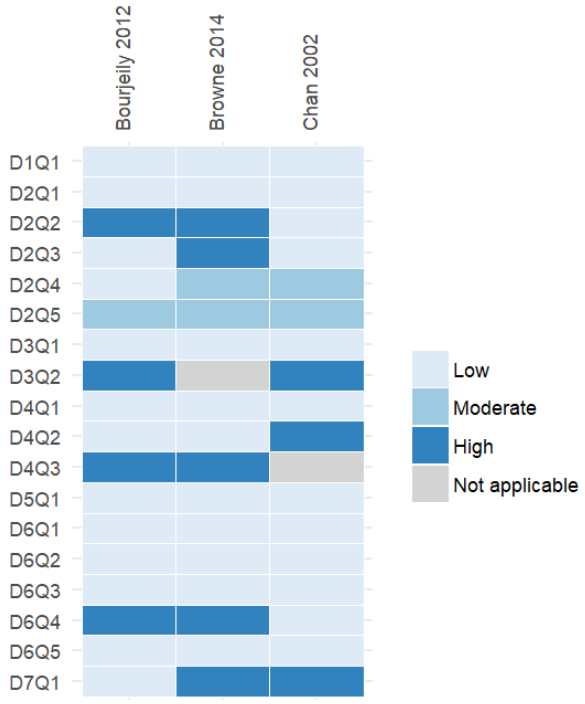


Figure 17-U : Moga checklist for utility and safety studies in pregnancy



Appendix 18: Individual Study Diagnostic Test Accuracy Data (Questions 2 and 3)

Notes to tables in Appendix 18: TP, FP, FN, TN are true positive, false positive, false negative, and true negative, respectively. SN is sensitivity, SP specificity, PPV positive predictive value, and NPV negative predictive value. 95% CI represents the 95% confidence interval.

Italicized entries in TP, FP, FN, TN columns have are derived data from other information provided in the study. Sensitivity, specificity, PPV, NPV and their confidence intervals are calculated from the 2x2 table, using the exact binomial formula for the confidence intervals.

Table 18-A: Diagnostic test accuracy data for CT as index test in non-pregnant patients

Study Information	Index	Reference	Post hoc/ subset	TP	FP	FN	TN	SN (95% CI)	SP (95% CI)	PPV (95% CI)	NPV (95% CI)
Mahdavi 2016 [127]	CT	VQ-SPECT	No/No	12	5	2	41	0.857 (0.572-0.982)	0.891 (0.764-0.964)	0.706 (0.44-0.897)	0.953 (0.842-0.994)
Okada 2015 [129]	CT	CC	No/No	*25*	*7*	*5*	*46*	0.833 (0.653-0.944)	0.868 (0.747-0.945)	0.781 (0.6-0.907)	0.902 (0.786-0.967)
Okada 2015 [129]	CT	CC	No/No	*28*	*0*	*2*	*53*	0.933 (0.779-0.992)	1 (0.933-1)	1 (0.877-1)	0.964 (0.875-0.996)
Lu 2014 [119]	CT	CC	No/No	13	0	0	37	1 (0.753-1)	1 (0.905-1)	1 (0.753-1)	1 (0.905-1)
Lu 2014 [119]	CT	CC	No/No	15	0	0	35	1 (0.782-1)	1 (0.9-1)	1 (0.782-1)	1 (0.9-1)
Megyeri 2014 [130]	CT	CC	No/No	36	4	2	184	0.947 (0.823-0.994)	0.979 (0.946-0.994)	0.9 (0.763-0.972)	0.989 (0.962-0.999)
Megyeri 2014 [130]	CT	CC	No/Yes (BW<100 kg)	17	2	1	90	0.944 (0.727-0.999)	0.978 (0.924-0.997)	0.895 (0.669-0.987)	0.989 (0.94-1)
Megyeri 2014 [130]	CT	CC	No/Yes (BW>=100 kg)	19	2	1	94	0.95 (0.751-0.999)	0.979 (0.927-0.997)	0.905 (0.696-0.988)	0.989 (0.943-1)
He 2012 [131]	CT	CC	No/No	*259*	*58*	*14*	*197*	0.949 (0.915-0.972)	0.773 (0.716-0.823)	0.817 (0.77-0.858)	0.934 (0.891-0.963)
He 2012 [131]	CT	CC	No/Yes (Low)	*69*	*6*	*19*	*119*	0.784 (0.684-0.865)	0.952 (0.898-0.982)	0.92 (0.834-0.97)	0.862 (0.793-0.915)
He 2012 [131]	CT	CC	No/Yes (Intermediate)	*131*	*5*	*31*	*61*	0.809 (0.74-0.866)	0.924 (0.832-0.975)	0.963 (0.916-0.988)	0.663 (0.557-0.758)
He 2012 [131]	CT	CC	No/Yes (High)	*59*	*3*	*8*	*17*	0.881 (0.778-0.947)	0.85 (0.621-0.968)	0.952 (0.865-0.99)	0.68 (0.465-0.851)
Thieme 2012 [120]	CT	CC	No/No	7	0	0	8	1 (0.59-1)	1 (0.631-1)	1 (0.59-1)	1 (0.631-1)
Thieme 2012 [120]	CT	VQ-SPECT-	No/No	*6*	*1*	*1*	*7*	0.857 (0.421-	0.875 (0.473-	0.857 (0.421-	0.875 (0.473-

Study Information	Index	Reference	Post hoc/ subset	TP	FP	FN	TN	SN (95% CI)	SP (95% CI)	PPV (95% CI)	NPV (95% CI)
		CT						0.996)	0.997)	0.996)	0.997)
Gutte 2009 [128]	CT	VQ-SPECT	No/No	*19*	*1*	*15*	*42*	0.559 (0.379-0.728)	0.977 (0.877-0.999)	0.95 (0.751-0.999)	0.737 (0.603-0.845)
Gutte 2009 [128]	CT	VQ-SPECT-CT	No/No	*20*	*1*	*10*	*50*	0.667 (0.472-0.827)	0.98 (0.896-1)	0.952 (0.762-0.999)	0.833 (0.715-0.917)
Wang 2009 [121]	CT	CC	No/No	36	1	1	37	0.973 (0.858-0.999)	0.974 (0.862-0.999)	0.973 (0.858-0.999)	0.974 (0.862-0.999)
Stein 2007 [133]	CT	SC	Yes/No	79	19	20	407	0.798 (0.705-0.872)	0.955 (0.931-0.973)	0.806 (0.714-0.879)	0.953 (0.929-0.971)
Stein 2007 [133]	CT	SC	Yes/No	59	4	8	136	0.881 (0.778-0.947)	0.971 (0.928-0.992)	0.937 (0.845-0.982)	0.944 (0.893-0.976)
Stein 2007 [133]	CT	SC	Yes/No	12	2	3	24	0.8 (0.519-0.957)	0.923 (0.749-0.991)	0.857 (0.572-0.982)	0.889 (0.708-0.976)
Stein 2006 [67]	CT	SC	No/No	150	25	31	567	0.829 (0.766-0.881)	0.958 (0.938-0.972)	0.857 (0.796-0.905)	0.948 (0.927-0.965)
Stein 2006 [67]	CT	SC	No/Yes (High)	22	1	6	9	0.786 (0.59-0.917)	0.9 (0.555-0.997)	0.957 (0.781-0.999)	0.6 (0.323-0.837)
Stein 2006 [67]	CT	SC	No/Yes (Intermediate)	93	8	15	121	0.861 (0.781-0.92)	0.938 (0.881-0.973)	0.921 (0.85-0.965)	0.89 (0.825-0.937)
Stein 2006 [67]	CT	SC	No/Yes (Low)	22	16	6	158	0.786 (0.59-0.917)	0.908 (0.855-0.947)	0.579 (0.408-0.737)	0.963 (0.922-0.986)
Reinartz 2004 [122]	CT	CC	No/No	32	1	5	45	0.865 (0.712-0.955)	0.978 (0.885-0.999)	0.97 (0.842-0.999)	0.9 (0.782-0.967)
Winer-Muram 2004 [123]	CT	PA	No/No	18	8	0	67	1 (0.815-1)	0.893 (0.801-0.953)	0.692 (0.482-0.857)	1 (0.946-1)
Coche 2003 [126]	CT	SC	No/No	27	1	1	65	0.964 (0.817-0.999)	0.985 (0.918-1)	0.964 (0.817-0.999)	0.985 (0.918-1)
Nilsson 2002 [124]	CT	PA	No/No	30	3	2	55	0.938 (0.792-0.992)	0.948 (0.856-0.989)	0.909 (0.757-0.981)	0.965 (0.879-0.996)
Blachere 2000 [132]	CT	CC	No/No	*64*	*7*	*4*	*104*	0.941 (0.856-0.984)	0.937 (0.874-0.974)	0.901 (0.807-0.959)	0.963 (0.908-0.99)
Qanadli 2000 [125]	CT	PA	No/No	56	3	3	89	0.949 (0.859-0.989)	0.967 (0.908-0.993)	0.949 (0.859-0.989)	0.967 (0.908-0.993)

CC = Complex composite; CT = Computed Tomography; SC = Simple composite; VQ = Ventilation-Perfusion.

Table 18-B: Diagnostic test accuracy data for CTCTV as index test in non-pregnant patients

Study Information	Index	Reference	Post hoc/subset	Details	TP	FP	FN	TN	Sn (95% CI)	SP (95% CI)	PPV (95% CI)	NPV (95% CI)
Stein 2007 [133]	CTCTV	SC	Yes/No		88	23	11	379	0.889 (0.81-0.943)	0.943 (0.915-0.963)	0.793 (0.705-0.864)	0.972 (0.95-0.986)
Stein 2007 [133]	CTCTV	SC	Yes/No		62	5	7	124	0.899 (0.802-0.958)	0.961 (0.912-0.987)	0.925 (0.834-0.975)	0.947 (0.893-0.978)
Stein 2007 [133]	CTCTV	SC	Yes/No		14	2	1	21	0.933 (0.681-0.998)	0.913 (0.72-0.989)	0.875 (0.617-0.984)	0.955 (0.772-0.999)
Stein 2006 [67]	CTCTV	SC	No/No		164	30	19	524	0.896 (0.843-0.936)	0.946 (0.924-0.963)	0.845 (0.787-0.893)	0.965 (0.946-0.979)
Stein 2006 [67]	CTCTV	SC	No/Yes (High)		27	1	2	9	0.931 (0.772-0.992)	0.9 (0.555-0.997)	0.964 (0.817-0.999)	0.818 (0.482-0.977)
Stein 2006 [67]	CTCTV	SC	No/Yes (Intermediate)		100	11	10	114	0.909 (0.839-0.956)	0.912 (0.848-0.955)	0.901 (0.83-0.949)	0.919 (0.857-0.961)
Stein 2006 [67]	CTCTV	SC	No/Yes (Low)		24	18	5	146	0.828 (0.642-0.942)	0.89 (0.832-0.934)	0.571 (0.41-0.723)	0.967 (0.924-0.989)

SC = Simple composite.

Table 18-C: Diagnostic test accuracy data for MRI as index test in non-pregnant patients

Study Information	Index	Reference	Post hoc/subset	Details	TP	FP	FN	TN	Sn (95% CI)	SP (95% CI)	PPV (95% CI)	NPV (95% CI)
Li 2017 [135]	MRI	CT	No/No	Yes/3D MRA	22	0	1	6	0.957 (0.781-0.999)	1 (0.541-1)	1 (0.846-1)	0.857 (0.421-0.996)
Pasin 2017 [136]	MRI	CT	No/No	No/MRA	17	1	3	70	0.85 (0.621-0.968)	0.986 (0.924-1)	0.944 (0.727-0.999)	0.959 (0.885-0.991)
Nyren 2016 [137]	MRI	CT	No/No	No/2D angio	*27*	*0*	*2*	*4*	0.931 (0.772-0.992)	1 (0.398-1)	1 (0.872-1)	0.667 (0.223-0.957)
Nyren 2016 [137]	MRI	CT	No/No	No/2D angio	*26*	*0*	*3*	*4*	0.897 (0.726-0.978)	1 (0.398-1)	1 (0.868-1)	0.571 (0.184-0.901)
Zhang 2013 [138]	MRI	CT	No/No	Yes/3D MRA	24	0	0	3	1 (0.858-1)	1 (0.292-1)	1 (0.858-1)	1 (0.292-1)
Zhang 2013 [138]	MRI	CT	No/No	Yes/3D MRA	24	1	0	2	1 (0.858-1)	0.667 (0.094-0.992)	0.96 (0.796-0.999)	1 (0.158-1)
Revel 2013 [139]	MRI	CT	Yes/No	Yes/3D MRA	*93*	*1*	*11*	*33*	0.894 (0.819-0.946)	0.971 (0.847-0.999)	0.989 (0.942-1)	0.75 (0.597-0.868)

Study Information	Index	Reference	Post hoc/subset	Details	TP	FP	FN	TN	Sn (95% CI)	SP (95% CI)	PPV (95% CI)	NPV (95% CI)
Revel 2013 [139]	MRI	CT	Yes/No	Yes/3D MRA	*86*	*0*	*18*	*46*	0.827 (0.74-0.894)	1 (0.923-1)	1 (0.958-1)	0.719 (0.592-0.824)
Revel 2013 [139]	MRI	CT	Yes/No	No/Perfusion	*69*	*8*	*35*	*56*	0.663 (0.564-0.753)	0.875 (0.768-0.944)	0.896 (0.806-0.954)	0.615 (0.508-0.716)
Revel 2013 [139]	MRI	CT	Yes/No	No/Perfusion	*80*	*8*	*24*	*47*	0.769 (0.676-0.846)	0.855 (0.733-0.935)	0.909 (0.829-0.96)	0.662 (0.54-0.77)
Revel 2013 [139]	MRI	CT	Yes/No	Yes/Perfusion	*78*	*3*	*26*	*29*	0.75 (0.656-0.83)	0.906 (0.75-0.98)	0.963 (0.896-0.992)	0.527 (0.388-0.663)
Revel 2013 [139]	MRI	CT	Yes/No	Yes/Perfusion	*82*	*14*	*22*	*54*	0.788 (0.697-0.862)	0.794 (0.679-0.883)	0.854 (0.767-0.918)	0.711 (0.595-0.809)
Revel 2013 [139]	MRI	CT	Yes/No	No/2D angio	*79*	*2*	*25*	*49*	0.76 (0.666-0.838)	0.961 (0.865-0.995)	0.975 (0.914-0.997)	0.662 (0.543-0.768)
Revel 2013 [139]	MRI	CT	Yes/No	No/2D angio	*71*	*1*	*33*	*77*	0.683 (0.584-0.771)	0.987 (0.931-1)	0.986 (0.925-1)	0.7 (0.605-0.784)
Revel 2013 [139]	MRI	CT	Yes/No	No/2D angio	*85*	*3*	*19*	*26*	0.817 (0.729-0.886)	0.897 (0.726-0.978)	0.966 (0.904-0.993)	0.578 (0.422-0.723)
Revel 2013 [139]	MRI	CT	Yes/No	No/2D angio	*67*	*1*	*37*	*65*	0.644 (0.544-0.736)	0.985 (0.918-1)	0.985 (0.921-1)	0.637 (0.536-0.73)
Revel 2012 [140]	MRI	CT	No/No	Yes/Combined	*87*	*1*	*16*	*94*	0.845 (0.76-0.909)	0.989 (0.943-1)	0.989 (0.938-1)	0.855 (0.775-0.915)
Revel 2012 [140]	MRI	CT	No/No	Yes/Combined	*92*	*2*	*11*	*93*	0.893 (0.817-0.945)	0.979 (0.926-0.997)	0.979 (0.925-0.997)	0.894 (0.819-0.946)
Revel 2012 [140]	MRI	CT	No/No	Yes/Combined	*81*	*0*	*22*	*88*	0.786 (0.695-0.861)	1 (0.959-1)	1 (0.955-1)	0.8 (0.713-0.87)
Revel 2012 [140]	MRI	CT	No/No	Yes/Combined	*86*	*1*	*17*	*87*	0.835 (0.749-0.901)	0.989 (0.938-1)	0.989 (0.938-1)	0.837 (0.751-0.902)
Stein 2010 [146]	MRI	CC	No/No	Yes/3D MRA	59	2	17	201	0.776 (0.666-0.864)	0.99 (0.965-0.999)	0.967 (0.887-0.996)	0.922 (0.878-0.954)
Stein 2010 [146]	MRI	CC	No/No	Yes/3D MRA	59	66	45	201	0.567 (0.467-0.664)	0.753 (0.697-0.803)	0.472 (0.382-0.563)	0.817 (0.763-0.863)
Pleszewski 2006 [149]	MRI	Sequential	No/No	Yes/3D MRA	*9*	*0*	*2*	*37*	0.818 (0.482-0.977)	1 (0.905-1)	1 (0.664-1)	0.949 (0.827-0.994)
Kluge 2006 [141]	MRI	CT	No/No	Yes/Combined	19	3	0	40	1 (0.824-1)	0.93 (0.809-0.985)	0.864 (0.651-0.971)	1 (0.912-1)

Study Information	Index	Reference	Post hoc/subset	Details	TP	FP	FN	TN	Sn (95% CI)	SP (95% CI)	PPV (95% CI)	NPV (95% CI)
Kluge 2006 [141]	MRI	CT	No/No	Yes/3D MRA	13	0	3	38	0.812 (0.544-0.96)	1 (0.907-1)	1 (0.753-1)	0.927 (0.801-0.985)
Kluge 2006 [141]	MRI	CT	No/No	Yes/Perfusion	19	4	0	39	1 (0.824-1)	0.907 (0.779-0.974)	0.826 (0.612-0.95)	1 (0.91-1)
Kluge 2006 [141]	MRI	CT	No/No	Yes/RT MRI	17	1	2	42	0.895 (0.669-0.987)	0.977 (0.877-0.999)	0.944 (0.727-0.999)	0.955 (0.845-0.994)
Ohno 2004 [147]	MRI	CC	No/No	Yes/3D MRA	10	2	2	34	0.833 (0.516-0.979)	0.944 (0.813-0.993)	0.833 (0.516-0.979)	0.944 (0.813-0.993)
Ohno 2004 [147]	MRI	CC	No/No	Yes/3D MRA	11	2	1	34	0.917 (0.615-0.998)	0.944 (0.813-0.993)	0.846 (0.546-0.981)	0.971 (0.851-0.999)
Ohno 2004 [147]	MRI	CC	No/No	Yes/3D MRA	11	2	1	34	0.917 (0.615-0.998)	0.944 (0.813-0.993)	0.846 (0.546-0.981)	0.971 (0.851-0.999)
Oudkerk 2002 [143]	MRI	PA	No/No	Yes/3D MRA	27	2	8	81	0.771 (0.599-0.896)	0.976 (0.916-0.997)	0.931 (0.772-0.992)	0.91 (0.831-0.96)
Gupta 1999 [144]	MRI	PA	No/No	Yes/3D MRA	11	1	2	22	0.846 (0.546-0.981)	0.957 (0.781-0.999)	0.917 (0.615-0.998)	0.917 (0.73-0.99)
Meaney 1997 [145]	MRI	PA	No/No	Yes/3D MRA	*8*	*1*	*0*	*21*	1 (0.631-1)	0.955 (0.772-0.999)	0.889 (0.518-0.997)	1 (0.839-1)
Erdman 1994 [148]	MRI	PA	No/No	No/Combined	19	3	2	10	0.905 (0.696-0.988)	0.769 (0.462-0.95)	0.864 (0.651-0.971)	0.833 (0.516-0.979)
Erdman 1994 [148]	MRI	SC	No/No	No/Combined	12	0	2	16	0.857 (0.572-0.982)	1 (0.794-1)	1 (0.735-1)	0.889 (0.653-0.986)
Grist 1993 [142]	MRI	CT	No/No	No/MRA	6	3	0	5	1 (0.541-1)	0.625 (0.245-0.915)	0.667 (0.299-0.925)	1 (0.478-1)

CC = Complex composite; CT = Computed Tomography; MRI = Magnetic Resonance Imaging; SC = Simple composite.

Table 18-D: Diagnostic test accuracy data for MRI-MRV as index test in non-pregnant patients

Study Information	Index	Reference	Post hoc/subset	TP	FP	FN	TN	Sn (95% CI)	SP (95% CI)	PPV (95% CI)	NPV (95% CI)
Stein 2010 [146]	MRIMRV	CC	No/No	64	165	33	101	0.66 (0.557-0.753)	0.38 (0.321-0.441)	0.279 (0.222-0.342)	0.754 (0.672-0.824)
Stein 2010 [146]	MRIMRV	CC	No/No	64	4	6	101	0.914 (0.823-0.968)	0.962 (0.905-0.99)	0.941 (0.856-0.984)	0.944 (0.882-0.979)

CC = Complex composite.

Table 18-E: Diagnostic test accuracy data for MRI-VQ as index test in non-pregnant patients

Study Information	Index	Reference	Post hoc/subset	TP	FP	FN	TN	Sn (95% CI)	SP (95% CI)	PPV (95% CI)	NPV (95% CI)
Ohno 2004 [147]	MRIVQ	CC	No/No	11	2	1	34	0.917 (0.615-0.998)	0.944 (0.813-0.993)	0.846 (0.546-0.981)	0.971 (0.851-0.999)

CC = Complex composite.

Table 18-F: Diagnostic test accuracy data for US as index test in non-pregnant patients

Study Information	Index	Reference	Post hoc/subset	TP	FP	FN	TN	Sn (95% CI)	SP (95% CI)	PPV (95% CI)	NPV (95% CI)
Abootalebi 2016 [150]	US	CT	No/No	*21*	*3*	*4*	*49*	0.84 (0.639-0.955)	0.942 (0.841-0.988)	0.875 (0.676-0.973)	0.925 (0.818-0.979)
Nazerian 2014 [151]	US	CT	No/No	*36*	*22*	*74*	*220*	0.327 (0.241-0.423)	0.909 (0.866-0.942)	0.621 (0.484-0.745)	0.748 (0.695-0.797)
Nazerian 2014 [151]	US	CT	No/No	*67*	*10*	*43*	*237*	0.609 (0.511-0.701)	0.96 (0.927-0.98)	0.87 (0.774-0.936)	0.846 (0.799-0.887)
Nazerian 2014 [151]	US	CT	No/No	*99*	*34*	*11*	*213*	0.9 (0.828-0.949)	0.862 (0.813-0.903)	0.744 (0.662-0.816)	0.951 (0.914-0.975)
Comert 2013 [152]	US	CT	No/No	27	8	3	12	0.9 (0.735-0.979)	0.6 (0.361-0.809)	0.771 (0.599-0.896)	0.8 (0.519-0.957)
Pfeil 2010 [153]	US	CT	No/No	7	7	3	16	0.7 (0.348-0.933)	0.696 (0.471-0.868)	0.5 (0.23-0.77)	0.842 (0.604-0.966)
Reissig 2004 [154]	US	CT	No/No	29	8	3	22	0.906 (0.75-0.98)	0.733 (0.541-0.877)	0.784 (0.618-0.902)	0.88 (0.688-0.975)

Study Information	Index	Reference	Post hoc/subset	TP	FP	FN	TN	Sn (95% CI)	SP (95% CI)	PPV (95% CI)	NPV (95% CI)
Mohn 2003 [155]	US	CC	No/No	22	10	9	33	0.71 (0.52-0.858)	0.767 (0.614-0.882)	0.688 (0.5-0.839)	0.786 (0.632-0.897)
Lechleitner 2002 [117]	US	MRI	No/No	29	1	6	16	0.829 (0.664-0.934)	0.941 (0.713-0.999)	0.967 (0.828-0.999)	0.727 (0.498-0.893)
Reissig 2001 [156]	US	MSC	No/No	35	2	9	23	0.795 (0.647-0.902)	0.92 (0.74-0.99)	0.946 (0.818-0.993)	0.719 (0.533-0.863)
Reissig 2001 [156]	US	CT	No/No	*23*	*7*	*9*	*23*	0.719 (0.533-0.863)	0.767 (0.577-0.901)	0.767 (0.577-0.901)	0.719 (0.533-0.863)
Lechleitner 1998 [158]	US	VQ	No/No	18	15	3	28	0.857 (0.637-0.97)	0.651 (0.491-0.79)	0.545 (0.364-0.719)	0.903 (0.742-0.98)
Lechleitner 1998 [158]	US	VQ	No/No	*18*	*33*	*3*	*36*	0.857 (0.637-0.97)	0.522 (0.398-0.644)	0.353 (0.224-0.499)	0.923 (0.791-0.984)
Mathis 1993 [157]	US	SC	No/No	41	4	1	8	0.976 (0.874-0.999)	0.667 (0.349-0.901)	0.911 (0.788-0.975)	0.889 (0.518-0.997)

CC = Complex composite; CT = Computed Tomography; MRI = Magnetic Resonance Imaging; SC = Simple composite; VQ = Ventilation-Perfusion;

Table 18-G: Diagnostic test accuracy data for Q as index test in non-pregnant patients

Study Information	Index	Reference	Post hoc/subset	Details	TP	FP	FN	TN	Sn (95% CI)	SP (95% CI)	PPV (95% CI)	NPV (95% CI)
Mazurek 2015 [166]	Q	CC	No/No	Unclear	19	33	7	25	0.731 (0.522-0.884)	0.431 (0.302-0.568)	0.365 (0.236-0.51)	0.781 (0.6-0.907)
van Es 2015 [167]	Q	CT	No/No	PISAPED	15	6	9	44	0.625 (0.406-0.812)	0.88 (0.757-0.955)	0.714 (0.478-0.887)	0.83 (0.702-0.919)
Lu 2014 [163]	Q	CC	No/No	PISAPED	19	6	3	78	0.864 (0.651-0.971)	0.929 (0.851-0.973)	0.76 (0.549-0.906)	0.963 (0.896-0.992)
Skarlovnik 2014 [161]	Q	CC	No/No	PISAPED	5	4	1	67	0.833 (0.359-0.996)	0.944 (0.862-0.984)	0.556 (0.212-0.863)	0.985 (0.921-1)
He 2012 [131]	Q	CC	No/No	PISAPED	*276*	*45*	*42*	*181*	0.86 (0.817-0.896)	0.812 (0.754-0.861)	0.868 (0.826-0.903)	0.801 (0.743-0.851)
He 2012 [131]	Q	CC	No/Yes (Low)	PISAPED	*16*	*22*	*72*	*108*	0.818 (0.722-0.892)	0.831 (0.755-0.891)	0.766 (0.667-0.847)	0.871 (0.799-0.924)
He 2012 [131]	Q	CC	No/Yes (Intermediate)	PISAPED	*140*	*15*	*25*	*56*	0.848 (0.785-0.899)	0.789 (0.676-0.877)	0.903 (0.845-0.945)	0.691 (0.579-0.789)

Study Information	Index	Reference	Post hoc/subset	Details	TP	FP	FN	TN	Sn (95% CI)	SP (95% CI)	PPV (95% CI)	NPV (95% CI)
He 2012 [131]	Q	CC	No/Yes (High)	PISAPED	*64*	*4*	*5*	*17*	0.928 (0.839-0.976)	0.81 (0.581-0.946)	0.941 (0.856-0.984)	0.773 (0.546-0.922)

0.941 (0.856-0.984) 0.773 (0.546-0.922) 0.928 (0.839-0.976) 0.81 (0.581-0.946)

Wang 2009 [121]	Q	CC	No/No	Modified PIOPED	33	3	4	35	0.892 (0.746-0.97)	0.921 (0.786-0.983)	0.917 (0.775-0.982)	0.897 (0.758-0.971)
Sostman 2008 [164]	Q	MSC	Yes/No	Modified PIOPED II	107	61	19	512	0.849 (0.775-0.907)	0.894 (0.865-0.918)	0.637 (0.559-0.71)	0.964 (0.945-0.978)
Sostman 2008 [164]	Q	MSC	Yes/No	Modified PIOPED II	113	23	20	557	0.85 (0.777-0.906)	0.96 (0.941-0.975)	0.831 (0.757-0.89)	0.965 (0.947-0.979)
Sostman 2008 [164]	Q	MSC	Yes/No	PISAPED	138	24	31	696	0.817 (0.75-0.872)	0.967 (0.951-0.979)	0.852 (0.788-0.903)	0.957 (0.94-0.971)
Sostman 2008 [164]	Q	MSC	Yes/No	PISAPED	134	25	35	695	0.793 (0.724-0.851)	0.965 (0.949-0.977)	0.843 (0.777-0.896)	0.952 (0.934-0.966)
Rubini 2007 [165]	Q	CT	No/No	PISAPED	22	7	7	71	0.759 (0.565-0.897)	0.91 (0.824-0.963)	0.759 (0.565-0.897)	0.91 (0.824-0.963)
Tondeur 2007 [162]	Q	SC	No/No	PISAPED	9	7	0	14	1 (0.664-1)	0.667 (0.43-0.854)	0.562 (0.299-0.802)	1 (0.768-1)
Collart 2002 [169]	Q	CC	No/No	Modified PIOPED	12	11	3	40	0.8 (0.519-0.957)	0.784 (0.647-0.887)	0.522 (0.306-0.732)	0.93 (0.809-0.985)
Miniati 1996 [168]	Q	PA	No/No	PISAPED	217	20	19	134	0.919 (0.877-0.951)	0.87 (0.807-0.919)	0.916 (0.873-0.948)	0.876 (0.813-0.924)
Miniati 1996 [168]	Q	PA	No/No	PISAPED	*347*	*14*	*27*	*192*	0.928 (0.897-0.952)	0.932 (0.889-0.962)	0.961 (0.936-0.979)	0.877 (0.826-0.917)

CC = Complex composite; CT = Computed Tomography; PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis; PISAPED = Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis; SC = Simple composite;

Table 18-H: Diagnostic test accuracy data for Q-SPECT as index test in non-pregnant patients

Study Information	Index	Reference	Post hoc/subset	Details	TP	FP	FN	TN	Sn (95% CI)	SP (95% CI)	PPV (95% CI)	NPV (95% CI)
Mazurek 2015 [166]	Q-SPECT	CC	No/No	Unclear	23	31	3	27	0.885 (0.698-0.976)	0.466 (0.333-0.601)	0.426 (0.292-0.568)	0.9 (0.735-0.979)
Bajc 2013 [173]	Q-SPECT	CC	No/No	EANM	53	5	6	88	0.898 (0.792-0.962)	0.946 (0.879-0.982)	0.914 (0.81-0.971)	0.936 (0.866-0.976)
Collart 2002 [169]	VQ-SPECT	CC	No/No		12	2	3	49	0.8 (0.519-0.957)	0.961 (0.865-0.995)	0.857 (0.572-0.982)	0.942 (0.841-0.988)

CC = Complex composite

Table 18-I: Diagnostic test accuracy data for Q-SPECT-CT as index test in non-pregnant patients

Study Information	Index	Reference	Post hoc/subset	Details	TP	FP	FN	TN	Sn (95% CI)	SP (95% CI)	PPV (95% CI)	NPV (95% CI)
Kumar (Group 1) 2015 [175]	Q-SPECT-CT	CC	No/No		36	1	6	153	0.857 (0.715-0.946)	0.994 (0.964-1)	0.973 (0.858-0.999)	0.962 (0.92-0.986)
Le Roux 2015 [174]	Q-SPECT-CT	VQ-SPECT	No/No	Revised PIOPED	97	42	13	241	0.882 (0.806-0.936)	0.852 (0.805-0.891)	0.698 (0.614-0.773)	0.949 (0.914-0.972)
Mazurek 2015 [166]	Q-SPECT-CT	CC	No/No	Unclear	26	10	0	48	1 (0.868-1)	0.828 (0.706-0.914)	0.722 (0.548-0.858)	1 (0.926-1)
Lu 2014 [163]	Q-SPECT-CT	CC	No/No		20	5	2	79	0.909 (0.708-0.989)	0.94 (0.867-0.98)	0.8 (0.593-0.932)	0.975 (0.914-0.997)

CC = Complex composite; CT = Computed Tomography; PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis; VQ = Ventilation-Perfusion.

Table 18-J: Diagnostic test accuracy data for VQ as index test in non-pregnant patients

Study Information	Index	Reference	Post hoc/subset	Details	TP	FP	FN	TN	Sn (95% CI)	SP (95% CI)	PPV (95% CI)	NPV (95% CI)
Watanabe 2015 [160]	VQ	CT	No/No	Modified PISAPED	*62*	*6*	*6*	*53*	0.912 (0.818-0.967)	0.898 (0.792-0.962)	0.912 (0.818-0.967)	0.898 (0.792-0.962)
Lu 2014 [163]	VQ	CC	No/No	PIOPED II	11	1	4	77	0.733 (0.449-0.922)	0.987 (0.931-1)	0.917 (0.615-0.998)	0.951 (0.878-0.986)
Skarlovnik 2014 [161]	VQ	CC	No/No		5	2	1	83	0.833 (0.359-0.996)	0.976 (0.918-0.997)	0.714 (0.29-0.963)	0.988 (0.935-1)
Skarlovnik 2014 [161]	VQ	CC	No/No	PIOPED II	3	1	1	77	0.75 (0.194-	0.987 (0.931-1)	0.75 (0.194-	0.987 (0.931-1)

Study Information	Index	Reference	Post hoc/subset	Details	TP	FP	FN	TN	Sn (95% CI)	SP (95% CI)	PPV (95% CI)	NPV (95% CI)
				Revised					0.994)		0.994)	
He 2012 [131]	VQ	CC	No/No	PIOPED II	*245*	*33*	*43*	*156*	0.851 (0.804-0.89)	0.825 (0.764-0.877)	0.881 (0.837-0.917)	0.784 (0.72-0.839)
He 2012 [131]	VQ	CC	No/Yes (Low)	PIOPED II	*66*	*18*	*15*	*93*	0.815 (0.713-0.892)	0.838 (0.756-0.901)	0.786 (0.683-0.868)	0.861 (0.781-0.92)
He 2012 [131]	VQ	CC	No/Yes (Intermediate)	PIOPED II	*123*	*10*	*23*	*47*	0.842 (0.773-0.897)	0.825 (0.701-0.913)	0.925 (0.866-0.963)	0.671 (0.549-0.779)
He 2012 [131]	VQ	CC	No/Yes (High)	PIOPED II	*56*	*5*	*5*	*16*	0.918 (0.819-0.973)	0.762 (0.528-0.918)	0.918 (0.819-0.973)	0.762 (0.528-0.918)
Gutte 2010 [176]	VQ	CC	No/No		7	7	4	18	0.636 (0.308-0.891)	0.72 (0.506-0.879)	0.5 (0.23-0.77)	0.818 (0.597-0.948)
Wang 2009 [121]	VQ	CC	No/No	Modified PIOPED	33	3	4	35	0.892 (0.746-0.97)	0.921 (0.786-0.983)	0.917 (0.775-0.982)	0.897 (0.758-0.971)
Sostman 2008 [180]	VQ	MSC	Yes/No	Modified PIOPED II	89	13	26	541	0.774 (0.687-0.847)	0.977 (0.96-0.987)	0.873 (0.792-0.93)	0.954 (0.934-0.97)
Ohno 2004 [147]	VQ	CC	No/No		8	8	4	28	0.667 (0.349-0.901)	0.778 (0.608-0.899)	0.5 (0.247-0.753)	0.875 (0.71-0.965)
Reinartz 2004 [122]	VQ	CC	No/No	PIOPED	28	6	9	39	0.757 (0.588-0.882)	0.867 (0.732-0.949)	0.824 (0.655-0.932)	0.812 (0.674-0.911)
Coche 2003 [126]	VQ	SC	No/No	PIOPED II	24	4	8	58	0.75 (0.566-0.885)	0.935 (0.843-0.982)	0.857 (0.673-0.96)	0.879 (0.775-0.946)
Lechleitner 2002 [117]	VQ	MRI	No/No	PIOPED	21	2	6	8	0.778 (0.577-0.914)	0.8 (0.444-0.975)	0.913 (0.72-0.989)	0.571 (0.289-0.823)
Blachere 2000 [132]	VQ	CC	No/No	PIOPED	*55*	*29*	*13*	*82*	0.809 (0.695-0.894)	0.739 (0.647-0.818)	0.655 (0.543-0.755)	0.863 (0.777-0.925)
Gray 1990 [178]	VQ	PA	No/No	Unclear	15	0	1	32	0.938 (0.698-0.998)	1 (0.891-1)	1 (0.782-1)	0.97 (0.842-0.999)
PIOPED Investigators 1990 [177]	VQ	PA	No/No	PIOPED	*102*	*14*	*44*	*249*	0.699 (0.617-0.772)	0.947 (0.912-0.971)	0.879 (0.806-0.932)	0.85 (0.804-0.889)
Woods 1989 [179]	VQ	PA	No/No	Modified Biello	6	2	2	11	0.75 (0.349-0.968)	0.846 (0.546-0.981)	0.75 (0.349-0.968)	0.846 (0.546-0.981)
Woods 1989 [179]	VQ	PA	No/No	PIOPED	6	1	3	12	0.667 (0.299-0.925)	0.923 (0.64-0.998)	0.857 (0.421-0.996)	0.8 (0.519-0.957)

CC = Complex composite; CT = Computed Tomography; MRI = Magnetic Resonance Imaging; PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis; PISAPED = Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis; SC = Simple composite; VQ = Ventilation-Perfusion.

Table 18-K: Diagnostic test accuracy data for VQ-SPECT as index test in non-pregnant patients

Study Information	Index	Reference	Post hoc/subset	Details	TP	FP	FN	TN	Sn (95% CI)	SP (95% CI)	PPV (95% CI)	NPV (95% CI)
Ibanez-Bravo 2016 [188]	VQ-SPECT	CT	No/No	EANMMI	18	8	3	19	0.857 (0.637-0.97)	0.704 (0.498-0.862)	0.692 (0.482-0.857)	0.864 (0.651-0.971)
Ibanez-Bravo 2016 [188]	VQ-SPECT	CT	No/Yes (High)	EANMMI	7	0	1	2	0.875 (0.473-0.997)	1 (0.158-1)	1 (0.59-1)	0.667 (0.094-0.992)
Ibanez-Bravo 2016 [188]	VQ-SPECT	CT	No/Yes (Intermediate)	EANMMI	11	8	2	17	0.846 (0.546-0.981)	0.68 (0.465-0.851)	0.579 (0.335-0.797)	0.895 (0.669-0.987)
Quirce 2014 [182]	VQ-SPECT	VQ	No/No	EANMMI	31	3	0	5	1 (0.888-1)	0.625 (0.245-0.915)	0.912 (0.763-0.981)	1 (0.478-1)
Skarlovnik 2014 [161]	VQ-SPECT	CC	No/No	EANM	9	1	0	39	1 (0.664-1)	0.975 (0.868-0.999)	0.9 (0.555-0.997)	1 (0.91-1)
Le Duc-Pennec 2012 [190]	VQ-SPECT	SC	No/No	Revised PIOPED	28	4	6	175	0.824 (0.655-0.932)	0.978 (0.944-0.994)	0.875 (0.71-0.965)	0.967 (0.929-0.988)
Le Duc-Pennec 2012 [190]	VQ-SPECT	VQ	No/No	Revised PIOPED	27	2	6	170	0.818 (0.645-0.93)	0.988 (0.959-0.999)	0.931 (0.772-0.992)	0.966 (0.927-0.987)
Le Roux 2012 [485]	VQ-SPECT	VQ	Yes/No	Revised PIOPED	26	2	12	171	0.684 (0.513-0.825)	0.988 (0.959-0.999)	0.929 (0.765-0.991)	0.934 (0.888-0.966)
Gutte 2010 [176]	VQ-SPECT	CC	No/No	Unclear	10	3	0	20	1 (0.692-1)	0.87 (0.664-0.972)	0.769 (0.462-0.95)	1 (0.832-1)
Gutte 2010 [176]	VQ-SPECT	VQ	No/No	Unclear	8	5	6	14	0.571 (0.289-0.823)	0.737 (0.488-0.909)	0.615 (0.316-0.861)	0.7 (0.457-0.881)
Gutte 2009 [128]	VQ-SPECT	CC	No/No	Unclear	28	6	1	42	0.966 (0.822-0.999)	0.875 (0.748-0.953)	0.824 (0.655-0.932)	0.977 (0.877-0.999)
Gutte 2009 [128]	VQ-SPECT	CC	No/No	Unclear	30	1	0	50	1 (0.884-1)	0.98 (0.896-1)	0.968 (0.833-0.999)	1 (0.929-1)
Gutte 2009 [128]	VQ-SPECT	CC	No/No	Unclear	26	2	20	21	0.565 (0.411-0.711)	0.913 (0.72-0.989)	0.929 (0.765-0.991)	0.512 (0.351-0.671)
Gutte 2009 [128]	VQ-SPECT	CC	No/No		21	0	10	50	0.677 (0.486-0.833)	1 (0.929-1)	1 (0.839-1)	0.833 (0.715-0.917)
Miles 2009 [183]	VQ-SPECT	CT	No/No	Unclear	19	1	3	56	0.864 (0.651-0.971)	0.982 (0.906-1)	0.95 (0.751-0.999)	0.949 (0.859-0.989)
Bajc 2008 [184]	VQ-SPECT	CT	No/No	Holistic	25	25	4	51	0.862 (0.683-0.961)	0.671 (0.554-0.775)	0.5 (0.355-0.645)	0.927 (0.824-0.98)
Weinmann 2008 [187]	VQ-SPECT	CT	No/No	PIOPED II	15	13	4	62	0.789 (0.544-0.939)	0.827 (0.722-0.904)	0.536 (0.339-0.725)	0.939 (0.852-0.983)

Study Information	Index	Reference	Post hoc/subset	Details	TP	FP	FN	TN	Sn (95% CI)	SP (95% CI)	PPV (95% CI)	NPV (95% CI)
Harris 2007 [185]	VQ-SPECT	CC	No/No	Modified PIOPED	17	2	0	18	1 (0.805-1)	0.9 (0.683-0.988)	0.895 (0.669-0.987)	1 (0.815-1)
Harris 2007 [185]	VQ-SPECT	CC	No/No	Modified PIOPED	8	0	4	35	0.667 (0.349-0.901)	1 (0.9-1)	1 (0.631-1)	0.897 (0.758-0.971)
Reinartz 2006 [186]	VQ-SPECT	CT	No/No	Unclear	20	1	2	30	0.909 (0.708-0.989)	0.968 (0.833-0.999)	0.952 (0.762-0.999)	0.938 (0.792-0.992)
Bajc 2004 [189]	VQ-SPECT	VQ	No/No	Holistic	11	5	0	37	1 (0.715-1)	0.881 (0.744-0.96)	0.688 (0.413-0.89)	1 (0.905-1)
Bajc 2004 [189]	VQ-SPECT	VQ	No/No	Unclear	11	4	0	37	1 (0.715-1)	0.902 (0.769-0.973)	0.733 (0.449-0.922)	1 (0.905-1)
Reinartz 2004 [122]	VQ-SPECT	CC	No/No	PIOPED	36	4	1	42	0.973 (0.858-0.999)	0.913 (0.792-0.976)	0.9 (0.763-0.972)	0.977 (0.877-0.999)

CC = Complex composite; CT = Computed Tomography; PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis; SC = Simple composite; VQ = Ventilation-Perfusion.

Table 18-L: Diagnostic test accuracy data for VQ-SPECT-CT as index test in non-pregnant patients

Study Information	Index	Reference	Post hoc/subset	Details	TP	FP	FN	TN	Sn (95% CI)	SP (95% CI)	PPV (95% CI)	NPV (95% CI)
Bhatia 2016 [192]	VQ-SPECT-CT	CT	No/No	Unclear	13	5	0	84	1 (0.753-1)	0.944 (0.874-0.982)	0.722 (0.465-0.903)	1 (0.957-1)
Le Roux 2015 [174]	VQ-SPECT-CT	VQ-SPECT	No/No	Revised PIOPED	97	0	13	283	0.882 (0.806-0.936)	1 (0.987-1)	1 (0.963-1)	0.956 (0.926-0.976)
Ling 2012 [191]	VQ-SPECT-CT	VQ-SPECT	No/No	Unclear	26	0	2	78	0.929 (0.765-0.991)	1 (0.954-1)	1 (0.868-1)	0.975 (0.913-0.997)
Gutte 2009 [128]	VQ-SPECT-CT	VQ-SPECT	No/No		*29*	*0*	*5*	*43*	0.853 (0.689-0.95)	1 (0.918-1)	1 (0.881-1)	0.896 (0.773-0.965)

CT = Computed Tomography; PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis; VQ = Ventilation-Perfusion.

Appendix 19: Individual Study Utility and Safety Data (Questions 2 and 3)

- Failure rates, nondiagnostic studies, and rates of incidental findings appear in Tables 19-A through 19-F.
- Details of incidental findings appear in Table 19-G.
- Safety data appears in Table 19-H.

Table 19-A: Failure rates, nondiagnostic studies, and incidental findings for CT as an index test

Study Information	Index	Reference	Failure, index	Failure, reference	Nondiagnostic, index	Nondiagnostic, reference	Incidental findings, index	Incidental findings, reference
Meier 2016 [198]	CT (CT low-CM)	CT	0/34 (0)	0/36 (0)	17/82 (0.207)	8/83 (0.096)		
Watanabe 2015 [160]	CT (CTPA)	FU			2/129 (0.016)			
Moores 2015 [199]	CT (CT)	CC	2/129 (0.016)	0/43 (0)			26/134	
Megyeri 2014 [130]	CT (CTPA (BW < 100kg))	CC	0/189 (0)	0/186 (0)				
He 2012 [131]	CT (CT)	CC			16/544 (0.029)			
Woo 2012 [205]	CT (CT)	None			21/1424 (0.015)			
Pesavento 2011 [202]	CT (CT)	FU	0/367 (0)		9/545 (0.017)		108/545	
Sodhi 2010 [204]	CT (CT)	CC	1/21 (0.048)	0/20 (0)			15/50	
Hantous-Zannad 2010 [196]	CT (CTPA)	FU	1/29 (0.034)					
Galipienzo 2010 [118]	CT (MCTPA)	FU	1/242 (0.004)					
Gimber 2009 [195]	CT (CTPA)	FU			21/353 (0.059)			
Wang 2009 [121]	CT (CTPA)	CC			2/82 (0.024)			
Anderson 2007 [57]	CT (CTPA)	VQ	2/500 (0.004)	6/100 (0.06)				
Stein 2006 [67]	CT (MDCT Angiography)	SC			51/824 (0.062)	87/824 (0.106)		
Huisman 2006 [197]	CT (CT)	FU	18/1385 (0.013)		40/1999 (0.02)			
Vigo 2006 [115]	CT (CT)	FU	6/536 (0.011)			15/702 (0.021)	144/536	
Perez de Llano 2006 [201]	CT (Helical CT)	FU	1/87 (0.011)					

Study Information	Index	Reference	Failure, index	Failure, reference	Nondiagnostic, index	Nondiagnostic, reference	Incidental findings, index	Incidental findings, reference
Hogg 2006 [110]	CT (CTPA)	FU	2/381 (0.005)					
Ghanima 2005 [109]	CT (MSCT (Spiral))	FU	2/211 (0.009)		15/329 (0.046)			
Revel 2005 [203]	CT (CT Angiography)	FU	2/109 (0.018)		20/220 (0.091)			
Coche 2003 [126]	CT (MDCT)	SC	0/65 (0)	0/58 (0)	1/94 (0.011)	7/94 (0.074)	19/66	
Donato 2003 [194]	CT (CT)	FU	4/239 (0.017)					
Bourriot 2003 [193]	CT (SCT)	FU	3/117 (0.026)			26/196 (0.133)		
Ost 2001 [200]	CT (Spiral CT)	PA	1/68 (0.015)		10/103 (0.097)			
Qanadli 2000 [125]	CT (Dual section Helical CT)	PA			17/314 (0.054)	11/316 (0.035)	1/158	
Blachere 2000 [132]	CT (CT angiography)	CC	3/107 (0.028)		5/179 (0.028)			

BW = body weight; CC = complex composite; CM = constrast medium; CT = computed tomography; CTPA = computed tomography pulmonary angiography; MDCT = multidetector computed tomography; SC = simple composite; VQ = ventilation-perfusion.

Table 19-B: Failure rates, nondiagnostic studies, and incidental findings for MRI as an index test

Study Information	Index	Reference	Failure, index	Failure, reference	Nondiagnostic, index	Nondiagnostic, reference	Incidental findings, index	Incidental findings, reference
Zhang 2013 [138]	MRI (MRPA)	CT			0/27 (0)	0/27 (0)		
Schiebler 2013 [54]	MRI (MRA)	FU	5/148 (0.034)		5/190 (0.026)			
Revel 2013 [139]	MRI (MRA Unenhanced free-breathing)	CT			128/274 (0.467)			
Revel 2013 [139]	MRI (MRA Unenhanced breath-hold)	CT			106/274 (0.387)			
Revel 2013 [139]	MRI (MRA Native Perfusion Reader)	CT			111/274 (0.405)			
Revel 2013 [139]	MRI (MRA Perfusion with mask subtraction)	CT			120/274 (0.438)			
Revel 2013 [139]	MRI (MRA Contrast-enhanced angiography)	CT			130/274 (0.474)			

Study Information	Index	Reference	Failure, index	Failure, reference	Nondiagnostic, index	Nondiagnostic, reference	Incidental findings, index	Incidental findings, reference
Revel 2012 [140]	MRI (MRI)	CT			80/274 (0.292)			
Stein 2010 [146]	MRI (MRA)	CC			92/371 (0.248)			
Kluge 2006 [209]	MRI (MRI)	MRI			0/218 (0)		97/218	
Kluge 2006 [209]	MRI (MRI)	MRI			1/218 (0.005)		97/218	
Kluge 2006 [209]	MRI (MRI)	MRI			26/218 (0.119)		97/218	
Kluge 2006 [141]	MRI (MRI)	CT			0/62 (0)			
Kluge 2006 [141]	MRI (MRI)	CT			0/62 (0)			
Kluge 2006 [141]	MRI (MRI)	CT			0/62 (0)		8/62 (0.145)	9/62 (0.145)

CC = complex composite; CT = computed tomography; MRI = magnetic resonance imaging.

Table 19-C: Failure rates, nondiagnostic studies, and incidental findings for US as an index test

Study Information	Index	Reference	Failure, index	Failure, reference	Nondiagnostic, index	Nondiagnostic, reference	Incidental findings, index	Incidental findings, reference
Mohn 2003 [155]	US (Transthoracic Sonography)	CC		0/43 (0)				
Lechleitner 2002 [117]	US (Chest ultrasound)	MRI			3/55 (0.055)	0/55 (0)		

CC = complex composite; MRI = magnetic resonance imaging.

Table 19-D: Failure rates, nondiagnostic studies, and incidental findings for Q as an index test

Study Information	Index	Reference	Failure, index	Failure, reference	Nondiagnostic, index	Nondiagnostic, reference	Incidental findings, index	Incidental findings, reference
Watanabe 2015 [160]	Q (Q-only PISAPED)	FU			0/129 (0)			
van Es 2015 [167]	Q (VQ with CXR)	CT		0/6 (0)	2/76 (0.026)	0/76 (0)		
Skarlovnik 2014 [161]	Q (No)	CC			21/98 (0.214)			
He 2012 [131]	Q (Q-only PISA-PED)	CC			0/544 (0)			
Sostman 2008 [164]	Q (Q + CXR Modified PIOPED II Reader 1)	DSA or CT			183/889 (0.206)			

Study Information	Index	Reference	Failure, index	Failure, reference	Nondiagnostic, index	Nondiagnostic, reference	Incidental findings, index	Incidental findings, reference
Sostman 2008 [164]	Q (Q + CXR PISAPED Reader 1)	DSA or CT			0/889 (0)			
Miniati 1996 [168]	Q (Q)	PA				21/413 (0.051)		

CC = complex composite; CT = computed tomography; CXR = chest X-ray; DSA = digital subtraction angiography; PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis; PISAPED = Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis.

Table 19-E: Failure rates, nondiagnostic studies, and incidental findings for Q-SPECT as an index test

Study Information	Index	Reference	Failure, index	Failure, reference	Nondiagnostic, index	Nondiagnostic, reference	Incidental findings, index	Incidental findings, reference
Bajc 2013 [173]	Q-SPECT (Q-SPECT)	CT	0/88 (0)	0/93 (0)	0/152 (0)			

CT = computed tomography; SPECT = single photon emission tomographpy.

Table 19-F: Failure rates, nondiagnostic studies, and incidental findings for VQ as an index test

Study Information	Index	Reference	Failure, index	Failure, reference	Nondiagnostic, index	Nondiagnostic, reference	Incidental findings, index	Incidental findings, reference
Watanabe 2015 [160]	VQ (VQ mod PISAPED)	FU			74/129 (0.574)			
Skarlovnik 2014 [161]	VQ (No)	CC			16/98 (0.163)			
He 2012 [131]	VQ (VQ PIOPED II)	CC			67/544 (0.123)			
Gutte 2010 [176]	VQ	CC			0/36 (0)	5/41 (0.122)		
Miles 2009 [183]	VQ	CT			25/99 (0.253)			
Wang 2009 [121]	VQ (VQ Perfusion and CR)	CC			2/28 (0.071)			
Sostman 2008 [180]	VQ (VQ High probability or very low/normal)	DSA or CT			241/910 (0.265)			
Coche 2003 [126]	VQ	CT			7/94 (0.074)	1/94 (0.011)	(0.242)	16/66 (0.242)
Lechleitner 2002 [117]	VQ (VQ scintigraphic scans)	MRI			18/55 (0.327)	0/55 (0)		

Study Information	Index	Reference	Failure, index	Failure, reference	Nondiagnostic, index	Nondiagnostic, reference	Incidental findings, index	Incidental findings, reference
PIOPED Investigators 1990 [177]	VQ (VQ)	PA	0/21 (0)		364/931 (0.391)			
Gray 1990 [178]	VQ	PA	0/28 (0)	0/51 (0)	30/78 (0.385)	0/78 (0)		

CC = complex composite; CT = computed tomography; DSA = digital subtraction angiography; MRI = magnetic resonance imaging; PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis; PISAPED = Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis; VQ = ventilation-perfusion.

Table 19-G: Details of alternative diagnoses and incidental findings, all modalities

Study	Number (%) of patients	Details
CT		
Moores 2015[199]	26/134 (19.4)	Pneumonia 13, emphysema 6, cancer 3, heart failure 3, pneumothorax 1.
Pesavento 2011[202]	108/545 (19.8)	Pneumonia 50, pleural effusion 27, malignancy 11, other 20.
Sodhi 2010[204]	15/50 (30.0)	Pleural effusion 8, mediastinal/hilar lymphadenopathy 6, pneumonia/air space consolidation 5, atelectasis/collapse 2, lung mass with metastasis 1.
Vigo 2006[115]	144/536 (28.9)	Pneumonia, lung malignancy, pleural disease, chronic obstructive lung disease, cardiopathies, interstitial lung disease, diseases of mediastinum, aortic dissection, subphrenic abscess, pneumothorax, pericarditis, other.
Coche 2003[126]	Non-PE: 19/66 (28.8)	Pneumonia 7, heart failure 5, small airways diseases 4, pleural diseases 2, and pulmonary fibrosis 1.
Qanadli 2000[125]	1/158 (0.6)	Intramural hematoma of ascending aorta 1.
MRI		
Kluge 2006[209]	97/218 (44.5)	Large pleural effusion 43, COPD 11, lobar atelectasis 11, aortic dissection 11, mediastinal bleeding 9, pneumonic infiltration 8, bronchiogenic carcinoma 2, lung metastases 1, lymphangitic carcinomatosis 1.
Kluge 2006[141]	MRI: 8/62 (12.9) CT: 9/62 (14.5)	Parenchymal lung disease 4 (emphysema 3, fibrosis, chronic bronchitis), aortic dissection 1, marked pleural effusion 2, breast carcinoma with lymphangitic carcinomatosis 1, polycystic liver disease 1, polycystic kidney disease 1.
Leichleitner 2002[117]	US: unreported MRI: 55/	(MRI findings). CHF 5, bronchopulmonary infection 4, pulmonary hypertension 3, and gastric ulcer 2, COPD 1, CAD 1, a musculoskeletal disorder 1, aortic valve disease 1, metastatic lung disease 1.

CAD = coronary artery disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease

Table 19-H: Safety, all modalities

	Index test	Reference test	Safety Outcome	Incidence and details
Pesavento 2011[202]	CT	None	Severe acute renal failure	CT: 1 (0.27%)
Stein 2006[67]	CT	CC	Allergic reaction	CT: 4 (>1%) Mild.
Yazici 2016[207]	CT	None	Contrast nephropathy (laboratory definition)	24 (13%)
Coche 2003[126]	CT	CT, VQ	Contrast nephropathy (creatinine increase)	1/69
Mitchell 2006[206]	CT	None	Contrast nephropathy (creatinine increase)	All: 44/1224 (4%) or paired: 44/354 (12%)
			Severe acute renal failure	0/1224
Revel 2012[140]	MRI	CT	Extravasation of contrast	MRI: 1 (patient could not complete protocol)
Stein 2010[146]	MRI	CT, VQ	Adverse events	No serious adverse events … related to MRA, venography, other tests. 3 month follow-up 93%, 6 months 84%.
Kluge 2006[209]	MRI-MRV	None	Adverse events	No complications related to MRI or contrast media
Pleszewski 2006[149]	MRI	Sequential	Adverse events	Reported "All 48 MR angiographic examinations were completed successfully without adverse effects"
Righini 2008[116]	PW (DD-leg US-CT)	APW (DD-CT)	Allergic reaction	PW: 1/509 (0.2) (rash) APW: 2/535 (0.4) (rash)
			Extravasation of contrast	PW: 1 APW: 2
			Severe acute renal failure	PW: 0 APW: 0
			Mortality (1 year follow-up)	PW: 37 APW: 22
Gray 1990[178]	VQ	PA	Mortality	4 (not related to imaging; due to underlying condition). 1 pericardial tamponade from malignant infiltration; 1 died of CHF, 1 of CRF+septicemia; 1 ruptured cardiac aneurysm, cardiac tamponade.

DD = D-dimer; PW = pathway; APW = alternative pathway.

Appendix 20: Study Characteristics of Studies in Pregnant Patients

Study	Study Design	Subject Characteristics	Intervention	Comparator	Study N	Mean age (years), range or SD
Gruning, 2016[219]	Retrospective case-control study	Pregnant women who underwent imaging for suspected pulmonary embolism; Stage of gestation: 16(10%) first trimester; 45 (27%) second trimester; 99 (59%) third trimester (8 patients without gestational age recorded)	VQ SPECT or Q SPECT	CT	168 (control group of 89 non-pregnant women)	28 (range 17 to 43; SD = 6)
Bajc, 2015[217]	Prospective cohort study	Pregnant women with suspected PE; Stage of gestation: 30(24%) first trimester; 59(46%) second trimester; 38(30%) third trimester	V SPECT; Q-SPECT; or VQ SPECT	CT	127	30 (range 18 to 48)
Browne, 2014[218]	Retrospective case control study	Pregnant (n = 70) and postpartum (n = 54) women; 124 non-pregnant controls; Stage of gestation 1(1.4%) first trimester; 31 (44.3%) second trimester; 38 (54.3%) third trimester	CT	Clinical follow-up	124	32 (range 15 to 46; SD = 5.62)
Bourjeily 2012[221]	Retrospective cohort study	Pregnant patients with suspected PE (inpatients or outpatients); Gestational age (27.5 [7.5] weeks)	CT	Clinical follow-up	343 patients (318 with complete follow-up data)	29 (6.7)
Shahir 2010[213]	Retrospective cohort study	Pregnant patients with suspicion of PE; Stage of gestation: 54 (27%) first trimester; 61 (31%) second trimester; 84 (42%) third trimester	CT	Q scintigraphy	199 (100 CT, 99 Q, 6 received both)	31 years (range 18 to 39)
Cahill 2009[214]	Retrospective cohort study	Pregnant or six weeks postpartum; Stage of gestation: 33(10.9%) first trimester; 49 (16.1%) second trimester; 117(38.5%) third trimester; 105(34.5%) postpartum	CT	VQ	304	29.2 (5.1) for CT; 30.8 (6.3) for VQ

Study	Study Design	Subject Characteristics	Intervention	Comparator	Study N	Mean age (years), range or SD
Ridge 2009[215]	Retrospective cohort study	Pregnant women with suspected PE; Stage of gestation NR	CT	VQ	50 (25 CTA; 25 VQ)	32.6 (5.6) for CT; 31.8 (5.4) for VQ
Scarsbrook 2007[220]	Prospective cohort study	Pregnant women with suspected PE; Stage of gestation 8% in first, 23% in second, 69% in third (n NR)	Q	CT	105	29.8 (range 16 to 48)
Chan 2002[216]	Prospective cohort study	Pregnant women with suspected PE (>12 weeks to <28 weeks gestation)	VQ	Clinical follow-up	120	32 (range 17 to 41)

CT = computed tomography; NR = not reported; PE = pulmonary embolism; Q = perfusion only; SD = standard deviation; SPECT = single photon emission computed tomography; VQ = ventilation perfusion scintigraphy

Appendix 21: Results of individual studies reporting stratified results and multiple imaging conditions

Table 21-A: Individual studies reporting stratified results

Study	Reference	Strata	N	Sensitivity (95% CI)	Specificity (95% CI)
CT					
Stein 2007[133]	SC (PA, VQ)	Age 18 to 58 years	559	0.80 (0.70 to 0.87)	0.96 (0.93 to 0.97)
		Age 60 to 79 years	221	0.88 (0.77 to 0.94)	0.97 (0.92 to 0.99)
		Age 80 to 99 years	44	0.80 (0.51 to 0.95)	0.92 (0.74 to 0.99)
Stein 2007[133]	SC (PA, VQ)	Men	318	0.88 (0.78 to 0.94)	0.93 (0.89 to 0.96)
		Women	506	0.79 (0.70 to 0.86)	0.97 (0.95 to 0.99)
He 2012[131]	CC (CT, VQ, PA)	Low risk (Wells)	213	0.784 (0.684 to 0.865)	0.952 (0.898 to 0.982)
		Moderate risk (Wells)	236	0.809 (0.740 to 0.866)	0.924 (0.832 to 0.975)
		High risk (Wells)	90	0.881 (0.778 to 0.947)	0.850 (0.621 to 0.968)
Stein 2006[67]	CC (VQ, DSA, US)	Low risk (Wells)	202	0.786 (0.59-0.917)	0.908 (0.855-0.947)
		Moderate risk (Wells)	237	0.861 (0.781-0.92)	0.938 (0.881-0.973)
		High risk (Wells)	38	0.786 (0.59-0.917)	0.9 (0.555-0.997)
Megyeri 2014[130]	CC (CT, US, VQ, FU)	Body weight <100 kg	114	0.944 (0.823 to 0.994)	0.978 (0.924 to 0.997)
		Body weight ≥100 kg	123	0.950 (0.751 to 0.999)	0.979 (0.927 to 0.997)
CTCTV					
Stein 2006[67]	CC (DSA, VQ, US)	Low risk (Wells)	193	0.828 (0.642-0.942)	0.89 (0.832-0.934)
		Moderate risk (Wells)	235	0.909 (0.839-0.956)	0.912 (0.848-0.955)
		High risk (Wells)	39	0.931 (0.772-0.992)	0.9 (0.555-0.997)
MRI					
Revel 2012[140]	CT	Low risk (Geneva)	74[a]	0.882 (0.636 to 0.985)[b] 0.684 (0.435 to 0.874)[b]	1.00 (0.900 to 1.00)[b] 1.00 (0.894 to 1.00)[b]
		Moderate risk (Geneva)	166[a]	0.837 (0.703 to 0.927)[b] 0.814 (0.666 to 0.916)[b]	0.986 (0.923 to 1.00)[b] 1.00 (0.947 to 1.00)[b]
		High risk (Geneva)	33[a]	0.833 (0.586 to 0.964)	1.00 (0.590 to 1.00)[b] 1.00 (0.631 to 1.00)[b]
Q					
He 2012[131]	CC (CT, VQ, PA)	Low risk (Wells)	218	0.818 (0.722-0.892)	0.831 (0.755-0.891)
		Moderate risk (Wells)	236	0.848 (0.785-0.899)	0.789 (0.676-0.877)
		High risk (Wells)	90	0.941 (0.856-0.984)	0.773 (0.546-0.922)
Sostman 2008[164]	PA or CT+Wells	Age <50 years	715	0.791 (0.705 to 0.856)	0.947 (0.926 to 0.962)
		Age ≥50 years	697	0.893 (0.832 to 0.932)	0.905 (0.878 to 0.927)

Study	Reference	Strata	N	Sensitivity (95% CI)	Specificity (95% CI)
VQ					
He 2012[131]	CC (CT, VQ, PA)	Low risk (Wells)	192	0.815 (0.713 to 0.892)	0.838 (0.756 to 0.901)
		Moderate risk (Wells)	236	0.842 (0.773 to 0.897)	0.825 (0.701 to 0.913)
		High risk (Wells)	90	0.918 (0.819 to 0.973)	0.762 (0.528 to 0.918)
VQ-SPECT					
Ibanez-Bravo 2016[188]	CT	Moderate	38	0.846 (0.546 to 0.981)	0.680 (0.465 to 0.851)
		High	10	0.875 (0.473 to 0.997)	1.00 (0.158 to 1.00)

[a] Total number of patients in risk category. Number of nondiagnostic exams was not reported for individual strata.
[b] Study reported results from two readers, which differed. Pooled results could not be calculated from available data.

Table 21-B: Individual studies reporting multiple MRI imaging conditions

Study	Comparator	Contrast / conditions	Sensitivity	Specificity
Revel 2013 [139]	CT	Yes/3D MRA[a]	0.894 (0.819-0.946)	0.971 (0.847-0.999)
	CT	Yes/3D MRA[a]	0.827 (0.74-0.894)	1 (0.923-1)
	CT	No/Perfusion[a]	0.663 (0.564-0.753)	0.875 (0.768-0.944)
	CT	No/Perfusion[a]	0.769 (0.676-0.846)	0.855 (0.733-0.935)
	CT	Yes/Perfusion[a]	0.75 (0.656-0.83)	0.906 (0.75-0.98)
	CT	Yes/Perfusion[a]	0.788 (0.697-0.862)	0.794 (0.679-0.883)
	CT	No/2D angio (breath-hold)[a]	0.76 (0.666-0.838)	0.961 (0.865-0.995)
	CT	No/2D angio (breath-hold)[a]	0.683 (0.584-0.771)	0.987 (0.931-1)
	CT	No/2D angio (free breathing)[a]	0.817 (0.729-0.886)	0.897 (0.726-0.978)
	CT	No/2D angio (free breathing)[a]	0.644 (0.544-0.736)	0.985 (0.918-1)
Kluge 2006 [141]	CT	Yes/Combined	1 (0.824-1)	0.93 (0.809-0.985)
	CT	Yes/3D MRA	0.812 (0.544-0.96)	1 (0.907-1)
	CT	Yes/Perfusion	1 (0.824-1)	0.907 (0.779-0.974)
	CT	Yes/RT MRI	0.895 (0.669-0.987)	0.977 (0.877-0.999)

[a] Study reported results from two readers, which differed. Pooled results could not be calculated from available data.

Appendix 22: Statistical Appendix (Questions 2 and 3)

This appendix contains:

- further details of data management
- how data were coded for analysis
- code for statistical models
- results for diagnostic test accuracy meta-analysis models
- details for explorations of heterogeneity

Diagnostic Test Accuracy

Data Management

Back-calculation of 2x2 tables

The 2x2 diagnostic test accuracy table consisting of true positive, true negative, false positive and false negative was extracted if available. If the 2x2 table was not available, then it was derived from available data for sensitivity and specificity (or positive predictive value and negative predictive value), number of cases as measured by the reference standard, and total number of patients contributing to the diagnostic test results. See Section 2.2.4 of the Centre for Reviews and Dissemination handbook, Systematic Reviews (https://www.york.ac.uk/crd/SysRev/!SSL!/WebHelp/SysRev3.htm).

If a study reported the comparison of multiple index tests with a common comparator and provided information on concordant or discordant results between the two index tests, as well as accounting for missing data, then in some cases it was possible also to extract the 2x2 table for a direct comparison. The best example of this is Watanabe 2015[160], which supplied a supplementary table listing discordant and missing results for all three modalities investigated, as well as 2x2 tables reporting comparisons with a common composite consisting of all information (and therefore excluded from the planned pool).

Data coding

Following data extraction, index tests and reference standards and covariates of interest were coded to reduce the number of categories. Covariates included:

- Study setting (Primary, Secondary or Tertiary healthcare setting)
- Patient origins (Inpatients, Outpatients, ER patients)
- Study funding

Modalities were pooled according to their index test category (Table 21A), and comparators were pooled according to their reference test category (Table 21B).

Table 21A: Coding of index test categories

Index test category	Index test description
CT	CTPA low dose
	CTPA
	CTA and leg US
CTCTV	CTA and CTV
MRI	1.5T
	3T

Index test category	Index test description
	Unknown T
MRIMRV	MRI and MRV
Ultrasound	Thoracic US
	Multiorgan US
	Transthoracic US
Q	Perfusion only
	Perfusion only and CXR
Q-SPECT	Perfusion only SPECT
Q-SPECT-CT	Perfusion only SPECT-CT
VQ	VQ
	VQ and CXR and leg US (optional)
VQ-SPECT	VQ SPECT
VQ-SPECT-CT	VQ SPECT CT
	Q-SPECT CT
Pathway	CPR and D-dimer and leg US and CTPA
	CT and CUS and VQ or DSA
	CPR and VQ and PA
	CPR and D-dimer and LUS and VQ
	CPR and D-dimer and VQ and CT
	CPR and D-Dimer and CT
	CT and Q and CXR
	D-dimer and US and CT
	D-dimer and VQ and CT

Table 21B: Coding of reference test categories

Reference test category	Reference test description
Complex Composite	All imaging and clinical FU
	All imaging and clinical information and clinical FU
	All imaging and clinical information
	Unspecified
Simple Composite	VQ and US
	VQ SPECT and clinical FU
	PA and clinical
	CT and clinical information
	All imaging
VQ or PA	VQ or PA
PA or CTA	PA or CTA
CT or VQ	CT or VQ
PA	PA
CT	CTPA
VQ	VQ

Reference test category	Reference test description
Other	Other
Alternative pathways	CPR and D-dimer and CTPA
Alternative pathways	Sequenced reference tree

Setting

Following the definitions in https://www.ehealthontario.on.ca/images/uploads/pages/documents/Health_Care_eBook_Final.pdf the type of centre was coded to indicate the level of healthcare

- Primary = First level of entry to healthcare system, physician's offices, nurse practitioner's offices, community health centres, nursing stations
- Secondary = Specialist and others, community hospital, acute care services
- Tertiary = Specialized care typically for inpatients, academic teaching facility or large community care facility
- Secondary / Tertiary = Secondary or Tertiary centre
- Secondary / ER = Secondary centre ER
- Tertiary / ER = Tertiary centre ER
- Secondary / Tertiary / ER = Secondary or Tertiary centre ER

Study centre

- Single = Single centre study
- Multi-national or regional = Multiple centres within a single country or region
- Multi-International = Multiple studies in more than one country

Patient origins

- Inpatients
- Outpatients
- ER = Patients presenting to an ER
- Inpatients / Outpatients = Study included both inpatients and outpatients
- Inpatients / Outpatients / ER = Study included inpatients, outpatients, and ER patients

Funding

- None
- Government or Academic/Institutional Grant
- Industry
- Private
- Multiple Sources
- Not reported

PE risk, according to structured assessment

- High
- Moderate
- Low
- Mixed (included a mixture of at least two of high, moderate, and low)
- Not reported

In addition, studies were coded as:

- Post-hoc analyses of studies already included
- Studies in which the index test was part of the reference
- Pregnant/Non-pregnant
- Interpretation criteria for Q and VQ

Exclusions from pooling

The following studies and comparisons were excluded from pooling:

- Studies that reported re-analysis of patient groups who were already included as part of another study, e.g., re-analyses of data to examine the effect of covariates or different interpretation criteria. These studies were incorporated where indicated in narrative reviews of the effect of covariates or interpretation criteria.
- Comparisons where the index modality was explicitly included in the reference standard. Where it is unclear whether this is the case, the study was retained. In some instances, it was possible to extract or derive an isolated comparison of the index modality with one of the imaging modalities used in the reference, in which case affected comparisons were excluded and the study was retained.

Handling of multiple sets of results from a single study

Where a study reported multiple sets of results, these were handled as follows:

- If results for more than one reader were reported, the four cells of the 2x2 tables were averaged across readers with rounding to the nearest integers, to create a summary 2xw table.
- If more than one contrast was reported, e.g., CT versus VQ and CT versus CC, then the 2x2 table that gave the highest accuracy (true positives plus true negatives, divided by the total number of patients) was included in the overall pool. The individual contrasts contributed to sub-pools, if there were enough studies.
- Where results from multiple scan conditions (MRI sequences) or multiple interpretation criteria (Q, VQ SPECT) that gave the highest accuracy (i.e., true positives plus true negatives / total patients) were included in the overall pool.
- Sensitivity analyses explored the effect of including results that gave the lowest accuracy, highest and lowest sensitivity, and highest and lowest specificity.

Handling of nondiagnostic tests

One or more studies reported data for nondiagnostic examinations for CT, MRI, Q, Q-SPECT, VQ, VQ-SPECT, and PW. Studies could be non-diagnostic on account of technical inadequacy, or non-diagnostic because, while technically adequate, their results were indeterminate. In clinical practice, studies that are non-diagnostic due to technical inadequacy are likely to be repeated, while patients with an indeterminate exam results usually undergo a different examination. For the nuclear medicine modalities in particular (Q, Q-SPECT, Q-SPECT-CT, VQ, VQ-SPECT, VQ-SPECT-CT), a substantial number of exams are technically adequate but non-diagnostic, assessed as intermediate probability, intermediate or low probability, or intermediate / low / very low probability, depending on the interpretation scale and the definitions used in the study.

Studies approached the reporting and analysis of nondiagnostic exams in different ways

- excluding patients with nondiagnostic exams from the diagnostic 2x2 table

- reporting only the total number of non-diagnostic tests (sometimes separating out non-diagnostic due to technical inadequacy from technically adequate but indeterminate)
- reporting the number of non-diagnostic cases and non-diagnostic non-cases
- a Bayesian adjustment of the sensitivity and specificity calculated from the results of exams were nondiagnostic.

An attempt was made to estimate the effect of non-diagnostic exams on the meta-analysis results by applying the conservative ITD assumption: non-diagnostic cases would be assumed to be FN, and non-diagnostic cases would be assumed to be FP. Because of the variability in approaches, and the number of studies that did not report usable data for the 3x2 diagnostic table, the resulting datasets were small and numerically heterogeneous, and a meta-analysis is not feasible at this time. The effect of non-diagnostic studies were summarized narratively.

The protocol definition of test failure was VTE in the first 30 days in a patient who had tested negative (negative DI) and was not receiving anticoagulation. Failure rate was reported in pathway studies and studies with index tests CT, MRI, Q-SPECT, VQ, VQ-SPECT, although the majority of studies reported failure rate over 3 or 6 months.

Diagnostic test meta-analysis: Sample WinBUGS programs

Program supplied by Dr. Nandini Dendukuri (http://www.nandinidendukuri.com/software)

Example for CT meta-analysis, with 11 studies and five reference standard classes. Reference standards are identified by their class, as described under data management. Non-informative priors were used for all parameters, and are specified within the WinBUGS program.

HSROC model assuming imperfect reference standard and conditional independence between index and reference test.

```
model {

        for(i in 1:11) {

                theta[i] ~ dnorm(THETA,prec[1])
                alpha[i] ~ dnorm(LAMBDA,prec[2])

                p[1,i] <- phi(-(theta[i] - 0.5*alpha[i])/exp(beta/2))
                p[2,i] <- phi(-(theta[i] + 0.5*alpha[i])*exp(beta/2))

                prob[i,1] <- pi[i]*( p[1,i] * s2[ref[i]] ) + (1-pi[i])*( p[2,i] * (1-c2[ref[i]]) )
                prob[i,2] <- pi[i]*( p[1,i] * (1-s2[ref[i]]) ) + (1-pi[i])*( p[2,i] * c2[ref[i]] )
                prob[i,3] <- pi[i]*( (1-p[1,i]) * s2[ref[i]] ) + (1-pi[i])*( (1-p[2,i]) * (1-c2[ref[i]]) )
                prob[i,4] <- pi[i]*( (1-p[1,i]) * (1-s2[ref[i]]) ) + (1-pi[i])*( (1-p[2,i]) * c2[ref[i]] )

                results[i,1:4] ~ dmulti(prob[i,1:4],n[i])
                n[i]<-sum(results[i,1:4])

                pi[i] ~ dbeta(1,1)

                se[i] <- p[1,i]
                sp[i] <- 1-p[2,i]

        }
```

```
        for(j in 1:2) {

                prec[j] <- pow(sigma[j],-2)
                sigma[j] ~ dunif(0,2)
        }

        THETA ~ dunif(-1.5,1.5)
        beta ~ dunif(-0.75,0.75)

 S_a ~ dnorm(0,1) # S_overall=phi(S_a)
 C_a ~ dnorm(0,1) # C_overall=phi(C_a)

        LAMBDA <- S_a*exp(beta/2) + C_a*exp(-beta/2)

        S_overall<-phi(-(THETA-LAMBDA/2)/exp(beta/2))
        C_overall<-phi( (THETA+LAMBDA/2)*exp(beta/2))

        theta_new ~ dnorm(THETA,prec[1])
        alpha_new ~ dnorm(LAMBDA,prec[2])

        S_new<-phi(-(theta_new-alpha_new*0.5)/exp(beta*0.5))
        C_new<-phi( (theta_new+alpha_new*0.5)*exp(beta*0.5))


        for(h in 1:5) {

                s2[h] ~ dunif(0.5,1) ;
                c2[h] ~ dunif(0.5,1) ;
        }

}
```

HSROC model assuming a perfect reference standard

```
model {

        for(i in 1:11) {

                theta[i] ~ dnorm(THETA,prec[1])
                alpha[i] ~ dnorm(LAMBDA,prec[2])

                p[1,i] <- phi(-(theta[i] - 0.5*alpha[i])/exp(beta/2))
                p[2,i] <- phi(-(theta[i] + 0.5*alpha[i])*exp(beta/2))

                prob[i,1] <- pi[i]*( p[1,i] * s2 ) + (1-pi[i])*(p[2,i] * (1-c2) )
                prob[i,2] <- pi[i]*( p[1,i] * (1-s2) ) + (1-pi[i])*( p[2,i] * c2 )
                prob[i,3] <- pi[i]*( (1-p[1,i]) * s2  ) + (1-pi[i])*( (1-p[2,i]) * (1-c2) )
                prob[i,4] <- pi[i]*( (1-p[1,i]) * (1-s2) ) + (1-pi[i])*( (1-p[2,i]) * c2 )

                results[i,1:4] ~ dmulti(prob[i,1:4],n[i])
                n[i]<-sum(results[i,1:4])

                pi[i] ~ dbeta(1,1)

                se[i] <- p[1,i]
```

```
            sp[i] <- 1-p[2,i]

        }


        for(j in 1:2) {

            prec[j] <- pow(sigma[j],-2)
            sigma[j] ~ dunif(0,2)
        }

        THETA ~ dunif(-1.5,1.5)
        beta ~ dunif(-0.75,0.75)

    S_a ~ dnorm(0,1)  # S_overall=phi(S_a)
    C_a ~ dnorm(0,1)  # C_overall=phi(C_a)

        LAMBDA <- S_a*exp(beta/2) + C_a*exp(-beta/2)

        S_overall<-phi(-(THETA-LAMBDA/2)/exp(beta/2))
        C_overall<-phi( (THETA+LAMBDA/2)*exp(beta/2))

        theta_new ~ dnorm(THETA,prec[1])
        alpha_new ~ dnorm(LAMBDA,prec[2])

        S_new<-phi(-(theta_new-alpha_new*0.5)/exp(beta*0.5))
        C_new<-phi( (theta_new+alpha_new*0.5)*exp(beta*0.5))


        s2 <- 1
        c2 <- 1

}
```

Diagnostic test accuracy meta-analyses: results

This section reports the results for the diagnostic test meta-analyses. Three models were run:

- Bivariate (Reitsma) = standard bivariate meta-analysis assuming perfect reference standard. All published systematic reviews retrieved so far used this model, therefore these were run for comparison with published work.
- HSROC perfect = hierarchical summary receiver operating characteristics (HSROC) model assuming perfect reference standard. This model was run for comparison with the adjusted model.
- HSROC imperfect = HSROC model assuming imperfect reference standard with conditional independence. This is the model that was reported.

The HSROC model assuming an imperfect reference standard with conditional independence was included in the main body of the report. The others are included for the purposes of comparison.

Table 21C: Pooled results for sensitivity and specificity of CT, MRI, US, VQ, and VQ-SPECT by three meta-analysis models.

	Analysis	Sensitivity (95% CI/CrI)	Specificity (95% CI/CrI)
CT	Bivariate (Reitsma)	0.894 (0.828-0.937)	0.944 (0.922-0.960)
n = 11	HSROC prefect	0.911 (0.840-0.966)	0.959 (0.925-0.983)
	HSROC imperfect	**0.973 (0.921-1.00)**	**0.987 (0.958-1.00)**
MRI	Bivariate (Reitsma)	0.865 (0.815-0.904)	0.947 (0.903-0.971)
n = 14	HSROC prefect	0.902 (0.843-0.958)	0.964 (0.927-0.986)
	HSROC imperfect	**0.958(0.898-0.998)**	**0.987 (0.955-1.00)**
US	Bivariate (Reitsma)	0.848 (0.791-0.892)	0.790 (0.697-0.860)
n = 10	HSROC perfect	0.858 (0.777-0.919)	0.793 (0.683-0.882)
	HSROC imperfect	**0.953 (0.868-0.999)**	**0.946 (0.828-1.00)**
VQ	Bivariate (Reitsma)	0.778 (0.704-0.837)	0.904 (0.853-0.939)
n = 10	HSROC prefect	0.789 (0.686-0.870)	0.920 (0.855-0.963)
	HSROC imperfect	**0.864 (0.734-0.967)**	**0.974 (0.916-1.00)**
VQ-SPECT	Bivariate (Reitsma)	0.869 (0.786-0.923)	0.849 (0.761-0.909)
n = 11	HSROC perfect	0.911 (0.805-0.978)	0.856 (0.738-0.935)
	HSROC imperfect	**0.973 (0.898-1.00)**	**0.914 (0.799-0.991)**

Diagnostic test meta-analysis: Exploration of heterogeneity

Figure 21A: Sensitivity versus 1-specificity for covariates for CT

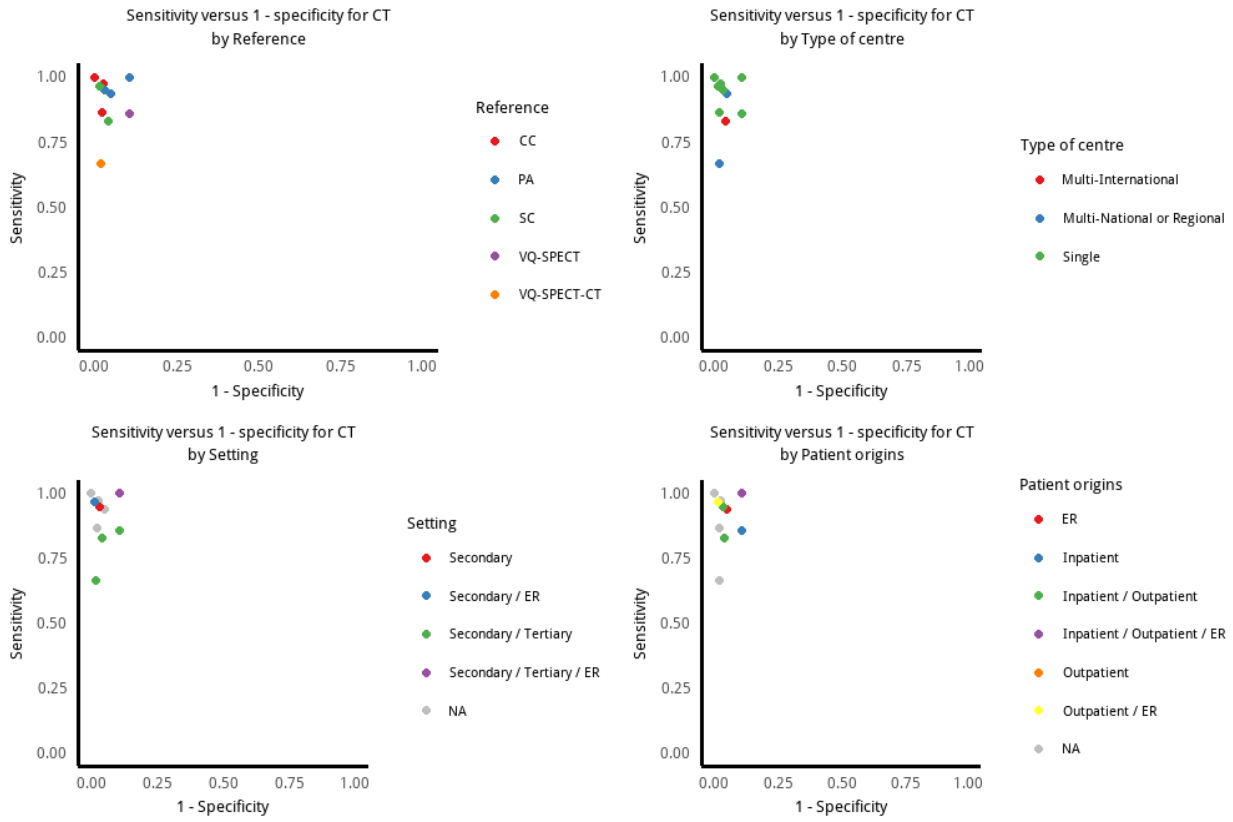


Figure 21B: Sensitivity versus 1-specificity for covariates for MRI

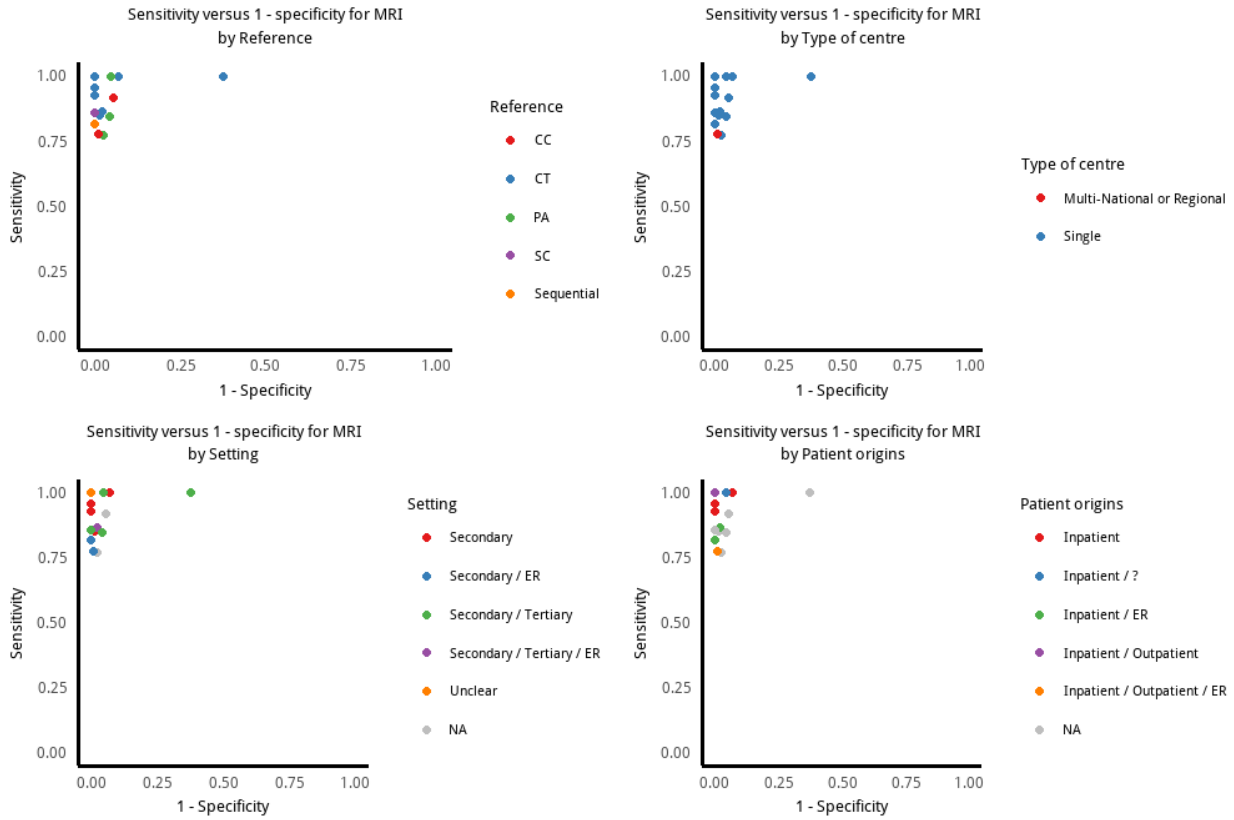


Figure 21C: Sensitivity versus 1-specificity for covariates for US

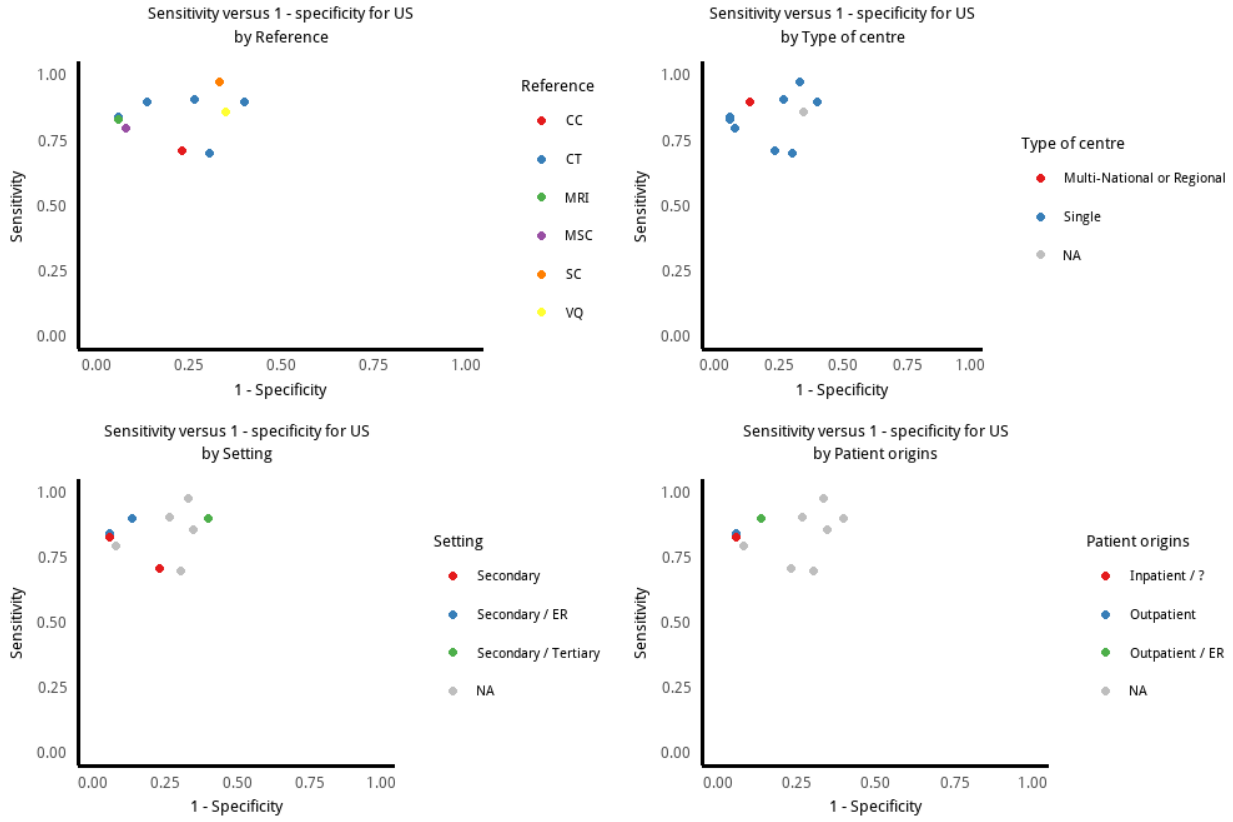


Figure 21D: Sensitivity versus 1-specificity for covariates for Q

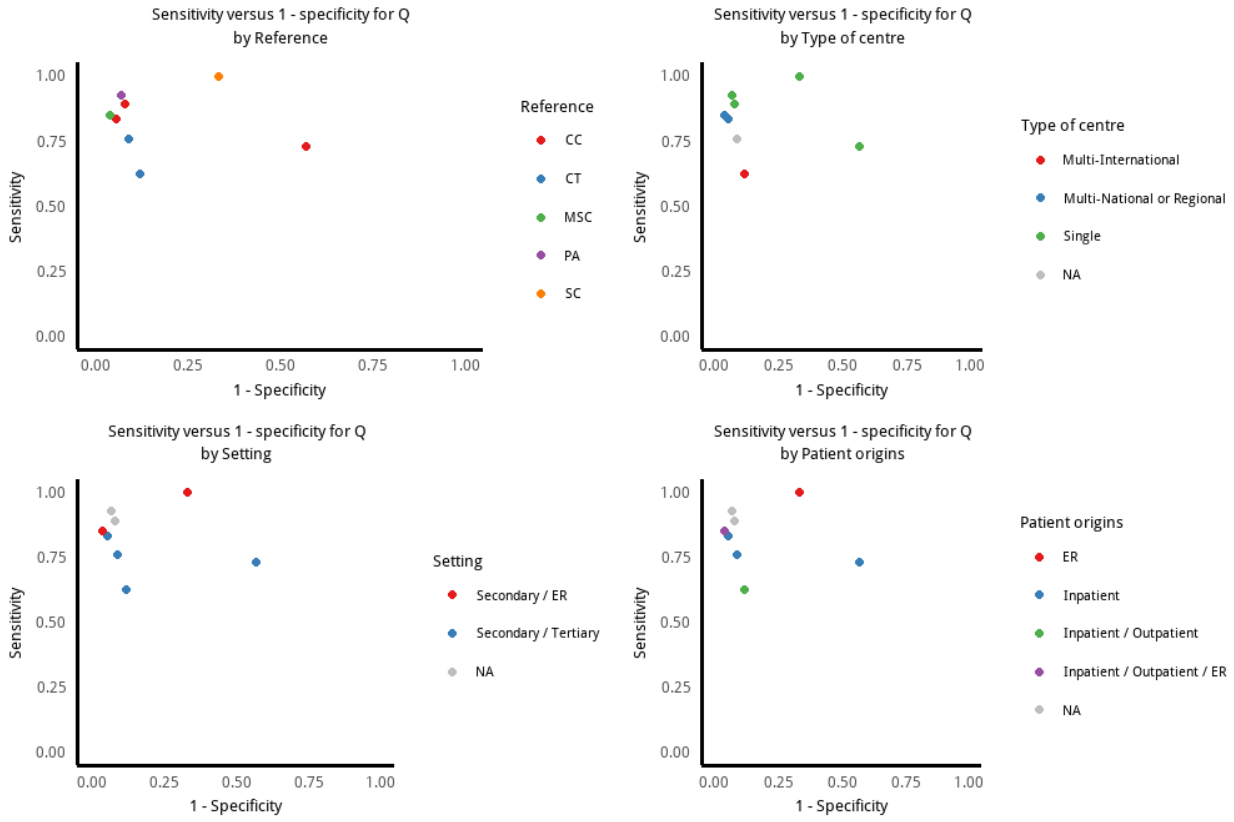


Figure 21E: Sensitivity versus 1-specificity for covariates for VQ

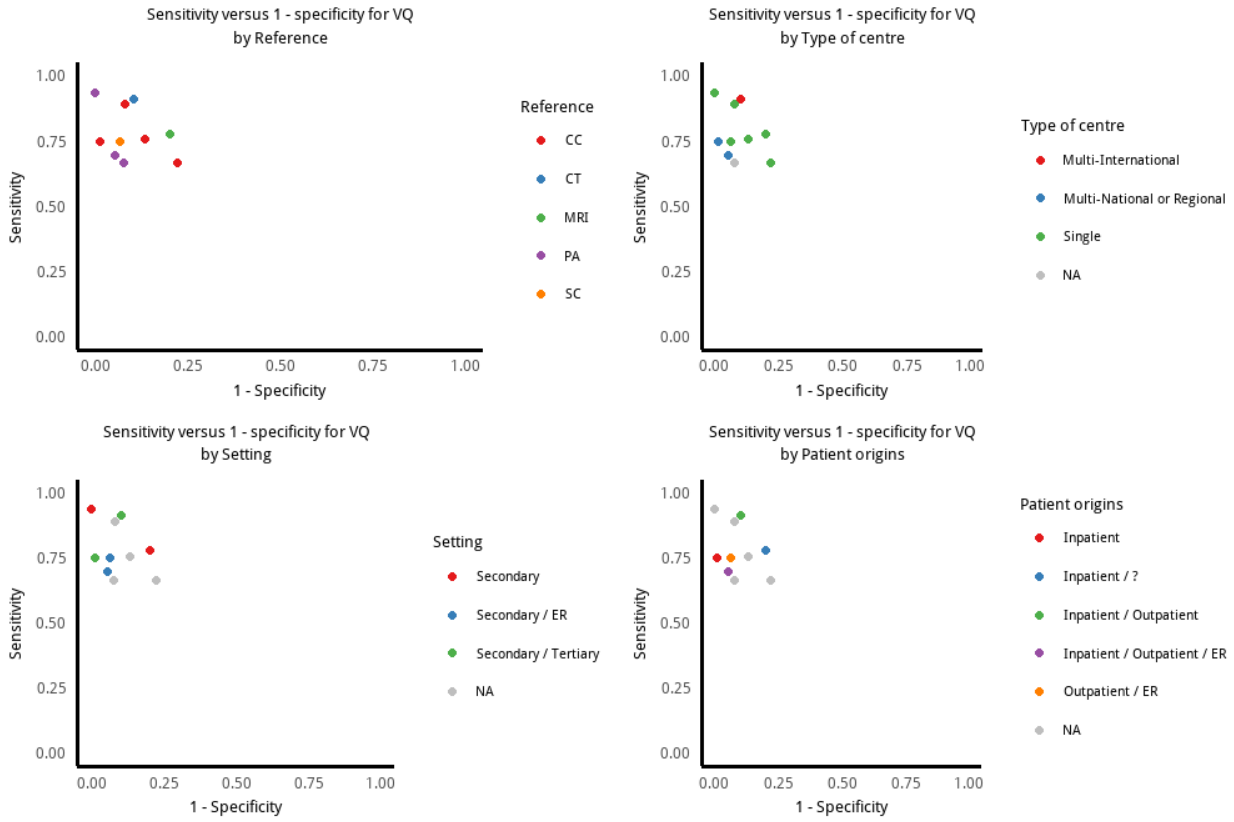
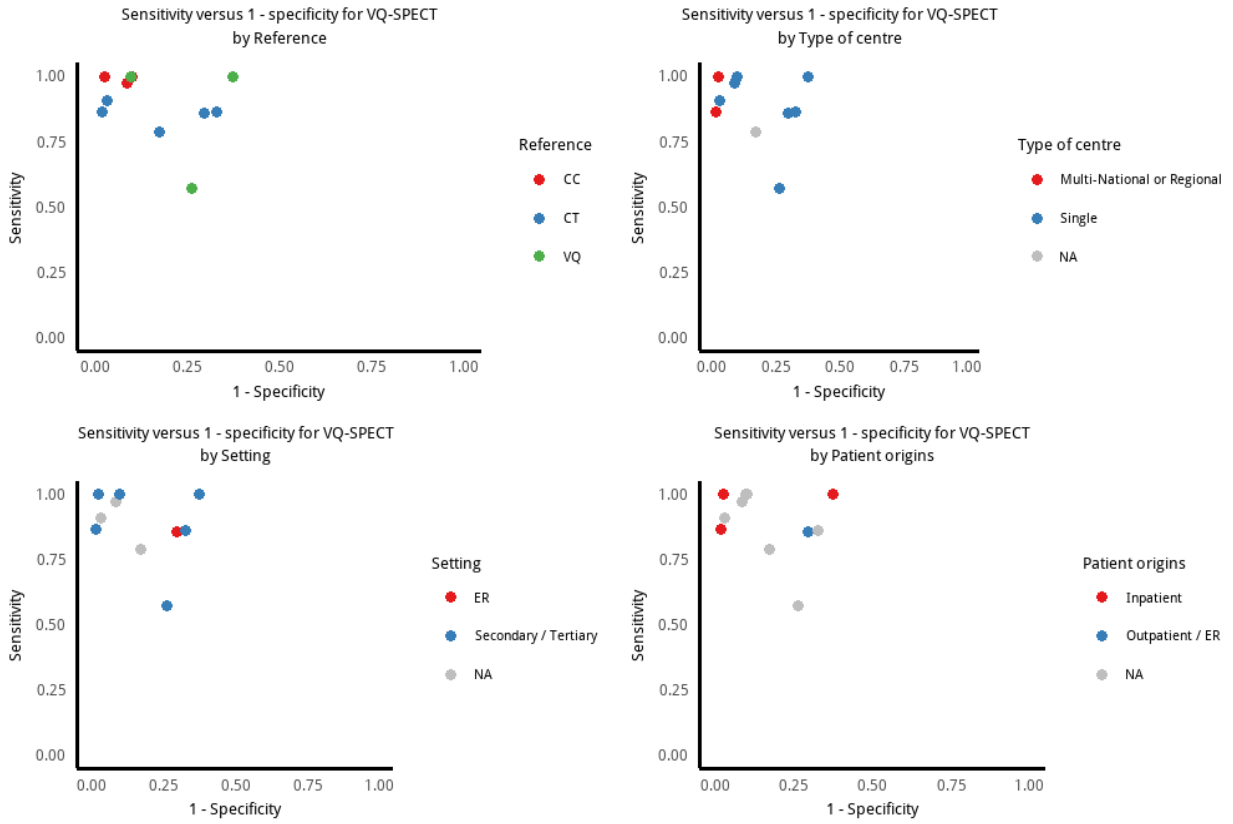


Figure 21F: Sensitivity versus 1-specificity for covariates for VQ-SPECT



Utilities and safety

Data management

Data coding

Utilities and safety data were coded using the same categories as described for the diagnostic test meta-analysis.

Exclusions from pooling

There were no exclusions from pooling based on comparators (e.g., composites, follow-up alone). One study was excluded from pooling for nondiagnostic studies of CT, as the patients were selected on the basis of prior imaging (indeterminate VQ).[200]

Handling of missing data

No imputation was attempted. Available data were included in summaries.

Meta-analysis of utilities data

No covariates were identified from the available data.

Table 21D: Results of random effects meta-analyses for utilities, all available pools

Modality	Outcome	Analysis	Value (95%CI)	I-squared (%)	Q [df] p-value
Unadjusted					
CT (n = 19)	Proportion test failure	All follow-up	0.008 (0.004-0.013)	55.0	38.5 [18] 0.003
CT (n = 14)	Proportion test failure	3 months subset	0.007 (0.003-0.012)	58.4	31.0 [13] 0.003
CT (n = 5)	Proportion test failure	6 months subset	0.015 (0.006-0.027)	0.0	5.1 [4] 0.275
CT (n = 5)	Risk ratio test failure	Comparative subset	RR 1.48 (0.309-7.077)	0.0	0.31 [4] 0.989
CT (n = 5)	Risk difference test failure	Comparative subset	RD -0.001 (-0.009-0.010)	0.0	0.63 [4] 0.959
CT (n = 13)	Proportion nondiagnostic		0.034 (0.023-0.047)	85.4	80.5 [13] <0.0001
MRI (n = 5)	Proportion nondiagnostic		0.106 (0.016-0.260)	97.7	113.3 [5] <0.0001
Q (n = 5)	Proportion nondiagnostic		0.049 (0.000-0.178)	98.4	360.6 [4] <0.0001
VQ (n = 10)	Proportion nondiagnostic		0.250 (0.157-0.358)	97.1	237.3 [9] <0.0001
VQ-SPECT (n = 10)	Proportion nondiagnostic		0.037 (0.010-0.079)	94.1	97.4 [9] <0.0001
Adjusted					
CT (n = 18)	Proportion test failure	Minus statistical outlier	0.009 (0.006-0.014)	29.6	25.4 [17] 0.086

Appendix 23: Risk Stratification: Parameters for the Economic Evaluation

Primary studies from SRs	CPR/ Author, Year of Source SR					
	3-Level Wells - assuming moderate goes to D-dimer/ Sanders, 2015[105]					
	Sensitivity	Specificity	TP	FN	FP	TN
Kabrhel et al, 2009	0.17	0.98	92	453	165	7230
Kabrhel et al, 2005	0.26	0.94	16	45	32	514
Chagnon et al, 2002	0.14	1.00	10	61	1	205
Sanson, 2000	0.02	0.98	3	119	5	287
Penaloza et al, 2013	0.13	0.96	43	282	31	682
	2-Level Wells/ Sanders, 2015[105]					
Kabrhel et al, 2005	0.59	0.78	36	25	122	424
Carrier et al, 2006	0.83	0.41	63	13	200	137
	Revised Geneva - assuming moderate Geneva goes to D-dimer / Sanders, 2015[105]					
Penaloza et al, 2013	0.21	0.96	68	257	31	682
Chagnon et al, 2002	0.11	0.98	8	63	4	202
	PERC/ Singh, 2013[385]					
Wolf, 2008	1.00	0.16	16	0	99	19
Hogg, 2005	0.88	0.53	23	3	186	213
Kline, 2004 (LR)	0.97	0.28	152	5	913	357
Kline, 2004 (VLR)	1.00	0.15	9	0	316	57
Dachs, 2010	1.00	0.25	18	0	147	48
Hugli, 2011	0.97	0.16	357	12	1097	209
Beam, 2007	1.00	0.19	8	0	147	34
Righini, 2005	0.97	0.15	190	6	483	83
Kline, 2008	0.96	0.26	593	25	5593	1927
Courtney, 2006	0.86	0.43	12	2	172	129
Crichlow, 2011	1.00	0.10	18	0	120	14
Penaloza, 2012	0.99	0.10	282	4	603	70
	LEG US/ Da Costa Rodrigues, 2016[33]					
Turkstra, 1997	0.29	0.97	43	106	5	173
Mac Gillavry, 2000	0.23	0.98	35	118	8	318
Elias, 2004	0.55	0.96	41	33	6	130
Le Gal, 2006	0.39	0.99	73	114	3	321
Velmahos, 2006	0.33	0.90	7	14	4	34
Mansencal, 2008	0.58	0.93	18	13	5	67
Nazerian, 2014	0.53	0.98	58	52	6	241

Appendix 24: Characteristics of existing published economic evaluation on diagnosis of PE

First Author, Year	Country, perspective	Population	Scope	Comparators	Approach	Timeframe	Findings (most cost-effective strategy)†
Doyle, 2004 [577]	USA, TPP	Pregnant patients suspected of PE	Ancillary test + diagnostic imaging	3 strategies: • Compression US+VQ+CT • VQ • CT	Model; decision tree	NR	CT
Duriseti, 2006 [230]	US, TPP	Patients suspected of PE in urban emergency department	Diagnostic pathway	60 strategies: permutations of varying d-dimer definition and diagnostic imaging modalities (i.e., CUS, VQ, CT)	Model; decision tree	• 6 months • Lifetime	CT
Duriseti, 2010 [231]	US, TPP	Patients (55 years of age) suspected of PE in urban emergency department presenting with undifferentiated symptoms	Diagnostic pathway	60 strategies: permutations of varying d-dimer definition and diagnostic imaging modalities (i.e., CUS, VQ, CT)	Model; unspecified	Lifetime (25 years)	D-dimer + US*
Elias, 2004 [239]	France, TPP	Not specified	Diagnostic pathway	9 strategies: VQ or CT, with or without d-dimer (Elisa or simpli RED) and leg US (limited or extended) and PA	Model, unspecified	3 months	US+ CT
Gospodarevskaya, [228]	Australia, TPP	Patients suspected of PE (≥18 years of age) presenting in emergency department	Diagnostic pathway, specifically varying the clinical prediction rule	2 strategies: • Gestalt+d-dimer+imaging (unspecified) • PERC+d-dimer+diagnostic imaging (unspecified)	Trial-based economic evaluation (before and after design)	NR	(solely on costs) Addition of PERC was the less costly option
Hull, 2001[229]	Canada, TPP	Patients who participated in PIOPED study	Sequence of diagnostic imaging modalities following	3 strategies: • VQ+CT • VQ+single leg US+CT	Trial-based economic evaluation	Undefined, noted as long-term	VQ+serial leg US+CT*

First Author, Year	Country, perspective	Population	Scope	Comparators	Approach	Timeframe	Findings (most cost-effective strategy)[†]
			non-confirmatory VQ findings	• VQ+serial leg US+CT			
Larcos, 2000[578]	Australia, NR	Patients suspected of PE	Ancillary test + diagnostic imaging	3 strategies: • CT • CT+ Leg US + PA • VQ + Leg US + CT	Model; decision tree	Lifetime	VQ
Lee, 2011 [236]	US, TPP	Patients suspected of PE, with varying clinical probability (i.e., high, intermediate, low)	Diagnostic pathway	9 strategies: diagnostic imaging modalities with or without d-dimer and leg US	Model; decision tree	3 months	D-dimer+CT
Paterson, 2001[238]	Canada, TPP	Patient suspect of PE (prevalence based on PIOPED)	Ancillary test + diagnostic imaging	7 strategies: leg US with diagnostic imaging modalities	Model; decision tree	3 months	VQ+leg US+CT
Perrier, 2003[240]	Switzerland, TPP	Not specified	Ancillary test + diagnostic imaging	8 strategies: diagnostic imaging modalities with or without d-dimer and leg US	Model; decision tree	3 months	• Low clinical probability: D-dimer+leg US_ VQ • Intermediate-to-high clinical probability: D-dimer+US+VQ+CT
Righini, 2007 [237]	Switzerland, TPP	Patients suspected of PE presenting in emergency department, based on two prospective studies	Diagnostic pathway	4 strategies: • Geneva+d-dimer+leg US+CT • Geneva+d-dimer+CT • Geneva+leg US+CT • CT	Model; decision tree	3 months	• < 80 years: Geneva+d-dimer+CT • ≥ 80 years:CT[‡]
Van Erkel, 1996[233]	Western Europe, hospital	Patient suspected of PE	Diagnostic pathway	12 strategies: CT with or without d-dimer or Leg US, or VQ with PA	Model; decision tree	3 months	Uninterpretable; average cost per life year presented
Van Erkel, 1998[232]	Netherlands, hospital	Patients suspected of PE (prevalence of PE=24%)	Diagnostic pathway	16 strategies: CT or PA with or without d-dimer and leg US	Model; decision tree	3 months	Uninterpretable; average cost per life year presented
Ward, 2011 [579]	US, Societal	59 year old, female suspected of new-onset PE	Ancillary test + diagnostic imaging NOTE: decision to obtain CT already made through risk	2 strategies: • Leg US+CT • CT	Model, hybrid model (decision tree [short-term diagnostic] and Markov model [long-term])	Lifetime	Leg US+CT

First Author, Year	Country, perspective	Population	Scope	Comparators	Approach	Timeframe	Findings (most cost-effective strategy)†
			stratification (not captured in the model)				

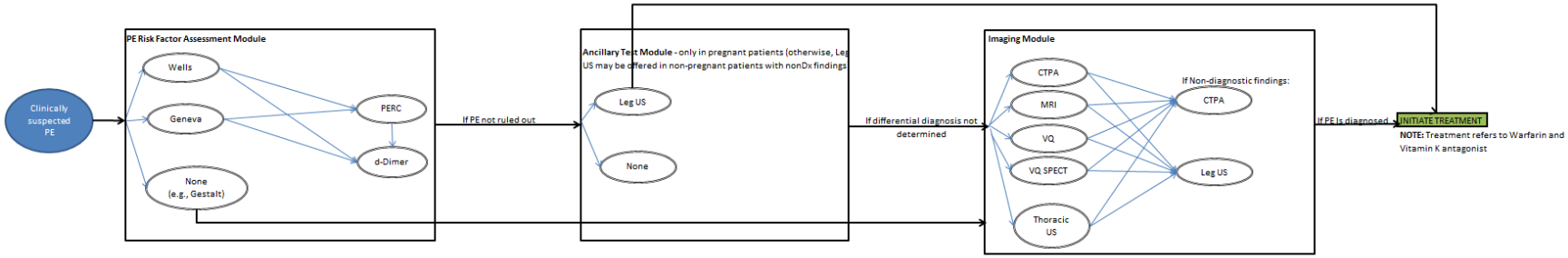
CT = computed tomography pulmonary angiogram; CUS = compression ultrasound; NR = not reported; PA = pulmonary angiography; PE = pulmonary embolism; RCT = randomized controlled trial; TPP = third-party payer; UK = United Kingdom; US = United States of America; VQ = ventilation-perfusion scan

*Incorrect conclusion reached regarding the most cost-effective strategy given incorrect analytical approach

†Defined either as the dominant strategy or the strategy that is cost-effective by the study author (typically willingness-to-pay ~$50,000 per unit of a clinical outcome). Clinical outcome may differ by study as some used QALYs while others used additional life saved.

‡ Difficult to confirm the accuracy of the author's conclusion as the results are not transparently reported.

Appendix 25: Diagnostic Pathway



Risk Factor Assessment Module (Risk stratification + Rule Out Test)

Risk Stratification			
STRATEGY	DFN OF OUTCOME	POSS. OUTCOME (IN TERMS OF CLINICAL MANAGEMENT)[λ]	SITUATION IN MODEL (condition| test result)
Wells (3-tier model) Outcome: Low, Moderate, High	Low: <2 points Moderate: 2-6 points High: >6 points	CONTINUE (within)	Patients w/ PE| Low
			Patients w/out PE| Low
		CONTINUE (NEXT)	Patient w/ PE| High/moderate
			Patient w/out PE| High/moderate
Wells (2-tier model) Outcome: PE Unlikely, PE Likely	PE Unlikely: 0-4 points PE Likely: >4 points	CONTINUE (within)	Patients w/ PE| "PE Unlikely"
			Patients w/out PE| "PE Unlikely"
		CONTINUE (NEXT)	Patient w/ PE| "PE Likely"
			Patient w/out PE| "PE Likely"
Geneva (revised) Outcome: Low, Intermediate, High	Low: 0-3 Intermediate: 4-10 High: >10	CONTINUE (within)	Patients w/ PE| Low or intermediate risk
			Patients w/out PE| Low or intermediate risk
		CONTINUE (NEXT)	Patients w/ PE| High risk
			Patients w/out PE| High risk
None (Gestalt)	Threshold in which considered	CONTINUE (within)	Patients w/ PE| Below threshold

Risk Stratification			
STRATEGY	DFN OF OUTCOME	POSS. OUTCOME (IN TERMS OF CLINICAL MANAGEMENT)[λ]	SITUATION IN MODEL (condition| test result)
	low risk can vary. Clinical review identified: <15%, <20% and undefined		Patients w/out PE| Below threshold
		CONTINUE (within or NEXT)†	Patients w/ PE| Above threshold
			Patients w/out PE| Above threshold
Rule Out Test			
PERC Outcome: negative, positive	Negative: No to all items Positive: Yes to any items	**STOP**	Patients w/ PE| Negative
			Patients w/out PE| Negative
		CONTINUE (to d-dimer)	Patient w/ PE| Positive
			Patient w/out PE| Positive
d-Dimer (standard) Outcome: negative, positive	Negative: d-dimer>500 mcg/L Positive: d-dimer≤500 mcg/L	**STOP**	Patients w/ PE| Negative
			Patients w/out PE| Negative
		CONTINUE (NEXT)	Patient w/ PE| Positive
			Patient w/out PE| Positive

[λ] Within refers to proceeding to a "rule out" test; NEXT refers to moving out of this module to the next module; STOP refers to the end of the screening process as patients ruled out of having PE
† Depends on the strategy

Ancillary Test Module (applies only to pregnant patients)

STRATEGY	DFN OF OUTCOME	POSS. OUTCOME (IN TERMS OF CLINICAL MANAGEMENT)[λ]	SITUATION IN MODEL
US Outcome: Positive, Negative	Positive: Either no compression of vein or absence of blood flow (=DVT) Negative: Compression and flow present	**PROCEED WITH TXT**	Patients w/ PE| Positive
			Patients w/out PE| Positive
		CONTINUE (NEXT)	Patients w/ PE| Negative/ Indeterminate
			Patients w/out PE| Negative/Indeterminate

[λ] NEXT refers to moving out of this module to the next module; PROCEED WITH TXT refers to end of screening as pt are diagnosed with PE

Imaging Module

STRATEGY	DFN OF OUTCOME	POSS. OUTCOME (CLINICAL MANAGEMENT)[λ]	SITUATION IN MODEL
CT Outcome: Positive, Negative	Positive: Thombus in segmental or larger pulmonary artery Negative: No evidence of thrombus	**PROCEED WITH TXT**	Patients w/ PE| Positive
			Patients w/out PE| Positive
		STOP	Patients w/ PE| Negative
			Patients w/out PE| Negative
MRI Outcome: Positive, Negative	Positive: Partially occlusive intra-luminal filling defect or complete arterial occlusion with termination of the contrast material Negative: Adequate opacification of sub-segmental branches	**PROCEED WITH TXT**	Patients w/ PE| Positive
			Patients w/out PE| Positive
		STOP	Patients w/ PE| Negative/ Indeterminate
			Patients w/out PE| Negative/Indeterminate
VQ Outcome: Abnormal, Normal/near-normal	High: ≥2 mismatched segmental defects Intermediate†	**PROCEED WITH TXT**	Patients w/ PE| High
			Patients w/out PE| High
		STOP	Patients w/ PE| Low

	Low: • Nonsegmental perfusion abnormalities; w/ no other perfusion defect in either lung • Perfusion defect smaller than corresponding radiographic lesion • ≥2 matched VQ defects w/ regionally normal CXR and some areas of normal perfusion elsewhere in the lungs • One to three small segmental defects (<25% of segment) • Solitary triple-matched defect in mid to upper lung zone confined to single segment • Stripe sign • Pleural effusion of ≥1/3 of pleural cavity with no other perfusion defect in either lung Non-diagnostic: All other findings		Patients w/out PE| Low
VQ SPECT Outcome: negative, positive	Positive: 1 segmental or 2 subsegmental mismatches Negative: Doesn't meet above criteria	**PROCEED WITH TXT**	Patients w/ PE| Positive
			Patients w/out PE| Positive
		STOP	Patients w/ PE| Negative
			Patients w/out PE| Negative
VQ SPECT/CT *Outcome: negative, positive*	Positive: ≥1 wedge-shaped peripheral defect (≥50% of pulmonary segmnet w/out CT image abnormality seen in three orthogonal plane Negative: Doesn't meet above criteria	**PROCEED WITH TXT**	Patients w/ PE| Positive
			Patients w/out PE| Positive
		STOP	Patients w/ PE| Negative
			Patients w/out PE| Negative
Thoracic US Outcome: lesion or no lesion	Positive: One or more typical pleural-based/subpleural hypoechoic lesions with or without pleural effusion Negative: Nonspecific subpleural lesions more than 5 mm in size, pure-free pleural effusion, normal sonographic findings	**PROCEED WITH TXT**	Patients w/ PE| Positive
			Patients w/out PE| Positive
		STOP	Patients w/ PE| Negative
			Patients w/out PE| Negative

*STOP refers to the end of the screening process as patients ruled out of having PE; PROCEED WITH TXT refers to end of screening as patients are diagnosed with PE
†Intermediate results is a form of non-diagnostic finding. In such case, patients were assumed to receive a CT scan to obtain a final diagnosis for PE.

Appendix 26: List of Diagnostic Strategies Considered in the Economic Model

Reference Case (i.e., non-pregnant population)

Strategy No	Risk Stratification	Rule Out Test	Diagnostic Imaging	Imaging modality for nonDx Findings
1	No screening			
2	None	None	CTPA	Leg US
3	None	None	MRI	Leg US
4	None	None	VQ Planar Scintigraphy	Leg US
5	None	None	VQ SPECT	Leg US
6	None	None	CTPA	CTPA
7	None	None	MRI	CTPA
8	None	None	VQ Planar Scintigraphy	CTPA
9	None	None	VQ SPECT	CTPA
10	Wells (3 criteria)	PERC+d-dimer	CTPA	Leg US
11	Wells (3 criteria)	PERC+d-dimer	MRI	Leg US
12	Wells (3 criteria)	PERC+d-dimer	VQ Planar Scintigraphy	Leg US
13	Wells (3 criteria)	PERC+d-dimer	VQ SPECT	Leg US
14	Wells (3 criteria)	PERC+d-dimer	CTPA	CTPA
15	Wells (3 criteria)	PERC+d-dimer	MRI	CTPA
16	Wells (3 criteria)	PERC+d-dimer	VQ Planar Scintigraphy	CTPA
17	Wells (3 criteria)	PERC+d-dimer	VQ SPECT	CTPA
18	Wells (3 criteria)	d-dimer	CTPA	Leg US
19	Wells (3 criteria)	d-dimer	MRI	Leg US
20	Wells (3 criteria)	d-dimer	VQ Planar Scintigraphy	Leg US
21	Wells (3 criteria)	d-dimer	VQ SPECT	Leg US
22	Wells (3 criteria)	d-dimer	CTPA	CTPA
23	Wells (3 criteria)	d-dimer	MRI	CTPA
24	Wells (3 criteria)	d-dimer	VQ Planar Scintigraphy	CTPA
25	Wells (3 criteria)	d-dimer	VQ SPECT	CTPA
26	Wells (2-level)	PERC+d-dimer	CTPA	Leg US
27	Wells (2-level)	PERC+d-dimer	MRI	Leg US
28	Wells (2-level)	PERC+d-dimer	VQ Planar Scintigraphy	Leg US
29	Wells (2-level)	PERC+d-dimer	VQ SPECT	Leg US
30	Wells (2-level)	PERC+d-dimer	CTPA	CTPA
31	Wells (2-level)	PERC+d-dimer	MRI	CTPA
32	Wells (2-level)	PERC+d-dimer	VQ Planar Scintigraphy	CTPA

Strategy No	Risk Stratification	Rule Out Test	Diagnostic Imaging	Imaging modality for nonDx Findings
33	Wells (2-level)	PERC+d-dimer	VQ SPECT	CTPA
34	Wells (2-level)	d-dimer	CTPA	Leg US
35	Wells (2-level)	d-dimer	MRI	Leg US
36	Wells (2-level)	d-dimer	VQ Planar Scintigraphy	Leg US
37	Wells (2-level)	d-dimer	VQ SPECT	Leg US
38	Wells (2-level)	d-dimer	CTPA	CTPA
39	Wells (2-level)	d-dimer	MRI	CTPA
40	Wells (2-level)	d-dimer	VQ Planar Scintigraphy	CTPA
41	Wells (2-level)	d-dimer	VQ SPECT	CTPA
42	Revised Geneva	PERC+d-dimer	CTPA	Leg US
43	Revised Geneva	PERC+d-dimer	MRI	Leg US
44	Revised Geneva	PERC+d-dimer	VQ Planar Scintigraphy	Leg US
45	Revised Geneva	PERC+d-dimer	VQ SPECT	Leg US
46	Revised Geneva	PERC+d-dimer	CTPA	CTPA
47	Revised Geneva	PERC+d-dimer	MRI	CTPA
48	Revised Geneva	PERC+d-dimer	VQ Planar Scintigraphy	CTPA
49	Revised Geneva	PERC+d-dimer	VQ SPECT	CTPA
50	Revised Geneva	d-dimer	CTPA	Leg US
51	Revised Geneva	d-dimer	MRI	Leg US
52	Revised Geneva	d-dimer	VQ Planar Scintigraphy	Leg US
53	Revised Geneva	d-dimer	VQ SPECT	Leg US
54	Revised Geneva	d-dimer	CTPA	CTPA
55	Revised Geneva	d-dimer	MRI	CTPA
56	Revised Geneva	d-dimer	VQ Planar Scintigraphy	CTPA
57	Revised Geneva	d-dimer	VQ SPECT	CTPA

Pregnant patients

Strategy No	Risk Stratification	Rule Out Test	Ancillary Tests	Diagnostic Imaging	Imaging modality for nonDx Findings
1	No screening				
2	None	None	Leg US	CTPA	CTPA
3	None	None	Leg US	MRI	CTPA
4	None	None	Leg US	VQ Planar Scintigraphy	CTPA
5	None	None	Leg US	VQ SPECT	CTPA
6	None	None	None	CTPA	Leg US
7	None	None	None	MRI	Leg US
8	None	None	None	VQ Planar Scintigraphy	Leg US
9	None	None	None	VQ SPECT	Leg US
10	Wells (3 criteria)	PERC+d-dimer	Leg US	CTPA	CTPA
11	Wells (3 criteria)	PERC+d-dimer	Leg US	MRI	CTPA
12	Wells (3 criteria)	PERC+d-dimer	Leg US	VQ Planar Scintigraphy	CTPA
13	Wells (3 criteria)	PERC+d-dimer	Leg US	VQ SPECT	CTPA
14	Wells (3 criteria)	PERC+d-dimer	None	CTPA	Leg US
15	Wells (3 criteria)	PERC+d-dimer	None	MRI	Leg US
16	Wells (3 criteria)	PERC+d-dimer	None	VQ Planar Scintigraphy	Leg US
17	Wells (3 criteria)	PERC+d-dimer	None	VQ SPECT	Leg US
18	Wells (3 criteria)	d-dimer	Leg US	CTPA	CTPA
19	Wells (3 criteria)	d-dimer	Leg US	MRI	CTPA
20	Wells (3 criteria)	d-dimer	Leg US	VQ Planar Scintigraphy	CTPA
21	Wells (3 criteria)	d-dimer	Leg US	VQ SPECT	CTPA
22	Wells (3 criteria)	d-dimer	None	CTPA	Leg US
23	Wells (3 criteria)	d-dimer	None	MRI	Leg US
24	Wells (3 criteria)	d-dimer	None	VQ Planar Scintigraphy	Leg US
25	Wells (3 criteria)	d-dimer	None	VQ SPECT	Leg US
26	Wells (2-level)	PERC+d-dimer	Leg US	CTPA	CTPA
27	Wells (2-level)	PERC+d-dimer	Leg US	MRI	CTPA
28	Wells (2-level)	PERC+d-dimer	Leg US	VQ Planar Scintigraphy	CTPA
29	Wells (2-level)	PERC+d-dimer	Leg US	VQ SPECT	CTPA
30	Wells (2-level)	PERC+d-dimer	None	CTPA	Leg US
31	Wells (2-level)	PERC+d-dimer	None	MRI	Leg US
32	Wells (2-level)	PERC+d-dimer	None	VQ Planar Scintigraphy	Leg US
33	Wells (2-level)	PERC+d-dimer	None	VQ SPECT	Leg US
34	Wells (2-level)	d-dimer	Leg US	CTPA	CTPA
35	Wells (2-level)	d-dimer	Leg US	MRI	CTPA

Strategy No	Risk Stratification	Rule Out Test	Ancillary Tests	Diagnostic Imaging	Imaging modality for nonDx Findings
36	Wells (2-level)	d-dimer	Leg US	VQ Planar Scintigraphy	CTPA
37	Wells (2-level)	d-dimer	Leg US	VQ SPECT	CTPA
38	Wells (2-level)	d-dimer	None	CTPA	Leg US
39	Wells (2-level)	d-dimer	None	MRI	Leg US
40	Wells (2-level)	d-dimer	None	VQ Planar Scintigraphy	Leg US
41	Wells (2-level)	d-dimer	None	VQ SPECT	Leg US
42	Revised Geneva	PERC+d-dimer	Leg US	CTPA	CTPA
43	Revised Geneva	PERC+d-dimer	Leg US	MRI	CTPA
44	Revised Geneva	PERC+d-dimer	Leg US	VQ Planar Scintigraphy	CTPA
45	Revised Geneva	PERC+d-dimer	Leg US	VQ SPECT	CTPA
46	Revised Geneva	PERC+d-dimer	None	CTPA	Leg US
47	Revised Geneva	d-dimer	None	MRI	Leg US
48	Revised Geneva	PERC+d-dimer	None	VQ Planar Scintigraphy	Leg US
49	Revised Geneva	PERC+d-dimer	None	VQ SPECT	Leg US
50	Revised Geneva	d-dimer	Leg US	CTPA	CTPA
51	Revised Geneva	d-dimer	Leg US	MRI	CTPA
52	Revised Geneva	d-dimer	Leg US	VQ Planar Scintigraphy	CTPA
53	Revised Geneva	d-dimer	Leg US	VQ SPECT	CTPA
54	Revised Geneva	d-dimer	None	CTPA	Leg US
55	Revised Geneva	d-dimer	None	MRI	Leg US
56	Revised Geneva	d-dimer	None	VQ Planar Scintigraphy	Leg US
57	Revised Geneva	d-dimer	None	VQ SPECT	Leg US

Appendix 27: Detailed Results of the Reference Case

Strategy No	Risk Stratification	Rule Out Test	Diagnostic Imaging	Imaging modality for nonDx Findings	Diagnostic Test Accuracy				Short-term		Costs ($)	QALYs	Sequential ICER
					TP	FP	TN	FN	Numer of patients undergoing imaging	Expected effective dose of radiation			
1	No screening				0.848	0	0	0.152	0	0	2,997	16.8286	
42	Revised Geneva	PERC+ d-dimer	CTPA	Leg US	0.131	0.038	0.810	0.021	0.56	2.93	3,927	17.4515	Extended dominance
10	Wells (3 criteria)	PERC+ d-dimer	CTPA	Leg US	0.131	0.039	0.809	0.020	0.57	2.96	3,935	17.4538	Extended dominance
46	Revised Geneva	PERC+ d-dimer	CTPA	CTPA	0.133	0.039	0.809	0.018	0.56	3.04	3,937	17.4632	1480.65022
14	Wells (3 criteria)	PERC+ d-dimer	CTPA	CTPA	0.134	0.040	0.809	0.018	0.57	3.07	3,945	17.4655	3706.04135
26	Wells (2-level)	PERC+ d-dimer	CTPA	Leg US	0.135	0.046	0.802	0.017	0.66	3.42	4,062	17.4702	Extended dominance
50	Revised Geneva	d-dimer	CTPA	Leg US	0.135	0.046	0.802	0.017	0.65	3.41	4,067	17.4691	Extended dominance
30	Wells (2-level)	PERC+ d-dimer	CTPA	CTPA	0.137	0.047	0.801	0.014	0.66	3.54	4,073	17.4822	7660.76761
18	Wells (3 criteria)	d-dimer	CTPA	Leg US	0.135	0.047	0.802	0.017	0.66	3.43	4,074	17.4702	Dominant
54	Revised Geneva	d-dimer	CTPA	CTPA	0.137	0.047	0.801	0.015	0.65	3.53	4,079	17.4811	Dominant
22	Wells (3 criteria)	d-dimer	CTPA	CTPA	0.137	0.048	0.801	0.014	0.66	3.56	4,085	17.4822	Extended dominance
43	Revised Geneva	PERC+ d-dimer	MRI	Leg US	0.121	0.038	0.810	0.031	0.56	0.00	4,166	17.4060	Dominant
34	Wells (2-level)	d-dimer	CTPA	Leg US	0.137	0.053	0.795	0.015	0.73	3.79	4,170	17.4782	Dominant
11	Wells (3 criteria)	PERC+ d-dimer	MRI	Leg US	0.121	0.038	0.810	0.031	0.57	0.00	4,177	17.4081	Dominant
38	Wells (2-level)	d-dimer	CTPA	CTPA	0.139	0.054	0.794	0.013	0.73	3.93	4,183	17.4903	13556.114
47	Revised Geneva	PERC+ d-dimer	MRI	CTPA	0.130	0.041	0.807	0.022	0.56	0.41	4,203	17.4495	Dominant
15	Wells (3 criteria)	PERC+ d-dimer	MRI	CTPA	0.131	0.041	0.807	0.021	0.57	0.41	4,214	17.4517	Dominant
44	Revised Geneva	PERC+ d-dimer	VQ Planar Scintigraphy	Leg US	0.107	0.060	0.788	0.045	0.56	1.24	4,246	17.3433	Dominant

Strategy No	Risk Stratification	Rule Out Test	Diagnostic Imaging	Imaging modality for nonDx Findings	Diagnostic Test Accuracy				Short-term		Costs ($)	QALYs	Sequential ICER
					TP	FP	TN	FN	Numer of patients undergoing imaging	Expected effective dose of radiation			
12	Wells (3 criteria)	PERC+ d-dimer	VQ Planar Scintigraphy	Leg US	0.108	0.061	0.787	0.044	0.57	1.25	4,259	17.3452	Dominant
48	Revised Geneva	PERC+ d-dimer	VQ Planar Scintigraphy	CTPA	0.126	0.066	0.782	0.026	0.56	2.05	4,319	17.4297	Dominant
16	Wells (3 criteria)	PERC+ d-dimer	VQ Planar Scintigraphy	CTPA	0.126	0.067	0.781	0.025	0.57	2.07	4,332	17.4319	Dominant
27	Wells (2-level)	PERC+ d-dimer	MRI	Leg US	0.125	0.046	0.802	0.027	0.66	0.00	4,341	17.4233	Dominant
51	Revised Geneva	d-dimer	MRI	Leg US	0.124	0.046	0.803	0.028	0.65	0.00	4,346	17.4223	Dominant
19	Wells (3 criteria)	d-dimer	MRI	Leg US	0.125	0.046	0.802	0.027	0.66	0.00	4,355	17.4233	Dominant
31	Wells (2-level)	PERC+ d-dimer	MRI	CTPA	0.134	0.050	0.799	0.018	0.66	0.48	4,384	17.4681	Dominant
55	Revised Geneva	d-dimer	MRI	CTPA	0.134	0.049	0.799	0.018	0.65	0.48	4,389	17.4669	Dominant
23	Wells (3 criteria)	d-dimer	MRI	CTPA	0.134	0.050	0.798	0.018	0.66	0.48	4,398	17.4681	Dominant
45	Revised Geneva	PERC+ d-dimer	VQ SPECT	Leg US	0.126	0.058	0.790	0.025	0.56	1.24	4,406	17.4290	Dominant
49	Revised Geneva	PERC+ d-dimer	VQ SPECT	CTPA	0.129	0.059	0.789	0.022	0.56	1.38	4,419	17.4434	Dominant
13	Wells (3 criteria)	PERC+ d-dimer	VQ SPECT	Leg US	0.127	0.059	0.789	0.025	0.57	1.25	4,420	17.4312	Dominant
17	Wells (3 criteria)	PERC+ d-dimer	VQ SPECT	CTPA	0.130	0.060	0.788	0.022	0.57	1.39	4,433	17.4457	Dominant
28	Wells (2-level)	PERC+ d-dimer	VQ Planar Scintigraphy	Leg US	0.111	0.073	0.775	0.041	0.66	1.44	4,443	17.3584	Dominant
52	Revised Geneva	d-dimer	VQ Planar Scintigraphy	Leg US	0.110	0.073	0.775	0.041	0.65	1.44	4,448	17.3575	Dominant
20	Wells (3 criteria)	d-dimer	VQ Planar Scintigraphy	Leg US	0.111	0.073	0.775	0.041	0.66	1.45	4,457	17.3584	Dominant
35	Wells (2-level)	d-dimer	MRI	Leg US	0.126	0.052	0.796	0.026	0.73	0.00	4,481	17.4307	Dominant
39	Wells (2-level)	d-dimer	MRI	CTPA	0.136	0.056	0.792	0.016	0.73	0.53	4,529	17.4760	Dominant
32	Wells (2-level)	PERC+ d-dimer	VQ Planar Scintigraphy	CTPA	0.130	0.080	0.768	0.022	0.66	2.39	4,529	17.4474	Dominant

Strategy No	Risk Stratification	Rule Out Test	Diagnostic Imaging	Imaging modality for nonDx Findings	Diagnostic Test Accuracy				Short-term		Costs ($)	QALYs	Sequential ICER
					TP	FP	TN	FN	Numer of patients undergoing imaging	Expected effective dose of radiation			
56	Revised Geneva	d-dimer	VQ Planar Scintigraphy	CTPA	0.129	0.080	0.768	0.022	0.65	2.39	4,533	17.4464	Dominant
24	Wells (3 criteria)	d-dimer	VQ Planar Scintigraphy	CTPA	0.130	0.081	0.767	0.022	0.66	2.40	4,543	17.4474	Dominant
2	None	None	CTPA	Leg US	0.138	0.077	0.771	0.013	1.00	5.20	4,553	17.4849	Dominant
6	None	None	CTPA	CTPA	0.141	0.079	0.769	0.011	1.00	5.39	4,571	17.4971	57097.2857
36	Wells (2-level)	d-dimer	VQ Planar Scintigraphy	Leg US	0.112	0.083	0.765	0.040	0.73	1.60	4,599	17.3647	Dominant
29	Wells (2-level)	PERC+ d-dimer	VQ SPECT	Leg US	0.130	0.070	0.778	0.022	0.66	1.44	4,628	17.4468	Dominant
53	Revised Geneva	d-dimer	VQ SPECT	Leg US	0.130	0.070	0.778	0.022	0.65	1.44	4,633	17.4457	Dominant
33	Wells (2-level)	PERC+ d-dimer	VQ SPECT	CTPA	0.133	0.072	0.777	0.018	0.66	1.60	4,643	17.4617	Dominant
21	Wells (3 criteria)	d-dimer	VQ SPECT	Leg US	0.130	0.071	0.778	0.022	0.66	1.45	4,643	17.4468	Dominant
57	Revised Geneva	d-dimer	VQ SPECT	CTPA	0.133	0.071	0.777	0.019	0.65	1.60	4,647	17.4606	Dominant
25	Wells (3 criteria)	d-dimer	VQ SPECT	CTPA	0.133	0.072	0.776	0.018	0.66	1.61	4,658	17.4617	Dominant
40	Wells (2-level)	d-dimer	VQ Planar Scintigraphy	CTPA	0.131	0.091	0.757	0.020	0.73	2.65	4,695	17.4549	Dominant
37	Wells (2-level)	d-dimer	VQ SPECT	Leg US	0.132	0.080	0.768	0.020	0.73	1.60	4,804	17.4542	Dominant
41	Wells (2-level)	d-dimer	VQ SPECT	CTPA	0.135	0.081	0.767	0.017	0.73	1.78	4,820	17.4693	Dominant
3	None	None	MRI	Leg US	0.128	0.076	0.772	0.024	1.00	0.00	4,981	17.4368	Dominant
7	None	None	MRI	CTPA	0.138	0.083	0.766	0.014	1.00	0.73	5,048	17.4825	Dominant
4	None	None	VQ Planar Scintigraphy	Leg US	0.113	0.122	0.727	0.038	1.00	2.20	5,167	17.3692	Dominant
8	None	None	VQ Planar Scintigraphy	CTPA	0.133	0.134	0.714	0.019	1.00	3.64	5,300	17.4602	Dominant
5	None	None	VQ SPECT	Leg US	0.134	0.117	0.731	0.018	1.00	2.20	5,443	17.4599	Dominant
9	None	None	VQ SPECT	CTPA	0.137	0.119	0.729	0.015	1.00	2.44	5,466	17.4751	Dominant

Pregnant patients

Strategy No	Risk Stratification	Rule Out Test	Ancillary Tests	Diagnostic Imaging	Imaging modality for nonDx Findings	Diagnostic Test Accuracy				Short-term		Costs ($)	QALYs	Sequential ICER
						TP	FP	TN	FN	Numer of patients undergoing imaging	Expected effective dose of radiation			
1	No screening					0.000	0.000	0.848	0.152	0	0	8,673	27.9556	
42	Revised Geneva	PERC+ d-dimer	Leg US	CTPA	CTPA	0.131	0.038	0.810	0.021	0.56	2.93	10,934	29.0014	2,162
10	Wells (3 criteria)	PERC+ d-dimer	Leg US	CTPA	CTPA	0.131	0.039	0.809	0.020	0.57	2.96	10,957	29.0053	5,892
43	Revised Geneva	PERC+ d-dimer	Leg US	MRI	CTPA							11,144	28.9245	Dominant
11	Wells (3 criteria)	PERC+ d-dimer	Leg US	MRI	CTPA	0.121	0.038	0.810	0.031	0.57	0.00	11,169	28.9280	Dominant
26	Wells (2-level)	PERC+ d-dimer	Leg US	CTPA	CTPA	0.135	0.046	0.802	0.017	0.66	3.42	11,295	29.0330	Extended dominance
50	Revised Geneva	d-dimer	Leg US	CTPA	CTPA	0.135	0.046	0.802	0.017	0.65	3.41	11,297	29.0312	Extended dominance
18	Wells (3 criteria)	d-dimer	Leg US	CTPA	CTPA	0.135	0.047	0.802	0.017	0.66	3.43	11,314	29.0331	Extended dominance
46	Revised Geneva	PERC+ d-dimer	None	CTPA	Leg US	0.138	0.052	0.796	0.014	0.48	2.60	11,373	29.0577	Extended dominance
14	Wells (3 criteria)	PERC+ d-dimer	None	CTPA	Leg US	0.139	0.053	0.795	0.013	0.49	2.63	11,402	29.0618	7,882
27	Wells (2-level)	PERC+ d-dimer	Leg US	MRI	CTPA	0.125	0.046	0.802	0.027	0.66	0.00	11,543	28.9537	Dominant
51	Revised Geneva	d-dimer	Leg US	MRI	CTPA	0.124	0.046	0.803	0.028	0.65	0.00	11,544	28.9520	Dominant
19	Wells (3 criteria)	d-dimer	Leg US	MRI	CTPA	0.125	0.046	0.802	0.027	0.66	0.00	11,563	28.9537	Dominant
34	Wells (2-level)	d-dimer	Leg US	CTPA	CTPA	0.137	0.053	0.795	0.015	0.73	3.79	11,577	29.0466	Dominant
47	Revised Geneva	d-dimer	None	MRI	Leg US	0.136	0.054	0.794	0.015	0.48	0.35	11,659	29.0452	Dominant
15	Wells (3 criteria)	PERC+ d-dimer	None	MRI	Leg US	0.137	0.055	0.793	0.015	0.49	0.35	11,691	29.0492	Dominant
44	Revised Geneva	PERC+ d-dimer	Leg US	VQ Planar Scintigraphy	CTPA	0.107	0.060	0.788	0.045	0.56	1.24	11,800	28.8192	Dominant
12	Wells (3	PERC+	Leg US	VQ Planar	CTPA	0.108	0.061	0.787	0.044	0.57	1.25	11,834	28.8223	Dominant

Strategy No	Risk Stratification	Rule Out Test	Ancillary Tests	Diagnostic Imaging	Imaging modality for nonDx Findings	Diagnostic Test Accuracy				Short-term		Costs ($)	QALYs	Sequential ICER
						TP	FP	TN	FN	Numer of patients undergoing imaging	Expected effective dose of radiation			
	criteria)	d-dimer		Scintigraphy										
54	Revised Geneva	d-dimer	None	CTPA	Leg US	0.142	0.063	0.785	0.010	0.57	3.07	11,834	29.0889	Extended dominance
30	Wells (2-level)	PERC+ d-dimer	None	CTPA	Leg US	0.142	0.063	0.785	0.009	0.57	3.08	11,834	29.0909	14,859
35	Wells (2-level)	d-dimer	Leg US	MRI	CTPA	0.126	0.052	0.796	0.026	0.73	0.00	11,854	28.9662	Dominant
22	Wells (3 criteria)	d-dimer	None	CTPA	Leg US	0.142	0.064	0.784	0.009	0.57	3.09	11,856	29.0909	Extended dominance
45	Revised Geneva	PERC+ d-dimer	Leg US	VQ SPECT	CTPA	0.126	0.058	0.790	0.025	0.56	1.24	11,931	28.9641	Dominant
13	Wells (3 criteria)	PERC+ d-dimer	Leg US	VQ SPECT	CTPA	0.127	0.059	0.789	0.025	0.57	1.25	11,966	28.9679	Dominant
55	Revised Geneva	d-dimer	None	MRI	Leg US	0.140	0.065	0.783	0.011	0.57	0.41	12,174	29.0760	Dominant
31	Wells (2-level)	PERC+ d-dimer	None	MRI	Leg US	0.141	0.066	0.783	0.011	0.57	0.41	12,175	29.0779	Dominant
38	Wells (2-level)	d-dimer	None	CTPA	Leg US	0.144	0.072	0.776	0.008	0.64	3.44	12,193	29.1050	Dominant
23	Wells (3 criteria)	d-dimer	None	MRI	Leg US	0.141	0.066	0.782	0.011	0.57	0.42	12,199	29.0779	Dominant
49	Revised Geneva	PERC+ d-dimer	None	VQ SPECT	Leg US	0.136	0.072	0.777	0.016	0.48	1.18	12,313	29.0397	Dominant
52	Revised Geneva	d-dimer	Leg US	VQ Planar Scintigraphy	CTPA	0.110	0.073	0.775	0.041	0.65	1.44	12,345	28.8433	Dominant
28	Wells (2-level)	PERC+ d-dimer	Leg US	VQ Planar Scintigraphy	CTPA	0.111	0.073	0.775	0.041	0.66	1.44	12,347	28.8449	Dominant
17	Wells (3 criteria)	PERC+ d-dimer	None	VQ SPECT	Leg US	0.137	0.073	0.776	0.015	0.49	1.19	12,354	29.0437	Dominant
20	Wells (3 criteria)	d-dimer	Leg US	VQ Planar Scintigraphy	CTPA	0.111	0.073	0.775	0.041	0.66	1.45	12,372	28.8449	Dominant
48	Revised Geneva	PERC+ d-dimer	None	VQ Planar Scintigraphy	Leg US	0.134	0.079	0.770	0.018	0.48	1.76	12,448	29.0268	Dominant
53	Revised Geneva	d-dimer	Leg US	VQ SPECT	CTPA	0.130	0.070	0.778	0.022	0.65	1.44	12,490	28.9925	Dominant
16	Wells (3 criteria)	PERC+ d-dimer	None	VQ Planar Scintigraphy	Leg US	0.135	0.080	0.769	0.017	0.49	1.78	12,490	29.0308	Dominant

Strategy No	Risk Stratification	Rule Out Test	Ancillary Tests	Diagnostic Imaging	Imaging modality for nonDx Findings	Diagnostic Test Accuracy				Short-term		Costs ($)	QALYs	Sequential ICER
						TP	FP	TN	FN	Numer of patients undergoing imaging	Expected effective dose of radiation			
29	Wells (2-level)	PERC+ d-dimer	Leg US	VQ SPECT	CTPA							12,491	28.9943	Dominant
21	Wells (3 criteria)	d-dimer	Leg US	VQ SPECT	CTPA	0.130	0.071	0.778	0.022	0.66	1.45	12,516	28.9944	Dominant
39	Wells (2-level)	d-dimer	None	MRI	Leg US	0.142	0.075	0.774	0.009	0.64	0.46	12,577	29.0919	Extended dominance
2	None	None	Leg US	CTPA	CTPA	0.138	0.077	0.771	0.013	1.00	5.20	12,622	29.0585	Dominant
36	Wells (2-level)	d-dimer	Leg US	VQ Planar Scintigraphy	CTPA	0.112	0.083	0.765	0.040	0.73	1.60	12,773	28.8558	Dominant
37	Wells (2-level)	d-dimer	Leg US	VQ SPECT	CTPA	0.132	0.080	0.768	0.020	0.73	1.60	12,927	29.0072	Dominant
57	Revised Geneva	d-dimer	None	VQ SPECT	Leg US	0.140	0.087	0.762	0.012	0.57	1.39	12,963	29.0701	Dominant
33	Wells (2-level)	PERC+ d-dimer	None	VQ SPECT	Leg US	0.140	0.087	0.761	0.012	0.57	1.39	12,967	29.0721	Dominant
25	Wells (3 criteria)	d-dimer	None	VQ SPECT	Leg US	0.140	0.087	0.761	0.012	0.57	1.40	12,995	29.0721	Dominant
3	None	None	Leg US	MRI	CTPA	0.128	0.076	0.772	0.024	1.00	0.00	13,009	28.9772	Dominant
56	Revised Geneva	d-dimer	None	VQ Planar Scintigraphy	Leg US	0.138	0.095	0.753	0.014	0.57	2.07	13,130	29.0568	Dominant
32	Wells (2-level)	PERC+ d-dimer	None	VQ Planar Scintigraphy	Leg US	0.138	0.095	0.753	0.014	0.57	2.08	13,134	29.0587	Dominant
24	Wells (3 criteria)	d-dimer	None	VQ Planar Scintigraphy	Leg US	0.138	0.096	0.752	0.014	0.57	2.09	13,163	29.0587	Dominant
41	Wells (2-level)	d-dimer	None	VQ SPECT	Leg US	0.142	0.099	0.750	0.010	0.64	1.56	13,476	29.0858	Dominant
6	None	None	None	CTPA	Leg US	0.146	0.106	0.742	0.006	0.90	4.85	13,541	29.1171	65,076
40	Wells (2-level)	d-dimer	None	VQ Planar Scintigraphy	Leg US	0.140	0.108	0.740	0.012	0.64	2.33	13,668	29.0722	Dominant
7	None	None	None	MRI	Leg US	0.144	0.109	0.739	0.008	0.90	0.65	14,089	29.1037	Dominant
4	None	None	Leg US	VQ Planar Scintigraphy	CTPA	0.113	0.122	0.727	0.038	1.00	2.20	14,381	28.8644	Dominant
5	None	None	Leg US	VQ SPECT	CTPA	0.134	0.117	0.731	0.018	1.00	2.20	14,568	29.0178	Dominant
9	None	None	None	VQ SPECT	Leg US	0.144	0.145	0.703	0.008	0.90	2.20	15,403	29.0968	Dominant

Strategy No	Risk Stratification	Rule Out Test	Ancillary Tests	Diagnostic Imaging	Imaging modality for nonDx Findings	Diagnostic Test Accuracy				Short-term		Costs ($)	QALYs	Sequential ICER
						TP	FP	TN	FN	Numer of patients undergoing imaging	Expected effective dose of radiation			
8	None	None	None	VQ Planar Scintigraphy	Leg US	0.142	0.159	0.689	0.010	0.90	3.28	15,696	29.0827	Dominant

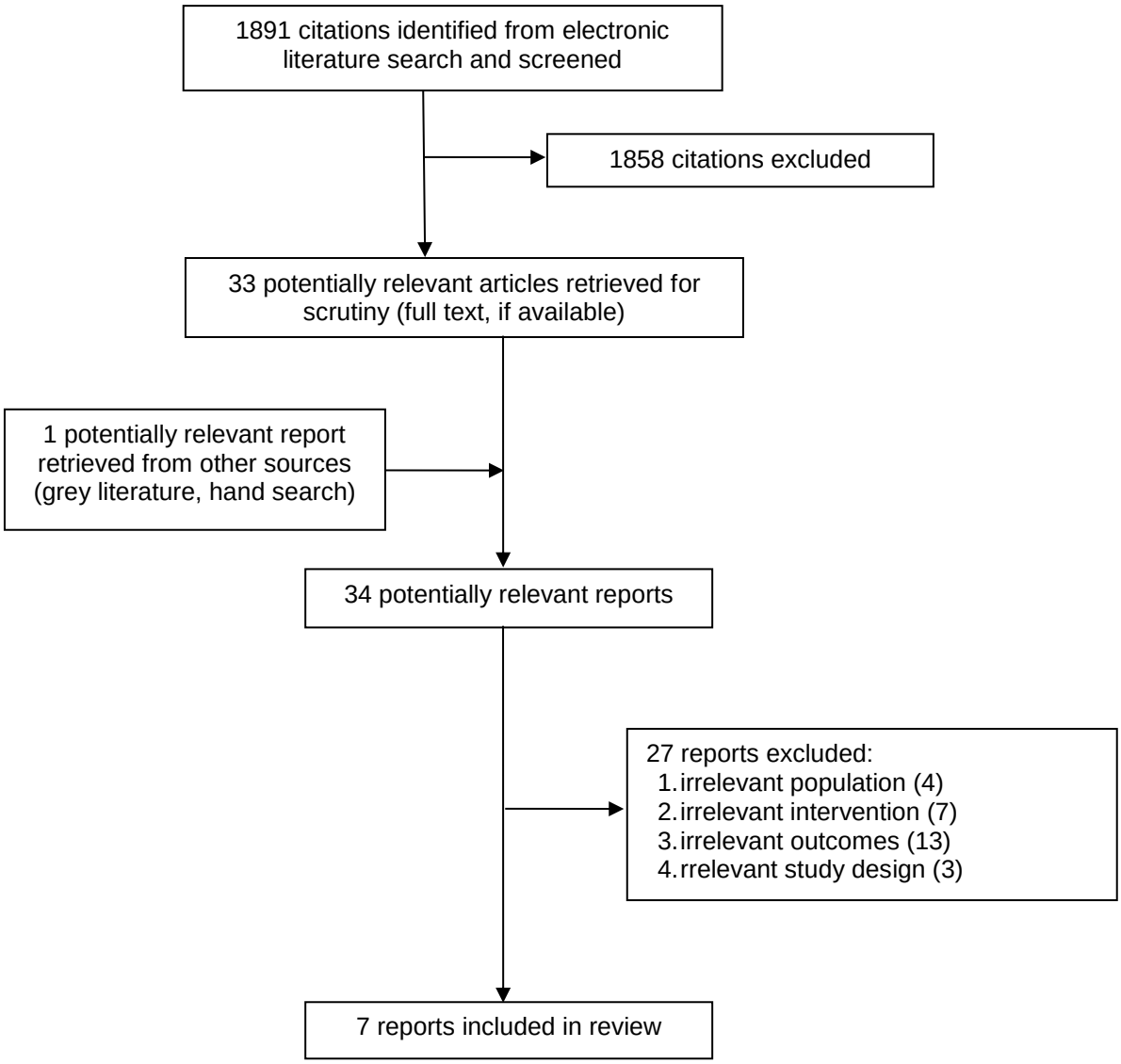
Appendix 28: Additional Sensitivity Analysis Results

Strategy				ICUR ($/QALYs)
Risk stratification		**Dx Imaging**	**Test for non-Dx findings**	
Discount rate (5%)				
No Imaging				-ref-
Revised Geneva	PERC>d-dimer	CT	CT	2,253
Wells: 3 tier	PERC>d-dimer	CT	CT	5,626
Wells: 2 tier	PERC>d-dimer	CT	CT	11,605
Wells: 2 tier	d-dimer	CT	CT	20,494
None		CT	CT†	84,250
Undiscounted (0%)				
No Imaging				-ref-
Revised Geneva	PERC>d-dimer	CT	CT	1,220
Wells: 3 tier	PERC>d-dimer	CT	CT	3,019
Wells: 2 tier	PERC>d-dimer	CT	CT	6,220
Wells: 2 tier	d-dimer	CT	CT	11,002
None		CT	CT†	47,084
Pooled DTA data (for Revised Geneva and 2-tier Wells)				
No Imaging				-ref-
Revised Geneva	PERC>d-dimer	CT	CT	1,489
Wells: 3 tier	PERC>d-dimer	CT	CT	1,543
Wells: 2 tier	PERC>d-dimer	CT	CT	8,393
Wells: 2 tier	d-dimer	CT	CT	17,391
None		CT	CT†	68,930
VQ, VQ SPECT, MRI (lower bound for proportion of non-diagnostic finding)[1]				
No Imaging				-ref-
Revised Geneva	PERC>d-dimer	CT	CT	1,481
Wells: 3 tier	PERC>d-dimer	CT	CT	3,706
Wells: 2 tier	PERC>d-dimer	CT	CT	7,661
Wells: 2 tier	d-dimer	CT	CT	13,556
None		CT	CT†	57,097
Alternative management of non-Dx findings				

Strategy				ICUR ($/QALYs)
Risk stratification		**Dx Imaging**	**Test for non-Dx findings**	
No Imaging				-ref-
Revised Geneva	PERC>d-dimer	CT [22]		1,481
Wells: 3 tier	PERC>d-dimer	CT		3,017
Wells: 2 tier	PERC>d-dimer	CT		6,158
Wells: 2 tier	d-dimer	CT		13,247
None		CT†		30,106
Longer duration of Initial treatment (6 months)				
No Imaging				-ref-
Revised Geneva	PERC>d-dimer	CT	CT	1,732
Wells: 3 tier	PERC>d-dimer	CT	CT	4,173
Wells: 2 tier	PERC>d-dimer	CT	CT	8,524
Wells: 2 tier	d-dimer	CT	CT	15,022
None		CT	CT†	66,108
Anticoagulation treatment (i.e., rivoraxaban)				
No Imaging				-ref-
Revised Geneva	PERC>d-dimer	CT	CT	145
Wells: 3 tier	PERC>d-dimer	CT	CT	2,131
Wells: 2 tier	PERC>d-dimer	CT	CT	5,649
Wells: 2 tier	d-dimer	CT	CT	10,875
None		CT	CT†	48,313
Utilities from original Markov model[245]				
No Imaging				-ref-
Revised Geneva	PERC>d-dimer	CT	CT	1,468
Wells: 3 tier	PERC>d-dimer	CT	CT	3,674
Wells: 2 tier	PERC>d-dimer	CT	CT	7,594
Wells: 2 tier	d-dimer	CT	CT	13,436
None		CT	CT†	56,509

CT= computed tomography; Dx= diagnostic; ICUR = incremental cost-utility ratio; PERC = Pulmonary embolism rule-out criteria; QALY= quality-adjusted-life-year; US = ultrasound
† This diagnostic strategy is also referred throughout the report as “All CT”
[1] Given the reference case findings where CT appeared on all strategies considered most likely cost-effective, higher rates of nondiagnostic findings for VQ or VQ-based imaging techniques would not change the findings

Appendix 29: Selection of Studies on Patient Perspectives and Experience



Appendix 30: Study Characteristics Table

First Author, Publication Year, Country	Data Collection Method	Study Objectives	Sample Size	Imaging Technology	Inclusion Criteria
Hinton, 2014, UK[286]	Semi-structured interviews	To explore the impact of a near-miss obstetric emergency, focusing particularly on partners.	46	N/A	Women who had experienced a near-miss event in childbirth and their partners
Thornton, 2015, USA[288]	Focus Groups	To identify opportunities for improving patient-centered communication about diagnostic imaging tests that involve the use of radiation in a cancer care setting.	30	MRI, CT, X-Ray, PET	People with a diagnosis of cancer and who underwent diagnostic imaging examinations that involved the use of ionizing radiation
Carlsson, 2013, Sweden[287]	Semi-structured interviews	To describe patients' expectations before and experiences during a head-first MRI scan.	10	MRI	Outpatients, ≥ 18 years old and able to understand and speak Swedish fluently.
Munn, 2011, Australia[289]	Systematic Review	To identify the patient experience of high technology medical imaging.	15 studies	CT and MRI	Studies that were qualitative design that explored the phenomenon of interest, the patient experience of high technology medical imaging.
Törnqvist, 2006, Sweden[290]	Conversational interviews	To illuminate patients' lived experience during MRI.	19	MRI	Speak and understand Swedish, be ≥ 18 years old and be outpatients scheduled for an MRI scan performed with the head inside the tunnel.
Nightingale, 2012, UK [285]	Semi-structured Interviews	To explore patients' experience of attending for a cardiac SPECT-CT procedure	22	SPECT-CT	Individuals ≥ 18 years old scheduled for SPECT-CT examination who had not undergone the examination before.
Strand, 2014, Sweden[284]	Semi-structured Interviews	To explore the experience of the MRI examination by patients with neoplasm metastasis in the spine.	12	MRI	Individuals ≥ 18 years old fluent in Swedish that have cancer with possible metastasis to the spine and were currently scheduled for an MRI to investigate possible metastasis.

Appendix 31: Critical Appraisal of Included Publications

Table A2: Strengths and Limitations of Qualitative Studies using Critical Appraisal Skills Programme (CASP) Qualitative Checklist[580]

Strengths	Limitations
Hinton, 2014[286]	
• The study goal to explore the impact of a near-miss obstetric emergency, focusing particularly on partners was clearly stated and is conducive to qualitative inquiry. • The use of a maximum variation sample of women in the UK was appropriate for including a variety of participants, including those of ethnic minorities. • The use of interviews supported by audio/video recordings and subsequent transcription was well suited for this qualitative inquiry. • Ethics committee approval was granted and all participants gave informed consent. • The authors indicate constructing a coding frame and then coding the data. • The use of a qualitative interpretive approach combining thematic analysis with constant comparison is appropriate for this type of study design. • The findings were explicit and appear grounded in the data. • The similarity of their results with that of other studies indicates the need for the development of guidance for supporting partners during and after complicated childbirth.	• Even though it was clear that the researchers used qualitative narrative interviews, an explicit study design was not used. • Rationale for the sample size is not provided. The authors do not discuss saturation of data. • There is no discussion of respondent recall bias, which is important in this study as some of the participants were asked to recall events that happened up to five years prior. • There was also no discussion reflexivity, and influence during analysis and selection of data for presentation.
Törnqvist, 2006[290]	
• The research aim to illuminate participants' lived experience during magnetic resonance imaging (MRI) was clearly stated and is conducive to use of hermeneutic phenomenological methodology. • Conversational interviews are used and are well suited to a phenomenological inquiry. • The authors discuss reflexivity and their potential impact on data collection and analysis • Ethics approval was obtained. • The analytical process was clearly detailed, including how the researchers came to consensus on the coding frame. • The findings were made explicit and clearly explained to demonstrate the variation in experience amongst participants. • The authors highlight the relevance of their findings to clinical practice: identifying patients' individual needs, although time-consuming, may save both time and money in the long run.	• While the author explains that patients who completed MRI were invited to take part in the study, no further justification is provided by means of a purposive strategy • Data saturation was not discussed, nor was a rationale provided for the sample size. • There is some mention that patients received oral and written information about the study. Considering the degree of panic that some patients experienced during the MRI, there is no discussion of how the authors dealt with that and whether and how that might have impacted on data collection.
Carlsson, 2013[287]	
• The research aims to describe patients' expectations before and experiences during a head-first MRI scan are clearly stated and well suited to qualitative inquiry. • Used semi-structured interviews with a variety of participants (in terms of age, gender, health) to create movement from prepared, open-ended questions to deeper	• The fact that one patient chose not to participate is mentioned but no discussion around why this happened. • There is no rationale provided as to the sample size of 10 participants, nor was data saturation was discussed. • Minimal reflexive practice

Strengths	Limitations
conversations on experience. • Ethical approval was obtained even though unnecessary according to Swedish law. • The authors provide sufficient detail regarding the analysis of the data including the use of systematic text condensation – an appropriate method of analysis to create a coding frame. • Details were provided around the validation of the findings using multiple analysts, as a strategy to enhance credibility • The findings were presented clearly using themes and subthemes, which were supported by direct quotes from the participants. • The relevance of the findings to clinical practice were highlighted as the need to adjust the patient-radiographer interaction to address patients' expressions of worries about the scanning procedure, or the coming result.	
Thornton, 2016[288]	
• The goal of the research to identify opportunities for improving patient-centered communication about diagnostic imaging test that involve the use of radiation in a cancer care setting was clearly stated and is appropriate for qualitative inquiry. • A purposive sampling recruitment strategy and subsequent use of focus groups are both well suited to address research goal. • The results were analyzed using inductive thematic textual analysis. This was an iterative process of transcript review, interpretation, and consensus discussions. • The research team worked together to analyze the transcripts and to come to consensus of the emerging themes, thereby enhancing the credibility of the data. • The findings were presented clearly using the six themes that were identified as key, high-level findings of the entire study by the research team during their consensus meetings. • The findings from this study are important and highlight the need for appropriate educational tools that healthcare providers can use to inform patients on medical imaging risks in a cancer care setting.	• Even though it was clear that the researchers used qualitative narrative interviews, an explicit study design was not used. • There is mention of six participants not attending the focus group, but no discussion of why and how researchers responded and adjusted the study. • There is no discussion about how the focus group guide was constructed. • There is no mention of data saturation, or other rationale provided for the sample size. • There is no discussion of researcher reflexivity, or any influence the researcher may have had on data collection or analysis. • It was mentioned that one participant refused to sign the consent form out of concerns over confidentiality, which was not discussed in detail. • Relatively minimal use of participant voice. Researchers tended to paraphrase or speak for the participants throughout.
Strand, 2014[284]	
• The study goal to explore the experience of a magnetic resonance imaging evaluation by patients with neoplasm metastasis in the spine was clearly stated and well suited for qualitative inquiry. • In-depth, semi-structured interviews were conducted immediately following the MRI scan and content analysis was used to understand participant experience. • Study participants were well informed of research goals and signed a written informed consent. Study conducted according to the ethical standards of Swedish law and the Declaration of Helsinki. • Some indication of reflexive practice prior to conducting the research.	• Sampling strategy was hampered by limited participant pool.

Strengths	Limitations
• Findings are well organized and presented, but could have benefited from more in-depth analysis. • Authors clearly indicate how this study could be beneficial to current clinical practice.	
Nightingale, 2012[285]	
• The study goal to explore the experience of patients referred for cardiac SPECT-CT across to clinical environments was clearly stated and well suited to the use of semi-structured interviews for data collection. • The use of thematic content analysis is both well defended by authors and appropriate for qualitative inquiry. • Utilized a third independent reviewer to verify initial findings and reduce the potential for bias. • Study participants were well informed of study goals. NHS research ethics committee and university ethics approval were obtained. • While findings seem under analyzed, they are well organized and presented. • Extensive section indicating opportunities for further research as well as applicability to current practice.	• No use of reflexive practice

Table A3: Strengths and Limitations of Systematic Reviews using Critical Appraisal Skills Programme (CASP) Systematic Review Checklist

Strengths	Limitations
Munn, 2011[289]	
• The review addressed a clearly focused question, the patient experience of high technology medical imaging, and appropriately contextualized the review within a body of relevant published research • The authors appropriately included articles that were of qualitative design that explored the phenomenon of interest. • The authors searched several relevant databases, and also searched for unpublished and grey literature. The search terms used were also appropriate to address the study aims. • The studies that were included in the review were assessed in duplicate using the Joanna Briggs Institute Qualitative Assessment and Review Instrument (JBI-QARI). The use of two assessors to perform the critical appraisal enhanced reliability in their analysis. • The results were pooled using the JBI-QARI, which involved the aggregation or synthesis of the findings to generate a set of statements. This was followed by a meta-synthesis to produce a single comprehensive set of synthesized findings.	• There was no discussion of any variations in the results that were obtained, for example by different patient populations, settings or conditions • There is no discussion of researcher reflexivity, or any influence the researcher may have had on data collection or analysis.

CADTH

Appendix 32: CADTH Survey Questions

Demographics and Clinical Setting

1. In which province/territory do you currently practice?
   - ☐ Alberta
   - ☐ British Columbia
   - ☐ Manitoba
   - ☐ New Brunswick
   - ☐ Newfoundland and Labrador
   - ☐ Northwest Territories
   - ☐ Nova Scotia
   - ☐ Nunavut
   - ☐ Ontario
   - ☐ Prince Edward Island
   - ☐ Quebec
   - ☐ Saskatchewan
   - ☐ Yukon

2. Please describe the centre you are representing and in which you predominantly practice (for example, teaching hospital, public health clinic, long-term care home, etc.). Please also describe the setting in which your centre is located (for example, large urban area, small town, remote area, etc.).

Diagnostic Strategy

3. Based on the setting you identified in Question 2, please describe how you diagnose suspected PE, including any strategies, guidelines, or shared decision making tools you might use, and who is involved in assessing patients (for example, nurses, primary care physicians, or specialists).

4. Are you aware of instances when the approach to diagnosing PE will differ depending on location within your province or territory (for example, teaching hospital, urban, rural, and remote)?
   ☐ Yes (please describe the strategy and setting below)
   ☐ No

5. Are you aware of instances when the approach to diagnosing PE will differ or when the usual diagnostic strategy cannot be followed? For example, might it differ depending on the type of patient and how they present (e.g., pregnant women, patients with potential contraindications to imaging, etc.)?
   ☐ Yes (please describe below)
   ☐ No

6. Do you currently use any of the following risk stratification tools when diagnosing PE? Please select all that apply.
   ☐ Pulmonary Embolism Rule-Out Criteria
   ☐ Wells' Criteria for Pulmonary Embolism
   ☐ Geneva Score
   ☐ None of the above
   ☐ Other (please describe):

7. Do you have ready access (i.e., equipment is available in your centre) to the following rule-out or ancillary tests when diagnosing PE? Please select all that apply.
   - ☐ Arterial blood gas
   - ☐ Capnography
   - ☐ Chest X-ray
   - ☐ D-dimer testing
   - ☐ Echocardiography
   - ☐ Electrocardiography
   - ☐ Leg compression ultrasound
   - ☐ None of the above
   - ☐ Other (please describe):

8. Do you have ready access (i.e., equipment is available in your centre) to the following imaging modalities when diagnosing PE? Please select all that apply.
   - ☐ Ventilation/Perfusion scintigraphy
   - ☐ Ventilation/Perfusion SPECT (single-photon emission computed tomography)
   - ☐ Ventilation/Perfusion SPECT-CT
   - ☐ CT (computerized tomography)
   - ☐ Thoracic ultrasound
   - ☐ MRI (magnetic resonance imaging)
   - ☐ PET (positron emission tomography) modalities
   - ☐ None of the above
   - ☐ Other (please describe):

9. If you had different or more resources available would that change your strategy for diagnosing PE? What additional resources would you use and how would your approach to diagnosing PE change?

10. What are the main challenges you face in diagnosing PE? For example, please describe any issues around clinical capacity and expertise to perform testing, available machinery being used for other purposes, time constraints, or any other challenges you might face.

11. Do you currently transport patients out of your centre to diagnose suspected PE?
☐ Yes (please proceed to question 12)
☐ No (please proceed to question 13)

12. Could you please tell us more about transporting patients out of your centre so that a PE diagnosis can be made? For example, how far do you send them, how are costs covered, what patient characteristics might warrant travel, and any other related issues.

Permission to Contact and CADTH Environmental Scan Use

13. Would you be willing to be consulted further on this topic, either through an informal phone call or by email?
☐ Yes
☐ No

Appendix 33: Survey Respondents – Self Identified Description

Province	Organization	Description of Centre or Practice
Manitoba	St. Boniface Hospital	Large, urban, teaching hospital
Manitoba	Diagnostic Services of Manitoba	Provides lab testing (provincial) and radiology (provincial – with the exception of Winnipeg and Brandon)
Manitoba	Winnipeg Regional Health Authority (2 respondents)	Large, urban, teaching hospital
New Brunswick	Horizon Health Diagnostic Imaging	Urban, teaching hospital
New Brunswick	Horizon Health	Rural hospital
New Brunswick	Horizon Health	Urban, teaching hospital
Ontario	The Ottawa Hospital	Large, urban, teaching hospital
PEI	Queen Elizabeth Hospital	Small teaching hospital
PEI	Health PEI	Community teaching hospital
Saskatchewan	Saskatoon Health Region	Teaching hospital
Saskatchewan	Regina Qu'Appelle Health Region	Teaching hospital

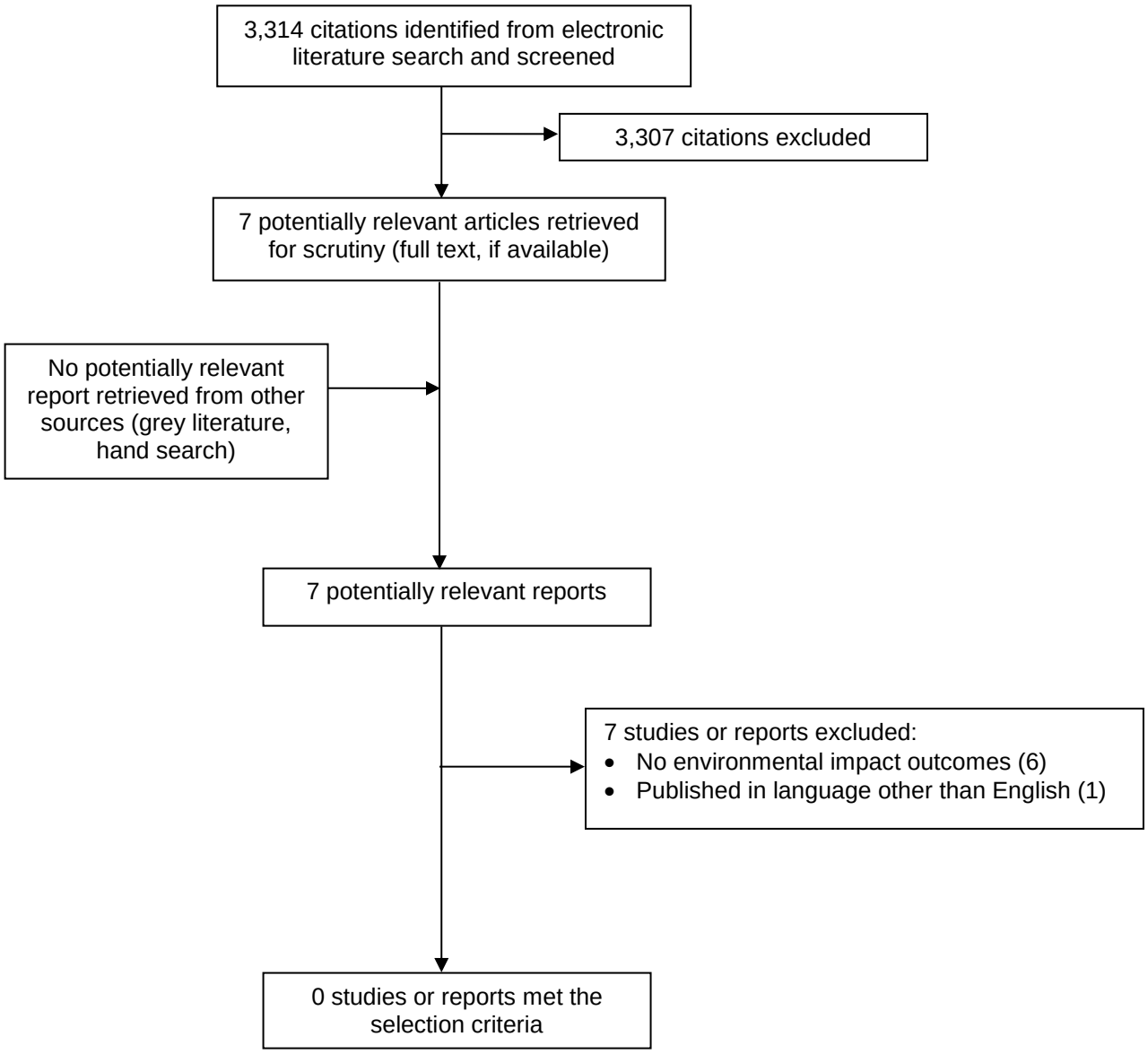
Appendix 34: Study Characteristics Table

First author, Publication year, Jurisdiction of origin	City/Town, Province or Territory	Study Objective	Data Collection Methods	Indication	Clinical Setting
Ahn, 2014[293]	London, Ontario	*"To assess the current level of knowledge and practice patterns of emergency physicians regarding radiation exposure from diagnostic imaging modalities for investigating acute pulmonary embolism (PE)."* (pg. 394)	Survey, retrospective chart review	PE	2 academic, tertiary care ED
Aranson, 2007[294]	Ottawa, Ontario	*"It was the objective of this study to determine the proportion of patients who undergo an appropriate diagnostic work-up following a D-dimer test performed to evaluate suspected PE or DVT."* (pg. 195)	Retrospective chart review	VTE	Academic, tertiary care hospital (ED and inpatient)
Ballantine, 2012[295]	Exeter, Ontario	*"The purpose of this study was to investigate the diagnostic approach for PE, time to access imaging and diagnostic utility of each modality in a rural emergency department (ED)."* (pg. 18)	Retrospective chart review	PE	Rural ED
Chen, 2015[296]	Toronto, Ontario	*"First, we sought to determine the utilization and PE diagnosis rate of CTPA among different patient age and gender groups in a tertiary academic emergency department (ED). Second, we sought to examine the inter-physician variation in CTPA use at our institution and correlate these metrics to physician characteristics including years in practice, gender, and training certification."* (pg. 222)	Retrospective chart review, review of physician characteristics	PE	Academic, tertiary care ED
Ingber, 2014[297]	Ontario	*"The objective of our study was to assess whether the introduction of a standardized clinical PTP assessment prior to ordering of D-dimer tests could reduce the use of subsequent radiologic imaging to investigate patients with suspected VTE in our ED."* (pg. 54)	Retrospective chart review	VTE	Academic, tertiary care ED
Le Roux, 2015[298]	Canada (un-specified)	*"There are currently no data available regarding current practices in nuclear medicine centers regarding the diagnosis of acute PE. In particular, little is known concerning the proportion of centers using SPECT or SPECT/CT rather than planar imaging, nor are there data regarding which criteria are currently used to interpret planar and VQ SPECT. The aim of this study was, therefore, to assess these practices in nuclear medicine centers."* (pg. 1213)	Survey	PE	48 nuclear medicine departments
Smith, 2008[36]	Hamilton, Ontario	*"Our objectives were to measure the documentation rate of PTP for ED patients on whom a SimpliRED D-dimer was performed for suspected venous*	Retrospective chart review	VTE	Academic, tertiary care centre

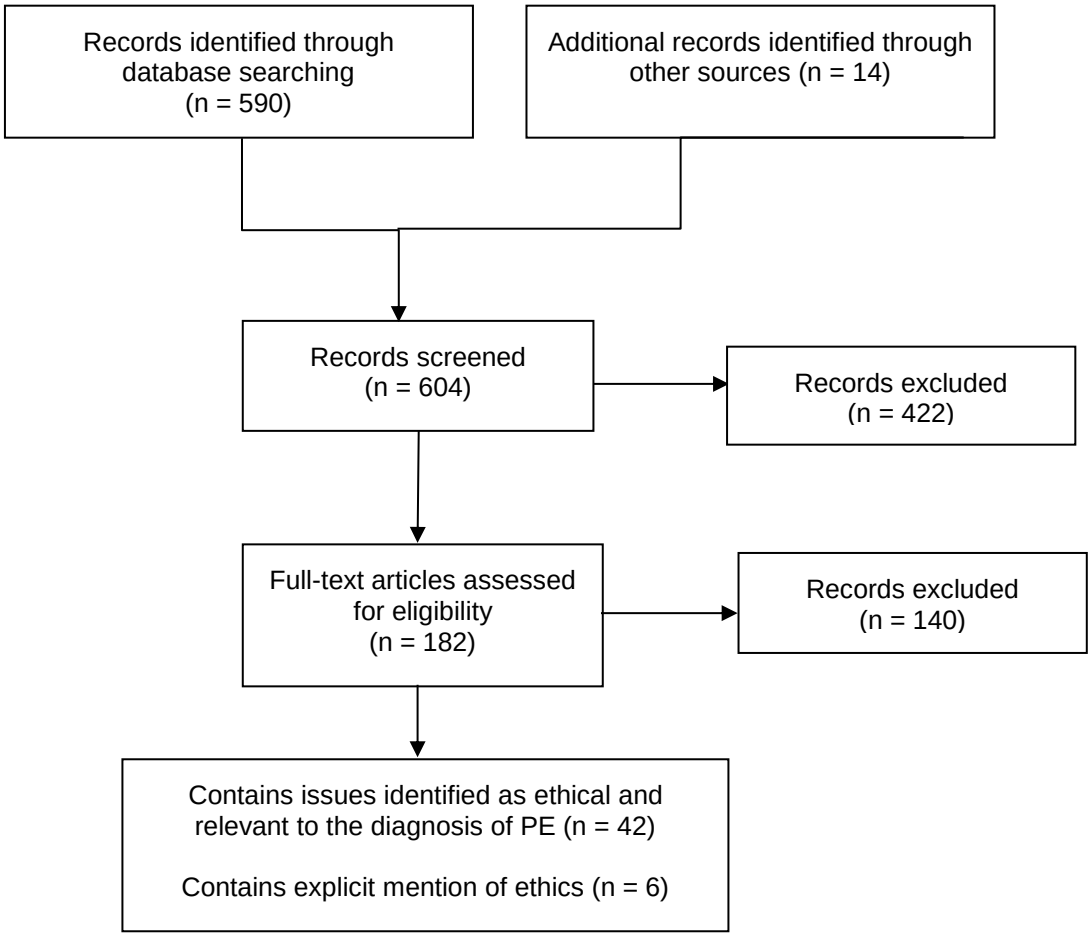
First author, Publication year, Jurisdiction of origin	City/Town, Province or Territory	Study Objective	Data Collection Methods	Indication	Clinical Setting
		thromboembolism (VTE) and to determine if the clinical management decisions by the clinicians were in keeping with current recommendations." (pg. 520)			
Southern, 2014[299]	pan-Canadian	*"We documented the infrastructure available in hospitals and health regions across Canada for provision of optimal diagnosis and therapy for VTE disease."* (no page number)	Surveys, interviews, GIS mapping	VTE	658 acute care hospitals across 10 provinces and 3 territories
Spencer Netto, 2012[300]	Toronto, Ontario	*"All trauma patients diagnosed with PE at our institution during a two year period were retrospectively reviewed in order to describe the timing of PE and to compare the clinical characteristics and natural history of trauma patients diagnosed with PE at different time intervals after injury. In particular, the clinical characteristics of patients with incidental, immediate PE were described."* (pg. 1502 to 1503)	Retrospective chart review	PE	Academic, trauma centre

CT = computed tomography; CTPA = computed tomography pulmonary angiogram; DVT = deep vein thrombosis; ED = emergency department; GIS = geographic information systems; PE = pulmonary embolism; PTP = pretest probability; SPECT = single-photon emission computed tomography; VQ = ventilation/perfusion; VTE = venous thromboembolism

Appendix 35: Selection of Studies on Environmental Impact



Appendix 36: Selection of Studies on Ethics Analysis



Appendix 37: Characteristics of Included Ethics Reports

CitationEthics	Country	Method	Topic	Normative claims/empirical results
Ethical issues related to imaging for pulmonary embolism				
Armao D, Semelka RC, Elias J. Radiology's ethical responsibility for healthcare reform: tempering the overutilization of medical imaging and trimming down a heavyweight. Journal of Magnetic Resonance Imaging. 2012;35(3):512-7.	United States	Opinion piece and normative analysis	Ethical issues related to overutilization of CT and MRI and health care reform responsibilities.	Dramatic increases in the use of diagnostic imaging have contributed to soaring medical costs and medical exposure to ionizing radiation. Principles of trust and right conduct are crucial guides for judging the appropriateness of actions to address overuitilization of imaging.
Gossner J, Nau R. Geriatric chest imaging: When and how to image the elderly lung, age-related changes, and common pathologies. Radiology Research and Practice [Internet]. 2013.	Germany	Opinion piece; normative analysis	Ethical implications related to the care of elderly patients with suspected cardiopulmonary disease.	Physicians should be confident imaging will provide potential diagnosis and treatment, but patients may still decline imaging. Frail elderly patients face unique challenges with having diagnostic imaging and the process of ageing must be separated from the disease itself.
Ethical issues related to diagnostic imaging				
Berlin LDR, Murphy, Siingh H. Breakdowns in communication of radiological findings: an ethical and medico-legal conundrum. Diagnosis. 2014;1(4): 263-268.	United States	Normative analysis; empirical ethics (survey)	Legal and ethical duty to disclose medical error and unexpected diagnostic findings.	The current patient and physician cultures interact to keep the physician disclosure rates of medical error low. Most physicians acknowledge that they should disclose and express sorrow to patients in the wake of an error, but decline to do so for fear of punitive action. Nevertheless, physicians are ethically and professionally bound to divulge errors to patients and should work with hospital risk management personnel or a representative of the professional liability insurance carrier for guidance on managing future communications about the incident.
Blumenthal-Barby JS, Cantor SB, Russell HV, Naik AD, Volk RJ. Decision aids: When 'nudging' patients to make a particular choice is more ethical than balanced, non-directive content. Health Affairs. 2013;32(2):303-310.	United States	Opinion, normative argument	Identification and discussion of three situations in which being as neutral, unbiased, and nondirective as possible should not be a goal in the development of patient decision aids.	Patient decision aids, such as instructional leaflets describing treatment options for prostate cancer, are designed to help educate patients so that they can share in decisions about their care. If the goal of medical decision making is to have patients make an informed decision based on a balanced consideration of the options, sometimes it is ethically appropriate for decision aids not to be balanced so that they can counter existing bias, framing effects, and cofiduciary responsibility and bring the patient to a balanced decision. Medical decision makers and decision aid developers must address the question of whether, under what

CitationEthics	Country	Method	Topic	Normative claims/empirical results
				circumstances, and how patients should be nudged toward one option or another.
Keefer, Raina. Ethical dilemmas in radiology and the vow to do no harm. March 9 2012 https://acrbulletin.org/acr-bulletin-march-2012/1087-ethical-dilemmas-in-radiology [Accessed 20 February 2018].	United States	Opinion/educational article	Description of key ethical challenges faced by interventional radiologists and thoughts on how ethical dilemmas might be approached.	Numerous questions arise on a daily basis that might not involve the question 'is this ethical?' but relate to the best care for a patient. Challenges include decisions about informed consent, appropriate utilization of imaging, communication of unexpected results and medical error, and overestimating expertise.
Rosenthal MS. Patient misconceptions and ethical challenges in radioactive iodine scanning therapy. Journal of Nuclear Medi Technol. 2006; 34:143-150.	United States	Opinion, education article, normative analysis.	Ethical issues in conveying accurate information about risks of radioactive iodine to patients.	Fear and anxiety over its use, misinformation in patient advocacy books and on the Internet, medical jargon, confusion regarding postscanning and posttreatment procedures, patient literacy, thyroid health status, and several other socioeconomic factors can create serious barriers to genuine informed consent in RAI scanning and treatment. There are inherent ethical and legal requirements for informed consent. Correcting misconceptions, misinterpreted facts, and even false information and appropriately warning patients about certain risks need to be raised as critical patient education issues for nuclear medicine practitioners.