

1 CADTH Optimal Use Report

2

3

4 **Optimal Strategies for the**
5 **Diagnosis of Acute Pulmonary**
6 **Embolism: A Health Technology**
7 **Assessment**

8

9 September 2017

10 Volume 6, Issue 3a

11

12 PROSPERO Registration Number: 42016046980

13

14 ABOUT THIS DOCUMENT

15
16 The information in this document is intended to help Canadian health care decision-makers, health care
17 professionals, health systems leaders, and policy-makers make well-informed decisions and thereby
18 improve the quality of health care services. While patients and others may access this document, the
19 document is made available for informational purposes only and no representations or warranties are made
20 with respect to its fitness for any particular purpose. The information in this document should not be used
21 as a substitute for professional medical advice or as a substitute for the application of clinical judgment in
22 respect of the care of a particular patient or other professional judgment in any decision-making process.
23 The Canadian Agency for Drugs and Technologies in Health (CADTH) does not endorse any information,
24 drugs, therapies, treatments, products, processes, or services.
25

26 While care has been taken to ensure that the information prepared by CADTH in this document is accurate,
27 complete, and up-to-date as at the applicable date the material was first published by CADTH, CADTH
28 does not make any guarantees to that effect. CADTH does not guarantee and is not responsible for the quality,
29 currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in any
30 third-party materials used in preparing this document. The views and opinions of third parties published in this
31 document do not necessarily state or reflect those of CADTH.
32

33 CADTH is not responsible for any errors, omissions, injury, loss, or damage arising from or relating to the
34 use (or misuse) of any information, statements, or conclusions contained in or implied by the contents of
35 this document or any of the source materials.
36

37 This document may contain links to third-party websites. CADTH does not have control over the content of
38 such sites. Use of third-party sites is governed by the third-party website owners' own terms and conditions
39 set out for such sites. CADTH does not make any guarantee with respect to any information contained on
40 such third-party sites and CADTH is not responsible for any injury, loss, or damage suffered as a result of
41 using such third-party sites. CADTH has no responsibility for the collection, use, and disclosure of personal
42 information by third-party sites.
43

44 Subject to the aforementioned limitations, the views expressed herein are those of CADTH and do not
45 necessarily represent the views of Canada's federal, provincial, or territorial governments.
46

47 This document is prepared and intended for use in the context of the Canadian health care system. The use of this
48 document outside of Canada is done so at the user's own risk.
49

50 This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse)
51 of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the
52 laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of
53 the Province of Ontario, Canada.
54

55 The copyright and other intellectual property rights in this document are owned by CADTH and its licensors. These
56 rights are protected by the Canadian *Copyright Act* and other national and international laws and agreements. Users
57 are permitted to make copies of this document for non-commercial purposes only, provided it is not modified when
58 reproduced and appropriate credit is given to CADTH and its licensors.
59

60 ISSN: 1927-0127
61

62 Cite as: [Click here to enter text.](#)
63
64

DRAFT

65 **EXECUTIVE SUMMARY**

66

67 To be developed.

68

DRAFT

69 RATIONALE AND POLICY ISSUES

70 Overview

71 Acute pulmonary embolism (PE) is the third most common acute cardiovascular disease, after
72 myocardial infarction and stroke.¹ It is part of the continuum of venous thromboembolism (VTE),
73 which also includes deep vein thrombosis (DVT).² Most PEs originate from thrombi in the leg or
74 pelvic veins, which can dislodge and travel through the venous system, eventually obstructing
75 blood vessels of the lung.³ Evidence of lower-limb DVT is found in about 70% of patients who
76 have sustained a PE,¹ but PE can also present in isolation.^{4,5} An accurate estimate of PE
77 incidence is difficult to obtain, because a significant proportion of pulmonary emboli are detected
78 on autopsy,⁶ not all of which are clinically relevant. It has been estimated that 80% of patients
79 identified with PE at autopsy are unsuspected or undiagnosed before death.⁷ Assuming the
80 incidence rate in Canada is similar to that in the United States (US), PE likely afflicts between
81 0.1% and 1% of the population.⁷

82 Mechanism and Outcomes

83 Blockages of the pulmonary artery and its branches can lead to obstruction of blood flow to the
84 heart. Resultant pressure in the lungs may increase right heart pressure, causing right
85 ventricular strain, which can lead to cardiovascular compromise and low oxygen levels.⁸ Other
86 complications include pulmonary hemorrhage and loss of oxygen supply. PE is a major cause of
87 emergency hospitalization, and clinical expression can range from asymptomatic disease to
88 sudden death. Acute PE can lead to chronic thromboembolic pulmonary hypertension, and right
89 ventricular failure if it is not promptly diagnosed and treated.⁹ Patients with delayed diagnosis
90 tend to have worse outcomes including endotracheal intubation, shock and hospital death.¹⁰
91 Case fatality is high and can vary depending on whether the condition is recognized and
92 treated. Approximately 2 to 10% of patients treated for PE die from causes attributable to the
93 condition.^{11,12} Untreated PE can be fatal in up to 30% of patients. If administered promptly,
94 anticoagulation therapy is highly effective at preventing extension of thrombus and can prevent
95 mortality and morbidity associated with PE.¹³

96 Diagnosis

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

101

102 Symptoms and Risk Factors

103

104 There are many challenges associated with diagnosing PE, one being the non-specific nature of
105 common PE symptoms, the most common including dyspnea and chest pain.^{14,15} A number of
106 conditions, including rib or vertebral body fracture, acute myocardial infarction, pulmonary
107 edema, pneumonia, cancer, or interstitial lung disease, can have similar symptoms to PE. On
108 the other hand, approximately 30% of patients with PE may be asymptomatic.¹⁶ Non-specific
109 patient symptoms can potentially lead to over-testing, as PE may be considered in the
110 differential diagnoses of a range of symptoms.

111

112 PE rarely occurs in the absence of risk factors and the likelihood of occurrence increases when
113 multiple risk factors are present. Factors associated with the development of PE can be
114 inherited or acquired. Some common risk factors include, but are not limited to, malignancy,
115 immobilization, surgery, extremity paresis, hormone replacement therapy and oral
116 contraception, and Factor V Leiden and other inherited and acquired thrombophilia conditions.¹⁷
117 Patients who have DVT or who are taking medications that alter coagulation of the blood are
118 also at risk of developing PE.^{5,18} In addition, pregnant women are four to five times more likely to
119 develop VTE, which is one of the leading causes of maternal death during childbirth.¹⁹ This is, in
120 part, due to physiological changes to coagulopathy and mechanical factors such as vein
121 compression in pregnancy. Because of these features, many symptoms of PE may overlap with
122 regular pregnancy symptoms such as shortness of breath and edema in the lower limbs.

123 **Risk Stratification**

124
125
126 The likelihood of PE can be estimated using various risk stratification approaches. A patient
127 may initially undergo assessment with a clinical prediction rule or clinical gestalt. Patients with
128 high probability of PE may proceed directly to imaging, while patients with low probability may
129 undergo further testing such as Pulmonary Embolism Rule-Out Criteria (PERC) or D-dimer
130 testing to further assess the need for diagnostic imaging. This may be supplemented by
131 additional biochemical or imaging studies to rule out differential diagnoses or strengthen
132 estimates of PE risk. Determining PE risk during initial assessment may reduce the overall need
133 for imaging, save diagnostic time and costs, and reduce complications, including downstream
134 risks of radiation exposure.²⁰

135 Clinical Prediction Rules

136 Evidence supports the practice of determining the clinical pretest probability of PE before
137 proceeding with diagnostic testing.²¹ The American College of Physicians (ACP) has provided
138 best practice advice on the evaluation of patients with suspected acute PE, noting that the first
139 step when evaluating a patient is to establish his or her pretest probability of PE.²² Clinical
140 prediction rules (also called clinical decision rules) aim to determine risk profile and the
141 necessity of undergoing diagnostic testing. The ACP recommends using either the Wells or
142 Geneva clinical prediction rules.²²

143
144 The Wells rule was designed in 2000 based on an analysis of 40 clinical variables associated
145 with PE. The analysis arrived at an approach that factors seven items based on both objective
146 criteria from patient history or physical examination, and physician judgment, into a total score.²³
147 Typically patients with scores lower than 4 are deemed low risk for PE, although there is
148 variation in the cut-offs applied. The Geneva score differs from Wells in that additional
149 diagnostic testing (electrocardiography, and/or chest radiography, and arterial blood gas) may
150 contribute to the score in addition to consideration of risk factors and clinical presentation.²³ A
151 revised Geneva score has been developed that can be determined independently of the
152 additional diagnostic tests.

153
154 There is controversy regarding which rules are the most accurate for stratifying risk for acute
155 PE,²⁴ but the Wells and Geneva rules have received the most extensive validation in the widest
156 range of settings.^{24,25} There is some evidence from systematic reviews (SRs) to suggest that the
157 Wells rule is more accurate than the Geneva rule, but that the most appropriate tool may
158 depend on the setting (i.e., low prevalence versus high prevalence [referred population]).^{24,26}
159 Adherence to protocols incorporating the Wells score and D-dimer testing has been

160 demonstrated to result in a 20% to 30% reduction in the number of computed tomography (CT)
161 examinations performed.²⁷

162 D-Dimer

163 D-dimer is one of several lab-based or imaging studies used to increase confidence in the
164 decision to forego testing or rule out PE. This test measures protein fragments produced either
165 when blood clots break down or in response to the use of fibrinolytic medication. Circulating
166 levels often elevate in patients with VTE. Patients judged to have a high probability of PE don't
167 usually undergo D-dimer testing and proceed straight to imaging. A negative D-dimer test in a
168 low-probability patient can support the decision to forego further investigation of PE.
169 Conversely, a positive D-dimer test indicates that further imaging is necessary. Various
170 quantitative (e.g., enzyme linked immunosorbent assay [ELISA]), semi-quantitative (e.g.,
171 immunofiltration latex agglutination) and qualitative (e.g., immunochromatography) D-dimer
172 assays are available and range in their sensitivity.²⁸ Cut-offs for normal concentrations vary by
173 assay and based on factors such as age, clinical conditions (e.g., cancer), recent surgery, and
174 pregnancy. D-dimer is available as a conventional lab-based test and as a point-of-care test.
175 Point-of-care tests can be performed during patient consultations and are available within 10 to
176 15 minutes,²⁹ thus overcoming limitations of limited access to central laboratories and delays in
177 receiving test results; however, lab-based tests may have higher sensitivity.³⁰

178 Pulmonary Embolism Rule-Out Criteria

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

184 Ancillary Tests

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

192 Limitations of Risk Stratification Tools

193 Given that symptoms of PE are not specific, clinical features alone cannot confidently diagnose
194 PE and risk stratification tools are rarely used in isolation.¹⁴ The positive predictive value of risk
195 stratification strategies, particularly clinical prediction rules, may be influenced to some extent by
196 the prevalence of disease in the population, as well as cut-off values used.²⁶ In addition, the use
197 of risk stratification strategies may not be appropriate in pregnancy. D-dimer levels increase
198 during the course of pregnancy and there is insufficient evidence for its use as a rule-out tool,
199 though trimester-specific cut-offs have been proposed.³³ Though the utility of clinical prediction
200 rules and D-dimer testing for ruling out unnecessary testing has been demonstrated,
201 implementation of such a strategy may be challenging due to lack of awareness about safety, as
202 well as concern about risks of omitting diagnostic imaging studies due to the high mortality rate

203 associated with acute PE.^{20,34,35} Nevertheless, these scores may improve the efficiency of PE
204 assessment and diagnostic yield of imaging studies,²⁵ and decrease the volume of unnecessary
205 imaging studies. Their use is in line with initiatives by Choosing Wisely and society partners,
206 which recommend that clinicians avoid CT angiography in patients who are stratified at low risk
207 of PE and receive either a negative PERC score or D-dimer measurement.³⁶

208

209 **Diagnostic Imaging**

210

211 Patients who are deemed at high risk of PE following risk stratification, or based on unstable
212 presentation, usually undergo diagnostic testing for confirmation of disease positivity.

213 Conventional pulmonary angiography (PA) has been previously regarded as the gold standard,
214 but due to its invasive nature and insufficient sensitivity, it has been overtaken by alternative
215 modalities.^{37,38} Other less-invasive methods of diagnosing PE include computed tomography
216 pulmonary angiography (CTPA), magnetic resonance angiography (MRA), ventilation-perfusion
217 (V/Q) modalities including ventilation-perfusion (V/Q) scanning planar scintigraphy, V/Q single-
218 photon emission computed tomography (SPECT), or V/Q SPECT-CT, positron emission
219 tomography–CT (PET-CT), and thoracic ultrasound.

220

- 221 • CT uses X-rays, radiation detectors, and computerized analysis to assemble cross-
222 sectional images of the body.³⁹ It allows for rapid imaging and diagnosis, as well as the
223 ability to visualize fine details of physical body structures, but is associated with
224 exposure to radiation. CT is used to visualize clot formation in the lung.⁴⁰⁻⁴²
- 225 • MRI uses electromagnetic and radiofrequency fields as well as computerized analysis to
226 assemble cross-sectional images of the body. It does not use ionizing radiation, thus
227 is preferred for patients with contraindications. MRI's high sensitivity enables
228 visualization of soft-tissue details, but the time to conduct an exam, requirement for the
229 patient to be motionless within a small space and inability to conduct exams in those
230 with pacemakers and other metallic implants are limitations. MRI is used to visualize clot
231 formation in the lung.⁴³⁻⁴⁶
- 232 • Several modalities are used to measure the V/Q ratio, which indicates the presence of a
233 blood clot based on mismatch between air and blood flow in the lung. In all cases,
234 radiopharmaceuticals are injected intravenously and inhaled and detected by
235 scintigraphy (2-dimensional), SPECT or SPECT-CT (both 3-dimensional).⁴⁷
 - 236 ○ V/Q scintigraphy utilizes X-rays to generate 2 dimensional images
 - 237 ○ V/Q SPECT uses nuclear medicine cameras to detect gamma rays from the
238 radiopharmaceuticals and generate cross-sectional images. Duration of the exam
239 tends to vary, but is generally longer than CT. There is exposure to ionizing
240 radiation and scan quality may be lower resolution. These scans also require a
241 supply of radiopharmaceuticals.
 - 242 ○ V/Q SPECT-CT combines SPECT and CT imaging to generate both anatomic
243 and functional information and improve resolution of the scan. One drawback is
244 the exposure to ionizing radiation involved with both scans.
- 245 • Thoracic ultrasound utilizes ultrasonic waves emitted and received by a transducer in
246 combination with computerized analysis to generate images of chest structures. It is
247 widely available at low cost and is not associated with exposure to ionizing radiation, but
248 quality of the output is highly operator dependant and tends to be lower resolution than
249 the other modalities mentioned.⁴⁸ In practice, it is more likely to be used for the unstable
250 patient who may not readily be transferred to diagnostic imaging.

251

252 As highlighted, each of these imaging modalities has strengths and limitations, and the
253 appropriate modality may depend on the availability of the technology as well as expertise of
254 health care providers, adherence to acquisition protocols, and whether specific patient risk
255 factors (e.g., allergy to contrast dye) and clinical conditions (e.g., pregnancy) are present.¹ Not
256 all modalities are widely available or in routine clinical use in Canada and other developed
257 countries. This may be due to lack of availability or expertise, or practical considerations such
258 as increased time required and complexity of performing the exam.⁴⁹ For instance, MRI appears
259 to be utilized far less than CT. In one study, over a two year period, MRA exams accounted for
260 less than 6% of imaging studies conducted for the investigation of PE.⁵⁰

261
262 V/Q scintigraphy was the first validated non-invasive procedure for the diagnosis of PE,⁵¹ but CT
263 overtook it as the most frequently used imaging modality to diagnose PE in 2001.⁵² Although CT
264 is widely considered to be a more definitive test, a large multi-centre study reported that both CT
265 and V/Q imaging used in conjunction with clinical probability assessment, D-dimer, and lower-
266 limb ultrasound testing resulted in similar low rates of VTE events during three-month follow-
267 up.⁵³ Because CT is associated with exposure to ionizing radiation and iodinated contrast
268 agents (with the associated risk of malignancy and contrast allergy), there is concern about its
269 overuse.⁵⁴ A surge in CT use and improvements in technology have led to an observed
270 escalation in the diagnosis of PE (including sub-segmental PEs of unclear clinical
271 importance),^{52,53} but there is no evidence linking its increased use with improved patient
272 outcomes.⁵⁵⁻⁵⁷ Major technical advances in CT technology have led to the use of CTPA
273 combined with indirect CT venography, electrocardiogram (ECG)-gated CTPA, and dual
274 source/dual energy CTPA.⁵⁸ However, in patients with known allergy to contrast media, those
275 with severe renal failure, and pregnant women, alternative imaging modalities are often
276 considered, especially in the emergency setting.⁹

277 **Policy Issues**

278 Of the total population of patients who are evaluated for suspected PE, few are confirmed to
279 have the condition, indicating a low diagnostic yield of current evaluation methods.^{26,59} Studies
280 report a range of values for the diagnostic yield of CTPA, ranging from less than 5% to 30%,
281 depending on the clinical characteristics of the patient pool, and use of risk stratification
282 strategies.⁶⁰⁻⁶³ False-positive test results, which, depending on pretest probability,⁶⁴ can occur in
283 approximately 10% to 42% of patients⁶⁵ who undergo CT scanning, can lead to unnecessary
284 anticoagulation therapy. This carries a substantial risk of adverse effects including hemorrhage
285 (occasionally fatal), drug interactions, inconvenience associated with repeated blood tests
286 (possibly requiring time off work), implications for future dental and medical procedures, and
287 costs (both to the patient and society).⁶⁶ False-negative CT results, which also occur at high
288 frequency (e.g., 1% to 11%),⁶⁷ can lead to bypass of necessary treatment, complications, and
289 death.

290
291 The uncertain benefit of increased testing and the significant expense of PE could suggest that
292 current CT utilization patterns for the diagnosis of PE are not cost-effective.²² This is reflected in
293 the increased diagnosis of small or clinically insignificant PEs, which, if treated, may increase
294 costs and possible harms (e.g., risk of bleeding), and may not reduce morbidity or mortality.⁶⁸
295 This is supported by statistics suggesting that diagnosed cases of PE have significantly
296 increased in the US, but there has not been a corresponding drop in PE-related morbidity or
297 mortality.⁶⁹⁻⁷¹ In light of these concerns, it is important to assess whether there are other cost-
298 effective and safe alternatives.

299

300 The optimal diagnostic strategy for suspected PE among experts remains controversial,^{72,73} and
301 it can differ based on factors related to the health care setting (i.e., urban, rural, or remote) that
302 may impact access to imaging. The optimal diagnostic strategy would, in theory, be one that has
303 high diagnostic accuracy and clinical utility, at an acceptable cost. However, issues of access
304 may also influence what is considered optimal for different populations. For instance, provision
305 of timely diagnosis may be more challenging in rural and remote facilities due to lack of access
306 to certain testing and imaging modalities and specialist expertise, as well as geographical
307 barriers to care. Inability to access optimal diagnostic testing in a timely manner could increase
308 the risk for missed diagnoses, as well as unnecessary anticoagulation due to either false-
309 positives or long wait times to receive assessment.⁷ Patient safety concerns associated with
310 exposure to radiation and contrast media that accompanies several imaging studies also
311 disproportionately affect specific patient groups, including pregnant women, and young women
312 for whom the risk of breast cancer associated with radiation is higher.⁷

313 **Summary and Project Goals**

314 Patients with suspected PE should be assessed using appropriate diagnostic tests in a timely
315 manner.^{3,74} Timing of access to diagnostic test results may have a significant impact on the
316 management of the condition and the effective use of health care resources.⁷ The
317 heterogeneous clinical presentation of PE and lack of specific symptoms can lead to myriad
318 problems. These include the wide application of testing, which can be very costly and may result
319 in over-diagnosis, false-positives, and unnecessary treatment. Although guidelines for PE
320 diagnosis recommend the use of imaging tests,¹⁵ the optimal diagnostic strategy for suspected
321 PE remains uncertain,^{72,73} and it may vary depending on the health care setting due to access to
322 the technology. Thus, the goal of this health technology assessment (HTA) is to conduct an
323 assessment of the evidence to inform formulation of recommendations regarding the optimal
324 diagnostic strategy, including risk stratification, for acute PE in the current context of care,
325 considering benefits, harms, and costs, as well as patient experiences, implementation issues,
326 and environmental impacts.

327 **POLICY QUESTION**

328
329 What is the optimal diagnostic strategy for acute PE in urban, rural, and remote settings? (For
330 the purposes of this report, urban, rural and remote settings will be discussed in the context of
331 availability of testing modalities, geographical barriers and other accessibility concerns, and
332 types of institutions [i.e., primary care to tertiary care].)

333 **OBJECTIVES**

334
335 The objective of this HTA is to address the policy question through an assessment of the
336 diagnostic test accuracy, clinical utility, safety, cost-effectiveness, patient experiences and
337 perspectives, implementation issues, and environmental impacts of strategies for the diagnosis
338 of adults with suspected PE.

339 **RESEARCH QUESTIONS**

340

341 The HTA will address the following research questions. Details on the specific interventions and
342 outcomes are included in Table 1.

343

344 **Clinical**

345

346 To acknowledge the order of assessment in the diagnostic pathway (note: a diagnostic pathway
347 is defined for this report as a specific and deliberate sequence of assessments comprising
348 strategies for initial risk stratification and ultimate determination of disease positivity. This is
349 distinct from the use of the term “diagnostic imaging studies,” which applies only to CT,
350 magnetic resonance imaging [MRI], V/Q, PET-CT, and thoracic ultrasound-based studies used
351 to diagnose PE) for PE, the clinical research questions are ordered by intervention, starting with
352 risk stratification strategies, and followed by complete diagnostic pathways and diagnostic
353 imaging studies. This does not reflect the priority of the research questions.

354

355 **Risk Stratification Strategies**

- 356 1. What are the A) diagnostic test accuracy, B) comparative clinical utility, and C) safety of
357 Wells or Geneva clinical prediction rules for the risk stratification of adult patients
358 presenting with PE symptoms in urban, rural, and remote settings:
- 359 a. with or without the use of PERC
 - 360 b. with or without the use of D-dimer testing
 - 361 c. with or without the use of other biochemical or imaging risk stratification
362 strategies?
- 363

364 **Diagnostic Pathways and Diagnostic Imaging Studies**

- 365
- 366 2. What are the A) diagnostic test accuracy, B) comparative clinical utility, and C) safety of
367 diagnostic pathways including imaging studies for the diagnosis of PE in adult patients in
368 urban, rural, and remote settings?
 - 369 3. What are the A) diagnostic test accuracy, B) comparative clinical utility, and C) safety of
370 imaging studies for the diagnosis of PE in adult patients in urban, rural, and remote
371 settings?
- 372

373 **Cost-Effectiveness**

374

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

377

378 **Patient Experiences and Perspectives**

379

- 380 5. What are the experiences with the diagnostic process from the perspective of those who
381 have undergone testing for acute PE, as well as their family members and non-clinical
382 caregivers?
 - 383
 - 384 6. What are the experiences with diagnostic imaging technologies for hematological,
385 pulmonary, or cardiac conditions from the perspective of patients and their family
386 members and non-clinical caregivers?
- 387

388 **Implementation Issues**

- 389
390 7. What are the issues associated with implementing the optimal use of diagnostic
391 strategies, including imaging, for acute PE in adults in urban, rural, and remote settings?
392

393 **Environmental Impact**

- 394
395 8. What are the environmental impacts associated with the use of diagnostic pathways,
396 including imaging studies, for the diagnosis of PE in adults in urban, rural, and remote
397 settings?
398

399 **Ethics**

- 400
401 9. What are the key ethical considerations identified in the literature on strategies for
402 diagnosing acute PE?
403

404 Questions 1 through 3 were addressed through a SR of available clinical evidence, Question 1
405 by a SR of systematic reviews, and Questions 2 and 3 by a SR of primary studies. Question 4
406 was addressed through a primary economic evaluation. The questions related to patient
407 experiences and perspectives (5 and 6) were addressed through a rapid review of the relevant
408 qualitative literature. Implementation issues (question 7), and environmental factors (question 8)
409 associated with imaging for PE diagnosis were addressed through literature searches and
410 narrative summaries. Question 9 on ethics was completed through an ethics analysis based
411 primarily on the bioethics literature.

412 **METHODS**

413

414 **CLINICAL REVIEW**

415

416 **Search Strategy**

417

418 The literature search was performed by an information specialist, using a search strategy peer-
419 reviewed according to the PRESS checklist - an evidence-based checklist for the peer review of
420 electronic search strategies.⁷⁵

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

429 Methodological filters were applied to limit retrieval to HTAs, SRs, meta-analyses (MAs),
430 network meta-analyses, and overviews of reviews. Retrieval was limited to documents

431 published since Jan 1, 2011. The search was also limited to English- or French-language
 432 publications. Conference abstracts were excluded from the search results. The detailed strategy
 433 can be found in Appendix 1.

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

441 Methodological filters were applied to limit retrieval to randomized controlled trials (RCTs) and
 442 non-randomized studies. Retrieval was limited to documents published since Jan 1, 2006. The
 443 search was also limited to English- or French-language publications. Conference abstracts were
 444 excluded from the search results. The detailed strategy can be found in Appendix 1.

445 The searches were completed on September 13, 2016. Regular alerts were established to
 446 update the searches until the publication of the final report. Regular search updates were
 447 performed on databases that do not provide alert services. Studies identified in the alerts and
 448 that met the selection criteria of the review were incorporated into the analysis if they were
 449 identified prior to the completion of the stakeholder feedback period of the final report. Any
 450 studies that were identified after the stakeholder feedback period were described in the
 451 discussion, with a focus on comparing the results of these new studies to the results of the
 452 analysis conducted for this report.

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

Table 1: Selection Criteria for Clinical Research Questions

Population	
Q1 to 3: Adult patients ≥ 18 years undergoing testing for acute PE ^a <u>Subgroups of interest:</u> <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • Composite reference standard (must include advanced diagnostic imaging tests [e.g., multidetector CT]) Q1 A, B, and C: <ul style="list-style-type: none"> • Any alternative clinical decision rule or modified or tailored tool (e.g., Wells, Geneva, or other) ± PERC criteria ± D-dimer ± additional biochemical or

Table 1: Selection Criteria for Clinical Research Questions

	<p>imaging-based risk stratification strategies^c</p> <ul style="list-style-type: none"> No clinical rule (Gestalt)
Q2 and 3: Diagnostic Imaging	
<p>Q2: Any of the below interventions, including at least 1 of any clinical decision rule, and/or biochemical or imaging-based risk stratification strategy)^c</p> <p>Q3: Any of the following imaging studies</p> <ul style="list-style-type: none"> CT technologies^d MRI technologies V/Q-based technologies^e PET-CT Thoracic ultrasound (+ echocardiography) 	<p>Q2 and 3A:</p> <ul style="list-style-type: none"> Composite reference standard (must include advanced diagnostic imaging tests [e.g., multidetector CT]) <p>Q2 and 3 A, B, and C:</p> <ul style="list-style-type: none"> Any alternative diagnostic imaging exam (± clinical decision rule ± biochemical or imaging-based risk stratification strategies)
Outcomes^f	
<p>Q1 to 3:</p> <p>A) Diagnostic test accuracy (i.e., sensitivity, specificity, PPV, NPV, PLR, NLR, DOR, AUROC, Youden's Index)</p> <p>B)</p> <p><u>Primary:</u></p> <ul style="list-style-type: none"> Clinical utility (failure rate [i.e., morbidity and mortality due to misdiagnosis at 30 days' follow-up])^g <p><u>Secondary:</u></p> <ul style="list-style-type: none"> Clinical utility (e.g., efficiency,^h identification of patients with different diagnoses, change in referring physician's diagnostic thinking, change in patient management, change in patient outcomes) <p>C) Harms (safety outcomes of imaging procedures [e.g., radiation exposure, CT-attributed malignancy, contrast nephropathy, patient discomfort, allergic reactions])</p>	
Study design	
<p>Q1: SRs with or without an MA, HTAs</p> <p>Q2 and 3:</p> <p>A) Diagnostic test accuracy outcomes: RCTs and non-randomized studies (i.e., controlled clinical trials, cohort studies, and cross-sectional studies)</p> <p>B) Clinical utility outcomes: RCTs and non-randomized controlled studies (i.e., controlled clinical trials, cohort studies, controlled before-and-after studies, and case-control studies)</p> <p>C) Safety outcomes: in addition to the above-mentioned study designs, non-randomized studies without a control group (excluding non-sequential case series and case reports) will also be included</p>	
Timeframe	
<p>Q1: Publications within the last 5 years (i.e., between January 2011 and September 2016)</p> <p>Q2 and 3: Publications within the last 10 years (i.e., between January 2006 and September 2016)</p>	

460 ± = with or without; AUROC = area under the receiver operating curve; COPD = chronic obstructive pulmonary disease; CT =
461 computed tomography; CTA/CTV = computed tomographic angiography in combination with venous-phase imaging; DOR =
462 diagnostic odds ratio; DVT = deep vein thrombosis; HTA = health technology assessment; ICU = intensive care unit; MA = meta-
463 analysis; MRI = magnetic resonance imaging; NLR = negative likelihood ratio; NPV = negative predictive value; PE = pulmonary
464 embolism; PET-CT = positron emission tomography – computed tomography; PLR = positive likelihood ratio; PPV = positive
465 predictive value; RCT = randomized controlled trial; SPECT = single-photon emission computed tomography; SR = systematic
466 review; V/Q = ventilation-perfusion.
467 ^a Excluding pediatric patients, patients with recurrent VTE, and patients with suspected DVT.
468 ^b For the purposes of this HTA, the term “risk stratification” refers to the determination of the likelihood of PE, rather than the
469 likelihood of adverse events or mortality resulting from PE.
470 ^c Leg compression ultrasound, capnography, electrocardiography, echocardiography, chest radiograph.
471 ^d Excluding single-detector, including CTA/CTV and triple-rule-out CT.
472 ^e Including planar V/Q scan, V/Q SPECT, V/Q SPECT-CT.
473 ^f No restriction on length of follow-up.
474 ^g Morbidity and mortality due to misdiagnosis such as A) morbidity and mortality in false-negative patients (the proportion of patients

475 classified as having low risk of PE who receive an ultimate diagnosis of PE based on the reference standard [false-negatives/true-
476 negatives + false-negatives], and B) risk of bleeding in false-positive patients who receive anticoagulation treatment.
477 ^hThe proportion of patients in the study cohort stratified to the group with low predicted probability of PEs (sum of true- and false-
478 negatives/total cohort).

DRAFT

Study Design

Risk Stratification

Systematic reviews were considered for inclusion if they examined the clinical probability of pulmonary embolism in adult patients using the Wells rule or the Geneva score. Eligible SRs were those that evaluated the Wells rule or the Geneva score and reported general findings specific to the individual CDRs. Therefore, SRs that examined CDRs in general, without specifying Wells or Geneva, or SRs that reported general findings without specific assignment to the Wells rule or the Geneva score were excluded. Systematic reviews which focused on PERC or D-dimer testing alone or without specifying the accompanying CDR were also excluded. Since some of the above exclusion criteria would have removed studies that would provide relevant inputs to the support the parameterization of the economic model (ECONOMIC REVIEW), the systematic reviews that do not meet the inclusion criteria for the overview of reviews but were identified relevant to the economic model are summarized in Appendix 22. Studies in a pediatric population were excluded.

To be included for research question 1, 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. Also, the literature search for the SR must have covered at least two electronic sources, adequately reported years searched and databases used, key words or MeSH terms, and where feasible, provided the search strategy). The included primary studies of the SRs must have been assessed for quality or risk of bias, and their findings synthesized quantitatively or qualitatively.

SRs were excluded if they did not meet the selection criteria outlined in Table 1 or if they were duplicate publications, or published before 2011. Multiple publications of the same SR were excluded unless they provided new outcomes of interest.

Diagnostic Pathways and Diagnostic Imaging Studies

Research questions 2 and 3 were addressed by a de novo systematic review of primary studies, studies were excluded if they did not meet the selection criteria outlined in Table 1, if they were case reports or case series, or if they are duplicate publications. 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 duration of time between symptom presentation and assessment, or length of follow-up. Studies were excluded if they are 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. Further, conference abstracts, published thesis documents, and evidence that was 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 SRs identified by the search. Either reviewer had to deem a citation to be potentially eligible for it to

be reviewed in full. 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 consensus. The study selection process is outlined in Appendix 7.

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 2. Articles were referred for full text review if any author considered them to be potentially eligible. Two reviewers then independently reviewed the full-text articles based on the pre-determined selection criteria outlined in Table 1 and in Appendix 2. The two reviewers then compared their included and included 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 is presented in Appendix 2.

The overall study selection process for all questions is presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart,⁵ which is presented in Appendix 7. A list of excluded studies, with reasons for exclusion after full-text review, can be found in Appendix 9. Characteristics of included studies are presented in Appendix 15 and Appendix 19 (for studies in pregnancy).

Data Extraction

Standardized data extraction forms (Appendix 3 and 4) were designed a priori to document and tabulate all relevant information from included studies. After piloting of pairs of randomly selected included studies by three pairs of reviewers, items 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 SRs, 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 included study and patient characteristics, technical characteristics of index and reference tests, and utility and safety data.

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 diagnostic test accuracy data was extracted. This included studies where,

- 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,⁷⁶ designed to assess the risk of bias in SRs of RCTs and non-randomized studies was used. Although the results of the methodological assessments were not used to exclude the included SRs, the conclusions and discussion of the final report focus on the findings of the SRs of higher quality.

Two reviewers piloted the quality assessment tool on two randomly chosen studies and, once consistency in assessments was reached, independently assessed the methodological quality of half of the remaining studies. Once complete, 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,⁷⁶ the SRs were assessed using the following four items from AMSTAR:

- a. Was the status of publication (i.e. grey literature) used as an inclusion criterion?
- b. Was a list of included studies provided?
- c. Was a list of excluded studies provided?
- d. 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).⁷⁷ RCTs addressing clinical utility or safety outcomes were assessed using the Cochrane Risk of Bias Tool.⁷⁸ Clinical non-randomized controlled studies were assessed using the Risk of Bias Assessment Tool for Nonrandomized Studies (ROBINS-I).⁷⁹ Non-randomized studies without a control group, which were eligible if they reported safety endpoints only, were addressed using the checklist developed by Moga et al.⁸⁰

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. A list of questions from the Cochrane, ROBINS-I, Moga and QUADAS II-II tools can be found in Appendix 10.

Summary of Evidence

Description of Study Characteristics and Findings

Risk Stratification

Data captured about the study characteristics covered the total number and designs of SRs, years of publication, and countries of development, as well as the patients (population) included in each SR, the interventions evaluated, the comparator and/or references, and the reported outcomes. A table of all the primary studies of the included SRs was prepared showing which had overlapped among the SRs. The relevant diagnostic accuracy and utility outcomes of the

risk stratification strategies evaluated by the SRs were recorded and reported. A summary of the characteristics of the included SRs and the findings have been provided in tabular form and described narratively.

Diagnostic Pathways and Diagnostic Imaging Studies

A summary of primary study characteristics — including the total number of studies by PICOS elements, and countries and years of publication — was 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 within the respective assessment tools are presented in the text and appendix as figures and tables.

Data Synthesis Methods

Risk Stratification

A narrative synthesis of the results of included SRs 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 SRs, 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. This was intended to accompany the narrative summary, to ensure consistency of presented information across all included SRs and to facilitate comparisons by the reader. Results were synthesized by outcome for the overall study population, and also for each subgroup listed in Table 1, if available.

Statistical Analysis

Data Synthesis Methods

The results of studies included for questions addressed by a SR of primary studies (questions 2 and 3) were pooled using MA, if appropriate. The decision 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 the 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, analysis were conducted for the overall study population and also for each subgroup listed in Table 1, as the data permitted.

Meta-Analysis of Diagnostic Test Accuracy Studies

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 τ^2 , the credible intervals of the summary estimates of sensitivity and specificity, and the point estimates and credible intervals of a new 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 between heterogeneity.⁸¹⁻⁸³ A marked difference between the credible intervals of the pooled estimate and of the predicted new study indicates substantial heterogeneity, although there are at this time no standard measures of heterogeneity in DTA studies.⁸¹ 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 the PICO. The combined list is:

- High versus low risk of PE
- Pregnant women
- Cancer patients
- Hemodynamically unstable versus stable
- OC or HRT users
- Obese patients
- Renal insufficiency
- Existing pulmonary disease (COPD)
- Elderly patients
- Access to imaging versus no access
- Inpatient versus ED 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.

Previous meta-analyses used models that assumed a perfect reference standard across all studies put forward for pooling, regardless of the reference standards used.^{67,84-86} Based on the studies that they included, 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 Gatsonis⁸⁷ that accommodates imperfect and composite reference standards.^{82,88} 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 combined tests, acknowledging evidence that suggests the results may be affected if test results correlated within positive and negative strata.^{89,90}

We also chose to pool studies using alternative statistical models (e.g. bivariate/Reistma, HSROC assuming preference reference) for comparison with published results; the results of these appear in Appendix 21.

Summaries of study characteristics, graphical explorations of heterogeneity and display of results were conducted using the statistical software R.⁹¹ DTA meta-analyses were conducted in WinBUGS⁹² using programs supplied by Dr. Nandini Dendukuri (<http://www.nandinidendukuri.com/software>). The bivariate model was run using R with package *mada*.⁹³ Details of all models and data are in the Statistical Appendix, Appendix 21.

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,⁹⁴ was to synthesize pooled risk ratios and odds ratios for comparative data for utility endpoints, 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 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% confidence interval were therefore calculated, by preference. Where comparative data were not available, utility data were synthesized as single proportions, e.g., proportion of patients with failure at 3 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*.⁹⁵ Cochran's Q test statistic was based on a level of statistical significance of $p=0.1$.

For most endpoints, sparse data limited the planned exploration of heterogeneity by subgroup (as prespecified 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 non-randomized studies reported on the same outcome, RCTs were considered separately from non-randomized studies. The small number of RCTs meant that this comparison was narrative. MAs were carried out using R with package *metafor*.⁹⁶

Where pooling was not indicated, a narrative synthesis was conducted, with the intent of synthesizing the direction and size of any observed effects across studies, and to assess the likelihood of clinical benefit or harm.

Given the sparse and uncontrolled 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.⁹⁴

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 at two levels. They were made up 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 grey literature search. Of the 50 full-text publications, six unique SRs^{24-26,97-99} were selected for inclusion while 44 were excluded for various reasons. The study selection process is outlined in Appendix 7. The degree of overlap between the included SRs with respect to primary studies was judged by building a matrix of primary studies included in the SRs (Appendix 8). A list of excluded studies, with reasons for exclusion, has been provided in Appendix 9.

For research question 1, a total of six SRs regarding the DTA, comparative clinical utility, or safety of strategies for the risk stratification of adult patients with suspected PE were identified. Four of the SRs^{24-26,98} reported that they included prospective and retrospective cohorts studies, while two SRs^{97,99} did not report the designs of their included primary studies (Appendix 11). One of the eight primary studies in the SR by Wang et al.²⁵ was a randomized controlled study.

Description of included Systematic Reviews

The six included SRs^{24-26,97-99} had a total of 82 unique primary studies, with thirteen of them included in multiple SRs (Appendix 8). One of these overlapping studies was included in three SRs,^{24,26,99} while each of the remaining 12 was included in two different SRs. The reviews by Siccama, 2011⁹⁷ and Wang, 2016²⁵ had no overlap of primary studies, with each including studies that were unique to them (Appendix 8).

The characteristics of the included SRs have been summarized in Appendix 11. Five of the six SRs reported that the primary studies they included were conducted in hospital settings and included emergency department (ED) patients, inpatient, or outpatients. The SR by Shen et al.²⁴ did not report information about the settings of its primary studies. Three SRs^{24,26,98} provided clear data about patients' ages while three did not.^{25,97,99} For SRs which stated ages, the mean

age of included patients ranged from 45 to 76.1 years. A summary description of the characteristics of the individual SRs is as follows.

Shen et al., 2016²⁴ assessed the diagnostic test accuracy of the 3-level Wells score and the 3-level Geneva score in a total of 3,613 patients with suspected pulmonary embolism (PE) in nine prospective and three retrospective cohort studies (Appendix 11). For each of the two clinical prediction rules, the probability of a patient being diagnosed with PE was classified into low, medium, and high. Patients assessed with the Wells rule were considered to have a low probability of PE if the score was <2.0 , moderate if the score was between 2.0 and 6.0, and high if the score was >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 and 10 points and high if the score was ≥ 11 points.

Lucassen et al., 2011²⁶ assessed diagnostic accuracy, and utility of the dichotomized Wells score, the dichotomized Geneva score, and clinical judgment (gestalt) in a total of 55,268 patients with suspected PE in 52 prospective cohort studies (Appendix 11). For the Wells rule, data were reported for cut-off <2 (Wells <2) and the Wells rule with cut-off ≤ 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 CDRs alone, and utility outcomes were reported when the CDRs were combined with a D-dimer test to rule out PE, following which patients were excluded from imaging or anticoagulation therapy.

Siccama et al., 2011⁹⁷ evaluated the diagnostic accuracy and safety of the Wells, the Geneva score, and the revised Geneva score in a total of 6,739 patients with suspected PE in nine primary studies (Appendix 11). The design of the included primary studies was not reported, and the cut-off scores of the CDRs were not specified.

Nine of the 31 primary studies in the SR by Sanders et al., 2015⁹⁹ 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 11). The remaining primary studies ($n=22$) of the SR⁹⁹ evaluated CDRs in different 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 comparison and was variously reported as $<15\%$ or $<20\%$, or without a numerical value as “low” or “alternate diagnosis not less like.”

Van Es et al.⁹⁸ 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 11). Outcomes were reported separately for strategies based on the conventional D-dimer assay with a fixed cut-off of 500 $\mu\text{g/L}$ and for the age-adjusted D-dimer testing in which the cut-off changes according to the patients' age (age $\times 10$ $\mu\text{g/L}$). Imaging and anticoagulant therapy were withheld in patients who had a Wells score ≤ 4 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 Wells score >4 or a Wells score ≤ 4 and a positive D-dimer. The age-adjusted D-dimer threshold was applied only in patients who were 50 years or older.

Wang et al., 2016²⁵ 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 non-randomized studies (Appendix 11). 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 3-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 SRs, the outcomes of the Charlotte rule or a stand-alone PERC are not of interest and have not been discussed.

Methodological quality of included SRs

Five SRs^{24,26,97-99} included in this overview evaluated their primary studies for quality or risk of bias with the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) instrument while one SR²⁵ performed a similar assessment using the Cochrane Group Effective Practice and Organization of Care instrument.

Overall most of the included SRs had a "Yes" or "Probably Yes" score across all the domains, indicating a very low or low potential bias (Appendix 10). All the SRs scored well with regards to study eligibility and criteria. Most concerns for the high or very high potential for bias were related to items in domain 4 (synthesis and findings) and is due in large part to two SRs.^{24,97} In addition to the ROBIS tool, selected items from the AMSTAR checklist were applied to evaluate the included SRs on some aspects of reporting, including the declaration of sources of potential conflicts of interest. All the included SRs listed their included primary studies, and all but one provided statements of potential conflicts interest. One SR⁹⁸ provided a list of excluded studies. Tables 3 summarized the results of the risk of bias assessment of the studies.

Outcomes of included Systematic Reviews

For the diagnostic accuracy, outcomes measures of interest were sensitivity and specificity. The yield, failure rate, and efficiency were outcome measures of utility of a diagnostic strategy. Broadly, the yield of an imaging modality referred to the proportion of studies with positive results for PE among all studies. The failure rate of a risk stratification strategy referred to the proportion of missed PE as determined by confirmed VTE or sudden unexplained death among patients who were excluded from imaging or anticoagulation based on a negative result of the strategy, during the follow-up period. The efficiency of a risk stratification strategy was defined as the proportion of suspected PE patients in whom imaging and anticoagulation therapy were withheld because the diagnosis of PE was ruled out by the strategy. Four SRs^{24,26,97,99} reported diagnostic accuracy outcomes. Four SRs^{25,26,98,99} reported utility outcomes, including two which also reported diagnostic accuracy outcomes..

Diagnostic Accuracy Findings

Four SRs^{24,26,97,100} reported diagnostic accuracy finding for clinical prediction rules which were not combined with D-dimer (Appendix 12).

Sensitivity and Specificity of 3-level Wells rule and 3-Level Geneva score

A SR of nine prospective cohort and three retrospective cohort studies (n=3,613 patients) found that the sensitivity of the 3-level Wells rule ranged from 63.8% to 79.3% compared with 55.3% to 73.6% for the 3-level revised Geneva score. The corresponding specificity values ranged 48.8% to 90.0% for 3-level Wells rule compared with 51.2% to 89.0% for the revised Geneva score. An SROC meta-analysis using a random-effect model showed that the diagnostic accuracy of the 3-level Wells rule was higher than the 3-level revised Geneva score. The Wells rule had an overall weighted AUC of 0.778 (95% confidence interval [CI]: 0.740 to 0.818) versus 0.693 (95% CI: 0.653 to 0.736) for the revised Geneva score (Appendix 12).

Sensitivity and Specificity of Dichotomized Wells rule and Dichotomized Geneva score

One meta-analysis²⁶ and one SR⁹⁹ reported outcomes for the dichotomized Wells rule and the dichotomized Geneva score. Overall, the sensitivity Wells <2 ranged 62% to 95% with its specificity ranging from 19% to 75%. The sensitivity of the revised Geneva score ranged 89% to 91% with specificity ranging from 33% to 37%. Further details are available in Appendix 8.

One SR⁹⁷ 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 <65 years to 22% in patients >75 years (Appendix 12). The authors did not specify whether the index CDR was the 3-level or the dichotomized Wells rule.

The SRs reported pooled sensitivities and specificities without specifying the nature of the correlation between these two measures. To support the data requirements to conduct a probabilistic economic evaluation (ECONOMIC REVIEW), the 2x2 tables from individual studies identified in select systematic reviews^{26,101} were retrieved and the data were meta-analyzed using a bivariate model that assumed perfect reference standards. Details of these additional analyses are presented in Appendix 22.

Utility Findings for the Wells and the Geneva Scores

Four SRs^{25,26,98,99} reported utility outcomes (yield, failure rate, and efficiency) for strategies involving CDRs and D-dimer testing (Appendix 13).

Yield of CTPA

In a pooled analysis of four before-and-after cohort studies (n=4,788), one SR²⁵ found that strategies which combined the Wells rule with D-dimer tests showed a CT yield of 12% compared to 9% for usual care where clinical decision support was not applied. Thus incorporating the decision support into the diagnostic strategy resulted in a 3% increase in the CT yield (Appendix 13).

Failure rate and efficiency of strategies combining CDR and quantitative D-dimer to rule out PE

One SR with meta-analysis²⁶ of prospective cohort studies reported that the failure rate and efficiency of strategies combining quantitative D-dimer testing with Wells ≤ 4 to rule out PE were 0.5% and 39%, respectively (4 studies). The failure rate was zero when the strategy combined quantitative D-dimer testing with the Geneva score, and 0.3% when combined with the

simplified Geneva score (2 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 CDR and qualitative D-dimer to rule out PE

One SR with meta-analysis²⁶ of prospective cohort studies reported that the failure rate and efficiency of strategies combining quantitative D-dimer testing with Wells <2 to rule out PE were 0.9% and 40%, respectively (4 studies). When Wells ≤4 was used in a similar strategy, the failure rate and efficiency were 1.7% and 42%, respectively (Appendix 13). There was no strategy combining qualitative D-dimer testing with the Geneva scores or revised Geneva score

Failure rate and efficiency of CDR without D-dimer to rule out PE

One SR⁹⁹ of seven studies (designs not specified) found that the failure rates and efficiency of Wells <2 to rule out PE ranged from 3.0% to 27.9% and from 17% to 73%, respectively. The the same SR,⁹⁹ the failure rates of Wells ≤4 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 PE

One SR⁹⁸ of six prospective cohort studies (n=7,268) reported that in combination strategies based on Wells ≤4, the overall failure rate was 0.65% with a fixed threshold D-dimer tests (cut-off 500µg/L) compared with 0.94% when the age-adjusted D-dimer tests were used (cut-off age X 10µg/L). The confidence intervals indicate that the failure rate did not reach the level of significance in either case (Appendix 13). 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 13). 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. Using a full random effect model and adding subgroup indicators as covariates, the investigators calculated the failure rates and efficiency of pre-specified subgroups, including age 51 to 74 years, age 75 years or older, patients with cancer, and patients with COPD.

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 to 2.1% in patients aged ≥75 years. Failure rate estimated were not calculated by age subgroups in the fixed D-dimer strategy. For patients with cancer, failure rate decreased from 2.6% with fixed threshold D-dimer to 1.45 when the age-adjusted was applied. However, in patients with 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 unclear.

Efficiency in subgroups

There was no difference in efficiency among patients aged ≤50 years regardless of whether the fixed threshold or the age-adjusted D-dimer test was used. However, in patients aged ≥75 years, 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, as well as those with cancer or COPD the age-adjusted D-dimer testing can increase the proportion of patients in whom imaging can be withheld safely.

Summary of findingsThe following are the summary findings from the individual SRs included in the overview without pooling.

The diagnostic accuracy scores of the CDRs

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

In all comparisons, 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 SR²⁶ which had data on all four, revised Geneva showed the highest sensitivity while the Wells ≤ 4 had the lowest, and Wells < 2 and Geneva tied in the middle.

The utility outcomes of CDR-based diagnostic strategies

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

Question 2. Diagnostic test accuracy

This section and the next (Question 3, utilities) includes the results of studies in non-pregnant patients, or studies which included very few pregnant patients and did not report pregnancy-specific outcomes. The results of studies specifically in pregnant patients are reported in a separate section of PE imaging in pregnancy (page 77).

Quantity of Research

For research questions 2 and 3, a total of 5455 citations were identified through the original database search (n = 4983), supplemental search (n = 352), and search alerts (alert 1: n = 61, alert 2: n = 57). After removal of duplicates and additional of records identified through other sources (n = 4) 5420 records remained. Of these 5420 articles, 5047 were excluded during screening of titles and abstracts and 373 full-texts were retrieved for review. Of these, 262 did not meet the inclusion criteria, leaving a total of 111 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 7.

Of the 111 studies, 70 reported diagnostic test outcomes for single imaging modalities, particularly CT, MRI, US, Q, Q-SPECT, Q-SPECT-CT, VQ, VQ-SPECT, and VQ-SPECT-CT, and combinations of modalities, specifically CT with CTV, MRI with MRV, and MRI with VQ. No diagnostic test accuracy (DTA) outcomes were available for pathway studies; these reported utility data only (see Results for Question 3, page 60). The remaining 45 studies reported utility or safety outcomes only, and are described in the section on utility and safety (page 60), or recruited pregnant or post-partum patients only, and are described in the section on PE imaging in pregnancy (page 77).

Table 2 shows the matrix of counts for comparisons of index and reference modalities for DTA studies, following classification of index and reference tests. Studies may have included more than one comparison, so the total number of comparisons may be greater than the number of studies in the pool.

Results for individual modalities (and combined modalities) follow.

Table 2 Matrix of counts for comparisons of index and reference modalities

Index	CC	CT	MRI	MSC	PA	SC	Sequential	VQ	VQ-SPECT	VQ-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-VQ	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
VQ	9	1	1	0	3	1	0	0	0	0	15
VQ-SPECT	6	5	0	0	0	1	0	4	0	0	16
VQ-SPECT-CT	0	1	0	0	0	0	0	0	3	0	4

^a Figures in brackets indicate the number of studies, where they differ from the number of contrasts

Abbreviations: CC = complex composite – comparator including imaging in combination with D-dimer; CT = computed tomography; CT-CTV = computed tomography and computed venous tomography; MRI = magnetic resonance imaging; MRI-MRV = magnetic resonance imaging and magnetic resonance venography; MRI-VQ = magnetic resonance imaging combined with ventilation-perfusion imaging; Q = perfusion imaging; Q-SPECT = perfusion-only SPECT; PA = pulmonary angiography; Q-SPECT = perfusion-only SPECT-CT; VQ = ventilation-perfusion planar scintigraphy; VQ-SPECT = ventilation-perfusion SPECT; VQ-SPECT-CT = ventilation perfusion SPECT-CT; SC = simple composite, only imaging modalities; Sequential = combination of imaging modalities used in sequence.

Pathways

No studies were found that reported DTA data for pathways against eligible comparators.

Computed Tomography

Sixteen studies reported DTA outcomes for CT.^{64,102-116}

Study and patient characteristics

Study information is summarized in **Table 3**, and detailed study characteristics are provided in Appendix 15.

Study design

One study was an RCT,¹⁰² and the rest were non-randomized studies.^{64,103-116}

Country and setting

Five studies were multi-centre, conducted in Denmark,¹¹¹ Sweden,¹⁰⁷ China,¹¹⁴ and in Canada and the US.^{64,116} The remaining studies were single-centre,^{102-106,108-110,112,113,115} Of these, two

were conducted in China,^{102,104} two in France,^{108,115} two in Germany,^{103,105} two in the US,^{106,117} one in each of Belgium,¹⁰⁹ Japan,¹¹² Switzerland.¹¹³ Four studies were conducted in a secondary setting,^{102,108,114,115} four in a secondary or tertiary setting,^{64,110,111,116} one in a secondary centre ER setting,¹⁰⁹ one in a tertiary centre / ER setting,¹¹³ and one in a secondary / tertiary ER setting.¹⁰⁶ Five studies did not specify the study setting.^{103-105,107,112}

Funding

Five studies had government/institutional funding,^{64,102,107,114,116}, one declared no funding,¹¹² and one had private funding.¹¹³ Nine reports did not declare the funding source.^{103-106,108-111,115}

Population

Studies recruited between 15¹⁰³ and 824 participants,^{64,116} although not all patients were represented in the final diagnostic 2x2 table (**Table 3**). The most common reason for exclusion from the 2x2 table was a non-diagnostic reference test result, meaning that patients could not be classified as cases and non-cases. Mean age ranged from 49.5 (SD 15)¹⁰⁷ to 66.1 years (SD not given),¹¹¹ and the sex distribution from a proportion of females 0.46¹⁰³ to 0.73¹¹¹. Four studies recruited a mixture of inpatient and outpatients,^{64,108,115,116} two selected outpatients,^{102,113} one selected a mixture of outpatients, inpatients, and patients presenting at the ER,¹⁰⁶ and one each selected inpatients¹¹⁰ outpatients and patients presenting to the ER,¹⁰⁹ and patients presenting to the ER alone.¹⁰⁷ One did not specify patient status.¹¹⁴ 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.^{64,104,108,109,113-116}

Comparators

Comparators were CC,^{102-105,112-115} PA,¹⁰⁶⁻¹⁰⁸ SC,^{64,109,116} VQ-SPECT,^{110,111} VQ-SPECT-CT.^{103,111} Studies could report more than one comparison.

Technical characteristics

The number of CT detectors ranged from 2¹⁰⁸ to 64,¹⁰² and was not reported in six articles.^{103,105,107,110,111,114} Two studies used dual energy sources.^{102,103}

Table 3 Summary of study information for CT

Study	Reference (composition of composite)	Diagnostic N	Mean age (years)	Risk of PE	Number of detectors
Lu 2014 ¹⁰²	CC (Consensus reading, history, clinical data, supplementary imaging)	50	53.5	Not reported	64
Reinartz 2004 ¹⁰⁵	CC (VQ, PA)	83	53.9	Mixed	Not reported
Thieme 2012 ¹⁰³	CC (Clinical, VQ-SPECT-CT), VQ-SPECT-CT	15	64.0	Not reported	Not reported
Wang 2009 ¹⁰⁴	CC (Consensus reading, all available)	75	51.0	Mixed	16
Okada 2015 ¹¹²	CC (CT)	83	64.5	Not reported	64
Megyeri 2014 ¹¹³	CC (CT, US, VQ)	137	58.6	Mixed	16
He 2012 ¹¹⁴	CC (CT, VQ, PA, leg US)	544	53.3	Mixed	Not reported
Blanchere 2000 ¹¹⁵	CC (CT, VQ, PA, US)	179	61	Mixed	4
Nilsson 2002 ¹⁰⁷	PA	90	49.5	Not reported	Not reported
Qanadli 2000 ¹⁰⁸	PA	151	58.0	Mixed	2
Winer-Muram 2004 ¹⁰⁶	PA	93	54.8	Not reported	4
Coche 2003 ¹⁰⁹	SC (VQ, DSA, CXR)	94	62.0	Mixed	4
Stein 2006 ⁶⁴	SC (CT, PA)	773	51.7	Mixed	4, 8, 16
Stein 2007 ¹¹⁶	SC (CT, PA)	773	51.7	Mixed	4, 8, 16
Mahdavi 2016 ¹¹⁰	VQ-SPECT	60	60.0	Not reported	Not reported
Gutte 2009 ¹¹¹	VQ-SPECT, VQ-SPECT-CT	81	66.1	Not reported	Not reported

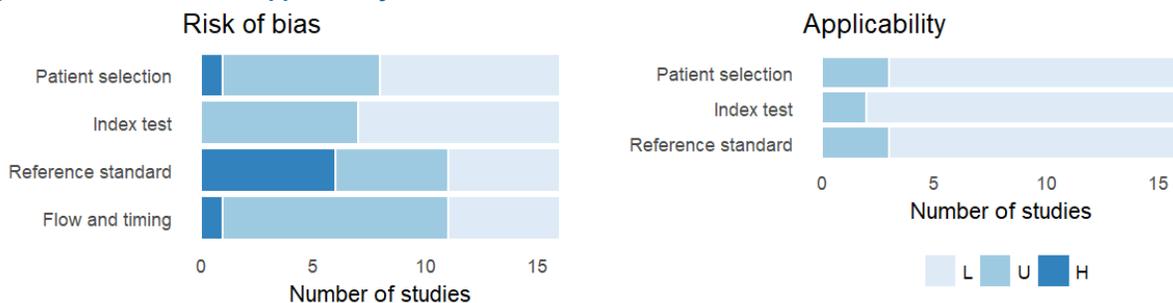
Abbreviations: CC = complex composite – comparator including imaging in combination with D-dimer; CT = computed tomography; CXR = chest X-ray; DSA = digital subtraction angiography; PA = pulmonary angiography; VQ = ventilation-perfusion planar scintigraphy; VQ-SPECT = ventilation-perfusion SPECT; VQ-SPECT-CT = ventilation perfusion SPECT-CT; SC = simple composite, only imaging modalities.

Quality appraisal

Figure 1 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, where the sequence of testing was frequently unclear. 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 high risk of bias for the reference standard, and have subsequently been excluded. Studies were generally applicable in patient selection, index test, and reference standard.

Figure 1 Risk of bias and applicability for all studies with CT as an index test



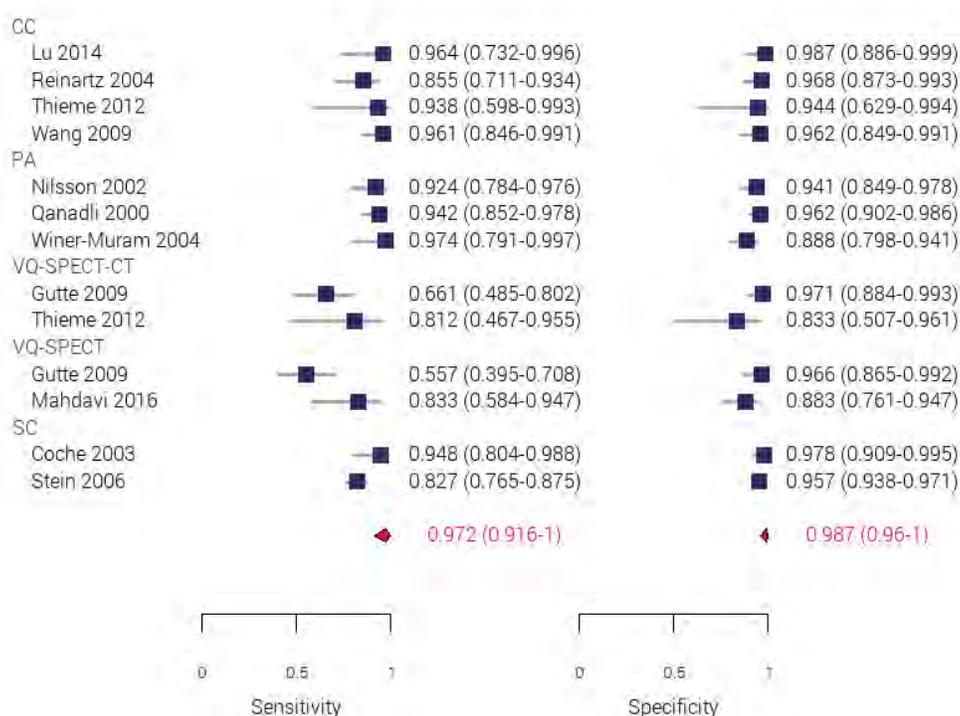
Detailed presentations of responses to individual signalling questions by study are shown in Appendix 16.

Summary of diagnostic test results

Of the sixteen studies, one was a post-hoc analysis of an included study, and was excluded from the overall pool but provided subgroup information.¹¹⁶ Four studies featured one or more comparisons where the index test was included in the reference assessment. These comparisons were excluded from the meta-analysis.¹¹²⁻¹¹⁵

The forest plot for the sensitivity and specificity for all included studies is shown in **Figure 2**, grouped by reference standard, and ordered by the frequency with which the reference standard appears.

Figure 2 Forest plot for studies with CT as index test



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

Abbreviations: CC = complex composite – comparator including imaging in combination with D-dimer; PA = pulmonary angiography; VQ-SPECT = ventilation-perfusion SPECT; VQ-SPECT-CT = ventilation perfusion SPECT-CT; SC = simple composite, only imaging modalities.

For patients in whom imaging was considered diagnostic, the overall pooled sensitivity with adjustment for imperfect reference standard, is 0.972 (95% CrI 0.916 to 1.00) and the pooled specificity is 0.987 (95% CrI 0.960 to 1.00). Therefore, of 1000 patients, 150 of whom had PE,¹¹⁸ an average of 4 patients (range 0 to 13) would receive a false negative diagnosis and would be at risk of recurrent PE, and an average of 11 patients (range 0 to 34) would receive a false positive diagnosis and would be at risk of complications (bleeding) from unnecessary treatment.

Heterogeneity

Both the forest plot above and ROC scatterplots of sensitivity versus 1-specificity (Appendix 21) 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 (another indication of heterogeneity) was wider for sensitivity (0.950 (95% CrI 0.718 to 1.00)) than for specificity (0.971 (95% CrI 0.810 to 1.00)).

There was 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 (inpatient, outpatient, ED), and PE risk, there was insufficient variation between studies for statistical adjustment (Appendix 21). 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,¹¹⁶ gender,¹¹⁶ prior PE risk,^{64,114} and body weight.¹¹³ With the exception of one study that found a statistically significant difference of gender on specificity,¹¹⁶ there were no studies that reported statistically significant effects of covariates on diagnostic performance. Detailed results appear in Appendix 20.

Computed Tomography and Computed Venous Tomography

One non-randomized multicentre study compared the composite of CT and CTV with a simple composite.⁶⁴

Study and patient characteristics

The study was conducted in the US and Canada, at a secondary / tertiary setting. Funding was from government sources. The study recruited 773 in- 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 were included.

The comparator was a simple composite using VQ and PA.

Technical characteristics

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

Detailed study characteristics are provided in Appendix 15.

Quality appraisal

The study was considered at low risk of bias for the domains of patient selection, index test, and reference standard, and at unclear risk of bias for flow and timing.

For applicability, the study was at low risk of bias for all three domains, patient selection, index test, and reference standard.

The study was quality appraised as part of the CT pool, with detailed quality appraisal results in Appendix 16.

Diagnostic test accuracy

For CTCTV, 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).⁶⁴

Effect of predicted risk of PE on diagnostic performance

This study also provided results stratified by Wells score. The confidence intervals for sensitivity in low risk patients and in high risk patients do not overlap, suggesting a significant effect of risk on sensitivity.

Magnetic Resonance Imaging

Fifteen studies compared MRI to a reference standard.¹¹⁹⁻¹³³

Study and patient characteristics

Table 4 shows study characteristics for the 15 MRI studies, including the composition of the comparators.

Study design

All studies were non-randomized. All studies were single-centre with the exception of one multi-centre study conducted in the US.¹³⁰

Country and setting

One single centre study was conducted in Canada¹³³ and four studies in the US.^{126,129,131,132} Two studies were conducted in China,^{119,122} two in France,^{123,124} and one study each in Germany,¹²⁵ Sweden,¹²¹ the Netherlands,¹²⁷ Brazil,¹²⁰ and Australia.¹²⁸ Nine studies were conducted in secondary^{119-121,123,125} or secondary and tertiary settings,^{126,128,129,132} and three studies were conducted in secondary or tertiary ER settings.^{124,130,133} One was unclear.¹²²

Funding

Six studies reported government funding,^{119,121-124,130} one study reported multiple funding sources,¹²⁸ one study did not receive funding,¹²⁰ one study reported private funding,¹²⁹ and six studies did not report their funding sources.^{125-127,131-133}

Population

The number of patients recruited ranged from 14¹³² to 818.¹³⁰ Three studies recruited inpatients,^{119,121,125,129} two recruited inpatients or patients presenting at the ER,^{124,133} one included a mix of inpatients and outpatients,¹²² and one included a mix of inpatients, outpatients, and patients presenting to the ER.¹³⁰ Seven did not specify the patient mix.^{120,123,126-128,131,132}

Four studies assessed prior probability of PE; in all cases, the studies recruited all risk-levels.^{121,124,125,130} The remaining studies did not report prior risk.

Comparators

Five comparators were used CC,^{130,131} CT,¹¹⁹⁻¹²⁶ PA,^{127-129,132} SC,¹³² Sequential.¹³³ Some studies reported more than one comparator.

Table 4 Summary of study information for MRI

Study	Reference	Diagnostic N	Mean age (years)	Risk of PE
Ohno 2004 ¹³¹	CC (PA, VQ, FU)	48	55.0	Not reported
Stein 2010 ¹³⁰	CC (CT, VQ)	273	49.0	Mix
Grist 1993 ¹²⁶	CT	14		Not reported
Kluge 2006 ¹²⁵	CT	62	60.9	Mix
Li 2017 ¹¹⁹	CT	29	55.0	Not reported
Nyren 2016 ¹²¹	CT	33		Mix
Pasin 2017 ¹²⁰	CT	91	63.0	Not reported
Revel 2012 ¹²⁴	CT	198	59.8	Mix
Revel 2013 ¹²³	CT	198	60	Not reported
Zhang 2013 ¹²²	CT	27	38.2	Not reported
Gupta 1999 ¹²⁸	PA	36	59.0	Not reported
Meaney 1997 ¹²⁹	PA	30	52.0	Not reported
Oudkerk 2002 ¹²⁷	PA	118	53.0	Not reported
Erdman 1994 ¹³²	PA, SC (VQ, Clinical)	30		Not reported
Pleszewski 2006 ¹³³	Sequential	48	55.0	Not reported

Abbreviations: CC = complex composite – comparator 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; VQ = ventilation-perfusion planar scintigraphy.

Technical characteristics

Table 5 shows a summary of technical information and exam sequences for the fourteen MRI studies.

Table 5 Summary of technical and sequence information for MRI studies

Author	Field	Slices	Contrast	Breath hold	Non-contrast enhanced	3D MRA	Perfusion
Ohno 2004 ¹³¹	1.5	5	Yes	Yes		x	
Stein 2010 ¹³⁰	1.5		Yes	Yes		x	
Grist 1993 ¹²⁶	1.5	5-10	No	Yes	x		
Kluge 2006 ¹²⁵	1.5	1.5-4	Yes	Yes	x	x	x
Li 2017 ¹¹⁹	3	4	Yes	Yes		x	
Nyren 2016 ¹²¹	1.5	4.5	No	No	x		
Pasin 2017 ¹²⁰	1.5	3-4	No	No	x		
Revel 2012 ¹²⁴	1.5	2.4-5	Yes	Yes	x	x	x
Revel 2013 ¹²³	1.5	2.4-5	Yes	Yes	x	x	x
Zhang 2013 ¹²²	3	1.3	Yes	Yes		x	
Gupta 1999 ¹²⁸	1.5	10	Yes	Yes		x	
Meaney 1997 ¹²⁹	1.5	3-4	Yes	Yes		x	
Oudkerk 2002 ¹²⁷	1.5	1.25	Yes	Yes		x	
Erdman 1994 ¹³²	0.35	10	No	Unclear	x		
Pleszewski 2006 ¹³³	1.5	2-4	Yes	Yes		x	

Quality appraisal

Figure 3 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 non-consecutive recruitment and inclusion of a subset of healthy patients. One study had high risk of bias due to lack of information about the index test. 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. Studies at high risk of bias for flow and timing were those that did not apply the same reference standard across all patients, without having defined a specific protocol or pathway, or that had an inappropriate interval between tests.

Figure 3 Risk of bias and applicability for all studies with MRI as an index test



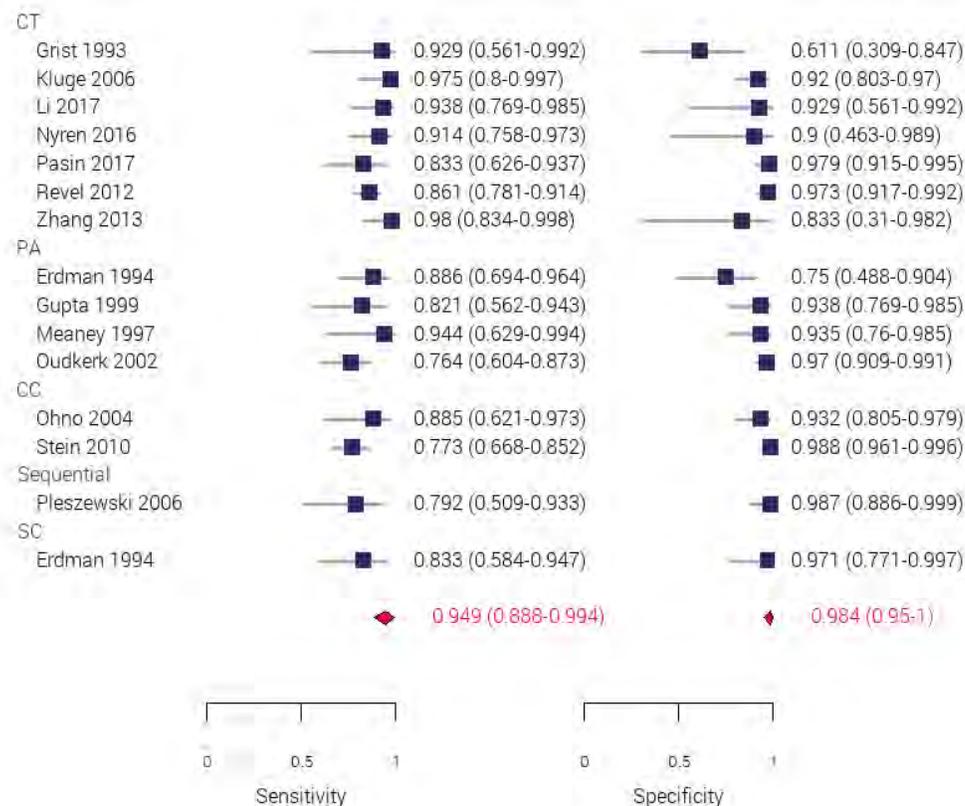
Detailed presentations of responses to individual signalling questions are given in Appendix 16.

Summary of diagnostic test results

One study was excluded from the main pool as having duplicate patients, but reported subgroups of interest, and is described below.¹²³

The forest plot for the sensitivity and specificity for all included studies is shown in **Figure 4**, grouped by reference standard, and ordered by the frequency with which the reference standard appears.

Figure 4 Forest plot for studies with MRI as index test



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

Abbreviations: CC = complex composite – comparator including imaging in combination with D-dimer; CT = computed tomography; PA = pulmonary angiography; SC = simple composite, only imaging modalities.

For patients in whom imaging was considered diagnostic, the pooled sensitivity with adjustment for imperfect reference standard is 0.949 (95%CrI 0.880 to 0.994) and the pooled specificity is 0.984 (95%CrI 0.950 to 1.00). Therefore, of 1000 patients, 150 of whom had PE,¹¹⁸ an average of 8 patients (range 1 to 18) would receive a false negative diagnosis and would be at risk of recurrent PE, and an average of 14 patients (range 0 to 43) would receive a false positive diagnosis and would be at risk of complications (bleeding) from unnecessary treatment.

Heterogeneity

Both the forest plot above and ROC scatterplots of sensitivity versus 1-specificity (Appendix 21) 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 (another indication of heterogeneity)

was wider for sensitivity for both sensitivity and specificity than for the pooled estimates, with predicted sensitivity 0.922 (95%CrI 0.651 to 1.00) and predicted specificity, 0.956 (95%CrI 0.693 to 1.00).

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 (inpatient, outpatient, ED), and PE risk, and the post-hoc variable of field-strength, there was insufficient variation between studies for statistical adjustment (Appendix 21). 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 or elevated D-dimer.¹²⁴ There was no consistent trend across risk strata. Detailed results appear in Appendix 20.

Effect of MRI sequence on diagnostic performance

Two studies compared the results of more than one set of imaging conditions.^{123,125} In Revel 2013,¹²³ both sensitivity and specificity were highest for contrast-enhanced 3D angiography. In Kluge 2006¹²⁵ the highest sensitivity was obtained by MR perfusion imaging, and the highest specificity by real time MRI. Detailed results appear in Appendix 20.

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

One nonrandomized, multicentre study reported the combination of MRI and MRV.

Study and patient characteristics

The study was conducted in the US, in secondary settings, and was supported by government funding.

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

The study comparator was a complex composite involving risk stratification, CT and VQ imaging.¹³⁰

Technical characteristics

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

Detailed study information are available in Appendix 15.

Quality appraisal

The study was considered at low risk of bias for the index test and reference standard, at high risk of bias for flow and timing, and at unclear risk of bias for patient selection.

For applicability, the study was at low risk of bias for all three domains, patient selection, index test, and reference standard.

The study was quality appraised as part of the MRI pool, with detailed quality appraisal available in Appendix 16.

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 non-cases 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 scintigraphy (MRI-VQ)

One nonrandomized, single-centre study reported the diagnostic properties of combined contrast-enhanced MRI and VQ,¹³¹ compared with a complex composite including PA, VQ 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 forty-eight in- and outpatients with an average age of 55 years. Detailed study information is available in Appendix 15.

Technical characteristics

The study used a magnet of field strength 1.5 T, with contrast-enhanced 3D MR angiography by 3D SPGRE. Ventilation scanning was carried out with 185 MBq 99mTc-MAA (perfusion) and 81mKr (ventilation).

Quality appraisal

The study was considered at low risk of bias for the domains of patient selection, and at unclear risk of bias for index test, reference standard, and flow and timing.

For applicability, the study was at low risk of bias for all three domains, patient selection, index test, and reference standard.

Detailed quality appraisal results are available in Appendix 16.

Diagnostic test results

The combination of contrast-enhanced MRI and VQ 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 VQ alone, the sensitivity was 0.67 and the specificity 0.78 (confidence intervals were not reported).

Thoracic Ultrasound

Ten studies compared thoracic US to a reference standard.¹³⁴⁻¹⁴³

Study and patient characteristics

Study information is summarized in Table 6, and detailed study characteristics are provided in Appendix 15.

Study design

All studies were of non-randomized design.

Country and setting

Three were conducted in Austria,^{140,142,143} three in Germany,^{137,138,141} and one each in France,¹³⁹ Italy,¹³⁵ Turkey,¹³⁶ and Iran.¹³⁴ One, the largest, was indicated as multi-centre,¹³⁵ eight as single-centre,^{134,136-142} and one was not specified.¹⁴³ Three were conducted in secondary or secondary / tertiary institutions,^{136,139,143} and two were conducted in secondary centre ERs.^{134,135} Five did not specify type of setting.^{137,138,141-143}

Funding

Three studies reported receiving no funding¹³⁴⁻¹³⁶ and seven did not report the type of funding.¹³⁷⁻¹⁴³

Population

The number of patients ranged from 33¹³⁷ to 357.¹³⁵ The mean age ranged from 52.8 years¹³⁴ to 71.0 years¹³⁵ Two studies involved outpatients and patients presenting to the ER,^{134,144} and one, inpatients.¹⁴⁰ Seven did not specify the patient mix.^{136-139,141-143} The prior risk of PE was formally assessed in six studies, three of whom recruited symptomatic patients with all levels of risk,^{139,140,143} and two of whom recruited symptomatic patients at moderate/high risk.¹³⁴⁻¹³⁶ Four studies did not report prior risk.^{137,138,141,142}

Comparators

Ten comparisons were reported for five comparators (CC,¹³⁹ CT,¹³⁴⁻¹³⁸ MRI,¹⁴⁰ SC,¹⁴² Sequential¹⁴³).

Technical characteristics

The most commonly used thoracic ultrasound probe frequencies were 3.5 to 5 MHz.^{135-137,139,140,142,143,145} Other probe frequencies were 3 MHz,¹⁴² 4 to 8 MHz,¹³⁵ 7 or 7.5 MHz,^{134,137,140,142,143} and 10 MHz.¹⁴⁰ 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 6 Summary of study information for Thoracic Ultrasound

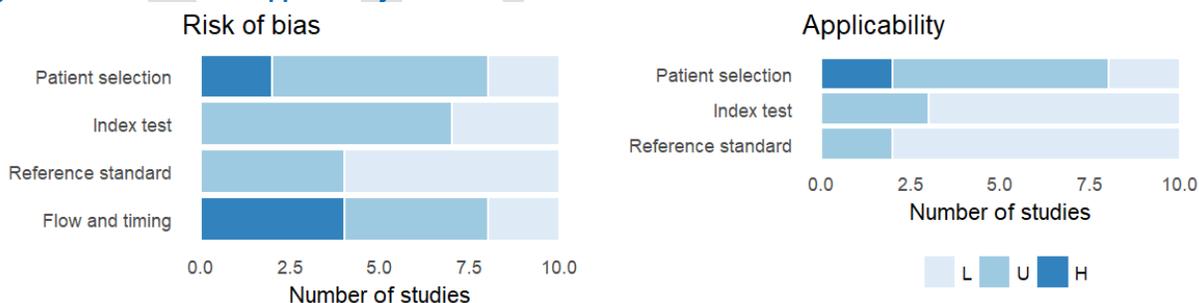
Study	Reference	N	Mean age (years)	Risk of PE	Probe
Mohn 2003 ¹³⁹	CC (VQ, LUS, PA, FU)	74	66.0	Mix	5 Mhz linear
Abootalebi 2016 ¹³⁴	CT	77	52.8	Mix	3.5 MHz, 5 MHz
Comert 2013 ¹³⁶	CT	50	54.1	Intermediate	3.5 MHz convex
Nazerian 2014 ¹³⁵	CT	357	71.0	Intermediate	4 to 8 MHz linear, 3.5 to 5 Hz convex
Pfeil 2010 ¹³⁷	CT	33	65.4	Not reported	3.5 to 5 MHz convex, 7.5 MHz linear
Reissig 2001 ¹⁴¹	CT	62	62.8	Not reported	Not reported
Reissig 2004 ¹³⁸	CT	62	62.2	Not reported	Not reported
Lechleitner 2002 ¹⁴⁰	MRI	52	69.0	Mix	3.5 MHz, 5 MHz
Mathis 1993 ¹⁴²	SC (VQ, PA)	54	63.0	Not reported	5 MHz (sometimes 3.5 MHz or 5 MHz)
Lechleitner 1998 ¹⁴³	VQ	64	66.0	Nix	3.5 MHz, 7.5 MHz, 10 MHz

Abbreviations: CC = complex composite – comparator including imaging in combination with D-dimer; CT = computed tomography; DSA = digital subtraction angiography; FU = follow-up; LUS = leg ultrasound; MRI = magnetic resonance imaging; PA = pulmonary angiography; SC = simple composite, only imaging modalities; VQ = ventilation-perfusion planar scintigraphy.

Quality appraisal

Figure 5 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 on account of insufficient detail or unclear reporting. Studies at high risk of bias for patient selection did not report exclusion criteria, and for the two studies at high risk for applicability, the patient selection was not clear. In two studies at high risk of bias for flow and timing, not all patients were included in the analysis, and in the other two, not all received the same reference standard.

Figure 5 Risk of bias and applicability for all studies with US as an index test

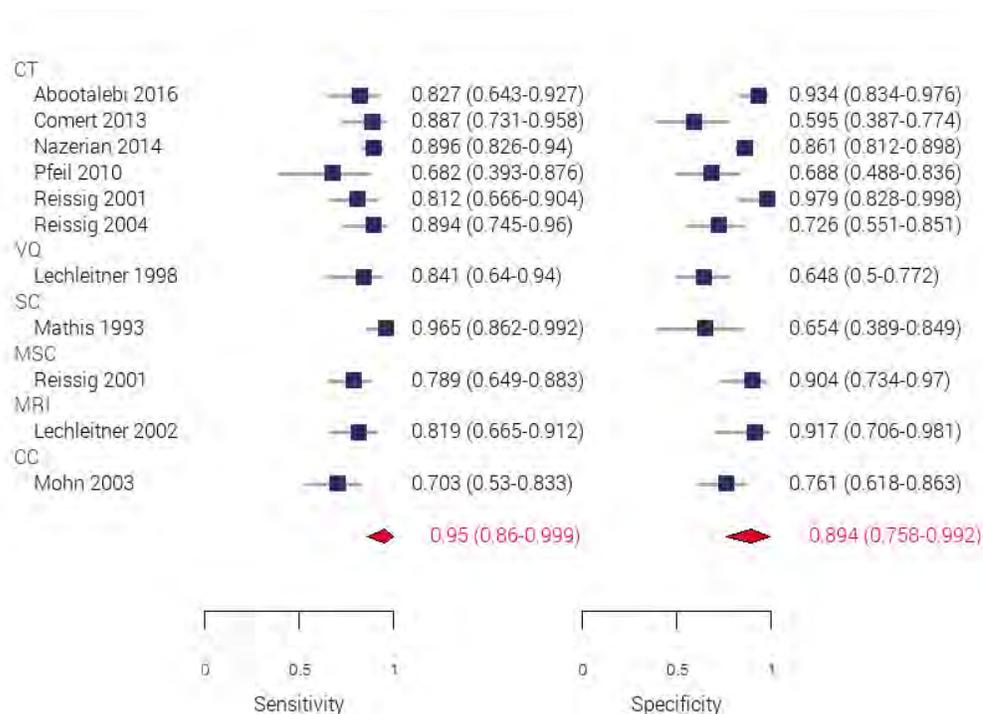


Detailed presentations of responses to individual signalling questions are given in Appendix 16.

Summary of diagnostic test results

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.

Figure 6 Forest plot for studies with thoracic US as index test



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

Abbreviations: CC = complex composite – comparator including imaging in combination with D-dimer; CT = computed tomography; MRI = magnetic resonance imaging; MSC = multiple simple composites – comparator was more than one combination of imaging modalities; PA = pulmonary angiography; SC = simple composite, only imaging modalities; VQ = ventilation-perfusion.

For patients in whom imaging was diagnostic, the pooled sensitivity with adjustment for imperfect reference standard is 0.950 (95% CrI 0.860 to 0.999) and the pooled specificity is 0.894 (95% CrI 0.758 to 0.992). Therefore, of 1000 patients, 150 of whom had PE,¹¹⁸ an average of 7 patients (range 0 to 21) would receive a false negative diagnosis and would be at risk of recurrent PE, and an average of 90 patients (range 7 to 206) would receive a false positive diagnosis and would be at risk of complications (bleeding) from unnecessary treatment.

The meta-analysis show a large increase in both sensitivity and specificity upon adjustment for imperfect reference standard (Appendix 21). For consistency with other analyses, the model with adjustment for imperfect reference standard is reported, but its interpretation must be qualified.

Heterogeneity

Both the forest plot above and an ROC scatterplot of sensitivity versus 1-specificity (Appendix 21) indicated heterogeneity for sensitivity and specificity. The predicted sensitivity for a new study is 0.918 (0.578 to 1.00) and the pooled specificity for a new study is 0.856 (95% CrI 0.403 to 0.999).

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 (inpatient, outpatient, ED), and PE risk, there was insufficient variation between studies for statistical adjustment (Appendix 21). 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)

Ten studies compared perfusion imaging with a reference standard.^{104,114,146-153}

Study and patient characteristics

Study design

All studies were non-randomised.

Country and setting

Four were multicentre, conducted in Slovenia,¹⁴⁶ the US,¹⁴⁹ China,¹¹⁴ and the Netherlands and Belgium.¹⁵² The rest were single centre studies, with two conducted in Italy,^{150,153} and one each in the US,¹⁴⁸ Belgium,¹⁴⁷ Poland,¹⁵¹ and China.¹⁰⁴ Five were in secondary or tertiary care centres,^{146,148,150-152} two were in a secondary centre ER,^{147,149} one was in a secondary centre,¹¹⁴ and two did not specify setting.^{104,153}

Funding

Four studies reported receiving government funding,^{114,149,151,153} three did not receive funding,^{147,148,152} and three studies did not report funding.^{104,146,150}

Population

Studies recruited between 53¹⁴⁷ and 890 patients.¹⁵³ The number of patients contributing to the diagnostic 2x2 table is shown in **Table 7**. Three studies recruited inpatients,^{146,150,151} one recruited inpatients and outpatients,¹⁵² one inpatients, outpatients and ER patients,¹⁴⁹ and one recruited from the ER.¹⁴⁷ Three did not report where patients were recruited from.^{104,148,153} Six studies reported the formally evaluated risk of PE, one as high¹⁵² and five as mixed.^{104,114,147,149,153} Four did not report risk.^{146,148,150,151}

Comparators

The reference standards were CC,^{104,114,146,148,151} CT,^{150,152} multiple simple composite (patients received different modalities as part of the simple composite),¹⁴⁹ SC,¹⁴⁷ and PA.¹⁵³

Technical characteristics

All studies used 99mTc-labelled micro-aggregated albumin injection for visualization, with doses ranging from 110 MBq¹⁴⁷ to up to 370 MBq.^{104,114} Seven studies used the PISAPED criteria for

PE diagnosis,^{114,146,147,149,150,152,153} two used a modified version of the PIOPED¹⁰⁴ or PIOPED II¹⁴⁹ criteria that allowed for the absence of ventilation results, and two used study-specific interpretations.^{112,151} 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 or equal in size and shape to chest radiograph abnormalities. All other findings were considered nondiagnostic.

Study information is summarized in **Table 7**, and detailed study characteristics are provided in Appendix 15.

Table 7 Summary of study information for Perfusion imaging

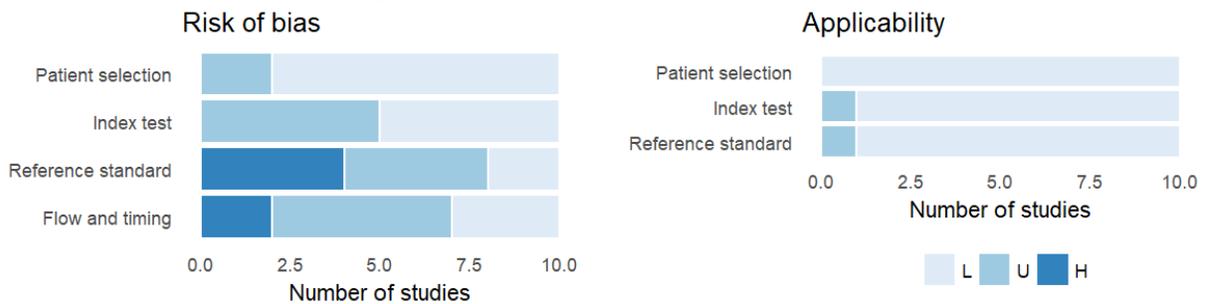
Study	Reference	N	Mean age (years)	Risk of PE	Dose (MBq) / Isotope	Index interpretation
Mazurek 2015 ¹⁵¹	CC (CT)	84	68.3	Not reported	185/99mTc	Study specific
Skarlovnik 2014 ¹⁴⁶	CC (Unclear)	77	71.5	Not reported	120-200/99mTc	PISAPED
Wang 2009 ¹⁰⁴	CC (Unclear)	75	51.0	Mix	185-370/99mTc	Modified PIOPED
Lu 2014 ¹⁴⁸	CC (leg US, Q-SPECT-CT, CT, VQ)	106	63	Not reported	4 mCi/99mTc	Study-specific
He 2012 ¹¹⁴	CC	544	53.3	Mix	185-370/99mTc	PISAPED
Rubini 2007 ¹⁵⁰	CT	107	60.0	Not reported	185/99mTc	PISAPED
van Es 2015 ¹⁵²	CT	74	38.0	High	148-155/99mTc	PISAPED
Sostman 2008 ¹⁴⁹	MSC (PA,CT)	910	51.7	Mix	4 mCi/99mTc	PISAPED, modified PIOPED II
Miniati 1996 ¹⁵³	PA	580	64.3	Mix	180/99mTc	PISAPED
Tondeur 2007 ¹⁴⁷	SC (CT, VQ)	30	60.0	Mix	110/99mTc	PISAPED

Abbreviations: CC = complex composite – comparator including imaging in combination with D-dimer; CT = computed tomography; MSC = multiple simple composite; PA = pulmonary angiography; SC = simple composite, only imaging modalities; Sequential = combination of imaging modalities used in sequence; VQ = ventilation-perfusion planar scintigraphy.

Quality appraisal

Figure 7 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 on account of insufficient detail or unclear reporting. Studies that were at high risk of bias for the reference standard had the index test included in the reference standard, or the reference test interpreted with knowledge of the index test results. 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.

Figure 7 Risk of bias and applicability for all studies with Q as an index test



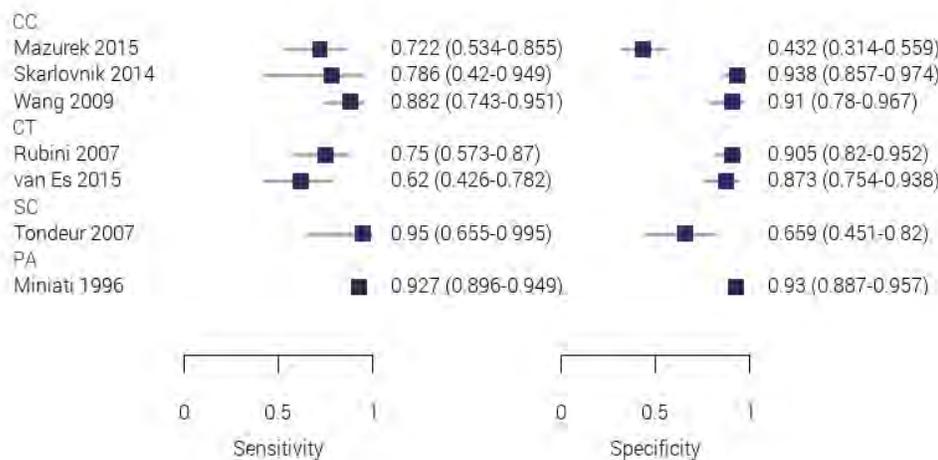
Detailed presentations of responses to individual signalling questions are given in Appendix 16.

Summary of diagnostic test results

Two contrasts were excluded because the index was included in the reference.^{114,148} Eight remaining studies reported eight comparisons, with five comparators: CC,^{104,146,154} CT,^{150,152} MSC,¹⁴⁹ PA,¹⁵³ SC.¹⁴⁷

The forest plot for the sensitivity and specificity for all included studies is shown in **Figure 8**, 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 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 8 Forest plot for studies with Q as index test



Dark blue – individual study estimates without adjustment.

Abbreviations: CC = complex composite – comparator including imaging in combination with D-dimer; CT = computed tomography; PA = pulmonary angiography; SC = simple composite, only imaging modalities.

The reported sensitivity of Q for the diagnosis of PE ranged from 0.62 (95% CI 0.426 to 0.782), against a reference standard of CT,¹⁵² to 0.927 (0.896 to 0.949) against a reference standard of PA.¹⁵³ The reported specificity of Q for the diagnosis of PE ranged from 0.432 (0.314 to

0.559)¹⁵¹ against a complex composite reference standard to 0.930 (0.889 to 0.956) against a reference standard of PA.¹⁵³

Heterogeneity

Both the forest plot above and an ROC scatterplot of sensitivity versus 1-specificity (Appendix 21) 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 (inpatient, outpatient, ED), and PE risk, there was insufficient variation between studies for statistical adjustment (Appendix 21).

Individual studies describing the effect of covariates on diagnostic test performance

One study¹¹⁴ reported results stratified by risk, and one study stratified results by age and assessed the effect of lung disease.¹⁴⁹ A third study included above restricted recruitment to patients less than 51 years old.¹⁵² Sensitivity appeared to increase with risk, while specificity was unaffected, although this was not statistically tested.¹¹⁴ Age and lung disease did appear to affect sensitivity and specificity,¹⁴⁹ but lung disease influenced the proportion of non-diagnostic scans.¹⁴⁹ Detailed results appear in Appendix 20.

Perfusion-Single Photon Emission Tomography (Q-SPECT)

Two studies compared SPECT-CT to a reference standard.^{151,155}

Study and patient characteristics

Both studies were single-centre, non-randomized studies, one conducted in Poland¹⁵¹ and the other in Sweden.¹⁵⁵ Both were conducted at a secondary or secondary / tertiary centre. One received government funding¹⁵¹ and the other private funding.¹⁵⁵

One study recruited 84 inpatients,¹⁵¹ and the other 152,¹⁵⁵ primarily outpatients. The mean age of patients in the first study was 58 years¹⁵⁵ and the second, 68.3 years.¹⁵¹ Neither study reported a formally assessed risk of PE.

One study used CT as in its composite,¹⁵⁵ and the other CT, thoracic US, and VQ-SPECT.¹⁵¹

Technical characteristics

Both studies used 99mTc-labelled micro-aggregated albumin, at doses of 120 MBq¹⁵⁵ and 185 MBq.¹⁵¹ One study used the European Association of Nuclear Medicine (EANM) criteria, under which a positive scan showed single or multiple wedge-shaped perfusion defects,¹⁵⁵ 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.¹⁵¹

Detailed study characteristics are provided in Appendix 15.

Quality appraisal

One study was at low risk for patient selection and one at unclear risk. One study was at low risk of bias for index test and one at unclear risk of bias. One study was at high risk of bias for the reference test, due to uncertainty about the independence of interpretation of the two tests and one at unclear risk of bias. One study was at high risk of bias for flow and timing, and one at unclear of bias.

All studies were at low risk for the applicability domains for patient selection, index test and reference standard.

Detailed presentations of responses to individual signalling questions are given in Appendix 16.

Diagnostic test accuracy results

In one study, the sensitivity of Q-SPECT was 0.898 (95%CI 0.722% to 0.962)¹⁵⁵ and the specificity 0.946 (95%CI 0.897 to 0.982).¹⁵⁵ In the other, the sensitivity of Q-SPECT was 0.885 (95% CI 0.698 to 0.976)¹⁵¹ and the specificity 0.466 (0.333 to 0.601).¹⁵¹

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 to a reference standard.^{148,151,156,157}

Study and patient characteristics

All studies were nonrandomized and single centre. Two studies were conducted in the US,^{148,157} one each in France¹⁵⁶ and Poland.¹⁵¹ Three were secondary/tertiary^{148,151,156} and one did not specify. One received government funding,¹⁵¹ one received none,¹⁴⁸ and two did not report funding.^{156,157}

Studies recruited between 49¹⁵⁷ and 393 patients.¹⁵⁶ One study recruited inpatients,¹⁵¹ one recruited inpatients and outpatients,¹⁵⁶ and two did not specify.^{148,157} None of the studies reported the prior risk of PE.

The comparator in one study was VQ-SPECT¹⁵⁶ and the other three used a complex composite.^{148,151,157} One composite consisted of leg US, CT, Q, VQ, Q-SPECT-CT,¹⁵⁷ another consisted of leg US, CT, VQ, Q-SPECT-CT,¹⁴⁸ and the third was unclear.¹⁵¹

Technical characteristics

The studies used 99mTc-labelled micro-aggregated albumin at doses ranging from 110¹⁵⁷ to 200 mBq.¹⁵⁶ A PE-positive scan required least one segmental (at least 50%)^{148,157} or one segmental or two subsegmental perfusion defects without lung parenchymal defects.^{151,156} 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.^{151,157}

Quality appraisal

For patient selection, two studies were at low risk of bias and two at unclear risk. For the index test, two studies were at low risk of bias, and one at unclear risk. For the reference test, three studies were high risk of bias, due to the inclusion of the index in the reference test, and one was unclear risk. For flow and timing, three studies were at low risk of bias, and one at unclear risk of bias.

For applicability of patient selection, index test and reference test, all studies were at low risk.

Diagnostic test accuracy results

Three studies included the index test in the reference standard.^{148,156,157}

Against the composite reference standard, the sensitivity of Q-SPECT-CT was 1.00 (95% CI 0.868 to 1.00) and the specificity, 0.828 (0.706 to 0.914).¹⁵¹

There were no reports on clinical subgroups of interest.

Ventilation-Perfusion Scintigraphy (VQ)

Fifteen studies compared VQ imaging with other imaging modalities.^{104,105,109,114,115,131,140,145,146,148,158-162}

Study and patient characteristics

Study information is summarized in **Table 8**, and detailed study characteristics are provided in Appendix 15.

Study design

All studies were non-randomized.

Country and setting

Four were multi-centre, one conducted in the US,¹⁵⁹ one in Slovenia,¹⁴⁶ one in China,¹¹⁴ and the third in Slovenia, Turkey, Czech Republic, Uruguay, and India.¹⁴⁵ The single centre studies were conducted in Canada,¹⁶² two in the US,^{131,148} two in Belgium,^{109,160} Scotland,¹⁶¹ Austria,¹⁴⁰ France,¹¹⁵ Germany,¹⁰⁵ Denmark,¹⁵⁸ and China.¹⁰⁴ The settings were secondary^{114,115,140,161} or secondary / tertiary healthcare,^{145,146,148,158,160} or secondary setting ER,^{109,159} with four studies not reporting setting.^{104,105,131,162}

Funding

One study received government funding,¹⁵⁹ and two reported receiving no funding.^{145,148} Eight studies did not report funding.^{104,105,109,115,131,140,146,158,160-162}

Population

Studies recruited between 38¹⁶² and 931 patients.¹⁵⁹ Two studies recruited inpatients,^{140,146} one recruited outpatients and ER patients,¹⁰⁹ one inpatients and outpatients,^{115,145} and one inpatients, outpatients and ER patients.¹⁵⁹ The other nine did not report the mix of patients they recruited.^{104,105,114,131,148,158,160-162} The mean age of patients ranged from 51.0 years¹⁰⁴ to 71.5

years.¹⁴⁶ The six studies that reported the results of formal assessment for risk of PE all recruited a mixture of risk levels.^{104,109,140,145}

Comparators

The studies compared VQ with five comparators, CC,^{104,105,114,115,131,146,148,158,160} CT,¹⁴⁵ MRI,¹⁴⁰ PA,^{159,161,162} SC.¹⁰⁹

Technical characteristics

For perfusion imaging, all studies used 99mTc microaggregates of albumin, administered intravenously at doses ranging from 74 MBq¹⁴⁰ to 370 MBq.^{104,114} For ventilation imaging, most studies used 99mTc as an isotope.^{104,105,114,140,145,146,148,161,162} Four studies^{109,131,158,160} used 81Kr. Two studies^{115,159} and one site in a multicentre study used 133Xe.¹⁴⁵ Interpretation criteria varied across the studies, with most using PIOPED or a revised or modified version of PIOPED or PIOPED II (**Table 8**).

DRAFT

Table 8 Summary of study information for VQ

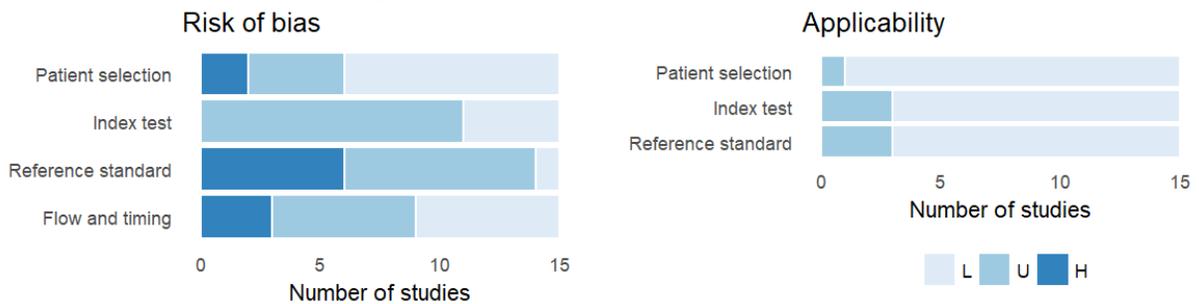
Study	Reference	Diagnostic N	Mean age (years)	Risk of PE	Index interpretation
Ohno 2004 ¹³¹	CC (VQ, PA)	48	55.0	Not reported	Modified PIOPED
Reinartz 2004 ¹⁰⁵	CC (PA)	82	53.9	Not reported	PIOPED
Skarlovnik 2014 ¹⁴⁶	CC (CT)	82	71.5	Not reported	PIOPED II Revised
Wang 2009 ¹⁰⁴	CC (Unclear)	75	51.0	Mix	Modified PIOPED
Blanchere 2000 ¹¹⁵	CC (PA,CT,VQ,US)	179	61	Mix	Study specific
Collart 2002 ¹⁶⁰	CC (CT,VQ)	66	Not reported	Not reported	PIOPED
Gutte 2010 ¹⁵⁸	CC (VQ), VQ	36	74	Not reported	Study specific
He 2012 ¹¹⁴	CC (CT,VQ,PA)	477	53.3	Mix	PIOPED
Lu 2014 ¹⁴⁸	CC (CT,VQ,Q-SPECT-CT)	93	63.4	Not reported	Study specific
Watanabe 2015 ¹⁴⁵	CT	127	59.0	Mix	Modified PIOPED
Lechleitner 2002 ¹⁴⁰	MRI	37	69.0	Mix	PIOPED
Gray 1990 ¹⁶¹	PA	48	56.0	Not reported	Study-specific
PIOPED Investigators 1990 ¹⁵⁹	PA	409	56.1	Not reported	PIOPED
Woods 1989 ¹⁶²	PA	22		Not reported	Modified Biello, PIOPED
Coche 2003 ¹⁰⁹	SC (VQ, PA)	94	62.0	Mix	PIOPED II

Abbreviations: CC = complex composite – comparator including imaging in combination with D-dimer; CT = computed tomography; PA = pulmonary angiography; PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis; PISAPED = Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis; SC = simple composite, only imaging modalities; VQ = ventilation-perfusion planar scintigraphy.

Quality appraisal

Figure 9 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. The studies at high risk of bias for patient selection both recruited non-consecutive patients. One, due to resource constraints, only recruited during the daytime. Six studies included the index test in the reference standard, or otherwise did not establish the diagnosis independently. In one study, not all patients received the same reference test, in one study, the allowed interval between the test and diagnostic confirmation was long enough for the patient’s status to change, and in two, not all included patients were in the diagnostic calculation.

Figure 9 Risk of bias and applicability for all studies with VQ as an index test



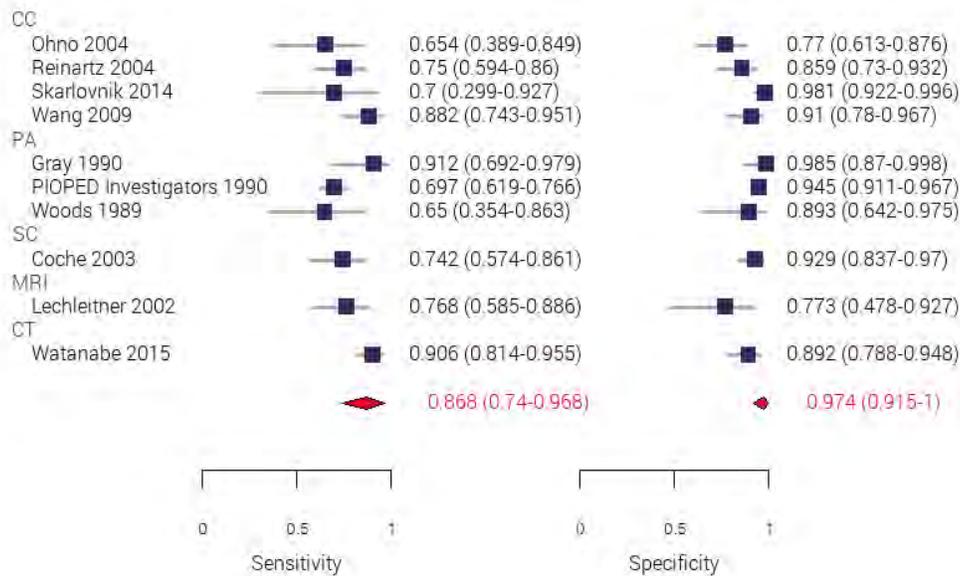
Detailed presentations of responses to individual signalling questions are given in Appendix 16.

Summary of diagnostic test results

Two studies were excluded as post-hoc analyses,^{163,164} and three comparisons were excluded because the index was included in the reference.^{114,148,160}

The forest plot for the sensitivity and specificity for all included studies is shown in **Figure 10**, grouped by reference standard, and ordered by the frequency with which the reference standard appears.

Figure 10 Forest plot of studies with VQ as index test



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

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

For patients in whom imaging was considered diagnostic, the pooled sensitivity with adjustment for imperfect reference standard is 0.868 (95% CrI 0.740 to 0.968) and the pooled specificity is

0.974 (95% CrI 0.915 to 0.999). Therefore, of 1000 patients, 150 of whom had PE,¹¹⁸ an average of 20 patients (range 5 to 39) would receive a false negative diagnosis and would be at risk of recurrent PE, and an average of 22 patients (range 1 to 72) would receive a false positive diagnosis and would be at risk of complications (bleeding) from unnecessary treatment.

Heterogeneity

Both the forest plot above and an ROC scatterplot of sensitivity versus 1-specificity (Appendix 21) suggest heterogeneity in both sensitivity and specificity for VQ, 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 credible intervals 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 is 0.836 (95% CrI 0.437 to 0.995) and the pooled specificity for a new study is 0.943 (0.628 to 1.00).

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 (inpatient, outpatient, ED), and PE risk, there was insufficient variation between studies for statistical adjustment (Appendix 21). All studies that assessed prior risk recruited a mixed population.

Individual studies describing the effect of covariates on diagnostic performance

One study¹¹⁴ reported results for VQ 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 20.

Ventilation-Perfusion Scintigraphy-Single Photon Emission Computed Tomography (VQ-SPECT)

Fourteen studies compared VQ-SPECT imaging with other imaging modalities.^{105,111,146,158,160,165-173}

Study and patient characteristics

Study information is summarized in **Table 9**, and detailed study characteristics are provided in Appendix 15.

Study design

All 14 studies were non-randomized.

Country and setting

Four were multi-centre, one conducted in each of Slovenia,¹⁴⁶ Denmark,¹¹¹ Slovenia,¹⁴⁶ and Australia.¹⁶⁷ Of the ten single centre studies, two were conducted in each of France,^{166,171} Germany,^{105,170} Sweden,^{168,173} and Spain,^{165,172} and one each in Belgium,¹⁶⁰ and Australia.¹⁶⁹

Eight studies were conducted in a secondary/tertiary setting,^{111,146,158,160,165-169,173} one in an ER setting,¹⁷² and for three the setting was unspecified.^{105,170,171}

Funding

Three received government funding,^{168,171,173} and one received industry funding.¹⁶⁷ Ten studies did not report funding sources.^{105,111,146,158,160,165,166,169,170,172}

Population

Studies recruited between 36¹⁵⁸ and 1785 patients.¹⁶⁸ Three studies recruited inpatients,^{146,165,167} one study recruited outpatients and patients presenting to the ER,¹⁷² and one recruited both.¹⁶⁶ Seven studies did not clearly report the source of their patients.^{105,111,158,160,168-171,173} The mean age of patients was 53.9¹⁷⁰ years to 79.6 years.¹⁶⁵ None of the studies reported a formal assessment of prior risk of PE.

Comparators

The studies reported sixteen comparisons involving four comparators, CC,^{105,111,146,158,160,169} CT,^{167,168,170-172} VQ,^{158,165,166,173} and SC.¹⁶⁶

Technical characteristics

For all studies, 99mTc-MAA was used as a tracer for perfusion, in doses of 100 MBq^{146,173} to 300 MBq.¹⁷¹ Ten studies used 99mTc as the tracer for ventilation,^{105,146,165,167-173} in the form of DTPA or Technogas, while four studies used 81Kr.^{111,158,160,166} Ventilation dose was variably reported, with four studies reporting the total dose used in inhalation, 445 MBq¹⁷¹ to 700 MBq,¹⁶⁵ four reporting the accumulated dose in the lungs as 20 MBq¹⁴⁶ to 50 MBq,¹⁷⁰ and the rest not reporting dose.^{158,166,167,169,172} Interpretation criteria were heterogeneous (**Table 9**).

Table 9 Summary of study information for VQ-SPECT studies

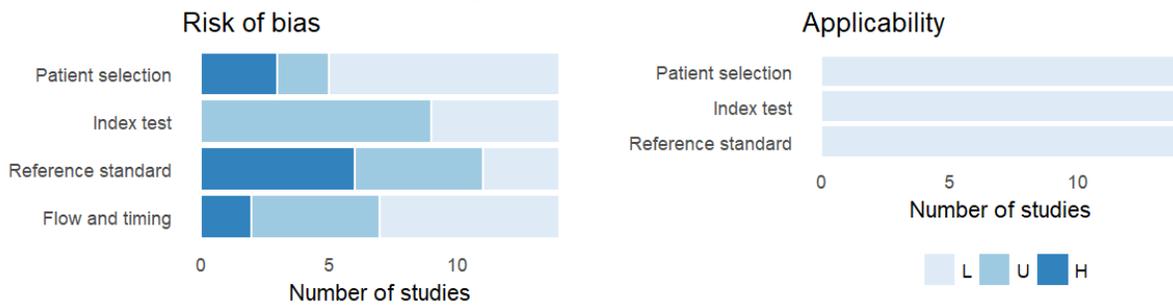
Study	Reference	Diagnostic N	Mean age (years)	Risk of PE	Index interpretation
Harris 2007 ¹⁶⁹	CC (VQ, CT, CTV)	37	66.0	Not reported	Modified PIOPED
Reinartz 2004 ¹⁰⁵	CC (PA)	83	53.9	Not reported	PIOPED
Skarlovnik 2014 ¹⁴⁶	CC (CT)	49	71.5	Not reported	EANM
Collart 2002 ¹⁶⁰	CC (CT,VQ)	70	Not reported	Not reported	PIOPED
Gutte 2009 ¹¹¹	CC (CT,VQ-SPECT)	81	65	Not reported	Study-specific
Bajc 2008 ¹⁶⁸	CT	105	Not reported	Not reported	Study-specific
Ibanez-Bravo 2016 ¹⁷²	CT	48	Not reported	Not reported	EANM
Miles 2009 ¹⁶⁷	CT	79	71.9	Not reported	Study-specific
Reinartz 2006 ¹⁷⁰	CT	53	56.4	Not reported	Study-specific
Weinmann 2008 ¹⁷¹	CT	94		Not reported	PIOPED II
Bajc 2004 ¹⁷³	VQ	52		Not reported	Study-specific
Gutte 2010 ¹⁵⁸	VQ	33	71.9	Not reported	Study-specific
Le Duc-Pennec 2012 ¹⁶⁶	VQ	205	64.3	Not reported	Revised PIOPED
Quirce 2014 ¹⁶⁵	VQ	39	79.6	Not reported	EANM

Abbreviations: CC = complex composite – comparator 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; VQ = ventilation-perfusion planar scintigraphy.

Quality appraisal

Figure 11 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. One study only included patients when the diagnostic imaging equipment was available, potentially producing a nonrepresentative population, and two were at high risk of bias due to possibly inappropriate exclusions. Studies that were at high risk of bias due to the reference standard included the index in the reference test, or had other concerns about the accuracy of their particular reference standard. In two studies, the number of patients excluded from the analysis represented a high risk of bias.

Figure 11 Risk of bias and applicability for all studies with VQ-SPECT as an index test



For flow and timing, two studies were at high risk of bias,^{167,171} seven studies at low risk,^{105,146,160,166,168,170,173} and five studies at unclear risk.^{111,158,165,169,172}

All studies were considered at low risk for applicability of patient selection, index test, and reference test.

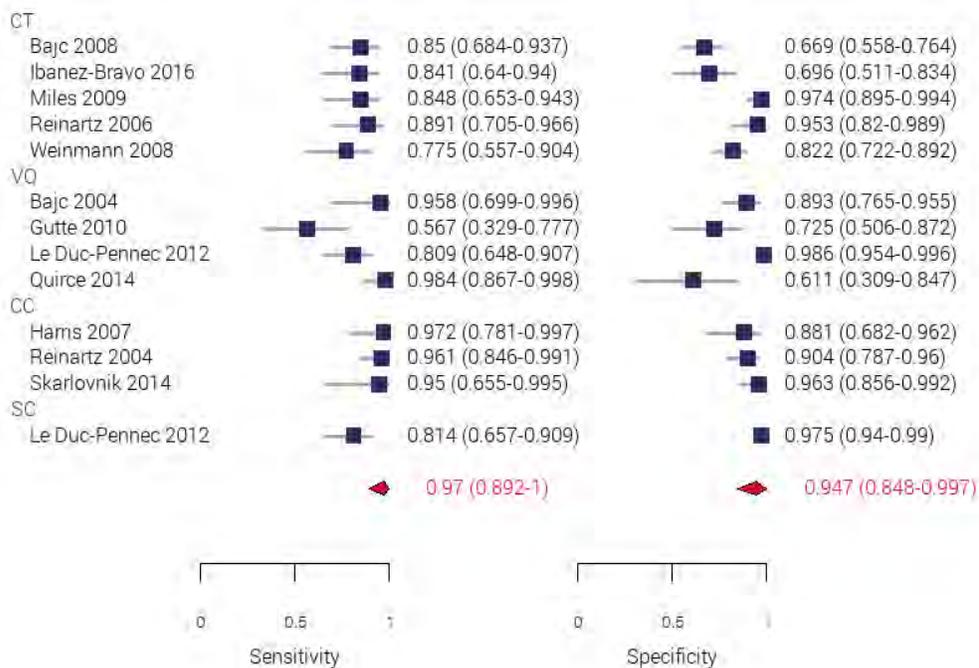
Detailed presentations of responses to individual signalling questions are given in Appendix 16.

Summary of diagnostic test accuracy

Three comparisons were excluded from the pool because the index was included in the reference.^{111,158,160}

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.

Figure 12 Forest plot of studies with VQ-SPECT as index test



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

Abbreviations: CC = complex composite – comparator including imaging in combination with D-dimer; CT = computed tomography; SC = simple composite, only imaging modalities; VQ = ventilation-perfusion.

For patients in whom imaging was considered diagnostic, the pooled sensitivity, with adjustment for an imperfect reference standard, is 0.970 (95% CrI 0.892 to 1.00) and the pooled specificity is 0.947 (95% CrI 0.849 to 0.998). Therefore, of 1000 patients, 150 of whom had PE,¹¹⁸ an average of 5 patients (range 0 to 16) would receive a false negative diagnosis and would be at risk of recurrent PE, and an average of 45 patients (range 2 to 128) would receive a false positive diagnosis and would be at risk of complications (bleeding) from unnecessary treatment.

Heterogeneity

Both the forest plot above and an ROC scatterplot of sensitivity versus 1-specificity (Appendix 21) 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 (another indication of heterogeneity) was very broad for both sensitivity (0.918 (95% CrI 0.453 to 1.00)) and specificity (0.884 (95% CrI 0.357 to 0.955)).

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 (inpatient, outpatient, ED), and PE risk, there was insufficient variation between studies for statistical adjustment (Appendix 21). Only one study reported risk of PE, and provided a stratified analysis (next section).

Effect of risk of PE on diagnostic performance

One study¹⁷² 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 20.

Ventilation-Perfusion Scintigraphy-Single Photon Emission Computed Tomography-Computed Tomography (VQ-SPECT-CT)

Four studies compared VQ-SPECT-CT imaging with two comparators.

Study and patient characteristics

Study information is summarized in **Table 10**, and detailed study characteristics are provided in Appendix 15.

All studies were non-randomized. One was a multi-centre study conducted in Denmark¹¹¹ and the others were single-centre studies conducted in Australia,^{174,175} and France.¹⁵⁶ All four were conducted in a secondary/tertiary setting.^{111,156,174,175} Three studies did not report funding,^{111,156,174} and one did not receive funding.¹⁷⁵

Studies recruited between 81¹¹¹ and 393¹⁵⁶ patients. Age ranged from a mean of 51.0¹⁷⁵ to a median of 71 years.¹¹¹ One study recruited inpatients or outpatients¹⁵⁶ and the others did not report the patients recruited.^{111,174,175} None reported the prior risk of PE.

The comparators used were CT¹⁷⁴ and VQ-SPECT-CT.^{111,156,175}

Technical characteristics

One of the four studies did not report imaging conditions.¹⁷⁵ The two others both used 99mTc-TAA for perfusion imaging, at 150 MBq¹¹¹ and 200 MBq.^{156,174} For ventilation imaging, two used 81mKr,^{111,156} and one 99mTc-Technogas (40 MBq accumulation).¹⁷⁴ All four studies used study-specific imaging criteria based on the identification of VQ mismatches not corresponding to anatomic abnormalities.

Table 10 Summary of study information for VQ-SPECT-CT studies

Study	Reference	Diagnostic N	Mean age (years)	Risk of PE	Index interpretation
Bhatia 2016 ¹⁷⁴	CT	102	53.0	Not reported	Study specific
Gutte 2009 ¹¹¹	VQ-SPECT	77	71.9	Not reported	Study specific
Ling 2012 ¹⁷⁵	VQ-SPECT	106	51.0	Not reported	Study specific
Le Roux 2015 ¹⁵⁶	VQ-SPECT	393	Median 71	Not reported	Study specific

Abbreviations: CT = computed tomography; VQ-SPECT = ventilation-perfusion single photon emission tomography.

Quality appraisal

For patient selection, three studies were at low risk of bias and one was unclear. For the index test, three studies were at low risk of bias and one was unclear. For the reference test, two studies were at high risk of bias, one because the index test was included in the reference and the other because all information was used for the final diagnosis, and two at unclear risk of bias. For flow and timing, two were at low risk of bias, and two at unclear risk of bias.

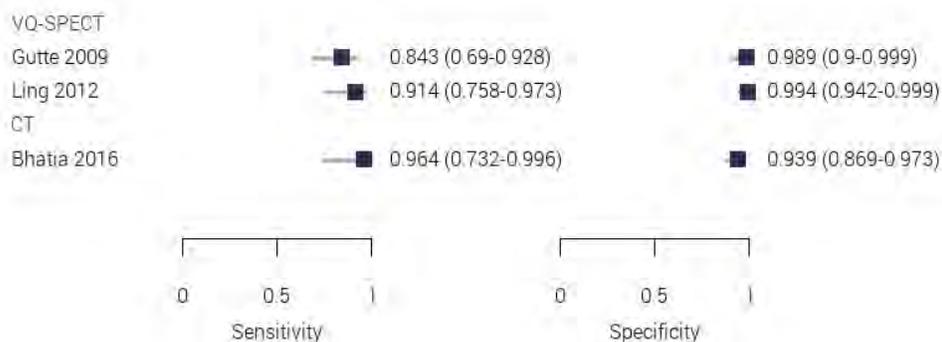
All studies were considered at low risk for applicability of patient selection, index test, and reference test.

Detailed presentations of responses to individual signalling questions are given in Appendix 16.

Summary of diagnostic test results

One comparison were excluded because the index was included in the reference.¹⁵⁶ The forest plot for the sensitivity and specificity for all included studies is shown in Figure 13, 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 13 Forest plot of studies with VQ-SPECT-CT as index test



Dark blue – individual study estimates without adjustment.

Abbreviations: CT = computed tomography; VQ = ventilation-perfusion single photon computed tomography.

The reported sensitivity of VQ-SPECT-CT for the diagnosis of PE ranged from 0.843 (95% CI 0.690 to 0.928), against a reference standard of VQ-SPECT,¹¹¹ to 0.964 (0.732 to 0.996) against a reference standard of CT.¹⁷⁴ The reported specificity of VQ-SPECT-CT for the diagnosis of PE ranged from 0.939 (0.869 to 0.973) against a reference standard of CT,¹⁷⁴ to 0.994 (0.942 to 0.999) against a reference standard of VQ-SPECT.¹⁷⁵

Individual studies describing the effect of covariates on diagnostic test performance

One study included above¹⁷⁴ found no significant difference in diagnostic test accuracy of VQ-SPECT-CT compared with CT of transplant or pre-existing lung disease.

Summary of diagnostic test accuracy results

Seventy-four studies reported results for diagnostic test accuracy for an eligible index imaging modality compared with an eligible reference modality in non-pregnant 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, VQ, VQ-SPECT, VQ-SPECT-CT, and combinations of modalities CT and CTV (CT venography), MRI and MRV (MR venography), and MRI and VQ.

Five modalities had sufficient data to allow for meta-analysis: CT, MRI, US, VQ, and VQ-SPECT (**Table 11**).

CT offered the best diagnostic test performance, with the narrowest credible intervals for pooled and predicted values. The pools for US, VQ, and VQ-SPECT were considerably more statistically heterogeneous, with lower bounds for prediction intervals for a new study in the region of 0.5, and the results for US depended to the greatest degree on the model used for synthesis. Thus the result for ultrasound is considered the least reliable.

It should be noted that the diagnostic test performance reported is for patients with a diagnostic test, and does not include those who had nondiagnostic or indeterminate findings. Studies did not consistently report the final diagnosis for indeterminate index tests to allow for analytic adjustment. The proportion of patients with non-diagnostic studies for CT was 0.036 (pooled,

95% CI 0.024 to 0.050), for MRI between 0 and 0.474, for VQ ranged from 0.071 to 0.574, and from VQ-SPECT ranged from 0 to 0.222. One small study reported no nondiagnostic exams for ultrasound.

Table 11 Summary of meta-analysis results

		Sensitivity (95% CrI)	Specificity (95% CrI)
CT (n = 11)	Pooled	0.972 (0.916 to 1.00)	0.987 (0.960 to 1.00)
	Predicted new	0.950 (0.718-1.00)	0.971 (0.810-1.00)
MRI (n = 14)	Pooled	0.949 (0.880 to 0.994)	0.984 (0.950 to 1.00)
	Predicted new	0.922 (0.651-1.00)	0.956 (0.693-1.00)
US (n = 10)	Pooled	0.950 (0.860 to 0.999)	0.894 (0.759 to 0.992)
	Predicted new	0.918 (0.578-1.00)	0.856 (0.406-0.999)
VQ (n = 10)	Pooled	0.868 (0.740 to 0.968)	0.974 (0.915 to 0.999)
	Predicted new	0.836 (0.437-0.995)	0.943 (0.628-1.00)
VQ-SPECT (n = 12)	Pooled	0.970 (0.892 to 1.00)	0.947 (0.849 to 0.998)
	Predicted new	0.918 (0.453-1.00)	0.884 (0.357-1.00)

For CT, individual studies assessed the effect of prior risk of PE, age and 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.

For MRI, one study assessed the effect of prior of 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 healthcare centres in urban settings; no studies were retrieved that were conducted in rural or remote settings, and therefore this aspect of the policy question could not be addressed. Where studies recruited a mix of inpatients, outpatients, and ER 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 3: Utility results

Of the 115 studies described under study selection, 65 contributed utility and safety outcomes (some also reported DTA outcomes). These are discussed by modality, below.

Pathway studies

Ten studies reported clinical utility and safety results for pre-specified diagnostic pathways.¹⁷⁶⁻¹⁸⁵

The ten studies included one RCT¹⁸⁵ and nine non-randomized studies.¹⁷⁶⁻¹⁸⁴ Three studies were multicentre, one conducted in Switzerland and France,¹⁸³ one conducted in Switzerland, France, and Brussels,¹⁸⁵ and one in Italy.¹⁸⁴ Two of the single-centre studies were conducted in France,^{176,180} and one each in Norway,¹⁷⁸ Italy,¹⁸¹ the UK,¹⁷⁹ Switzerland,¹⁸² and Spain.¹⁷⁷ Eight studies were conducted in secondary^{176,180-183} and secondary/tertiary settings,^{179,184,185} and the setting of two studies was unclear.^{177,178} Seven studies had government funding,^{176-178,181-183,185} one private funding,¹⁷⁹ and two articles did not detail funding.^{180,184} Reported follow-up was for 3 months in nine studies^{176-180,182-185} and one year in the tenth.¹⁸¹

The number of participants ranged from 114¹⁸² to 1819 patients.¹⁸⁵ Seven studies described pathways for diagnosis of PE in non-pregnant patients only (Table 31).^{176-179,182,184,185} Three studies allowed the recruitment of pregnant patients,^{180,181,183} but they represented between 0.5%¹⁸⁰ and 1.7%¹⁸³ of patients, therefore the studies were summarized together. Three studies recruited inpatients,^{176,180,182} three studies recruited ER patients,^{177,180,183} one study recruited outpatients,¹⁴⁰ and one study recruited outpatients and inpatients.¹⁸⁴ Two studies did not report which patients were included.^{179,181} Seven studies reported a formal assessment of prior PE risk, six of which were mixed-risk,^{176,177,181,183-185} and one high risk.¹⁷⁸ Three studies did not report a formal assessment of risk.^{179,180,182}

Pathway characteristics

The schematics in **Figure 14** 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^{176-179,182-185} of probability of PE. Six studies used clinical probability to select the next test,^{176,177,179,182,183,185} one used clinical probability in combination with probability by VQ imaging,¹⁸¹ and one did not report how the information was used.¹⁸⁴ All but two of the pathways^{180,181} 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.^{176-179,182,183,185}

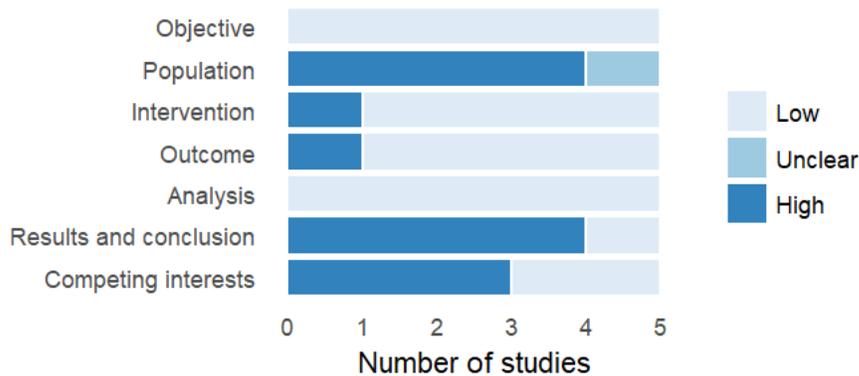
Two studies included a single imaging modality, CT.^{177,185} Four studies included two imaging modalities: Four studies used CT combined with VQ,^{176,180,183,184} one each with CT combined with PA,¹⁷⁸ and two with VQ combined with PA.^{181,182} One study included three modalities, CT, VQ, and PA.¹⁷⁹ No pathway studies reported the other imaging modalities. In four studies, CT was the final imaging modality in the pathway,^{176,177,183,185} and in four, PA was the final imaging modality.^{178,179,181,182} In the remaining studies, VQ was the final imaging modality in one,¹⁸⁴ and DSA in one.¹⁸⁰

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

Five studies were appraised by the Moga checklist.^{178,180,181,183,184} The summary of findings is shown in Figure 15. Most studies were single centre and therefore assessed as high risk of bias by the checklist. One study was considered at high risk of bias due to lack of clarity about anticoagulation, and in the same study, not all outcomes were reported. The most common reason for risk of bias in results and conclusions was lack of adverse event reporting.

Detailed presentations of responses to individual signalling questions by study are shown in Appendix 16.

Figure 15 Risk of bias for single-arm pathway studies



Outcomes

Failure rate

Ten studies of diagnostic pathways reported failure rates.¹⁷⁶⁻¹⁸⁵ One study reported the results for multiple sequences, 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 0.017,¹⁷⁶⁻¹⁸⁵ and the other two reported rates of 0.033 and 0.055, respectively (**Table 12**).

Table 12 Summary of modalities, endpoints and failure rate recorded for pathways for diagnosis of PE

Study	Sequence	Endpoints	Failure rate
Galipienzo 2012 ¹⁷⁷	W, DD, CT	3-month VTE	0/57 0.00 (0.00 to 0.063)
Righini 2008 ¹⁸⁵	rG, DD, US, CT	3-month VTE, AE, treatment outcome	6/649 0.009 (0.003 to 0.020)
Bosson 2007 ¹⁷⁶	W, DD, leg US, VQ, CT	3-month VTE	6/182 0.033 (0.012 to 0.070)
Jouveshomme 2007 ¹⁸⁰	CT, leg US, VQ, DSA	3-month VTE or death	12/218 0.055 (0.029 to 0.094)
Vigo 2006 ¹⁸⁴	C, CT, DD, VQ	3-month VTE	3/239 0.013 (0.003 to 0.036)
Hogg 2006 ¹⁷⁹	mW, DD, VQ, CT, PA	Safety	3/408 0.007 (0.002 to 0.021)
Ghanima 2005 ¹⁷⁸	DD, CT, PA	3-month VTE, % diagnosed	2/221 0.009 (0.001 to 0.032)
Perrier 2005 ^{183*}	C, DD, CT	3-month VTE, AE, treatment outcome	5/292 0.017 (0.006 to 0.040)
Miniati 2003 ¹⁸¹	C, VQ, PA	% definitive diagnosis, recurrence in 1 year	1/230 0.004 (0.00 to 0.024)
Miron 1999 ¹⁸²	VQ, C, DD, leg US, PA	% diagnosed	0/73 0.00 (0.00 to 0.049)

* Pregnant patients were not excluded

C = clinical assessment of risk; CT = computed tomography; DD = D-dimer measurement; PA = pulmonary angiography; rG = revised Geneva scale; US = ultrasound; VQ = ventilation-perfusion; VTE = venous thromboembolism; W = Wells score

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.^{176-178,183,185} The other studies did not incorporate that sequence,^{180,184,186} or did not report these patients separately.¹⁷⁹

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.¹⁸⁰

Computed Tomography

Twenty-six studies reported utility and/or safety results for CT.^{53,64,104,108,109,113-115,145,178,179,184,186-199}

Study and patient characteristics

Study design

One study was a RCT,⁵³ and twenty-five were nonrandomised studies.^{64,104,108,109,113-115,145,178,179,184,186-199}

Country and setting

Seven studies were multi-centre, two in Canada and the US,^{53,64} one in Slovenia, Turkey, Czech Republic, Uruguay, and India,¹⁴⁵, and one each in Canada,¹⁹⁹ the Netherlands,¹⁹¹ Italy,¹⁸⁴ and China.¹¹⁴ Nineteen studies were single centre, five were conducted in France,^{108,115,187,192,197} three in Spain,^{186,193,195} three in the US,^{188,189,194} one in Italy,¹⁹⁶ and one each in the UK,¹⁷⁹ Belgium,¹⁰⁹ Norway,¹⁷⁸ Switzerland,¹¹³ Tunisia,¹⁹⁰ China,¹⁰⁴ and India.¹⁹⁸ Seventeen studies were conducted in secondary^{108,109,114,115,186,187,190,195,196} or secondary or tertiary settings,^{53,64,145,184,188,191,193,199} two in a tertiary setting,^{113,198} and one in an ER.¹⁷⁸ In five studies, the setting was not specified.^{104,189,192,194,197}

Funding

Seven studies received government funding,^{53,64,114,178,186,191,193} one study received private funding,¹¹³ one study received industry funding,¹⁷⁹ and two studies did not receive funding.^{145,192} Fifteen studies did not report funding sources.^{104,108,109,115,184,187-190,194-199}

Population

The total number of included participants ranged from 50¹⁹⁸ to 3306.¹⁹¹ The mean age ranged from 38.3¹⁷⁹ to 71,¹⁸⁴ and the proportion of women from 0.26¹¹³ and 0.70.¹⁰⁹ One study recruited inpatients,¹⁸⁷ three recruited outpatients,^{109,113,178} five recruited inpatients and outpatients,^{64,108,115,145,184} two recruited inpatients and ER patients,^{195,196} and one recruited inpatients, outpatients, and ER patients,⁵³ and two recruited ER patients alone.^{186,191,193} Eleven studies did not identify which group were recruited.^{104,114,179,188-190,192,194,197-199} In the studies that reported a formal assessment of risk, five studies selected high risk patients,^{178,187,193,194,198} one selected intermediate risk patients,⁵³ and 13 selected a mixed population of patients.^{64,104,108,109,113-115,145,184,186,195,196,199} Seven studies did not report the prior risk.^{179,188-192,197}

Technical characteristics

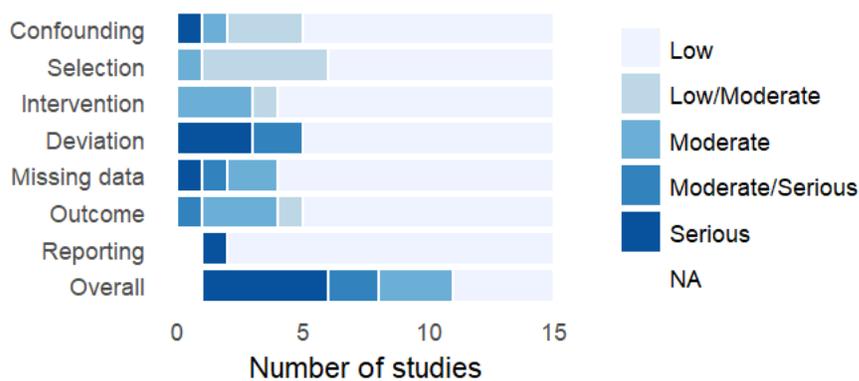
The number of CT detectors ranged from one¹⁹⁵ to 384.¹⁹² Five studies did not report the number of detectors.

Quality Appraisal

The single RCT⁵³ was assessed as low risk of bias in six of seven domains of the Cochrane Risk of Bias tool and unclear risk of bias for performance bias due to knowledge of allocated interventions.

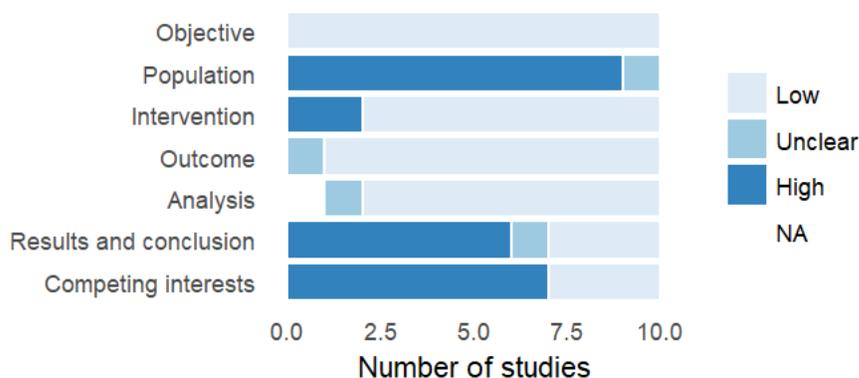
Fifteen studies were assessed as comparative studies by the ROBINS-I tool.^{53,64,104,108,109,113-115,145,179,188-191,193,194} Summary results are shown in Figure 16. Sources of serious risk of bias were exclusions of patients who had both a negative CT and anticoagulation (confounding), different reference standards applied across the study, a high proportion of indeterminate results in the reference standard (VQ or VQ-SPECT), which might be associated with PE severity, or exclusions due to missing data. For most of the outcomes of interest, studies did not report comparative data. The most relevant domains for these summaries were of selection, intervention, and outcome, which were at low to moderate risk of bias for all studies. Studies included in the comparison of failure rates ranged from moderate to serious risk of bias, with serious risk of bias predominately arising from inconsistent imaging across all patients.

Figure 16 Risk of bias for comparative studies of CT as index test



Ten studies were assessed as single-arm studies by the Moga checklist.^{178,184,186,187,192,195-199} Summary results are shown in Figure 17. Most studies were single centre and therefore assessed as high risk of bias by the checklist. Two studies did not clearly describe interventions or co-interventions (anticoagulation). Studies assessed at high risk of bias for reporting did not report one or more of all outcomes, loss to follow-up, or uncertainty around estimates. The majority of studies did not report funding. Studies all included an objective, and presentation of outcome and analysis were at low risk of bias.

Figure 17 Risk of bias for single-arm studies of CT



Detailed presentations of responses to individual signalling questions by study are shown in Appendix 16.

Outcomes

Failure rates

Single arm studies of failure rates

Nineteen studies reported failure rates (proportion of patients with negative imaging results who were diagnosed with VTE during follow-up) for CT as an index test, although none of them reported failure rate for the first 30 days alone.^{53,109,113,115,178,179,184,186-188,190-198} The majority of the studies reported failure in patients who were not anticoagulated.

The proportion of diagnostic failure individual studies ranged from 0^{109,113,192,196} to 0.048.¹⁹⁸ For all studies the pooled proportion of failure was 0.008 (95% CI 0.004 to 0.013; $I^2 = 55.0\%$, Q (df = 19) = 38.5, $P = 0.003$). 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 characteristics.

There was 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 (inpatient, outpatient, ED), and PE risk, there was insufficient variation between studies for statistical adjustment (Appendix 21). A graphical summary of the proportion of failures by setting suggested that failure might be higher in the Secondary category alone, but given the small number of centres in each setting, this is liable to be a result of random variation.

Fourteen studies reported failure in the first 3 months after imaging.^{53,113,115,178,179,184,186,191-193,195-198} Individual study failure rates ranged from 0^{109,113,192,196} to 0.048.¹⁹⁸ The pooled failure rate in the first 3 months was 0.007 (95%CI 0.003 to 0.012; $n = 14$; $I^2 = 58.4\%$; Q (df = 14) = 31.0, $P = 0.003$).

Five studies reported failure in the first 6 months after imaging.^{109,187,188,190,194} Individual failure rates ranged from 0¹⁰⁹ to 0.034.¹⁹⁰ The pooled failure rate in the first 6 months was 0.015 (95% CI 0.006 to 0.027; $n = 5$; $I^2 = 0$, Q (df = 4) = 5.1, $P = 0.275$).

Comparative studies of failure rates

Six studies,^{53,109,113,192,193,198} including one RCT⁵³ reported failure rates compared with reference standards: CC,^{113,193,198} CT (different imaging conditions),¹⁹² SC,¹⁰⁹ and VQ.⁵³

In the RCT, patients with suspected PE were randomized to undergo CT (CT pulmonary angiography) or VQ, with a primary outcome of failure rate over 3 months.⁵³ Two of 516 patients with negative CT developed VTE in 3 month follow-up (0.4%), compared with six of 611 patients (1%) with a negative (normal) VQ scan, a non-significant difference of -0.006 [95%CI -0.016 to 0.030]. One patient with negative CT experienced a PE within 30 days follow-up (0.2%). Two patients with negative VQ experienced a PE within 30 days (0.3%), and one experienced a proximal DVT. One PE was fatal, at 49 days in a patient with negative VQ.

The pooled risk difference across the five nonrandomized studies was also non-significant, 0.001 (95%CI -0.009 to 0.010; $I^2 = 0.0\%$; Q (df = 4) = 0.635, $P = 0.959$).

Nondiagnostic examinations

Fourteen studies reported on the number of exams that were nondiagnostic.^{64,104,108,109,114,115,145,178,189,191,194,196,197,199} For CT, nondiagnostic exams were due to technical inadequacy, such as insufficient filling of pulmonary vessels with contrast. The proportion of studies that was nondiagnostic ranged from 0.011¹⁰⁹ to 0.097.¹⁹⁴ The pooled rate of nondiagnostic exams was 0.036 (95%CI 0.024 to 0.050, n = 14; I² = 86.5%; Q (df = 13) = 89.2, P < 0.0001).

There was 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 (inpatient, outpatient, ED), and PE risk, there was insufficient variation between studies for statistical adjustment (Appendix 21). We could not investigate whether prior risk of PE explained heterogeneity due to insufficient data.

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.^{109,184,193,196,198} A sixth study reported a single alternative diagnosis.¹⁰⁸ Pneumonia and parenchymal lung disease were the most common alternative diagnoses (Appendix 18).

Safety

Contrast nephropathy and acute renal failure

Three studies involving CT reported the incidence of severe acute renal failure.^{185,196} An RCT investigating the effect of adding leg US to a pathway consisting of D-dimer and CT, reported no acute renal failure of initiation of hemodialysis, 0/509 (0%) patients undergoing DD-leg US-CT and 0/535 (0%) patients undergoing DD-CT.¹⁸⁵ Nonrandomized studies of safety and utility outcomes in CT reported none (in 1224 patients)²⁰⁰ and one instance of severe acute renal failure (0.27%).¹⁹⁶

Three studies involving CT reported the incidence of patients with serum creatinine increased above baseline of 1.4%,¹⁰⁹ 13%,²⁰¹ and 4%.²⁰² The clinical significance of this is unclear.

Allergic reaction

Two studies involving CT reported allergic reactions.^{64,185} In a randomized comparison of pathways including CT (DD-US-CT versus DD-CT), 1/509 (0.2%) patients in the DD-US-CT pathway and 2/535 (0.4%) patients in the DD-CT pathway had a mild cutaneous skin reaction on contrast administration.¹⁸⁵ In a nonrandomized study involving CT, 4 (<1%) had a mild allergic reaction, described as itching, swollen eyelids, or vomiting.⁶⁴ No anaphylactic reactions were reported.

Extravasation of contrast

One study involving CT reported extravasation of contrast.¹⁸⁵ An RCT investigating the effect of adding leg US to a pathway consisting of D-dimer and CT, one patient and two patients had extravasation of contrast in the DD-US-CT and DD-CT arms respectively.¹⁸⁵

Magnetic Resonance Imaging

Seven studies reported utility and/or safety results for MRI.^{50,122,123,125,125,130,203}

Study and patient characteristics

Study design

All studies were nonrandomized.

Country and setting

One study was multi-centre, conducted in the US,¹³⁰ and six were single-centre. Of the six, two were conducted in Germany,^{125,203} two in France,^{123,124} and one each in the US,⁵⁰ and China.¹²² Six studies were conducted in secondary^{50,123,125,130,203} or secondary/tertiary centres,¹²⁴ while the setting of one was unclear.¹²²

Funding

Four studies received government funding,^{122-124,130} one received no funding,⁵⁰ and two did not report the funding.^{125,203}

Population

The number of patients recruited ranged from 27¹²² to 818.¹³⁰ The mean age ranges from 38.9 years (SD 14.4 years)¹²² to 60.9 years (SD 15.7 years),¹²⁵ and the proportion of women from 0.22⁵⁰ to 0.59.¹³⁰ Two studies recruited only inpatients,^{125,203} one recruited inpatients, outpatients, and ER patients,¹³⁰ and one recruited inpatients and ER patients.¹²⁴ Three did not report on the patients recruited.^{50,122,123} Three studies reported the prior risk of PE, all of which recruited patients at mixed risk,^{124,125,130} and four did not report the risk.^{50,122,123,203}

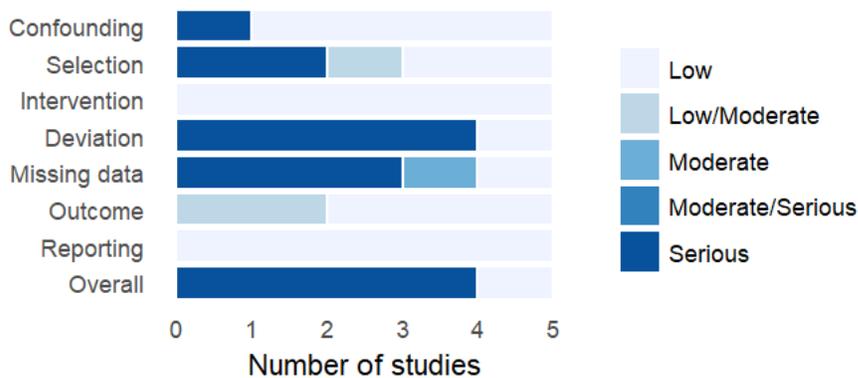
Technical characteristics

Five studies used 1.5 Tesla units,^{50,123-125,130} one study used a 3 Tesla unit,¹²² and one did not report field strength.²⁰³

Quality appraisal

Five studies were assessed as comparative studies by the ROBINS-I tool.^{122-125,130} Summary findings are shown in Figure 18. Overall risk of bias was low for one study, and serious for four. Serious risk of bias was predominately due to the exclusion of patients with nondiagnostic index test results, which contributed to selection bias, deviation from the protocol, and missing data, and means 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 MRI as index test



Two studies were assessed as single-arm studies by the Moga checklist.^{50,203} 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 or 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 16.

Outcomes

Failure rates

One study⁵⁰ reported 4 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 exams that were nondiagnostic,^{50,122-124,130,203} primarily due to technical inadequacy. Two studies reported results for multiple sequences (discussed below), and the highest rate was selected for pooling. Proportions of nondiagnostic exams ranged from 0¹²² to 0.474¹²³. The dataset was too statistically heterogeneous to pool ($I^2 = 98.5$; $Q(df = 5) = 212.1, P < 0.0001$).

The variability in the proportion of nondiagnostic exams across studies did not appear to be related to the type of MRI examinations conducted. From review of the patient flow, studies did not obviously differ in their approach to excluding patients, which might have been reflected in the proportion of nondiagnostic exams. Studies generally used a pragmatic definition for nondiagnostic exams, and 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 0.129¹²⁵ and 0.445²⁰³ of patients. One study of US as an index test also reported findings for MRI. Details are shown in Appendix 18.

Safety

Adverse event outcomes

One study of MRI compared with CT and VQ imaging 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 6-month follow-up that included 84% of patients.⁶⁴

Extravasation of contrast.

In one study 1/275 patients was unable to complete the MRI protocol due to extravasation of contrast.¹²⁴

Thoracic ultrasound

Two studies reported utility and/or safety results for US studies.^{139,140}

Study and patient characteristics

Both studies were nonrandomized, single-centre studies at secondary settings, conducted in Austria¹⁴⁰ and France.¹³⁹ Neither reported funding.^{139,140}

The number of patients recruited was 55 in one study¹⁴⁰ and 74 in the other.¹³⁹ The mean age in one study was 69 years¹⁴⁰ and in the other 66 years (SD 17).¹³⁹ One study recruited inpatients,¹⁴⁰ and the other did not report which.¹³⁹ Both recruited a mixed-risk group of patients.^{139,140}

Technical characteristics

One study used a 5 MHz transducer,¹³⁹ and the other used frequencies of 3.5, 7.5 and 10 MHz.¹⁴⁰

Quality appraisal

One study was assessed by ROBINS-I.¹⁴⁰ Most domains were assessed as low risk of bias, but there were significant deviations from the protocol, leading to an overall assessment of moderate risk of bias.

One study was assessed by the Moga checklist.¹³⁹ 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 were at low risk of bias.

Outcomes

Nondiagnostic exams

One study using US as an index test reported three nondiagnostic (indeterminate) examinations, out of 55 patients imaged with ultrasound.¹⁴⁰

Alternative diagnoses and incidental findings

One study reported alternative diagnoses and incidental findings in 19 of 55 patients.¹⁴⁰ Details are in Appendix 18.

Perfusion only (Q)

Six studies reported utility and/or safety results for perfusion-only studies.^{114,145,146,149,152,153}

Study and patient characteristics

Study design

All studies were nonrandomized

Country and setting

Five studies were multi-centre, conducted in the US,¹⁴⁹ Netherlands and Belgium,¹⁵² Slovenia, Turkey, Czech Republic, Uruguay and India,¹⁴⁵ Slovenia,¹⁴⁶ and China.¹¹⁴ One single centre study was conducted in Italy.¹⁵³ Five studies were conducted in secondary^{114,149} and secondary / tertiary settings,^{145,146,152} and one did not identify the setting.¹⁵³

Funding

Three studies received government funding,^{114,149,153} two reported receiving no funding,^{145,152} and one study did not report funding.¹⁴⁶

Population

Studies recruited between 76¹⁵² and 910 patients.¹⁴⁹ The age ranged from a median of 40 years (29 to 45 years)¹⁵² to a median of 72 years.¹⁴⁶ One study recruited inpatients,¹⁴⁶ two recruited inpatients and outpatients,^{145,152} one recruited inpatients, outpatients, and ER patients.¹⁴⁹ Two did not report the patients they recruited.^{114,153} Four studies recruited a mixed-risk group of patients,^{114,145,149,153} and one recruited patients at high prior-risk of PE.¹⁵² One study did not report prior risk.¹⁴⁶

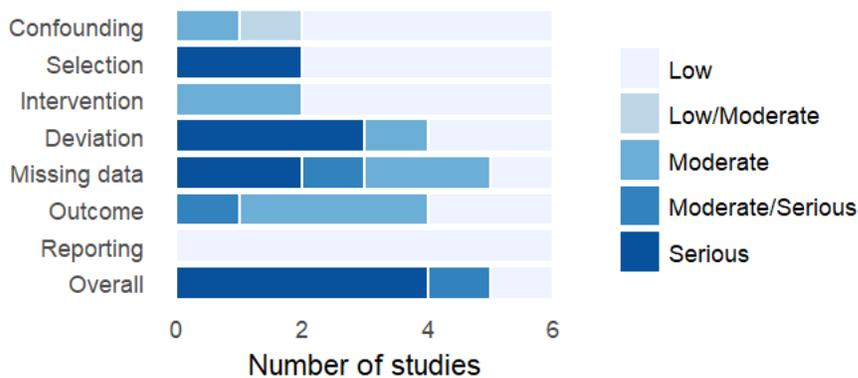
Technical characteristics

All studies used 99mTc-labelled micro-aggregated albumin injection for visualization, with doses ranging from 120 MBq¹⁴⁶ to 200 MBq.¹⁴⁶ Studies used the PISAPED,^{114,149,152,153} PIOPED II,^{114,149} and EANM guidelines¹⁴⁶ for interpretation.

Quality appraisal

Six studies were assessed by ROBINS-I. A summary of findings is shown in Figure 19. Studies were noted as being at high risk of bias for protocol deviation or from missing data due to a high proportion of indeterminate studies. One study excluded these patients, and another referred only patients with an abnormal lung scan for further testing, resulting in a selection bias and possibly biasing the interpreter of the lung scan. 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 (Q) as an index test



Outcomes

Nondiagnostic exams

Five studies reported the number of perfusion exams that were nondiagnostic, primarily due to technically adequate but indeterminate exams. Proportions of nondiagnostic exams ranged from 0^{114,145} to 0.214.¹⁴⁶ The dataset was heterogeneous to pool ($I^2 = 98.4$; $Q(df = 4) = 360.6$, $P < 0.0001$).

From available data, the source of heterogeneity could not be determined. For perfusion exams, nondiagnostic exams are predominately technically adequate exams with indeterminate results. The variability in the proportion of nondiagnostic exams across studies did not appear to be related to the interpretation criteria. From review of the patient flow, studies did not obviously differ in their approach to excluding patients, which might have been reflected in the proportion of nondiagnostic exams.

Perfusion-Single Photon Emission Tomography (Q-SPECT)

One nonrandomized study reported utility and/or safety for Q-SPECT.¹⁵⁵

Study and patient characteristics

The study was a single-centre study conducted at a secondary setting in Sweden.¹⁵⁵ Funding was not reported.

The study recruited 152 patients, primarily outpatients.¹⁵⁵ Prior risk of PE was not reported.¹⁵⁵

Technical specifications

The study used 99mTc-Technogas or 99mTc-DTPA for visualization, and EANM criteria for interpretation.¹⁵⁵

Quality appraisal

One study was assessed by ROBINS-I.¹⁴⁰ Two domains (intervention and missing data) were assessed as low risk of bias, and four as low/moderate (risk of confounding, risk of selection bias, deviation from the protocol, and overall reporting). Overall risk of bias was low/moderate.

Outcomes

Failure rate

One study¹⁵⁵ reported no failures in patients with negative scans over 3 months of follow-up.

Nondiagnostic exams

One study reported no non-diagnostic exams for Q-SPECT.¹⁵⁵ Non-diagnostic 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 (VQ)

Eleven studies reported utility and/or safety results for VQ.^{104,109,114,140,145,146,158,159,161,163,167}

Study and patient characteristics

Study design

All studies were nonrandomized

Country and setting

Six were multicentre studies, one conducted in Slovenia, Turkey, Czech Republic, Uruguay, and India,¹⁴⁵ two conducted in the US,^{159,163} Australia, and one each conducted in Slovenia,¹⁴⁶ Australia,¹⁶⁷ and China.¹¹⁴ The five single centre studies were conducted in Belgium,¹⁰⁹ Denmark,¹⁵⁸ Scotland,¹⁶¹ Austria,¹⁴⁰ and China.¹⁰⁴ All studies were conducted in a secondary^{109,114,140,159,161,163} or secondary/tertiary setting,^{145,146,158,167} with the exception of one whose setting was not reported.¹⁰⁴

Funding

Three studies received government funding,^{114,159,163} one received industry funding¹⁶⁷, one reported no funding,¹⁴⁵ and six did not report the funding received.^{104,109,140,146,158,161}

Population

The studies recruited between 36¹⁵⁸ and 951 patients.¹⁶³ Three studies recruited inpatients,^{140,146,167} one recruited outpatients,¹⁰⁹ one recruited inpatients and outpatients,¹⁴⁵ and two recruited inpatients, outpatients, and ER patients.^{159,163} Four studies did not report the patient origins.^{104,114,158,161} Six studies recruited a mixed-risk group of patients,^{104,109,114,140,145,163} and five did not report the prior PE risk.^{146,158,159,161,167}

Technical characteristics

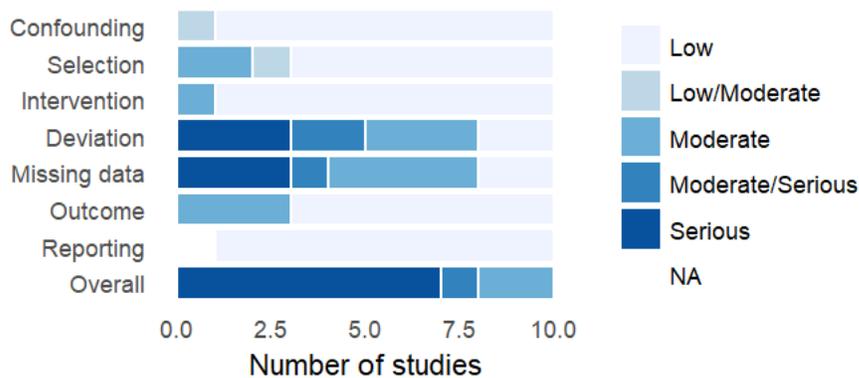
With the exception of one study that did not provide details,¹⁴⁵ all studies used 99mTc-labelled micro-aggregated albumin injection for perfusion visualization, with doses ranging from 100 MBq¹⁴⁶ to 370 MBq.¹¹⁴ For ventilation, six studies used 99mTc-labelled DTAP or Technogas,^{104,109,114,145,146,167} two used 81mKr,^{109,158} and three used 113Xe.^{145,159,161}

Interpretation criteria varied widely, with studies using PLOPED, PISAPED and modifications and revisions, and study-specific criteria.

Quality appraisal

Ten studies were assessed by ROBINS-I.^{104,109,114,140,145,146,158,159,161,167} The summary of findings was shown in Figure 20. Seven studies were considered at serious risk of bias, primarily due to post-hoc exclusions from the analysis, for unspecified reasons or for indeterminate findings.

Figure 20 Risk of bias for comparative studies of VQ as index test



Detailed presentations of responses to individual signalling questions by study are shown in Appendix 16.

Outcomes

Failure rate

Two studies^{159,161} reported no failures in patients with negative scans, out of 21¹⁵⁹ and 28 patients,¹³⁸ respectively. Duration of follow-up was one year¹⁵⁹ and unknown.¹⁶¹

One study reported comparative failure rates,¹⁶¹ with no failures in 28 patients who had a VQ 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 exams

Ten studies reported the number of VQ exams that were nondiagnostic,^{104,109,114,140,145,146,159,161,163,167} primarily due to technically adequate but indeterminate exams. Two studies reported the results for multiple sequences, and the highest rate was selected for pooling. The proportion of nondiagnostic exams ranged from 0.071¹⁰⁴ to 0.574,¹⁴⁵ and the dataset was too heterogeneous to pool ($I^2 = 97.1\%$; $Q(df = 9) = 237.3$, $P < 0.0001$).

Ventilation-Perfusion Scintigraphy-Single Photon Emission Computed Tomography (VQ-SPECT)

Eleven nonrandomized studies reported utility and/or safety results for VQ-SPECT.^{110,146,158,165,167-169,172,173,204,205}

Study and patient characteristics

Two studies were multi-centre, conducted in Slovenia¹⁴⁶ and Australia.¹⁶⁷ One single centre study was conducted in Canada,²⁰⁵ one in the US,¹¹⁰ two in Sweden,^{168,173} two in Spain,^{165,172}

and one each in the UK.²⁰⁴ Denmark,¹⁵⁸ Australia.¹⁶⁹ Nine studies were conducted in a secondary care setting,^{110,146,158,165,167-169,172,173,204,205} and the setting for two was unclear.

Studies recruited between 36¹⁵⁸ and 1785 participants.¹⁶⁸ Four studies involved inpatients,^{110,146,165,167} one involved outpatients,¹⁷² and six did not report the origins of patients.^{158,168,169,173,204,205} None of the studies reported prior clinical risk of PE.

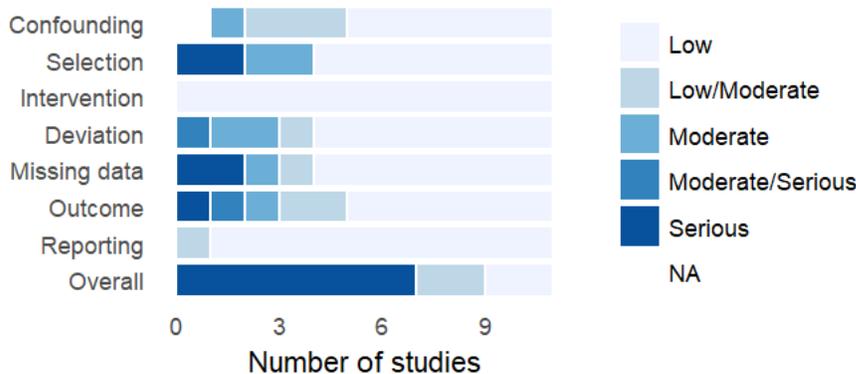
Technical characteristics

With the exception of one study that did not provide details,¹⁴⁵ all studies used 99mTc-labelled micro-aggregated albumin injection for perfusion visualization, with doses ranging from 100 MBq¹⁴⁶ to 185 MBq.¹⁶⁷ For ventilation, eight studies used 99mTc-labelled DTAP or Technogas,^{110,146,165,167,168,172,173,205} two used 81mKr,^{158,204} and one did not report.¹⁶⁹ 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. Studies were considered at serious risk of bias. Three studies were at serious risk of bias due to inappropriate exclusions, for unclear reasons, or in such a way as to bias results by greater or lesser severity. Three studies were at serious risk of bias due to the handling of missing data, indeterminate studies. In two studies, treatment with anticoagulation was not primarily determined by imaging results.

Figure 21 Risk of bias for comparative studies of VQ-SPECT as index test



Detailed presentations of responses to individual signalling questions by study are shown in Appendix 16.

Outcomes

Failure rate

One study reported no failures in 405 patients with negative scans at 3 month follow-up.²⁰⁶

Nondiagnostic exams

Ten studies reported the number of VQ-SPECT exams that were non-diagnostic,^{110,146,165,167-169,172,173,204,205} primarily due to technically adequate but indeterminate results. The proportion of

nondiagnostic exams ranged from 0^{146,167} to 0.220,¹⁶⁹ and the dataset was too statistically heterogeneous to pool ($I^2 = 94.1\%$; $Q(df = 9) = 97.4$, $P < 0.0001$).

Removing Harris 2007 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.

Summary of utility findings

The pooled proportion of patients presenting with recurrent VTE following a negative scan at three and six months were available for CT, 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 VQ 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% 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, VQ, VQ-SPECT), or no studies reporting failure rates (US, Q, VQ-SPECT-CT).

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

The proportion of patients with non-diagnostic studies for CT was 0.036 (pooled, 95% CI 0.024 to 0.050), for MRI from 0 and 0.474, for VQ from 0.071 to 0.574, and for VQ-SPECT from 0 to 0.222. One small study reported a proportion of 0.053 nondiagnostic exams for ultrasound, 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 ultrasound and the nuclear medicine modalities.

Safety data was sparsely reported, and adverse events were generally not serious.

Question 3: PE Imaging in Pregnancy

Thirteen studies^{147,180,181,183,207-215} included populations or subgroups of pregnant or postpartum women. Four studies did not report on outcomes in the pregnancy subgroup so are not included in the following summary.^{147,180,181,183}

Summary of Study Characteristics

Study characteristics for the nine studies reporting on pregnant populations are presented in Appendix 19.

Study Design

All studies were non-randomized, six were retrospective, and three were prospective cohorts.^{210,211,214} The six retrospective studies were cohort studies,^{207-209,215} and case-control

studies^{212,213} Six studies were comparative,^{207-209,211,213,214} and three were non-comparative studies with safety data.^{210,212,215}

Country of Origin

The studies were conducted in Canada²¹⁰ Ireland^{209,212} Sweden,²¹¹ the US,^{207,208,215} and the UK.^{213,214} There were a mix of multi-centre^{207,210} and single centre studies.^{208,209,211-215} All studies were conducted in secondary or tertiary care community or academic hospitals.²⁰⁷⁻²¹⁵

Patient Population

All study participants were pregnant women suspected of acute pulmonary embolism. Information on patient status (e.g., inpatient, outpatient and emergency room), and geographical setting (urban vs rural vs remote) was limited. One study¹⁹⁶ reported including both inpatients 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.

Interventions and Comparators

Two studies compared Q-SPECT, V-SPECT or V/Q-SPECT and CT.^{211,213} Three non-comparative studies reporting on safety outcomes were included, two investigating the use of CT against clinical follow-up,^{212,215} and one²¹⁰ assessing V/Q scintigraphy against clinical follow-up. Two studies compared CT against Q scintigraphy,^{207,214} and two studies compared CT and V/Q scintigraphy.^{208,209}

Outcomes and Funding

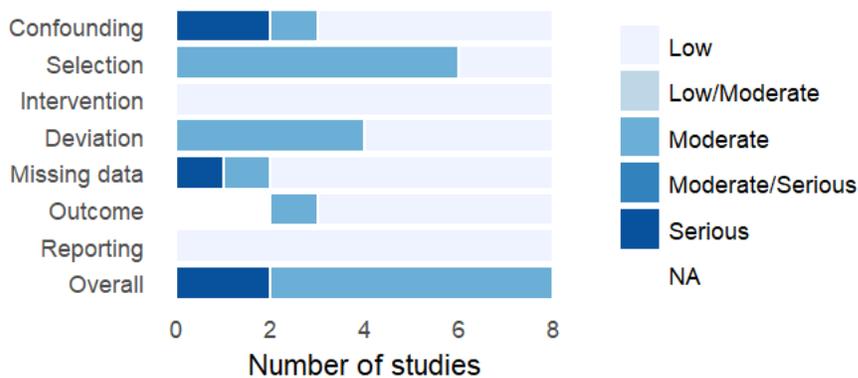
Studies included data on clinical utility and safety. No studies reported on diagnostic test accuracy against an appropriate reference standard. Funding was provided through government or academic grants,^{210,211,213} otherwise the source was not disclosed.^{207-209,212,214,215}

Quality Appraisal

Non-randomized controlled Studies (ROBINS-I)

Eight studies contained comparative data, and were assessed using the ROBINS-I tool.^{207-209,211-215} A summary of findings is shown in Figure 22. All studies compared two groups who received different imaging, and the studies at high risk of bias were those that did so without adjustment and were at risk of baseline confounding. Another study was at high risk of bias due to missing data due to a substantial number of nondiagnostic studies.

Figure 22 Risk of bias for comparative studies in pregnancy



Also, it should be noted that a systematic review by van Mens published in early 2017²¹⁶ reported that they could not include Cahill 2009²⁰⁸ due to discrepancies identified between the original study results and additional data provided on the pregnant patient subgroup that could not be resolved by the authors.

Non-Comparative Studies (MOGA)

One non-comparative study was assessed using the MOGA tool.²¹⁰ The authors stated a clear hypothesis. It was not clear whether there was consecutive recruitment and disease severity of patients at entry to the study was unclear, suggesting risk of selection bias. The intervention was clearly described but co-interventions received by the patients were not reported. The outcome measures were clearly defined in the methods section, but some of the follow-up measured relied on maternal recall and mining of hospital records, which may have introduced recall bias and subjectivity into the assessment. Due to exclusion of women who were anticoagulated from the analysis, the authors may be underestimating potential harms. Study grant funding is disclosed but other conflicts of interest were unknown.

Detailed presentations of responses to individual signalling questions by study are shown in Appendix 16.

Summary of Diagnostic Test Results

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

Summary of Utility Results

Failure Rate

Failure rates (i.e., morbidity and mortality due to misdiagnosis at 30 days' follow-up),⁹ presented by modality for comparison, are reported in Table 13. Overall, rates of VTE or isolated PE in patients with negative or indeterminate test findings were low.

Several studies only reported on the failure rate 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 diagnosed with PE.²¹¹ In one non-comparative study, no patients with non-diagnostic or normal VQ scans who did not receive anticoagulation had an incidence of VTE during follow-

up.²¹⁰ In one study, no patients with indeterminate V/Q scans ended up with VTE upon CT or during follow-up.²¹⁴ In two other non-comparative studies, no patients negative for PE with CT had VTE during follow-up.^{212,215}

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 each of two studies^{207,209} in the CT group, and no patients in the VQ²⁰⁹ or perfusion scanning²⁰⁷ groups.

Table 13 Failure Rate by Modality

Study	CT, n/N (%)	VQ, n/N (%)	p-value
Browne 2014 ²¹²	0/70 (0%)	---	---
Bajc, 2015 ²¹¹	---	0/116 (0) ^b	---
Bourjeily, 2012 ²¹⁵	0/318 (0%)	---	---
Shahir 2010 ²⁰⁷	1/94 (1)	0/94 (0)	NR
Ridge 2009 ²⁰⁹	1/8	0/0	NR
Scarsbrook 2007 ²¹⁴	---	0/7	---
Chan 2002 ²¹⁰	---	0/0	---

^bVQ-SPECT

Indeterminate or Non-Diagnostic Tests

Rates of indeterminate tests by modality are presented in **Table 14**. The trend was towards a greater number of indeterminate or non-diagnostic tests in the CT group when the comparison was made to V/Q modalities; however, the rates were generally low.

Two studies^{211,213} reported numerically higher rates of indeterminate tests for patients who received CT versus V/Q SPECT, but did not report on statistical significance.

One study²⁰⁷ reported numerically higher rates of indeterminate tests in the CT group versus perfusion-only scanning and did not report statistical significance. One study²⁰⁹ reported significantly higher rates of indeterminate tests in the CT versus VQ group. One study reported higher rates of technically inadequate testing in the CT group, but more similar rates if non-diagnostic V/Q scans were considered in the comparison.²¹⁴

Another study reported numerically higher rates of indeterminate VQ versus CT scans, with no significant difference between groups.²⁰⁸ 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 (2.1 to 13.8), including when adjusted for gestational age, postpartum status, hypoxia and chest pain.²⁰⁸

One study did not compare modalities but reported over a quarter of tests as indeterminate for VQ scintigraphy.²¹⁰ Another study reported a low rate of inconclusive (0.9%) and technically limited (20%) CT exams.²¹⁵

Table 14 Summary of indeterminate or non-diagnostic tests

Study	CT, n/N (%)	V/Q-based modality, n/N (%)	p-value
Gruning 2016 ²¹³	1/23	0/89 ^a	NR
Bajc 2015 ²¹¹	6/61(10)	0/127 ^a	NR
Bourjeily 2012 ²¹⁵	3/340 (0.9) ^b	---	---
Shahir 2010 ²⁰⁷	6/106 (5.6)	3/99 (3.3) ^c	0.0058
Cahill 2009 ²⁰⁸	17% ^d	13.2% ^d	0.38
Ridge 2009 ²⁰⁹	10/28 (35.7)	1.25 (4)	0.0058
Scarsbrook 2007 ²¹⁴	1/9 (11)	7/96 (7) ^e	NR
Chan 2002 ²¹⁰	---	29/120 (24.2)	---

CT = computed tomography; NR = not reported; V/Q = ventilation perfusion scintigraphy

^aV/Q SPECT

^b68/340 (20%) technically limited

^cPerfusion only scan

^dTotal n not reported

^e0/96 were technically inadequate

Alternative Diagnoses and Incidental Findings

Two studies^{211,213} reported on incidental findings in pregnant women. Pneumonia was detected by V/Q SPECT in 15(12%) patients, two of whom also had PE.²¹¹ In addition, one occurrence of both airway obstruction and left heart failure were detected.²¹¹ One study²¹³ 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 15**.

Mortality

Maternal mortality rates were rarely reported on and the rates were very low in both studies that presented data.^{207,210}

Obstetrical and pediatric outcomes

One retrospective study of VQ imaging reported obstetrical and pediatric outcomes in 121 pregnant women with suspected PE.²¹⁰ 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 of previously diagnosed primary pulmonary hypertension after a normal scan.²¹⁰ 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%).²¹⁰ 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 (VQ scan at 22 weeks gestation, followed by low dose heparin until delivery); duplicate ureters (VQ scan at 11 weeks gestation); transposition of the great arteries identified prior to the VQ scan; and a small hemangioma (normal VQ scan at 28 weeks gestation).²¹⁰ 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 VQ scanning at 26 weeks. No childhood cancers or leukemias were reported, although the mean follow-up on the mothers was less than 2 years (mean 20.6 months, 0.5 to 108 months).

The authors concluded that pediatric risks from VQ 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^{211,213} radiation dose to maternal tissue, maternal breast tissue, was higher with CT versus 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 15 Mortality and Radiation Dose Results by Modality

Study	CT, n/N (%)	VQ, n/N (%)	p-value
Mortality			
Shahir 2010 ^{207a}	0/NR(0)	0/NR(0)	NR
Chan 2002 ²¹⁰	2/121	---	NR
Radiation Dose			
Bajc 2015 ²¹¹		0.6 mGy (V/Q SPECT)	NR
		0.25 mGy (Q SPECT only)	
		0.34 to 0.48 mGy ^b (V/Q SPECT)	NR
		0.14 to 0.20 mGy ^b (Q SPECT only)	
Gruning 2016 ²¹³	7.8 (2 to 18)	1.4 (0.7 to 2.8) (Q SPECT)	NR
		0.82 (V SPECT)	
		1.6 (0.70 to 3.6) (V/Q SPECT)	
	20 (4 to 50)	0.49 (0.24 to 1.0) (Q SPECT)	NR
		0.29 (V SPECT)	
		0.56 (0.24 to 1.3) (V/Q SPECT)	
	110 (3.7 to 380)	71 (33 to 130) (Q SPECT)	NR
		22 (V SPECT)	
		77 (33 to 150) (V/Q SPECT)	

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

^aRates not disclosed, authors stated that “none of the patients died”²⁰⁷

^bDepending on trimester of pregnancy²¹²

Search updates for Question 2 and 3

The meta-analysis incorporated studies retrieved to February 16, 2017. Four monthly update searches, with a latest search date of July 28, 2017, retrieved a total of 443 articles. Twenty-five articles were retrieved for full text review, and three eligible studies were identified, reporting DTA²¹⁷ and utility outcomes.²¹⁷⁻²¹⁹ The results of these studies were consistent with the those already identified.

Mila 2017²¹⁷ compared VQ-SPECT-CT with full dose CT, and VQ 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, while those with contraindications underwent imaging without contrast (46.8%).

The sensitivity of VQ-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 VQ-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 VQ-SPECT-CT performed better than VQ-SPECT or CT.

The rate of indeterminate studies was 0.022 for VQ-SPECT-CT and 0.032 for VQ-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 2017²¹⁸ conducted a patient-level meta-analysis of test failure for four studies of a diagnostic algorithm that used Wells, D-dimer and CT to exclude PE. The combined four studies included 7975 patients, of whom 6148 patients were eligible for the study. The mean age was 57 years (SD 17 years), and 0.58 were male. The pre-test probability of PE was likely in 4254 and unlikely in 1894; 1307 were diagnosed with PE at baseline, leaving 4421 with negative imaging.

The three months VTE rate ranged from 0.005 to 0.058 across the four studies. The three months VTE rate in patients with a normal CT and Wells ≤ 4 (unlikely) was 0.0085 (95% CI 0.004 to 0.02) and Wells >4 (likely) was 0.02 (0.01 to 0.04). The three months rate for fatal PE in patients with a normal CT and Wells ≤ 4 (unlikely) was 0.0012 (0.0001 to 0.014) and Wells >4 (likely) was 0.0048 (95% CI 0.002 to 0.011).

Pelletier-Galarneau 2017²¹⁹ conducted a retrospective study of diagnostic yield of studies for VQ in patients with suspected PE according to referral source (emergency department, inpatient, 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 PLOPED 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 inpatients. The proportion of women ranged from 0.538 for inpatients 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 inpatients.

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 inpatients.

DRAFT

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.²²⁰ The systematic review identified thirteen economic evaluations, published between 1990 to 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), USA (n=5), Canada (n=1), and Australia (n=1). Two additional studies were identified from our literature search : one each from Australia²²¹ and Canada.²²² 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),²²¹ while the study from Canada assessed the cost-effectiveness of different imaging modalities upon a non-diagnostic VQ lung scan (i.e., pulmonary angiography, leg US ± pulmonary angiography, or leg US ± evaluation of cardiorespiratory reserve ± pulmonary angiography or serial leg US). Appendix 23: Characteristics of existing published economic evaluation on diagnosis of PE 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,²²³⁻²²⁶ the majority of studies compared fewer than ten 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 regards to the diagnostic strategy that would be considered most likely cost-effective (Appendix 23: Characteristics of existing published economic evaluation on diagnosis of PE). Furthermore, only one study formally compared CDR (e.g., Geneva/ Wells) as part of its diagnostic pathway.²²¹ The majority of studies were found to have adopted a short time frame (i.e., < one year) and, in the few studies with a lifetime perspective, the approach to conduct long-term extrapolation was rarely described.^{223,224}

Given that existing economic evaluations do not fully address all possible diagnostic pathways of interest, largely do not explore the long-term implications of a PE diagnosis, and 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 **Error! Reference source not found.**), a de novo economic analysis on the cost-effectiveness of different diagnostic strategies in adult suspected of acute PE was conducted as part of the economic review. The economic models identified from the literature provided insights towards 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 suspected of 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.⁹⁴

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 suspected of a 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 with 41.4% males. The underlying prevalence of PE (15.2%, 171/1126) reflected Canadian reported rates.¹¹⁸ It was further assumed that the initial contact with the health care system would be in an outpatient setting although an inpatient 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. As the implementation review noted, some imaging modalities and biochemical test (i.e., d-dimer) are not readily available in rural and remote settings. Scenario analyses were conducted in which access to d-dimer was removed thereby, removing any diagnostic strategies that involved d-dimer.

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.²²⁵⁻²³¹

Although the original protocol specified that the reference case would be discounted at a rate of 5% per annum, recently revised Canadian guideline for the conduct of economic evaluations now recommended a lower discount rate of 1.5% per annum.²³² 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%.²³³

4. Diagnostic Algorithms

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 multistep sequential algorithm that may include risk stratification, rule-out tests, ancillary testing and diagnostic imaging.²³⁴ The economic model therefore explored the cost-effectiveness of the entire diagnostic algorithms for PE, as depicted in Appendix 5: Pulmonary Embolism Diagnosis and Management Strategies and Subsequent Outcomes, instead of most published models which focus on specific step in the diagnostic management.

Risk stratification refers to CDR which assign a risk score reflecting patient's likelihood of having PE. Objective clinical prediction rules of interest to this review include the Wells Score and Geneva rule. Application of these validated algorithms allows for the determination of a pre-test probability for PE. Despite this, CDR 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 CDR alone. In patients categorized as having a low pre-test probability of PE (i.e., low risk), they will proceed to ‘rule out’ test to establish a PE diagnosis. In addition, subjective pre-test probability assessment (i.e., clinical gestalt) was also evaluated.

As noted above, if patients were deemed to be at sufficiently low risk based on one of the CDR, the following biochemical tests or decision rules may be further applied to formally ‘rule out’ PE:

- i. D-dimer testing: A negative d-dimer assay result combined with a low pre-test probability, as determined by the CDR, is considered sufficient to rule out PE. No further workup is required.
- ii. PERC > d-dimer: PERC is another CDR 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 down the diagnostic algorithm by receiving ancillary test or diagnostic imaging.

The most common ancillary test is leg US. PE, together with DVT, is considered to be one disease entity commonly referred to as venous thromboembolism (VTE). These conditions often co-occur, with research suggesting over 70% of patients presenting with PE are found to have DVT in the legs^{5,18} and 25 to 50% of patients with PE have clinically evident DVT.²³⁵ Leg US is an alternative option to obviate the need for radiological imaging tests as patients diagnosed with a DVT by leg US are treated in the same manner as those diagnosed with PE (i.e., initiation of anticoagulant therapy).

In patients still suspected of PE after risk stratification and ancillary testing, diagnostic imaging is offered. A variety of imaging modalities are used, and based on the clinical review, the economic review assessed CT, MRI and VQ-based technologies (e.g., VQ planar scintigraphy and VQ SPECT). Thoracic US was explored in an exploratory analyses given that this imaging modality is commonly employed on unstable patients who are not readily sent to diagnostic imaging and given the limitations with the clinical data, as highlighted in the clinical review (Thoracic Ultrasound: Summary of diagnostic test results).

Details on the clinical decision of different diagnostic findings associated with each test are described in Appendix 24: Diagnostic Pathway. When factoring all clinically-possible permutations involving the diagnostic exams and tests, a total of 120 diagnostic pathways were of interest to this review (Figure 23). The list of all possible diagnostic strategies of interest to this review can be found in Appendix 25: List of 120 Diagnostic Algorithms Considered in the Economic Model.

Figure 23: Summary of the types of diagnostic tests and exams evaluated in the reference case; combined together in all clinically relevant permutations results in 120 diagnostic strategies

Clinical prediction rule	‘Rule out’ test	Ancillary test	Diagnostic Imaging
None (i.e., clinical gestalt)	None*	None	CT
Wells: Three levels vs.	d-Dimer	Leg US	MRI

simplified			
Revised Geneva	PERC>d-dimer		VQ Planar scintigraphy
			VQ SPECT

CT= computed tomography; MRI = magnetic resonance imaging; PERC = Pulmonary embolism rule-out criteria; SPECT = single-photon emission computed tomography; US = ultrasound; VQ = ventilation/perfusion

*Note: A 'rule out' test is always given after performing a formal CDR (i.e., Wells or Geneva) if the patient is deemed of low or moderate (if applicable) post-test probability. No 'rule out' test is only applicable in strategies involving no objective CDR (e.g., Gestalt).

5. Perspective

The perspective of a Canadian Ministry of Health was adopted, consistent with CADTH guidelines for the conduct of economic evaluations.²³² As such, direct and indirect medical costs were captured including the cost of laboratory and diagnostic tests, emergency visits, in-patient visits and medical services.

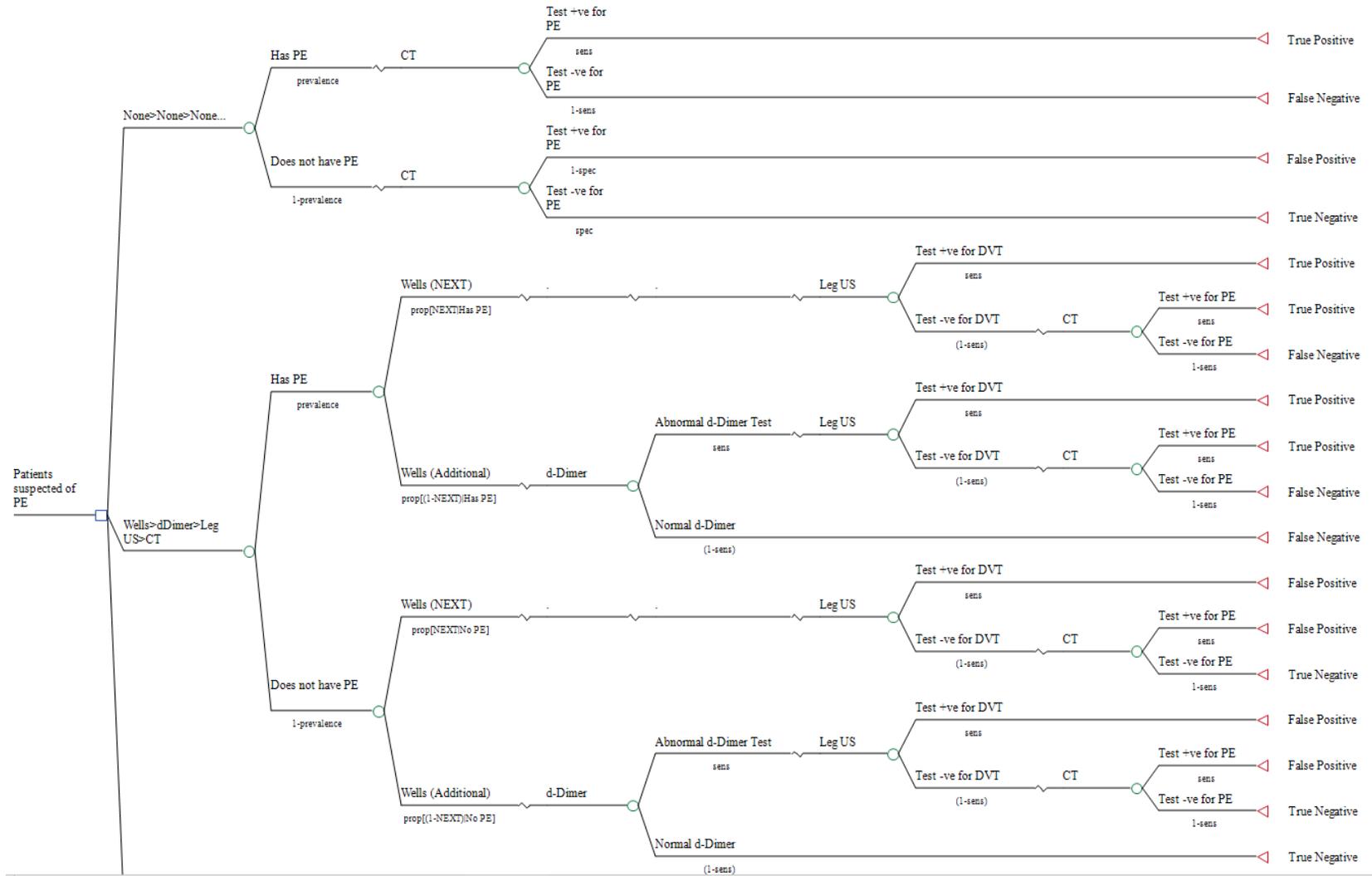
6. Decision Analytic Model

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 24 illustrates the structure of the decision tree and presents two of the 120 diagnostic algorithms evaluated in this review. The patient cohort, suspected of PE, proceeds through the decision tree and, conditional to the diagnostic accuracy of upstream tests, this determines their progression through the next step of diagnostic pathway in terms of whether they will receive further downstream tests or whether a diagnosis can be reached (i.e., of having or not having PE). The sensitivity and specificity of each test and the test order impacts the proportion of correct and misdiagnosis of PE.

DRAFT

Figure 24: Illustration of decision tree of 2 of the 120 diagnostic algorithms modelled

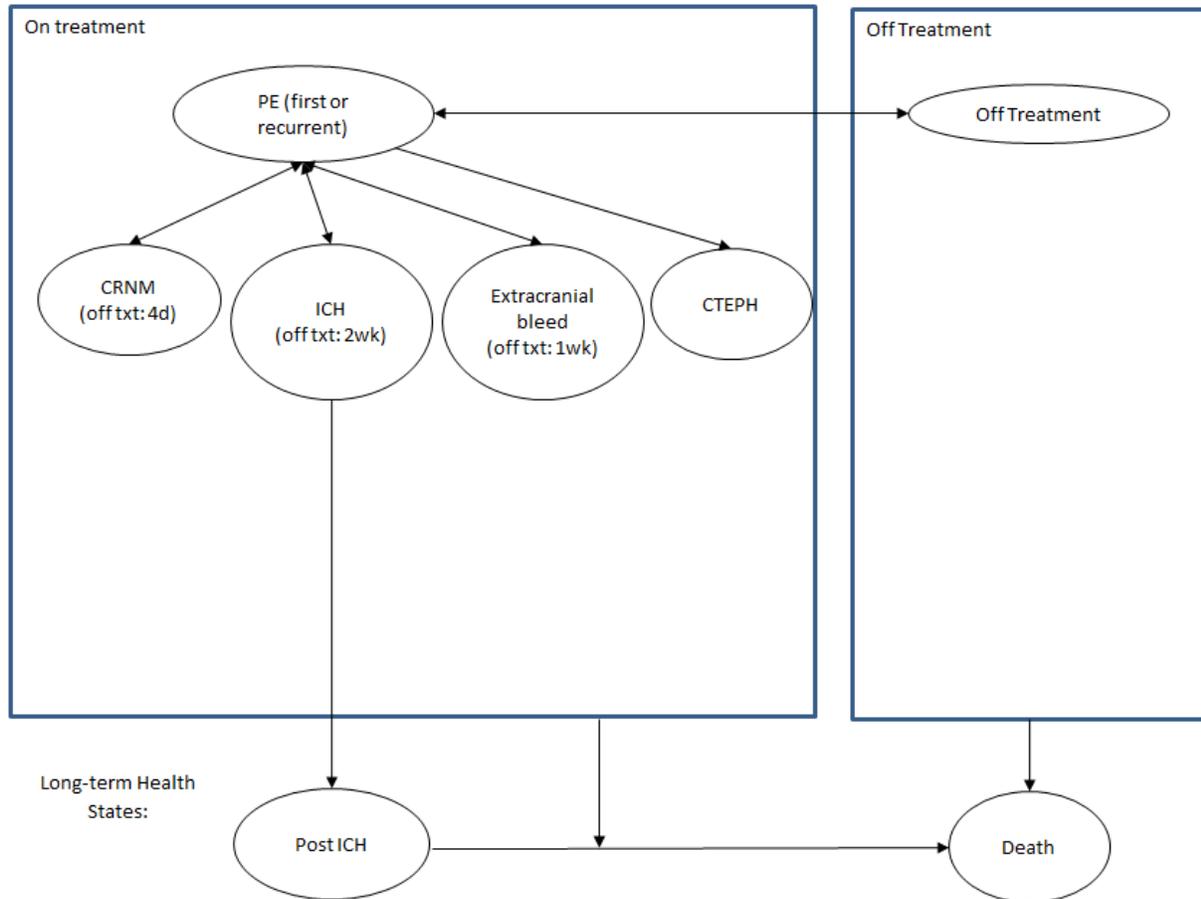


CT= computed tomography; DVT = deep vein thrombosis; PE = pulmonary embolism; sens= sensitivity; spec = specificity; US = ultrasound

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 and, in this report, this model will be referred to as the original Markov model.²³⁶ 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 bleeds (i.e., intracranial or extracranial bleed), clinically relevant non-major bleeds, post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension (CTEPH). To reflect more accurately 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 25**). Based on external validation, it was determined that the incidence of CTEPH was underestimated as this complication could only occur following a recurrent PE. 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 above-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 that would result 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. Non-fatal PE recurrence (in the true positive and false negative arms) was assumed to be correctly diagnosed and managed.

Figure 25: Conceptual design of the Markov component of the economic model. Patients diagnosed with PE enter the “on treatment” state while patients not diagnosed with PE enter the “Off treatment” state. After each cycle, patients may 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 can lead to death.



D= day; ICH = intracranial hemorrhage, CRNM = clinically relevant non-major; CTEPH = chronic thromboembolic pulmonary hypertension; txt = treatment; wk= week
 Adapted from CADTH, 2016²³⁶

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 11: Characteristics of Included Systematic Reviews for Clinical Review of Risk Stratification (Question 1). As multiple thresholds to interpret a test may exist and, given the correlation between test sensitivity and specificity, a trade-off exists between the proportion of false negative and false positive results. As such, 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 of pooling the clinical data using a bivariate model that assumed perfect reference standards (Table 16). 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. Both the pooled diagnostic test accuracy data and the diagnostic test accuracy from individual studies were applied as inputs to the economic model to see which scenario provided the closest

predictions in terms of test outcomes (i.e., proportion of positive test, proportion of negative tests, 3-month risk of PE) 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 16). 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 non-diagnostic test results that had to be accounted for in the model. The proportion of non-diagnostic test results were based on pooling the rates reported in individual clinical study, as reported in the clinical review. As per advice from the clinical experts, it was assumed that, in non-CT-based diagnostic management strategies, non-confirmatory imaging results would be handled by offering patients CT. 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, review by the clinical experts suggested considerable clinical heterogeneity to how a non-confirmatory 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 non-confirmatory CT scan based on the feedback from clinical experts. One approach was to assume that, if leg US was not part of the diagnostic pathway, patients would receive a leg US for a confirmatory diagnosis for VTE. Another approach evaluated in sensitivity analysis was a blended strategy in which patients with low-to-moderate pre-test probability of PE based on the CDR and no diagnosis could be reached from rule out or ancillary tests, were not offered treatment while high-risk patients were treated.

Table 16: Diagnostic test accuracy

Diagnostic Test Accuracy					
		Point estimates		hsROC (st dev)	Sources (number of studies)
		Sensitivity	Specificity		
Clinical Prediction Rules	3-tier Wells	0.132	0.972	β : -0.230 Θ : -2.82 (0.37) α : 2.28 (0.27)	Pooled (5) ⁹⁹
	2-tier Wells	0.590	0.777	N/A	Kabrhel et al, 2005 ²³⁷
	Revised Geneva	0.113	0.981	N/A	Chagnon et al, 2002 ²³⁸
	Gestalt (<15%)	0.697	0.702	N/A	Pooled (3) ⁹⁹
	Gestalt (<20%)	0.889	0.259	N/A	Pooled (2) ⁹⁹
	Gestalt (undefined)	0.883	0.446	β : 0.214 Θ : 0.60 (1.07) α : 1.90 (0.27)	Pooled (19) ²⁶
'Rule Out Test'	D-dimer (undefined methods, ELISA)	0.97	0.41	N/A	Carrier, 2009 ²³⁹
	PERC	0.962	0.215	β : 0.186	Pooled (12) ²⁴⁰

				Θ: 2.36 (0.39) α: 2.36 (0.001)	
Ancillary Test	Leg US	0.410	0.960	β: 0.013 Θ: -1.84 (0.22) α: 2.95 (0.37)	Pooled (6) ³²
Diagnostic Test Imaging	CT	0.972	0.987	β: 0.053 Θ: 0.12 (0.50) α: 4.55 (0.63)	Clinical review
	MRI	0.949	0.984	β: 0.304 Θ: -5.3x10 ⁻⁴ (0.37) α: 4.03 (0.57)	
	Thoracic US	0.950	0.888	β: -0.025 Θ: -0.21 (0.39) α: 3.17 (0.57)	
	VQ/SPECT	0.970	0.947	β: -0.036 Θ: -0.14 (0.37) α: 3.87 (0.68)	
	VQ Planar Scintigraphy	0.868	0.974	β: 0.298 Θ: 0.24 (0.31) α: 3.20 (0.57)	

Proportion of Nondiagnostic Findings

	Point estimate	95% CI	Sources
CT	0.036	0.05-0.024	Clinical review
MRI	0.153	0.338-0.033	
Thoracic US	0.055. [†]	Not computed	
VQ/SPECT	0.037	0.079-0.01	
VQ Planar Scintigraphy	0.25	0.358-0.157	

CT= computed tomography; ELISA = enzyme-linked immunosorbent assay; MRI = magnetic resonance imaging; PERC = Pulmonary embolism rule-out criteria; SPECT = single-photon emission computed tomography; US = ultrasound; VQ = ventilation/perfusion

[†]Based on one clinical study. The clinical review noted reporting issues in this study.

Radiation Exposure

A potential argument in favor of a multistep diagnostic algorithm for PE that incorporates risk stratification and ancillary testing is the potential reduction in 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 17 presents the estimated range of radiation associated with each imaging modality.

Table 17: Radiation exposure associated with each diagnostic test

Imaging Modality	Estimated 'effective dose' of radiation	Reference
CT: Chest ¹	5.2 mSv ³ Range reported: 2.7 to 15	Kanal, 2017 ²⁴¹ Range from Jones, 2012 ²⁴² and Janbabanezhad, 2015 ²⁴³
Doppler US	0	Assumed
MRI	0	Assumed
Thoracic US	0	Assumed

VQ ²	2.2	Jones, 2012 ²⁴²
VQ/ SPECT ²	2.2	Assumed similar to VQ SPECT

¹ In pregnant patients, mean fetal dose from chest CT is estimated between 0.03-0.66 mGy²⁴⁴

² In pregnant patients, mean fetal dose from VQ-based tests is estimated between 0.32-0.74 mGy²⁴⁴

Treatment model (for Markov model)

Detailed description relating to the clinical inputs of the treatment model have been published elsewhere.²³⁶ Compared to 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 to the revised model.²⁴⁵ The decision problem for the original Markov model focussed primarily on a VTE cohort whereas the scope of this review was narrower with an interest on patients with PE. As such, 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 18.

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, false positive patients 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 of false positive patients was modelled to be similar to the general population who do not have a PE diagnosis. Contrary, false negative patients were at an increased risk of death and an increased risk of recurrent PE in the first month given that treatment was withheld (Table 18). Thereafter, the prognosis of these patients in terms of mortality and recurrence risks was assumed to be similar to PE patients off anticoagulant treatment (i.e., risks were higher than a general population but lower than those with an incident PE). True negatives were modelled to reflect a general Canadian population with general Canadian mortality rates applied.

Table 18: PE-specific probabilities

Parameter		Value (probabilistic)	References
Recurrent PE	On Treatment		
	3-month probability of recurrent PE (short-term LMWH+VKA) [†]	0.017 (Beta: $\alpha=14$; $\beta=811$)	Quinlan, 2004 ²⁴⁶
	Annual probability of recurrent PE (lifetime LMWH+VKA) [‡]	0.031 (Normal: $\mu=0.031$; $\sigma=0.012$)	Agnelli, 2003 ²⁴⁷
	Off Treatment/ Untreated		
	First month probability of recurrent PE	0.263 (Beta: $\alpha=5$; $\beta=14$)	Barritt, 1960 ²⁴⁸
	Annual probability of recurrent PE	0.041 (Normal: $\mu=0.041$; $\sigma=0.009$)	Agnelli, 2003 ²⁴⁷
Treatment-related bleeds	On Treatment		
	3-month probability of major bleed (short-term LMWH+VKA)	0.014 (Beta: $\alpha=14$; $\beta=1,009$)	Quinlan, 2004 ²⁴⁶
	6-month probability of CRNM bleed (short-term LMWH+VKA)	0.082 (Beta: $\alpha=1,111$; $\beta=12,452$)	CADTH, 2016 ²³⁶
	Annual probability of major bleed (lifetime LMWH/VKA)	0.027 (Normal: $\mu=0.012$; $\sigma=0.010$)	Aujesky, 2005 ²⁴⁹
PE-related mortality*	On Treatment		
	Case fatality rate, treated \pm	0.6 (Beta: $\alpha=23,040$; $\beta=288,580$)	Stein, 2002 ²⁵⁰
	Probability of death (short-term, month)	0.008 (Normal: $\mu=0.008$; $\sigma=0.008$)	Wells, 2016 ²⁵¹

	2 to 3)	$\sigma=0.0005$	
	Off Treatment		
	Case fatality rate, untreated \pm	0.263 (Beta: $\alpha=5$; $\beta=14$)	Barritt, 1960 ²⁴⁸

CRNM = clinically relevant non-major bleed; LMWH = low molecular weight heparin; PE = pulmonary embolism; VKA = vitamin K antagonist

[†] Applies for the first six months of the model

[‡] Applies from the seventh month onwards

\pm Applied to the cycle of an incident PE

*After PE, mortality rates return to the Canadian general population age-specific mortality rate.²⁴⁵

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.²³⁶ 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 CTEPH. Given that diagnosis of PE occurs rapidly (i.e., under a month), no utility weights were applied to the outcomes associated with the decision tree. Table 19 summarizes the utility values with a more detailed description available elsewhere.²³⁶

Some changes in utility weights were made from the original Markov model for this adaptation. 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, age-specific Canadian population utilities were used. In addition, the utility values in the original model were reviewed to determine if 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 utilities values in the original model were determined through the standard gamble method, with the exception of post intra-cranial bleed and CTEPH which were obtained from a generic (i.e., EQ-5D) and 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.²⁵²

Table 19: Utility values associated with each health states

Parameter description	Description	Utility value	Reference
Population norm	General population (n=1,555); EQ-5D Canada	Age-specific utility value	Johnson, 2000 ²⁵³
PE	Lower extremity DVT or PE patients (n=215); standard gamble	0.75 (Beta: $\alpha=161.25$; $\beta=53.75$)	Hogg, 2013 ²⁵⁴
EC bleed	Canada	0.65 (Beta: $\alpha=139.75$; $\beta=75.25$)	
Major ICH		0.15 (Beta: $\alpha=32.25$; $\beta=182.75$)	
Post ICH	Population-based cohort (n=2,425); EQ-5D UK	0.713 (Beta: $\alpha=1,729.03$; $\beta=695.98$)	Rivero-Arias, 2010 ²⁵⁵
CTEPH	CTEPH patients (n=15); EQ-5D Spain	0.648 (Beta: $\alpha=9.72$; $\beta=5.28$)	Roman, 2013 ²⁵²
Death		0	Assumption

EC= extracranial; EQ-5D= EuroQoL – 5 dimensions; ICH = intracranial hemorrhage, CTEPH = chronic thromboembolic pulmonary hypertension; PE = pulmonary embolism; UK = United Kingdom

9. Costs

Costs are described in Table 20. 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 2016/2017 Canadian dollar. As treatment and event costs were available in the original Markov model, these costs were reviewed to determine if 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.²⁵⁶ If Canadian costs were unavailable, costs were estimated from comparable health systems. Conversion of currency was conducted using the Bank of Canada currency converter.²⁵⁷

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 purposes 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 (OCCI) (2010/2011 fiscal year inflated to 2016 Canadian dollar values)²⁵⁸ with the exception for the cost of d-dimer, which came from a published Canadian paper.²⁵⁹ Physician fees were obtained from the Ontario Schedule of Benefit for Physician Services (OSB).²⁶⁰

The clinical experts consulted in this project suggested that the interpretation of CT is performed immediately and, if a scan appears non-diagnostic, a repeat scan is done 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 non-diagnostic scan.

Table 20: Diagnostic costs (2017 \$)

Imaging Modality	Diagnostic Tests 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
VQ	581 (Gamma: $\alpha = 2.71$; $\beta = 214.47$)	219.55	OCCI, OSB
VQ/ 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; VQ = ventilation-perfusion

Treatment Costs

The treatment costs of patients with positive test results for pulmonary embolism 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,²³⁶ the most cost-effective treatment was selected for the reference case analysis: initial parenteral anticoagulation (i.e., LMWH) followed by at least three-months of oral administration of VKAs with LMWH provided until systemic anticoagulation is achieved. Drug costs were determined using the Ontario Drug Benefit Formulary and based on recommended dosing.²⁶¹ No additional markup or dispensing fee was applied. VKA requires monitoring of INR and dose titration. Laboratory tests for monitoring anticoagulant therapy was based on an existing published Markov model and further details can be found elsewhere.²³⁶

Event Costs

Costs to manage PE and treatment-related complications were based on the original Markov model.²³⁶ The cost of PE management reflected a weighted cost based on an assumption that 67% would be in an inpatient setting (i.e., average length of hospital stay of 7.8 days) while the remaining would be managed in an outpatient service.

10. Statistical Analysis & 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 impacts 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 were characterized by beta distribution and costs were characterized by gamma distributions. Where possible, the diagnostic test accuracy (i.e., sensitivity and specificity) were 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 CDR with the exception of 3-tier Wells) and 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 ICER was presented unless otherwise specified. Strategies that were dominated (i.e., another strategy that has lower expected costs and higher expected QALYs) or 'extended dominated' (i.e., at least one possible combination of two treatment strategies exist that would be less costly and results in higher QALYs) were identified and did not inform the calculation of the efficiency frontier (which presents 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 (CEAC), whereby 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 the degree to which uncertainty in the model parameters (i.e., parameter uncertainty) and its assumptions (i.e., structural uncertainty) would impact 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 as it reflects the commonly selected time horizon used in economic models conducted for this topic to capture the immediate impact diagnostic strategies.²²⁵⁻²³¹
- Discount rate: The reference case selected the most recent recommended discount rate of 1.5%²³² with sensitivity analyses conducted on the previously recommended discount rate of 5% and an undiscounted scenario (i.e., discount rate = 0%).²³³
- Risk of PE: In the reference case, the general population prevalence of PE was 0.15.¹¹⁸ However, some patients are at increased risk of PE such as post-surgery, patients on hormonal contraception and thrombophilia.²⁶² As many economic model on 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 VQ 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 VQ-based imaging techniques and MRI (Magnetic Resonance Imaging and Ventilation-Perfusion Scintigraphy (VQ)). Sensitivity analyses were conducted to explore an optimistic estimate that would favor these imaging modalities. For each, the smallest estimate reported in an individual study was selected.^{104,122,165}
 - Management of Gestalt findings: In the reference case, it was assumed that patients with a low pre-test probability of PE according to Gestalt would proceed with additional testing which could include rule out tests, ancillary tests or diagnostic imaging as dictated by the diagnostic strategy modelled. This is reasonable given that the cut-off from the clinical studies were often defined as a probability of PE under 15 or 20% and reflects existing clinical management practice. However, this would mean that a strategy involving Gestalt followed directly by diagnostic imaging (i.e., CT, MRI, VQ or VQ/SPECT) would have all patients scanned. This reflects a more conservative stance given the seriousness of a PE diagnosis. However, it is also possible that some clinicians use Gestalt to exclude PE as it considered to be an acceptably low risk. To test this scenario, we conduct a sensitivity analysis whereby patients assessed with low-pretest risk by Gestalt are assumed “ruled out” and excluded from further diagnosis.
 - Management of non-diagnostic CT findings: In the reference case, it was assumed that, if the initial CT was non-diagnostic, the procedure would be repeated immediately with the second imaging tests being diagnostic (the entire process would incur one billing). According to the clinical experts consulted as part of this review, this is a simplification given that the management of a non-diagnostic CT varies in clinical practice. Alternatives include anticoagulating patients with non-diagnostic findings or employing leg US (if it was not part of the diagnostic pathway) to confirm diagnosis. Both alternatives were modelled.
 - Treatment duration for PE: According to most treatment guidelines for pulmonary embolism, the duration of treatment should be dictated by the nature of the event and the clinical context. Anticoagulation therapy is recommended to be continued for at least three months²³⁵ and in the therapeutic review in which 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.²³⁶ 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 on treatment for VTE found that the historical standard of care (low molecular weight heparin with vitamin

K antagonist) was the most likely cost-effective intervention under a willingness-to-pay threshold of \$170,00/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 narratively 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. The implementation review did suggest that some patients may be contra-indicated 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.

The implementation review found that not all diagnostic tests are readily available and that there is jurisdictional variation in terms of access to certain diagnostic tests. A separate scenario analysis was conducted to evaluate settings without access to d-dimer (i.e., removal of diagnostic strategies with d-dimer). In addition, 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 with 67% subsequently admitted into the hospital.

Given concerns noted in the clinical review with regards to the pooled diagnostic test accuracy data for thoracic US, an exploratory analysis was conducted incorporating this imaging modality to determine if different conclusions could be reached if thoracic US was added as a possible diagnostic modality. The pooled hsROC curve and the pooled proportion of non-diagnostic 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 being 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 the mathematical calculations were performed correctly and were consistent with the model specification and logical discrepancies were assessed by evaluating it 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.²³⁶ 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.^{263,264} To externally validate the decision tree, the model's outputs in terms of diagnostic accuracy (i.e., true positive, true negatives, false positive, false negatives) and short-term outcomes (i.e., three-month PE recurrence) was compared to diagnostic management studies identified in the clinical review.^{176,177,183,185,265-270}

12. Model Assumptions

The reference case economic analysis was conducted under the following assumptions (Table 21).

Table 21: Assumptions used to populate the economic model

Assumption	Strategy in which applicable:	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	All	Varied prevalence of PE at both ends of the estimated range. Subgroup analysis by age.
Initial contact by patients with the healthcare system is in an outpatient setting.	All	Initial contact with the health care system in an inpatient 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.	All	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	All	
If the initial diagnostic imaging test was non-confirmatory, it was assumed all patients would proceed with CT. This subsequent test was assumed to be able to provide confirmatory findings.	All non-CT strategies	
Nondiagnostic CT scans were assumed detected immediately with a scan repeated immediately resulting in a single billing fee.	CT-strategies	Two different scenarios tested: i. Use of Leg US to provide a confirmatory diagnosis ii. Patients deemed of high-risk for PE would receive treatment; patients deemed of low-to-moderate risk would have treatment with-held.
Time between diagnosis and initiation of treatment was not explicitly modelled. In other words, the duration required to reach diagnosis was assumed to not impact patient prognosis.	All	
Anti-coagulation therapy is initiated only after a diagnosis is complete.	All	
Treatment following an established diagnosis of PE entailed LMWH with VKA.	All	Treatment entailed apixaban, a direct oral anticoagulant therapy. The regimen involved apixaban 10 mg BID in the first week followed by 5 mg BID thereafter.
Treatment was three-months in duration. Recurrent PE would lead to indefinite anticoagulant therapy.	All	Following initial diagnosis of PE, patients would receive six months or lifetime anticoagulant therapy.
In patients incorrectly diagnosed as false positives and are on treatment, they are at the same risk of adverse bleeding events as those with PE who are on anticoagulant therapy.	All	
Treatment compliance was not explicitly captured in the model and it was assumed that patients remained perfectly compliant to their treatment regimen.	All	
In patients with nonfatal recurrent PE initially classified as false negatives, they were assumed to receive a correct diagnosis upon recurrence and to initiate lifetime anticoagulant therapy.	All	

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 22 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.,²⁷¹ the risk of death at three-to-six months in patients with PE is below 5% in most RCTs evaluating therapeutic strategies while, 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 on mortality were compared to these clinical studies. At three months post-diagnosis, the cumulative mortality rate in cohort and registry studies are reported to range from 5.07% to 10.3%.^{263,264} The observed range may reflect differences in patient baseline characteristic (e.g., age, comorbidities). Lobo et al.²⁶⁴ recruited patients with symptomatic acute PE without co-existing chronic lung disease or chronic heart failure while Pengo et al.²⁶³ included first-time acute PE patients without pre-existing conditions that can cause nonthromboembolic pulmonary hypertension or had pre-existing exertional dyspnea. The model predicted a three-month cumulative mortality of 7.87%. Over a ten year period, the model predictions slightly underestimated mortality although it remained within the reported 95% confidence interval (Table 21).²⁶³

In terms of other clinical outcomes, the model closely predicted the 3-month cumulative incidence of several clinical events reported in Lobo et al.²⁶⁴ (major bleeding: 1.39% [reported] vs 1.34% [predicted] and recurrent PE: 1.71% [reported] vs 1.62% [predicted]). However, Pengo et al.²⁶³ reported recurrent PE at the same time period and their incidence was higher than our model's predictions (i.e., 4.9% (95% CI: 1.9 to 7.9) [reported] vs 1.61% [predicted]). Over a longer duration, the model predictions aligned closer to the reported rate.

Only one study reported on the incidence of CTEPH.²⁶³ In using the original published model,²³⁶ 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 if it is an incident or recurrent case. The Markov model structure was revised to reflect this and, although this improved model's predictions, the revised model underestimates CTEPH incidence (6 months: 1.0% (0.0 to 2.4) vs. 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 to change the incidence of CTEPH to determine its impact on the robustness of the model.

Table 22: Comparison of Markov model's prediction on disease progression with published studies

Parameter	Study Description	Reported Results (95%CI)	Model Prediction
Major bleeding	<i>Lobo, 2006²⁶⁴</i> <i>Registry of 4,145 patients</i> <i>Age NR; 43.0% males</i> <i>Setting: Spain</i> <i>Total follow up: 3 months after hospital discharge</i>	Cumulative Incidence 3 months: 1.39%	Cumulative Incidence 3 months: 1.34%
		Cumulative Mortality 3 months: 5.07%	Cumulative Mortality 3 months: 7.86%
All-cause mortality	<i>Pengo, 2006²⁶³</i>	Cumulative Mortality	Cumulative Mortality [in

Table 22: Comparison of Markov model's prediction on disease progression with published studies			
Parameter	Study Description	Reported Results (95%CI)	Model Prediction
	Case study involving 223 patients Age 60.8; 42.2% males [anticoagulant was minimum of 6 months and extended on an individualized decision]	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)	true positive cohort] 3 months: 7.86% 6 months: 8.74% 1 year: 9.21% 5 years: 13.54% 10 years: 20.77%
CTEPH	Setting: Italy Total follow up: 10 years	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) <i>No reports of CTEPH thereafter</i>	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, 2006 ²⁶⁴	Cumulative Incidence 3 months: 1.71%	Cumulative Incidence: 3 months: 1.93%

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

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, however, can 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^{176,177,185} 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 number of total positives and total negatives). Overall, for diagnostic tools and imaging tests in which the clinical review provided robust meta-analytic diagnostic test accuracy data (e.g., CT, VQ, 3-levels Wells), the model predictions were found to align closely to each study's reported outcomes. However, the predictions were more divergent for diagnostic tools whose pooled sensitivity/specificity were based on fewer than three studies (e.g., 2-level Wells, revised Geneva, 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 diagnostic test accuracy data from individual studies. Across multiple clinical studies, better model predictions were observed when the diagnostic test accuracy was taken from Kabrhel et al²³⁷ for 2-level Wells and by Chagnon et al²³⁸ for revised Geneva. The diagnostic test accuracies from both these studies were therefore taken towards our reference case. As only one study provided Gestalt (<20%), we conducted the same exercise and, although Carrier et al, 2006²⁷² resulted in better predictions, the pooled analysis was selected for the reference case with a sensitivity analyses conducted using this diagnostic test accuracy reported by Carrier.

It is important to note that no clinical pathway studies involving Gestalt (with a threshold of <15), PERC or MRI were identified that could be used to compared with the model predictions.

DRAFT

Table 23: Comparison of decision tree prediction on diagnostic results against clinical studies

Study	Pathway	Outcomes reported	Model Prediction	
			Based on Pooled DTA	(if applicable) DTA from single source
Righini, 2008 ^{185*} 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 (181+23) Prediction negative: 712 (704+8) 3-month VTE risk: 0.56% (3.75)	Chagnon, 2002 Prediction positive: 203 (180+23) Prediction negative: 713 (705+8) 3-month VTE risk: 0.53% (3.75)
	Revised Geneva→ D-dimer→ CT (n=903)	Prediction positive (i.e., TP +FP): 186 Prediction negative (i.e., TN+ FN): 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, 2002 Prediction positive: 181 (176+5) Prediction negative: 721 (711+10) 3-month VTE risk: 0.67% (4.82)
Perrier, 2005 ¹⁸³ Prevalence: 26% [†]	Geneva→D-dimer→leg US→ CT (n=756) [Strategy 66 in model]	Prediction positive: 190 (2+109+1+78) Prediction negative: 554 (232+318+1+3) 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, 2002 Prediction positive: 205 (188+17) Prediction negative: 550 (542+8) 3-month VTE risk: 0.73% (4.04)
Bosson, 2007 ^{176*} Prevalence: 20%	3-level Wells→ d-dimer→ legUS→VQ (n=997)	Prediction positive: 210 (109+49+52) Prediction negative: 787 (299+116+117+255) 3-month VTE risk: 7/787 (0.9%)	Prediction positive: 212 (182+30) Prediction negative: 785 (768+17) 3-month VTE risk: 1.06% (8.33)	
Galipienzo ^{177*} Prevalence: 23.6% (95% CI: 18.2 to 29.6%)	[Dichotomized] Wells→ ddimer→ CT (n=241)	Predictive positive: 57 Predictive negative: 179 3-month VTE risk: 0	Predictive positive: 57 (55+2) Predictive negative: 184 (182+2) 3-month VTE risk: 0.43% (0.79)	Kabrhel, 2005 Predictive positive: 56 (55+1) Predictive negative: 185 (183+2) 3-month VTE risk: 0.43% (0.80)
Hendriksen, 2016 ²⁶⁸ Prevalence:	Gestalt (<20%) (n=598)	Gestalt <20%: 196 Gestalt >20%: 402	Gestalt <20%: 144 Gestalt >20%: 454	Carrier, 2009 Gestalt <20%: 211 Gestalt >20%: 387

12.04%		TP: 66 TN: 189 FP: 336 FN: 7	TP: 64 TN: 136 FP: 390 FN: 8	TP: 62 TN: 201 FP: 325 FN: 10
	[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, 2005 Wells ≤ 4: 439 Wells >4: 160 TP: 42 TN: 409 FP: 118 FN: 30
Di Marca, 2015 ²⁶⁹ Prevalence: 21.6%	3-level Wells → d-dimer → CT (n=102)	Wells, Low + Intermediate: 94 Wells, High: 8 <i>Probability of PE based on pre-test results</i> High: 88% Intermediate/Low: 16%	Low + Intermediate: 97 (19+78) High: 5 (3+2) <i>Probability of PE based on pre-test results</i> High: 55.5% Intermediate/Low: 19.2%	
	Revised Geneva → D-dimer → CT (n=102)	rGeneva, Low + Intermediate: 89 rGeneva, High: 13 <i>Probability of PE based on pre-test results</i> High: 54% Intermediate/Low: 16.9%	rGeneva, Low + Intermediate: 96 (77+18) rGeneva, High: 6 (4+2) <i>Probability of PE based on pre-test results</i> High: 57.7% Intermediate/Low: 18.8%	Chagnon, 2002 rGeneva, Low + Intermediate: 98 (78+20) rGeneva, High: 4 (2+2) <i>Probability of PE based on pre-test results</i> High: 60.3% Intermediate/Low: 19.4%
	3-level Wells → d-dimer → CT (n=101)	Wells, Low + Intermediate: 92 Wells, High: 9 <i>Probability of PE based on pre-test results</i> High: 100% Intermediate/Low: 16%	Low + Intermediate: 96 (21+75) High: 5 (3+2) <i>Probability of PE based on pre-test results</i> High: 58.4% Intermediate/Low: 21.1%	
	Revised Geneva → D-dimer → CT (n=101)	rGeneva, Low + Intermediate: 85 rGeneva, High: 16 <i>Probability of PE based on pre-test results</i> High: 56% Intermediate/Low: 17%	Low + Intermediate: 95 (75+20) High: 6 (4+2) <i>Probability of PE based on pre-test results</i> High: 60.6% Intermediate/Low: 20.7%	Chagnon, 2002 Low + Intermediate: 96 (75+21) High: 5 (3+2) <i>Probability of PE based on pre-test results</i> High: 63.1% Intermediate/Low: 21.4%
Klok, 2008 ²⁷⁰	3-level Wells	Low+Intermediate: 287	Low+Intermediate: 287 (42+245)	

Prevalence: 16%	(n=300)	High:13	High:13 (6+7)	
	Revised Geneva (n=300)	Low+Intermediate: 293 High: 7	Low+Intermediate: 284 (40+244) High: 16 (8+8)	Chagnon, 2002 Low+Intermediate: 290 (43+247) High: 10 (5+5)

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

† NOTE: In this study, physicians could override Geneva score by clinical judgement.

DRAFT

2. Reference-case Findings

Cost utility analysis

Lifetime probabilistic results for the reference case analysis are presented in Table 24 and

DRAFT

Figure 26 with disaggregated clinical outcomes and costs presented in Table 25 and Table 26, respectively. Most non-CT strategies were ruled out by dominance (i.e., more expensive and provided worse clinical outcomes compared to a diagnostic strategy) or extended dominance (i.e., more expensive and provide worse clinical outcomes than a combination of two diagnostic strategies),

DRAFT

Figure 26. This was expected given the clinical review suggested that CT had better diagnostic tests accuracy compared to other imaging modalities, was associated with one of the lowest rates of nondiagnostic findings and had the lowest technical costs.

The diagnostic strategy with the lowest costs was revised Geneva>PERC> d-dimer>CT. Clinically, this strategy involves providing revised Geneva to all patients suspected of PE to classify their risk. In those considered of low-to-moderate pre-test probability of PE, PERC followed by d-dimer was used to rule out PE and, of those who could not be ruled out or in patients with high pre-test probability of PE according to revised Geneva, CT is offered.

Eight strategies provided better clinical outcomes but at greater costs (Table 24). As noted above, all of the strategies included CT as the diagnostic imaging modality but differed in terms of the risk stratification and ancillary tests performed. Employing risk stratification and ancillary testing was less costly than a corresponding strategy that involved only the diagnostic imaging modality. The use of systematic risk stratification and ancillary testing can result in the avoidance of further diagnostic imaging in a proportion of the population (Table 25). For instance, PERC-based strategies were associated with the lowest expected costs and, consequently, lower ICER values as patients with negative PERC could be ruled out of PE without incurring additional costs for imaging. A similar argument can be applied for d-dimer and leg US. As d-dimer is less costly than leg US, a diagnostic strategy with d-dimer was associated with lower expected costs than a similar strategy that omitted d-dimer but included leg US. D-dimer was found to be present in eight of the diagnostic strategies on the cost-effectiveness frontier. Only the strategy with the highest ICUR value, Gestalt>LegUS>CT (ICUR=\$196,369/QALY), did not include d-dimer testing to stratify a patient's risk, and as such, the proportion of patients proceeding to CT was the highest in this strategy. Leg US emerged on the upper-end of the cost-effectiveness frontier for diagnostic strategies. This was expected as leg US would be more costly than d-dimer but functions differently in that, given its high specificity, it provides confirmatory diagnoses of patients with DVT, which alongside PE, falls under the clinical spectrum of VTE. It can therefore prevent patients with DVT from requiring additional diagnostic imaging (Table 25).

Therefore, upon ordering strategies by ascending ICUR values, a trade-off was observed between false positives and false negative findings. Diagnostic strategies with higher ICERs had fewer false negatives but more false positives findings (Table 24). These findings reflect the implications of incorrectly missing a PE diagnosis (i.e., false negative) as patients with PE that have treatment withheld are 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 initial three months after diagnosis. The incremental difference in QALYs among strategies was small. For instance, between the reference strategy (i.e., strategy with the lowest expected costs) and the strategy with the highest ICUR (i.e., Gestalt>Leg US>CT), the QALY difference was only 0.055 which can be converted as 20 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 averted and the number of adverse bleeding events (Table 25).

Figure 26 presents the incremental cost-effectiveness plane in which, when factoring parameter uncertainty, highlights the diagnostic pathways that were most likely cost-effective across different willingness-to-pay values. It allows identification of the preferred strategy based on one's willingness-to-pay. At a willingness to pay of \$50,000/QALY, the strategy of Gestalt(<15>d-dimer>Leg US>CT was the most likely cost-effective diagnosis pathway (probability = 86.7%).

Cost effectiveness analysis

Results, based on the incremental cost per life years saved, are presented in Table 27. The findings were very similar to those in which QALYs were the clinical outcome. The diagnostic strategy with the lowest costs was revised Geneva>PERC>d-dimer>CT and eight CT-based strategies were identified that provided better clinical outcomes at higher costs.

DRAFT

Table 24: Lifetime costs, and QALYs of different diagnostic strategies (Reference Case)- Sequential Incremental Cost-Utility Ratio

The 111 strategies that were dominated or extendedly dominated are not presented below.

Strategy				Diagnostic Test Accuracy				Costs	QALYs	Incremental		ICUR (cost/QALYs)
Risk stratification		Ancillary Tests	Dx Imaging	TP	FP	TN	FN			Costs	QALYs	
Revised Geneva	PERC>d-dimer	None	CT	0.135	0.045	0.803	0.017	3,968	17.4431	-ref-		
Wells: 3 tier	PERC>d-dimer	None	CT	0.135	0.046	0.802	0.016	3,977	17.4455	9	0.0024	3,816
Wells: 2 tier	PERC>d-dimer	None	CT	0.139	0.055	0.793	0.013	4,111	17.4662	134	0.0171	7,854
Gestalt: <15	PERC>d-dimer	None	CT	0.140	0.058	0.790	0.012	4,163	17.4670	51	0.0043	11,874
Wells: 2 tier	d-dimer	None	CT	0.141	0.062	0.786	0.011	4,227	17.4710	64	0.0041	15,734
Gestalt: <15	d-dimer	None	CT	0.141	0.065	0.783	0.011	4,266	17.4732	40	0.0021	18,803
Gestalt: <15	d-dimer	Leg US	CT	0.146	0.084	0.764	0.006	4,910	17.4926	1	0.290	33,016
Gestalt (pooled)	d-dimer	Leg US	CT	0.146	0.096	0.752	0.005	5,121	17.4962	211	0.0035	60,247
Gestalt	None	Leg US	CT	0.147	0.118	0.730	0.005	5,514	17.4982	393	0.0020	196,369

Table 25: Expected clinical outcomes- diagnostic strategies on the efficiency frontier

Strategy				Short-term		Long-term		
Risk stratification		Ancillary Tests	Dx Imaging	Number of patients undergoing CT	Expected 'effective dose' of radiation (mSv)	Number of recurrent PE	Number of adverse bleeding	Number of CTEPH
Revised Geneva	PERC>d-dimer	None	CT	0.563	3.04	0.143	0.044	0.020
Wells: 3 tier	PERC>d-dimer	None	CT	0.569	3.08	0.143	0.044	0.020
Wells: 2 tier	PERC>d-dimer	None	CT	0.657	3.55	0.142	0.043	0.019
Gestalt: <15	PERC>d-dimer	None	CT	0.669	10.40	0.142	0.043	0.019
Wells: 2 tier	d-dimer	None	CT	0.728	3.94	0.141	0.043	0.019
Gestalt: <15	d-dimer	None	CT	0.754	4.08	0.141	0.043	0.019
Gestalt: <15	d-dimer	Leg US	CT	0.664	3.59	0.140	0.043	0.019
Gestalt (pooled)	d-dimer	Leg US	CT	0.746	4.03	0.140	0.043	0.019
Gestalt	None	Leg US	CT	0.904	13.63	0.140	0.043	0.019

Table 26: Expected Lifetime Costs in Selected Categories - diagnostic strategies on the efficiency frontier

Strategy				Diagnostic Costs (\$)	Treatment and Management Costs (\$)		
Risk stratification		Ancillary Tests	Dx Imaging		First three months	Long term	Total
Revised Geneva	PERC>d-dimer	None	CT	469	1,310	2,187	3,497
Wells: 3 tier	PERC>d-dimer	None	CT	473	1,316	2,186	3,502

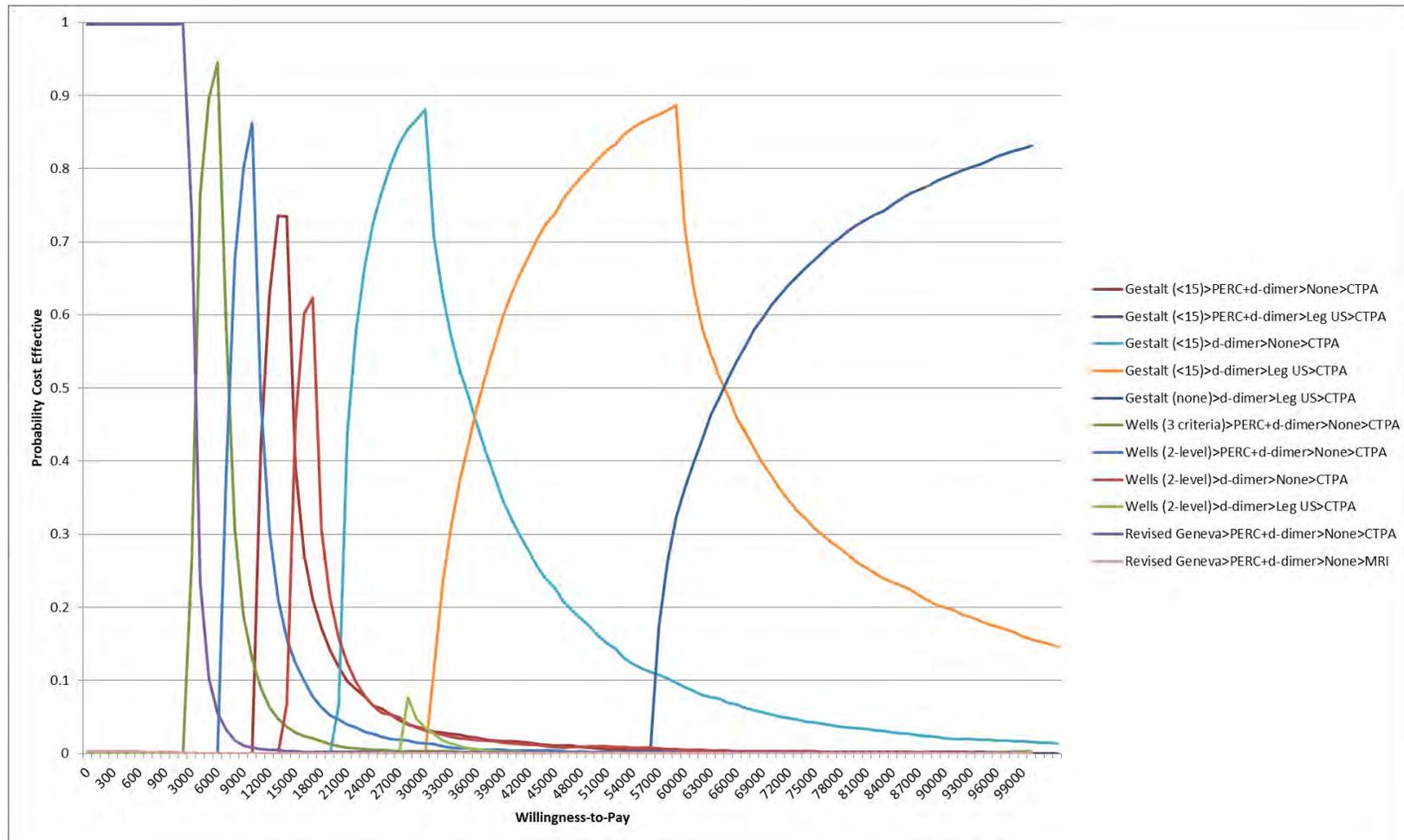
Wells: 2 tier	PERC>d-dimer	None	CT	539	1,390	2,181	3,570
Gestalt: <15	PERC>d-dimer	None	CT	564	1,416	2,180	3,597
Wells: 2 tier	d-dimer	None	CT	599	1,446	2,180	3,627
Gestalt: <15	d-dimer	None	CT	618	1,466	2,180	3,646
Gestalt: <15	d-dimer	Leg US	CT	1,123	1,606	2,179	3,785
Gestalt (pooled)	d-dimer	Leg US	CT	1,250	1,687	2,183	3,870
Gestalt	None	Leg US	CT	1,485	1,835	2,192	4,027

Table 27: Lifetime costs and LYs of different diagnostic strategies - Sequential Incremental Cost-Effectiveness Ratio

The 111 strategies that were dominated or extendedly dominated are not presented below.

Strategy				Diagnostic Test Accuracy				Costs	Life Years	Incremental		ICER (cost/LYs)
Risk stratification		Ancillary Tests	Dx Imaging	TP	FP	TN	FN			Costs	Life Years	
Revised Geneva	PERC>d-dimer	None	CT	0.135	0.045	0.803	0.017	3,968	18.329	-ref-		
Wells: 3 tier	PERC>d-dimer	None	CT	0.135	0.046	0.802	0.016	3,977	18.335	9	0.002	3,816
Wells: 2 tier	PERC>d-dimer	None	CT	0.139	0.055	0.793	0.013	4,111	18.400	134	0.017	7,854
Gestalt: <15	PERC>d-dimer	None	CT	0.140	0.058	0.790	0.012	4,163	18.423	51	0.004	11,874
Wells: 2 tier	d-dimer	None	CT	0.141	0.062	0.786	0.011	4,227	22.421	64	0.004	15,734
Gestalt: <15	d-dimer	None	CT	0.141	0.065	0.783	0.011	4,266	22.424	40	0.002	18,803
Gestalt : <15	d-dimer	Leg US	CT	0.146	0.084	0.764	0.006	4,910	22.447	644	0.020	33,016
Gestalt (pooled)	d-dimer	Leg US	CT	0.146	0.096	0.752	0.005	5,121	22.452	211	0.004	60,247
Gestalt	None	Leg US	CT	0.147	0.118	0.730	0.005	5,514	22.456	393	0.002	196,369

Figure 26: Cost-Effectiveness Acceptability Curve, clinical outcome defined as QALYs (Reference Case). At different willingness-to-pay thresholds (x-axis), the y-axis highlights the proportion of simulations (n=1,000) 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 28, Table 29 and Table 30. Sensitivity analyses with minimal impact on the ICUR or conclusion included: the proportion of nondiagnostic findings in VQ-based modalities and MRI, alternative approaches to manage low pre-test probability of PE as assessed by Gestalt, alternative approaches to the management of non-diagnostic CT findings and alternative therapies for anticoagulation (see Appendix 26: Additional Sensitivity Analysis Results).

Prevalence of PE: The model was sensitive to the prevalence of PE. With lower PE prevalence, the ICERs increased for most diagnostic strategies while, with higher PE prevalence, the ICERs 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 while the opposite holds true when more patients are at risk of PE. In both analyses, the lowest cost strategy remained revised Geneva> PERC>d-dimer>CT. The strategies on the cost-effectiveness frontier differed based on the prevalence of PE with the general trends observed in the reference case remaining valid. At a willingness-to-pay threshold of \$50,000/QALY, Gestalt (<15)>d-dimer>CT was the most likely cost-effective intervention (probability= 79.2%) in patients with lower prevalence (9%) . With higher prevalence of PE, the addition of Leg US (i.e., Gestalt (none)>d-dimer>Leg US> CT) was the most cost-effective diagnostic strategy (96.7%) given that the additional higher costs of leg US was offset by the reduced rates of false negatives.

Treatment duration for index PE event: The model was sensitive to the duration of anticoagulation therapy. A trade-off was present as the cost of treatment increased as the duration lengthened but this resulted in a reduction in the risk of recurrent PE. Assuming a six-month treatment duration, there was greater impact of parameter uncertainty. At a willingness-to-pay threshold of \$50,000/QALY, 50.1% and 31.7% of the simulations found that Wells (2-level)>d-dimer>leg US>CT and Gestalt(<15)>d-dimer>CT, respectively, were the most-likely cost-effective interventions.

Settings without d-dimer: As the implementation review noted, not all settings will have access to d-dimer. To assess these situations, all strategies involving d-dimer were removed in the economic evaluation. This would mean that all strategies involving an objective CDR (i.e., Wells and Geneva) were removed from the analysis as, according to the clinical expert, the utility of CDR is in the application of subsequent rule out test such as d-dimer as this reduces the need for patients to undergo unnecessary diagnostic imaging.

In this case, only 24 diagnostic strategies involving permutations of Gestalt, leg US and different imaging modalities were assessed. The findings were similar to the reference case except that the least expensive strategies was Gestalt assessment with all patients receiving CT(Table 28). By adding leg US, the diagnostic strategy became more expensive given the additional costs of the diagnostic procedure. However, this permitted the diagnosis of VTE in a subset of patients and led to higher rates of true positives and lower rates of false negatives findings. From a willingness-to-pay greater than \$45,730/QALY, Gestalt>Leg US> CT would be considered the most likely cost-effective diagnostic strategy according to the analysis.

Patients contraindicated for CT: 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

52 therefore conducted to explore this scenario whereby all strategies involving CT were removed
 53 (Table 28). In terms of diagnostic imaging modalities, at willingness-to-pay threshold under
 54 \$43,229/QALY, MRI-based strategies emerged as cost-effective while strategies involving VQ
 55 SPECT were cost-effective at $\lambda \geq \$43,229/\text{QALY}$. This was expected given the trade-off in costs
 56 (MRI, \$383 vs. VQ/SPECT, \$932) and test sensitivity (MRI, 0.949 vs. VQ-SPEC, 0.9702).
 57 Similar to the reference case, rule-out test involving PERC and d-dimer were cost-effective at
 58 the lower end of the willingness-to-pay threshold ($\lambda < \$22,351/\text{QALY}$), d-dimer alone was cost-
 59 effective when $\$22,351/\text{QALY} \leq \lambda < \$261,122/\text{QALY}$, and beyond a willingness-to-pay of
 60 \$261,122/QALY, no rule-out tests were considered cost-effective. Strategies involving leg US
 61 was associated with greater costs given the diagnostic costs but resulted in improved QALYs as
 62 more PE patients would receive treatment (i.e., more true positives) and would be cost-effective
 63 if $\lambda \geq \$14,360/\text{QALY}$.

64
 65 The CEAC suggests the model was more sensitive to parameter uncertainty when CT-based
 66 strategies were removed from the analysis, especially as the willingness-to-pay threshold
 67 increased. At a willingness-to-pay of \$50,000/QALY, Gestalt(<15)>PERC>d-dimer>Leg US>VQ
 68 SPECT was the most likely cost-effective strategy for the diagnosis of PE (probability = 47.8%)
 69 (Figure 27).
 70
 71

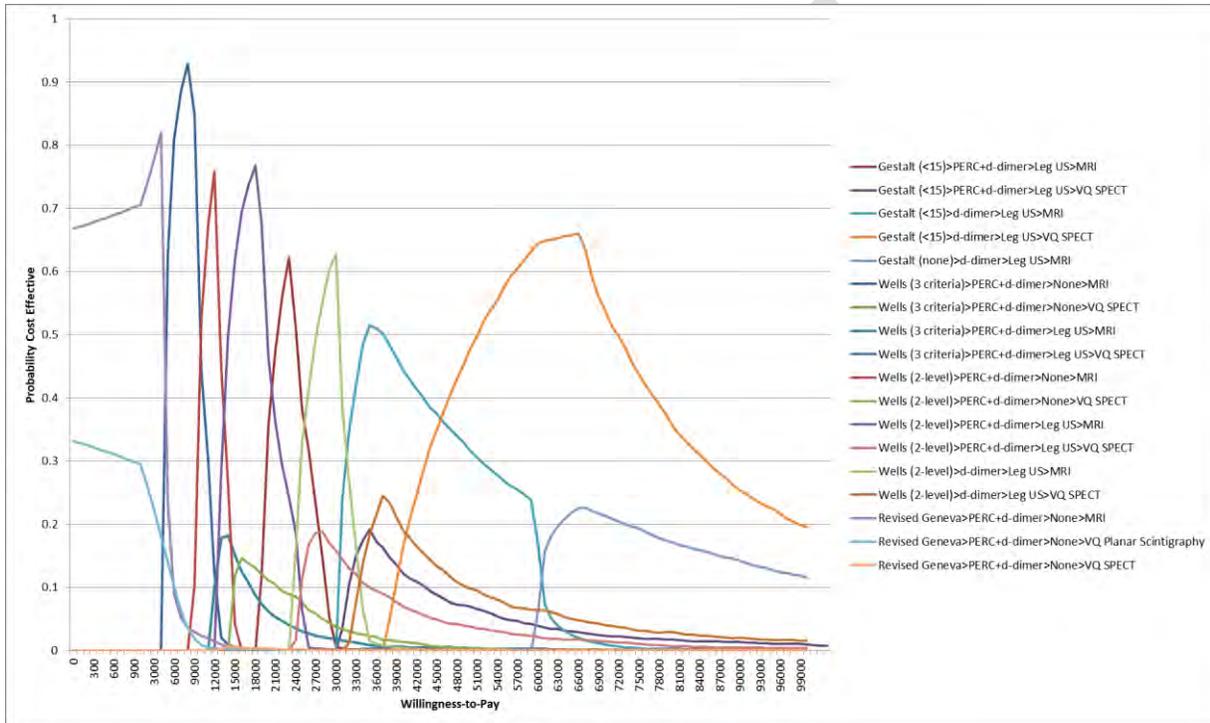
Table 28: General Sensitivity Analyses Results (diagnostic strategies that are dominated are not shown)

Strategy				ICUR (cost/QALYs)
Risk stratification		Ancillary Tests	Dx Imaging	
Prevalence of PE (0.09)				
Revised Geneva	PERC>d-dimer	None	CT	-ref-
Wells: 3 tier	PERC>d-dimer	None	CT	2,488
Wells: 3 tier	d-dimer	None	CT	15,262
Gestalt: <15	d-dimer	None	CT	24,813
Gestalt: <15	d-dimer	Leg US	CT	59,138
Gestalt (pooled)	d-dimer	Leg US	CT	116,995
Gestalt: <15	None	Leg US	CT	461,027
Prevalence of PE (0.28)				
Revised Geneva	PERC>d-dimer	None	CT	-ref-
Wells: 3 tier	PERC>d-dimer	None	CT	868
Gestalt: <15	PERC>d-dimer	None	CT	4,203
Gestalt: <15	d-dimer	None	CT	8,027
Gestalt (pooled)	d-dimer	None	CT	17,198
Gestalt <15	d-dimer	Leg US	CT	17,512
Gestalt (pooled)	d-dimer	Leg US	CT	27,504
Gestalt	None	Leg US	CT	81,419
Longer duration of Initial treatment (6 months)				
Revised Geneva	PERC>d-dimer	None	CT	-ref-
Wells: 3 tier	PERC>d-dimer	None	CT	4,651
Wells: 2 tier	PERC>d-dimer	None	CT	9,695
Gestalt: <15	PERC>d-dimer	None	CT	17,724
Wells: 2 tier	d-dimer	None	CT	25,140
Gestalt: <15	d-dimer	None	CT	36,120
Wells: 2 tier	d-dimer	Leg US	CT	50,526
Gestalt: <15	d-dimer	Leg US	CT	70,943
Setting without d-dimer				
Gestalt	None	Leg US	VQ SPECT	-ref-
Gestalt	None	Leg US	CT	96,062
Patients contra-indicated for CT				
Revised Geneva	PERC>d-dimer	None	MRI	-ref-
Wells: 3 tier	PERC>d-dimer	None	MRI	5,141

Wells: 2 tier	PERC>d-dimer	None	MRI	10,568
Wells: 3 tier	PERC>d-dimer	Leg US	MRI	14,360
Wells: 2 tier	PERC>d-dimer	Leg US	MRI	14,705
Gestalt (<15)	PERC>d-dimer	Leg US	MRI	22,351
Wells: 2 tier	d-dimer	Leg US	MRI	28,340
Gestalt (<15)	d-dimer	Leg US	MRI	35,882
Gestalt (<15)	d-dimer	Leg US	VQ SPECT	43,229
Gestalt (pooled)	d-dimer	Leg US	VQ SPECT	78,835
Gestalt (<15)	None	Leg US	VQ SPECT	261,122

72
73
74

Figure 27: Cost-Effectiveness Acceptability Curve (Patients Contra-indicated for CT Imaging)



75
76
77

Scenario analysis

78 Several structural and methodological uncertainties were evaluated. It was found that the model
79 was not sensitive to the discount rate selected, in employing alternative diagnostic test accuracy
80 data for Gestalt (<20) or in applying the utility values from the original Markov model²³⁶
81 (Appendix 26: Additional Sensitivity Analysis Results). Below, we highlight the structural or
82 methodological uncertainties in which the economic model was sensitive to:
83

84

85 **Different analytical time horizons:** By truncating the time horizon to three months, as
86 commonly observed in many economic evaluations in this topic area, revised Geneva >
87 PERC > d-dimer > CT was the most likely cost-effective strategy when the willingness to pay was
88 under \$569,588/QALY. Although the order of diagnostic strategies considered cost-effective
89 remained mostly the same compared to the reference case (with the exception that
90 Gestalt(<15)> d-dimer>CT became dominated), the ICER values associated with each
91 diagnostic strategy were much higher. These findings were expected as the difference in
92 incremental costs between strategies lay primarily in the cost of diagnosis, while the incremental
93 benefits were lower given that the overall benefits of imaging tend to be realized over a longer

94 time period from the avoidance of PE-related morbidity and mortality, and the prevention of
 95 recurrent PE.

96
 97 **Pooled diagnostic test accuracy data:** As noted in the external validation section, the inputs
 98 for diagnostic test accuracy for revised Geneva and 2-tier Wells were selected based on
 99 comparing the outputs of the model prediction to diagnostic pathway clinical studies. As
 100 predicted outcomes were better aligned when diagnostic test accuracy data were taken from
 101 Kabrhel et al²³⁷ for 2-level Wells and by Chagnon et al²³⁸ for revised Geneva, these were
 102 selected in reference case analyses. When using the pooled sensitivity and specificity values
 103 instead, the strategies forming the efficiency frontier differed from the reference case in that 2-
 104 tier Wells strategies became dominated and were no longer present on the efficiency frontier. In
 105 one case, the 2-tier Wells strategy that was considered part of the reference case's efficiency
 106 frontier switched to the corresponding 3-tier Wells strategy (i.e., Wells > d-dimer > CT).
 107 However, the interpretation was similar in many instances. Between a willingness-to-pay
 108 threshold of \$34,420/QALY to \$204,016/QALY, Gestalt>d-dimer>Leg US>CT was the most
 109 likely cost-effective diagnostic strategies, differing by what threshold was employed to define
 110 low pre-test PE probability by Gestalt.

Strategy				ICUR
Risk stratification		Ancillary Tests	Dx Imaging	(cost/QALYs)
Time horizon: 3 months				
Revised Geneva	PERC>d-dimer	None	CT	-ref-
Wells: 3 tier	PERC>d-dimer	None	CT	569,588
Wells: 2 tier	PERC>d-dimer	None	CT	1,459,155
Gestalt: <15	PERC>d-dimer	None	CT	3,229,661
Wells: 2 tier	d-dimer	None	CT	5,988,319
Gestalt: <15	PERC>d-dimer	Leg US	CT	10,156,770
Wells: 2 tier	d-dimer	Leg US	CT	24,479.161
Time horizon: 3 months				
Pooled diagnostic test accuracy (pooled sensitivity for 2-level Wells and revised Geneva)				
Revised Geneva	PERC>d-dimer	None	CT	-ref-
Wells: 3 tier	PERC>d-dimer	None	CT	1,542
Wells: 3 tier	d-dimer	None	CT	8,750
Gestalt: <15	PERC>d-dimer	None	CT	9,216
Gestalt: <15	d-dimer	None	CT	17,217
Gestalt: <15	d-dimer	Leg US	CT	34,420
Gestalt (pooled)	d-dimer	Leg US	CT	62,160
Gestalt	None	Leg US	CT	204,016

112
 113 **Subgroup analysis**

114 **Age:** Under the assumption that the prevalence of PE remains constant at 15.8%, in the
 115 subgroup analysis, at both the ages of 40 or 70, the ICER increased for the diagnostic
 116 strategies on the efficiency frontier (Table 29). Of note, a trend was observed when comparing
 117 between the same strategies across these two age cohorts that younger patients incurred
 118 higher costs but also had a greater gain in QALY improvement. This reflects the impact of a PE
 119 diagnosis in that it has greater impact on improving a patient's QALY but at a cost, as patients
 120 may require a longer duration of anticoagulation therapy, especially as overall prevalence of
 121 recurrent PE are higher.

122
 123 Of note, the model did not explore the relationship between age and PE prevalence and how it
 124 may impact cost-effectiveness. Clinical studies have suggested that the incidence of PE is
 125 linearly related to age with older patients presenting a higher incidence of PE.²⁷³

Table 29: Lifetime Results, by varied patients' age (diagnostic strategies that are dominated are not shown)

Strategy				Diagnostic Test Accuracy				Costs	QALYs	Incremental		ICUR (cost/QALYs)
Risk stratification	Ancillary Tests	Dx Imaging	TP	FP	TN	FN	Costs			QALYs		
Age: 40												
Revised Geneva	PERC >d-dimer	None	MRI	0.127	0.039	0.809	0.025	11,203	23.6617	-ref-		
Revised Geneva	PERC >d-dimer	None	CT	0.135	0.045	0.803	0.017	11,238	23.7095	35	0.0478	738
Wells: 3 tier	PERC >d-dimer	None	CT	0.136	0.046	0.802	0.016	11,265	23.7128	27	0.0033	8,340
Wells: 2 tier	PERC >d-dimer	None	CT	0.139	0.055	0.793	0.013	11,682	23.7364	416	0.0236	17,644
Gestalt: <15	PERC >d-dimer	None	CT	0.140	0.058	0.790	0.012	11,842	23.7424	161	0.0060	26,898
Wells: 2 tier	d-dimer	None	CT	0.141	0.062	0.786	0.011	12,030	23.7480	187	0.0056	33,394
Gestalt: <15	d-dimer	None	CT	0.142	0.065	0.783	0.010	12,156	23.7509	126	0.0029	43,368
Gestalt: <15	PERC >d-dimer	Leg US	CT	0.144	0.075	0.773	0.008	12,949	23.7687	793	0.0178	44,579
Wells: 2-tier	d-dimer	Leg US	CT	0.145	0.080	0.768	0.007	13,207	23.7744	258	0.0057	45,036
Gestalt: <15	d-dimer	Leg US	CT	0.146	0.084	0.764	0.006	13,384	23.7774	176	0.0030	59,283
Gestalt	d-dimer	Leg US	CT	0.147	0.096	0.752	0.005	13,961	23.7823	577	0.0049	118,895
Gestalt	None	Leg US	CT	0.147	0.118	0.730	0.005	15,036	23.7851	1,075	0.0028	384,087
Age: 70												
Revised Geneva	PERC >d-dimer	None	CT	0.135	0.045	0.803	0.017	2,968	10.2005	-ref-		
Wells: 3 tier	PERC >d-dimer	None	CT	0.136	0.046	0.802	0.016	2,977	10.2018	9	0.0013	6,591
Wells: 2 tier	PERC >d-dimer	None	CT	0.139	0.055	0.793	0.013	3,108	10.2114	131	0.0095	13,761
Gestalt: <15	PERC >d-dimer	None	CT	0.140	0.058	0.790	0.012	3,158	10.2138	50	0.0024	20,964
Wells: 2 tier	d-dimer	None	CT	0.141	0.062	0.786	0.011	3,221	10.2160	63	0.0022	27,936
Gestalt: <15	d-dimer	None	CT	0.142	0.065	0.783	0.010	3,260	10.2172	39	0.0012	33,542
Gestalt: <15	d-dimer	Leg US	CT	0.146	0.084	0.764	0.006	3,899	10.2278	639	0.0106	60,118
Gestalt (pooled)	d-dimer	Leg US	CT	0.147	0.096	0.752	0.005	4,108	10.2297	209	0.0019	111,924

Gestalt	None	Leg US	CT	0.147	0.118	0.730	0.005	4,496	10.2306	388	0.0009	419,644
---------	------	--------	----	-------	-------	-------	-------	-------	---------	-----	--------	---------

128
129
130
131
132
133
134
135
136
137
138

Inpatient Setting: If PE were diagnosed and managed in an in-patient setting (changing the proportion of patients treated from 67% to 100% and the prevalence of PE to 20%), this would have a minimal impact compared to the reference case analysis. The order of diagnostic strategies on the cost-effectiveness frontier remained the same although the ICER for each respective diagnostic strategy reduced (Table 30).

Table 30: Lifetime Results - Different Scenarios (diagnostic strategies that are dominated are not shown)

Strategy				Diagnostic Test Accuracy				Costs	QALYs	Incremental		ICUR (cost/QALYs)
Risk stratification	Ancillary Tests	Dx Imaging	TP	FP	TN	FN	Costs			QALYs		
In-patient setting												
Revised Geneva	PERC >d-dimer	None	CT	0.178	0.043	0.757	0.022	5,645	17.3073			-ref-
Wells: 3 tier	PERC >d-dimer	None	CT	0.178	0.043	0.757	0.022	5,657	17,3104	11	0.0031	3,697
Wells: 2 tier	PERC >d-dimer	None	CT	0.183	0.052	0.748	0.017	5,815	17,3324	158	0.0220	7,175
Gestalt: <15	PERC >d-dimer	None	CT	0.184	0.055	0.745	0.016	5,874	17.3380	59	0.0056	10,624
Wells: 2 tier	d-dimer	None	CT	0.185	0.059	0.741	0.015	5,946	17.3432	72	0.0052	13,795
Gestalt: <15	d-dimer	None	CT	0.186	0.061	0.739	0.014	5,991	17.3459	45	0.0027	16,554
Gestalt: <15	d-dimer	Leg US	CT	0.192	0.079	0.721	0.008	6,674	17.3711	683	0.0252	27,127
Gestalt (pooled)	d-dimer	Leg US	CT	0.193	0.090	0.710	0.007	6,903	17.3757	229	0.0046	49,886
Gestalt	None	Leg US	CT	0.193	0.111	0.689	0.007	7,327	17.3785	424	0.0028	154,023

139
140
141
142
143
144
145
146
147
148

4. Exploratory Analysis

By adding the 30 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. Firstly, the clinical review highlighted that the diagnostic test accuracy (i.e., sensitivity and specificity) of CT was superior to thoracic US. In addition, the proportion of non-diagnostic findings were lower with CT than thoracic US (mean proportion= 0.036 [CT] vs. 0.055 [thoracic US]). Lastly, the cost of performing CT was lower than thoracic US. Combined, this resulted in the findings observed.

149 Summary of Findings

150 Over a lifetime perspective, the economic model estimated a small difference in health benefits
151 (QALYs and life years gained) between different diagnostic strategies for PE. The rank order of
152 strategies, by increasing ICUR (Table 24), can be explained by the properties of each test in
153 terms of diagnostic performance and costs. For instance, employing risk stratification and
154 ancillary testing was less costly than a corresponding strategy with only the diagnostic imaging
155 modality as it can result in the avoidance of further diagnostic imaging in a proportion of the
156 population. However, in the proportion of the population with PE, avoidance of imaging is not
157 optimal as it leads to misdiagnosis (i.e., false negatives). Indeed, a trade-off emerged between
158 false positives and false negatives as diagnostic strategies with higher ICURs had fewer false
159 negatives but more false positives findings. These findings were not surprising given the implicit
160 trade-off between sensitivity and specificity within each diagnostic test and the morbidity and
161 mortality implications of incorrectly missing a PE diagnosis.

162
163 The least costly strategy was Revised Geneva>PERC>d-dimer>CT. At a willingness to pay of
164 \$50,000/QALY, the diagnostic strategy involving Gestalt(<15)>d-dimer>Leg US>CT was found
165 to be most likely cost-effective (probability = 86.7%),

DRAFT

166 Figure 26, Table 24. This strategy was in fact found to be cost-effective from a willingness-to-
167 pay ranging from \$33,016/QALY to \$60,247/QALY. Clinically, this entails providing subjective
168 Gestalt assessment to all patients suspected of PE to classify their risk. In those whose pre-test
169 PE probability is under 15%, d-dimer is offered to rule out PE and, of those who could not be
170 ruled out of PE by d-dimer or in patients with pre-test PE probability greater than 15%, leg US is
171 performed to diagnose DVT. Of these patients in which DVT can not be diagnosed from leg US,
172 CT is then offered to reach a conclusive diagnosis.

173
174 In the efficiency frontier, only CT-based strategies were present. This was not unexpected: the
175 clinical review highlighted that CT was associated with greater sensitivity and specificity than
176 other imaging modalities and, according to the fee schedules, CT is also associated with the
177 lowest costs. The emergence of CT-based strategies on the efficiency frontier is important when
178 understanding the economic results in the context of rural and remote communities. The
179 Canadian Medical Imaging Inventory³⁹ has highlighted that, in rural and remote areas, CT is the
180 most common modality across Canada. As such, no further exploration of rural and remote
181 settings were performed given that the imaging modality most likely cost-effective was also the
182 most readily accessible one in rural and remote communities.

183
184 The economic results were found to be sensitive to the analyzed time horizon, the prevalence of
185 PE and the treatment duration for an index PE event. These parameters had a more
186 pronounced impact on cost-effectiveness given its influence on the cost-benefit ratio of
187 diagnosing and treating PE. For instance, in truncating the analysis to three months as is
188 commonly observed in most economic evaluation on diagnostic strategies for PE, the initial
189 costs of diagnosis is more prominent compared to the long-term benefit of anticoagulation
190 therapy to reduce PE recurrence. With a lower prevalence of PE, the cost-effectiveness
191 increased as there is less benefit from more costly screening as fewer cases will be identified.
192 The opposite argument can be applied when the prevalence of PE is suspected to be higher as
193 more intense and more costly screening strategies become more preferred (i.e., lower ICER)
194 given that the cost and clinical impact of missing a diagnosis for PE is greater. Similarly, a
195 longer period of treatment for an index PE case would result in higher cost per case of PE
196 diagnosed (true positive and false positives). A tradeoff was present as patients with a correct
197 diagnosis (i.e., true positive) had a reduced likelihood of recurrent PE but all patients treated
198 (i.e., true positive and false positives) similar had an increase risk of bleeding complications
199 while on treatment.

200

201

202 **PATIENT PERSPECTIVES AND EXPERIENCES**

203 **Study Design**

204
205 A rapid review of the published qualitative literature was conducted to gain an understanding of
206 patients', family members', and non-clinical caregivers' perspectives and experiences of the
207 process of undergoing diagnosis for acute PE.

208 209 **Research Questions**

210
211 The research questions were developed in response to the policy issues and in consultation
212 with subject and content matter experts. As is typical in qualitative research, the questions were
213 refined in an iterative process through the course of the review to respond to the quantity and
214 nature of relevant published literature. The goal was to provide a relevant response to the policy
215 concern based on the available qualitative literature. The first research question, listed below,
216 focuses on the experience of diagnostic processes for PE as well as experiences with the
217 technologies of interest. Following an initial literature search, it was deemed there was
218 insufficient literature to answer the stated question and so an additional research question, and
219 corresponding literature search, was added to broaden the focus onto the experiences of
220 diagnosis in any setting, including the emergency room, for any condition.

- 221
- 222 1. What are the experiences with the diagnostic process from the perspective of those who
223 have undergone testing for acute PE, in any setting, including emergency room setting,
224 from the perspective of patients and their family members and non-clinical caregivers?
225
 - 226 2. What are the experiences with diagnostic imaging for any reason and in any setting,
227 including the emergency room, from the perspective of patients, their family members,
228 and/or their non-clinical caregivers?
229

230 **Methods**

231 Literature Search Methods

232 The literature search was performed by an information specialist, using a search strategy peer-
233 reviewed according to the PRESS checklist - an evidence-based checklist for the peer review of
234 electronic search strategies.⁷⁵

235 Patient experiences information was identified by searching the following bibliographic
236 databases: MEDLINE (1946-), with in-process records and daily updates, via Ovid; Embase
237 (1974-) via Ovid; PsycINFO (1967-) via Ovid; CINAHL (1981-) via EBSCO; PubMed; and
238 scopus. The search strategy comprised both controlled vocabulary, such as the National Library
239 of Medicine's MeSH terms, and keywords. The main search concept was medical imaging
240 modalities and terms related to patient experiences, perspectives, beliefs, and values.
241 Methodological filters were applied to limit retrieval qualitative studies. Retrieval was limited to
242 documents published since January 1, 2006. Results were limited to English- or French-
243 language publications. Conference abstracts were excluded from the search results. The
244 detailed strategy can be found in Appendix 1.

245 The search was completed on December 14, 2016. Regular alerts were established to update
 246 the search until the publication of the final report. Regular search updates were performed on
 247 databases that do not provide alert services. A supplemental search was conducted on
 248 December 16, 2016 for qualitative studies on anticoagulant drugs.

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

254

255 Eligibility Criteria

256

257 All English and French language reports of studies of any qualitative design that describe the
 258 perspectives of adults who: 1) have undergone testing for acute pulmonary embolism; 2) have
 259 experience with diagnostic imaging technologies for any reason and in any setting, including the
 260 emergency room, were eligible for this review. We were also interested in reports describing
 261 related perspectives and experiences of family members, and other non-clinical caregivers. To
 262 be eligible, studies must have explored or assessed the perspectives of patients and caregivers
 263 directly and not indirectly, for example through another person. Studies that assessed only
 264 clinician perspectives were excluded. The following types of publications were also excluded:
 265 theses and dissertations, data presented in abstract form only, book chapters, editorials, and
 266 letters to the editor.

267

268 The Eligibility Criteria are listed in Table 1 below.

269

Population	Adults (≥ 18 years), and their non-clinical caregivers (e.g., partners and family members), who have either: <ul style="list-style-type: none"> • undergone testing for suspected acute PE using any diagnostic strategy <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> • experience with diagnostic imaging technologies for any reason and in any setting, including the emergency room
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

270 CT = computed tomography; MRI = magnetic resonance imaging; PE = pulmonary embolism; PET =
271 positron emission tomography; Q = research question; SR = systematic review; V/Q = ventilation-
272 perfusion.

273

274 **Screening and Selecting Studies for Inclusion**

275 One reviewer screened citations identified through the literature search. In the first level of
276 screening, titles and abstracts were reviewed and the full text of potentially relevant articles
277 were retrieved and assessed for inclusion by the same reviewer. The final selection of full-text
278 articles was based on the eligibility criteria in Table 1. The study selection process is presented
279 in a PRISMA flow chart (Appendix 1).

280 **Critical Appraisal of Individual Studies**

281

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

289

290 **Data Collection and Extraction**

291

292 From each eligible article, descriptive data were extracted by one reviewer into an a priori
293 developed standardized electronic form. Descriptive data included such items as first author,
294 article title, study objectives, participant characteristics, and study design. Further, result
295 statements from all eligible articles relevant to the research question were captured for analysis,
296 or coded, using NVivo qualitative data analysis software (QSR International Pty Ltd. Version
297 11,2015).

298

299 **Data Analysis**

300

301 *Descriptive Analysis*

302

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

306

307 *Thematic Analysis*

308

309 A thematic analysis was conducted by a single reviewer using NVivo 11.3.2. To begin, the data
310 were coded line by line for meaning and content starting with an a priori list of codes that was
311 developed based on the research questions. The start list included, for example, harms and
312 benefits of testing and expected outcomes of testing. During the coding process, other codes
313 that were not on the start list emerged from the data and were included, for example to capture
314 the personal emotional experience of the diagnostic imaging process. When new codes
315 emerged, all data were recoded to search for further instances of the meaning captured by that
316 code.

317

318 Once all data were coded, the codes were organized into related areas to construct descriptive
319 themes. In this process, the reviewer looked for similarities and differences between codes and
320 grouped together similar codes. Once descriptive themes were identified, a summary of the
321 results across the studies organized by each theme was written by the reviewer. A group
322 discussion then took place, involving other researchers with experience in qualitative research,
323 to review and discuss the emergent themes and identify further analytic ideas.
324

325 Preliminary results were presented to the CADTH Health Technology Expert Review Panel
326 (HTERP), in a manner similar to peer debriefing. This impartial, multidisciplinary panel helped to
327 raise new and relevant areas to consider in the final analysis. For example, the panel discussed
328 the challenge of using a shared decision-making model or obtaining informed consent given the
329 urgent circumstances when diagnosing PE. Also, the finding that some patients preferred to
330 have emotional support from another person during the imaging process led to a discussion of
331 the perspectives of health care providers on the feasibility of implementing routines that would
332 meet the emotional and information needs of patients and their family members. The panel also
333 questioned the strength of the link between the reported results and the original research
334 questions, following which the data were revisited to assess the credibility of the results and
335 subsequent revisions were made to increase the clarity of those linkages.
336

337 The results presented below represent a synthesis that remains close to the original results of
338 the included studies, with minimal interpretation.
339

340 **Summary of Evidence**

341

342

343 Quantity of Research Available

344

345 A total of 1,891 citations were identified in the literature search. Following screening of titles and
346 abstracts by one reviewer, 1,858 citations were excluded and 34 potentially relevant articles
347 from the electronic search were retrieved for full-text review. Of these potentially relevant
348 articles, 27 were excluded as they did not fit the study criteria and the remaining seven were
349 selected for inclusion in this report. All seven studies are relevant to the second research
350 question.²⁷⁴⁻²⁸⁰ No eligible studies were identified that addressed the first research question.
351

352 **Summary of Study Characteristics**

353

354 *Study Design*

355 Seven studies of various designs were included as relevant to this report (See Table A1,
356 Appendix 2). One was a systematic literature review,²⁷⁹ two used a phenomenological
357 design,^{277,280} while four did not report a study design,^{274-276,278} and appeared to follow a
358 descriptive approach with no theoretical orientation.
359

360 *Place and time of studies*

361 The systematic review was conducted in Australia,²⁷⁹ while three primary studies were
362 conducted in Sweden,^{274,277,280} two in the United Kingdom^{275,276} and one in the United States of
363 America.²⁷⁸ Two studies were published in 2014^{274,276} and one study each in 2015,²⁷⁸ 2013,²⁷⁷
364 2012,²⁷⁵ 2011,²⁷⁹ and 2006.²⁸⁰
365

366 *Patient Population*

367 A range of patient populations and experiences with diagnostic imaging technologies were
368 covered in the studies included in this review. One study included women and their partners
369 who had experienced a near-miss event in childbirth (defined as “severe maternal illnesses
370 which, without urgent medical attention would have led to a mother’s death”).²⁷⁶ Of the 35
371 women included in this study, five women had experienced a pulmonary embolism. Three
372 studies included adults who presented at the MRI department to undergo a scan where the
373 head was to be fully inside the tunnel.^{274,277,280} One study included adults who had undergone a
374 SPECT-CT examination²⁷⁵ and another study included adults who were diagnosed with
375 colorectal, breast, testicular, thoracic, and lung cancers and thereby who underwent diagnostic
376 imaging examinations that involved the use of ionizing radiation.²⁷⁸ The systematic review
377 included literature describing the patient experience of high technology imaging.²⁷⁹
378

379 *Types of Technologies*

380 Three studies included patients who underwent MRI,^{274,277,280} one included individuals who had
381 undergone SPECT-CT,²⁷⁵ and one study explored perspectives on a range of strategies to
382 diagnose cancer, including x-rays, computed tomography (CT), positron emission tomography
383 (PET) mammography, and MRI.²⁷⁸ The study including women who experienced near-miss
384 events in childbirth did not report the types of technologies used in their diagnosis.²⁷⁶ The focus
385 of the systematic review was on high technology imaging, including MRI, CT, PET and SPECT;
386 however, each of the five included studies focused on either MRI or CT.²⁷⁹
387

388 Summary of Critical Appraisal

389 Overall studies included in this report are of moderate to high quality. There are, however, a few
390 exceptions described below. All studies were well conducted and demonstrated congruence
391 between the research methods and objectives. A summary of the strengths and limitations is
392 included below and details are available in Appendix 3, and Tables A2 and A3.
393

394 *Primary studies*

395 Each of the six included primary studies provided a clear statement of the research objectives or
396 purpose and all study objectives fit well for qualitative inquiry and synthesis. Four studies did not
397 report a study design, although appeared to follow a qualitative descriptive design, which was
398 appropriate for the descriptive intentions of the study.^{274-276,278} Two primary studies described
399 using a phenomenological approach, thereby applying a stronger theoretical orientation to guide
400 data collection, analysis and interpretation.^{277,280}
401

402 Three of the six primary studies identified using a purposive sampling strategy,²⁷⁶⁻²⁷⁸ which is
403 appropriate for qualitative research of all designs. No mention, however, was made within any
404 primary study report regarding data saturation. It is therefore unclear whether the final samples
405 were able to represent the diversity of participant experiences. The final three primary
406 studies^{274,275,280} made no mention of a particular sampling strategy, however one did report
407 including men and women of different ages and with different experiences of their MRI scans.²⁸⁰
408 This description therefore appears to follow a maximum variation strategy, which is appropriate
409 to ensure a broad range of experiences can be represented.
410

411 Both focus groups and interviews were used across the included primary studies. Four studies
412 described using semi-structured interviews,²⁷⁴⁻²⁷⁷ and one used focus groups and an interview
413 guide,²⁷⁸ in each case which allowed for a consistent set of topics to be raised with all individual
414
415

416 and focus group participants. One study used unstructured interviews to allow issues as
417 experienced by participants to emerge as important.²⁸⁰ Three studies reported that the
418 interviews were conducted by a researcher; however, none of the studies discussed how
419 rapport was built with the participants and thus making it unclear whether a rapport was built at
420 all.^{276,277,280} The five studies that used interviews as their data collection method, identified using
421 content analysis,^{274,275} a systematic text condensation approach,²⁷⁷ a qualitative interpretive
422 approach,²⁷⁶ and a hermeneutic phenomenological analysis²⁸⁰ to analyze their data. The study
423 using focus groups described an iterative thematic textual analysis process, which allowed for
424 the emergence of inductive themes.²⁷⁸ All six studies described strategies to enhance rigor that
425 primarily focused on reliability in coding including coding by more than one researcher and
426 consensus meetings amongst the researchers with regards to the final code list.^{274-278,280}
427

428 Reflexivity refers to the process of systematically reflecting and collecting data throughout the
429 research process to determine the potential effect of the researcher on the data collected and
430 analyzed. It is important to consider reflexivity as it is aimed at the threat to the confirmability of
431 qualitative research results. One of the six primary studies detailed the researchers'
432 backgrounds and efforts to put aside personal beliefs during data collection and analysis,²⁷⁴
433 while the remaining five were silent on the issue.^{275-278,280} Further, the same study included a
434 discussion of the relationship between the researcher and the participants, and the researcher
435 and the topic,²⁷⁴ while again the remaining five were silent.^{275-278,280}
436

437 *Systematic Review*

438

439 There was one systematic review that met the eligibility criteria for this review.²⁷⁹ The authors of
440 this review outlined a clear objective for their study that is well suited for a systematic review of
441 primary qualitative research studies. The research question falls clearly from the objective and
442 the eligibility criteria are congruent with each. A comprehensive literature search was conducted
443 that included both grey and published literature, with no date limits. The search was, however,
444 limited to articles published in the English language, which means relevant studies published in
445 other languages would not have been identified. Quality appraisal of all included studies was
446 conducted using the JBI-QARI tool, and was conducted independently by two reviewers, which
447 would enhance the reliability of the assessments. It is unclear, however, whether citation
448 screening and study identification were conducted by more than one reviewer, which raises the
449 potential for some studies to be inappropriately classified. Similarly, it is unclear whether data
450 extraction and analysis involved more than one reviewer. In particular for data synthesis,
451 involving more than one reviewer would help to ensure reliability in coding and ultimately
452 credibility in the emergent synthesis. A detailed list of eleven synthesized results are presented
453 however alongside all 127 result statements that were extracted from the primary study reports,
454 which allows for an assessment of the comprehensiveness of the synthesized results. Based
455 on this assessment, it appears that the emergent synthesis dependably reflects the primary
456 study results. An important limitation of this review is the authors' failure to speak to any efforts
457 seeking to enhance rigor within the review process. For example, no description was provided
458 of the researchers' background and their relationship to the topic and no other attempts were
459 made to remain reflexive and aware of their influence on data collection, synthesis or
460 interpretation. Similarly, no mention was made of team meetings or peer debriefing, or the
461 maintenance of an audit trail. While it is unclear whether strategies to enhance rigor were not
462 conducted, or not reported, it remains possible that the synthesis lacks credibility as a result.
463

464 Summary of Findings

465
466 Perceived Benefits and Risks of Diagnostic Imaging
467

468 All but one of the studies included participants who spoke to the perceived benefits of a range of
469 diagnostic imaging techniques.^{274,275,277-280} In one study, some participants even tied their lives
470 to these technologies stating “I might not be here [without that CT scan]” or “I owe my life to an
471 x-ray” (p. 5).²⁷⁸
472

473 In most cases, however, benefits were articulated in terms of the technology’s non-invasive
474 potential to peer within²⁷⁸ and deliver images capable of mapping out current or prospective
475 health concerns. Strand et al.²⁷⁴ point to one individual who could find nothing positive about
476 their experience with an MRI scan for neoplasm metastases in their spine aside from it offering
477 the potential to “get help and know what can be done” (p. 194). Whether the resultant images
478 indicated a positive or negative diagnosis, this ability to “know” was often perceived as valuable
479 in and of itself.²⁷⁷ So much so that several individuals indicated that reminding themselves of
480 this potential helped to mitigate varied levels of discomfort experienced during their actual
481 examination.^{274,277,278,280}
482

483 While these perceived benefits of imaging technologies tended to be discussed more often than
484 risks, Thornton et al.’s²⁷⁸ study with individuals navigating cancer care from a variety of
485 perspectives (i.e., lung cancer screening, chemotherapy for stage IV colorectal carcinoma,
486 thoracic cancer survivorship) also explored perceptions of risk. The cumulative ionizing radiation
487 risks of repeated CT scans during chemotherapy treatments, the potential for kidney damage
488 from intravenous contrast material, or safety concerns about excretion of radioactive tracers
489 weighed heavily.²⁷⁸ For some individuals in Nightingale et al.’s study on experiences with
490 cardiac SPECT-CT, perceptions of risks emanated from an association of terms like “nuclear”
491 with “atom bombs.”²⁷⁵ Nonetheless, for both studies, individuals expressed that the value of
492 imaging strategies far outweighed any long-term risks of ionizing radiation.^{275,278}
493
494

495 Experience of Diagnostic Testing
496

497 The primary themes to emerge from the literature regarding patient or partner experience with
498 diagnostic imaging were identified as “threats to self-control,” “the importance of family or staff,”
499 the importance of “clear and honest communication,” and “long-term psychological effects.”
500 While perceived benefits and risks of undergoing imaging revolved around the post-examination
501 experience, this section focuses much more on “heat-of-the-moment” experience. As individual
502 interviews for all of the primary studies aside from Hinton et al.²⁷⁶ occurred on the same day as
503 examination, it is possible to understand them as presenting a more visceral glimpse into what it
504 could be like on the examining table.
505

506 *Threat to Self-Control*
507

508 Some patients stated that the experience of undergoing diagnostic imaging examinations
509 challenged their self-control and their ability to manage the situation.^{277,279,280} Patients attributed
510 this feeling of loss of control to being isolated, confined, dependent on others and also reported
511 a loss of control over their thoughts and reactions.^{279,280} In one study, outpatients undergoing
512 an MRI indicated that this feeling of loss of control started before even coming into the MRI
513 department.²⁸⁰ Some stated that the sight of the machine and the narrow tunnel triggered the

514 feeling. One participant described feeling calm before the scan but that the procedure triggered
515 stressful memories of being buried in a previous accident, which was unexpected.²⁸⁰ One author
516 reported that the variation in experiences highlights the need for individualized support to
517 manage feelings of threats to self-control.²⁸⁰

518
519 While no specific imaging technologies are discussed in Hinton et al.'s study on near-miss
520 events during childbirth or, "severe life threatening obstetric complications,"²⁷⁶ non-birthing
521 partners likewise described feeling out of control watching their partner in the emergency
522 situation. Unable to help on their own and feeling powerless, these partners often described the
523 experience as shocking and distressing.²⁷⁶ Because of the nature of the emergency situation,
524 partners also explained feeling excluded by the health care team as they worked to save the
525 patient.²⁷⁶

526 527 *Importance of support from family or staff*

528
529 Similar to the way in which the spatial confines of these technologies had the ability to pull at
530 one's sense of self-control, several individuals indicated feeling unmoored from reality both
531 during and leading up to their examination. Whether causing the perception of time to slow^{275,277}
532 or ushering the individual to "another world",²⁸⁰ the unfamiliarity of the setting could increase
533 anxiety or fear for some people. In an extreme example, Tornqvist et al. note some individuals
534 associated their MRI scan with being in a coffin or "lying almost as for cremation" (p. 957).²⁸⁰
535 Perhaps little more than a passing comment, by drawing upon these spaces reserved for dead
536 and inert bodies as a means of explanation, some participants seem to signal a form of isolation
537 or reality separated from the living.

538
539 In order to be drawn back, several individuals spoke to the importance of knowing someone was
540 sharing this space with them.^{274,275,277,280} Again in Tornqvist et al., reminiscing on his own
541 experience, one participant said, "My wife is there with me now. I can feel her hand on my leg,
542 and then I know there is someone, she is there. It's an enormous support" (p. 958).²⁸⁰ By simply
543 laying a hand on her husband's leg, this woman was able to pull him back and help him remain
544 calm. For others, radiographers tended to play the role of anchor. Whether counting down
545 remaining time aloud,²⁷⁵ providing an emergency buzzer in case the participant needed to
546 prematurely end the exam,^{274,277,279,280} or simply reminding the participant that they were
547 there,²⁸⁰ radiographers could act as mediators between reality and the individual.

548
549 Another form of support, this one coming prior to the actual examination, took the form of
550 spending time customizing the experience for each participant. Individuals in Strand et al.'s
551 study note this customizability as incredibly valuable due to the potentially painful positions
552 required in MRI scanning for potential neoplasm metastasis in the spine.²⁷⁴ By providing pillows
553 or thicker mattresses to suit individual needs, radiographers were able to add a certain level of
554 humanity to such a surreal experience.

555
556 Support appears to enable patients to relax during the procedure and increase their feeling of
557 control over the situation.²⁸⁰ There also appears to be a link between threat to self-control and
558 the need for support; those feeling a greater threat to self-control were more likely to need
559 support from others, and conversely the availability of support could improve the ability to
560 cope.²⁸⁰

561
562 For some families who had experienced near-misses in childbirth, non-birthing partners similarly
563 acknowledged the importance of family and staff support.²⁷⁶ One husband, telling the story of
564 his family's near-miss, recounted the empathy shown by a staff member after their daughter had

565 been delivered. As he held his daughter and wife who was “down for the count” he remembered
566 the way in which the anesthetist “put her arm around [me] and she was stroking [my wife’s] hair
567 as well” (p.5)²⁷⁶ Though unable to completely resolve the partner’s feelings of powerlessness or
568 distress throughout the imaging and intervention processes (as discussed in the previous
569 section), showing a keen awareness of these feelings was experienced as both appreciated and
570 calming.

571
572 *Clear, honest communication from medical staff was highly valued by patients and their partners*
573

574 Support could also come in the form of clinicians or radiographers taking time to talk about the
575 examination prior to the actual procedure.^{275,277-279} While individuals in Carlsson and Carlsson’s
576 study reported being satisfied with the written information they received regarding their
577 upcoming MRI scan, those same individuals emphasized the importance of reviewing this
578 information in person as several realized once undergoing the examination that they had not
579 fully understood the written information.²⁷⁷

580
581 Nightingale et al.²⁷⁵ similarly report that patients appreciated pre-appointment conversations
582 with their radiologists. For those individuals who were quite anxious to even attend the imaging
583 procedure, this background and being on a first name basis with the radiographers was
584 beneficial.

585
586 The synthesized findings from the systematic review by Munn and Jordan²⁷⁹ indicate that being
587 aware of what to expect during a MRI scan (i.e. the sound during MRI and invasive aspects of
588 the scan) helped patients to deal with the anxiety they experience during the test. Where
589 participants reported receiving information from their healthcare providers some also indicated
590 being unsatisfied with it and having to turn to self-directed internet searches for further
591 information.^{278,279} In particular, participants in the systematic review²⁷⁹ as well as a further
592 primary study²⁷⁸ expressed a desire for information regarding the availability of different
593 diagnostic imaging options and the risks and benefits associated with each.

594
595 Several participants in the study by Thornton et al.²⁷⁸ reported benefit-risk discussions about
596 ionizing radiation from medical imaging as rare and seldom initiated by clinicians. While some
597 indicated this would be a valuable conversation, perceptions of the importance seemed to vary
598 based on stage of illness and personal feelings toward imaging technologies. For instance,
599 advanced stage oncologic patients reported preferring to leave all decision-making responsibility
600 about imaging tests to their physician during active phases of therapy while others had low
601 interest in shared decision-making processes when they understood the importance of an
602 imaging test.²⁷⁸ Several participants indicated a lesser need for discussion of the benefits and
603 risks of diagnostic imaging due to trust and the confidence that their physician or hospital will
604 protect them by using the best imaging equipment and protocols.²⁷⁸

605
606 Although in each study patients expressed the need for clear communication and information,
607 the circumstances or local format of the imaging procedures may prevent optimal
608 communication or shared-decision making. Variation in hospital or clinic procedures, and the
609 circumstances of the suspected PE could account for why some patients felt satisfied and
610 others did not.

611
612 Even though the partners of women facing imaging for near-misses understood that it was an
613 emergency situation and information needed to be moved along quickly, sometimes without
614 their knowledge, they explained that having clear and honest communication from the
615 healthcare professionals made a difference in their experience.²⁷⁶ For instance, one partner

616 recalled walking into the ICU room where his wife was and thinking that she was dead for an
617 hour before being told that she was on life support and would be fine.²⁷⁶

618
619 *Long-term emotional effects*

620
621 Psychological distress was also expressed in two studies, including anxiety, uncertainty, dread,
622 and fear that lasted until the results of the scan were known.^{278,279} In Hinton et al.'s study on
623 near-miss events in childbirth, many of the partners and patients were interviewed several years
624 after the emergency experience and some reported suffering from posttraumatic stress disorder
625 as a result of their overall experience. Others explained they were unable to re-visit the past
626 experience through recollection with their family members or clinician.²⁷⁶

627
628

629 **Summary of Findings**

630 Of those individual experiences that were explored within the studies included for this review,
631 several spoke to the ways in which the power of these diagnostic technologies to map out both
632 current and prospective health concerns helped to mitigate various levels of discomfort felt
633 throughout their respective exam. Nonetheless, however powerful this prognostic potential "to
634 know" may be, many participants still framed their experience in terms of their concerns with
635 self-control, isolation and being unprepared. Self-control could be placed under threat at any
636 point throughout the imaging process. Whether beginning somewhere within the walk toward
637 the imaging room or rising and falling throughout the actual examination, these feelings of
638 powerlessness could heighten levels of anxiety or discomfort for both patients and their
639 caregivers (or partners). At times, this discomfort could be expressed through metaphors related
640 to death, dying or other forms of extreme alienation. More than merely signaling a basic sense
641 of isolation, the use of these extreme metaphors seem to indicate feelings of disconnect or
642 unmooring from reality. With that in mind, physical reminders of the presence of loved ones or
643 more verbal or visual reminders of a radiographer's presence could serve as anchors
644 throughout the imaging process and help alleviate related concerns. Similarly, though potentially
645 irrelevant to the emergency room diagnostic process for PE, clear lines of communication
646 between individual and clinicians prior to examination could help to alleviate these concerns.
647 While reading material was noted as helpful when preparing for an upcoming scan, many
648 participants felt as though spending time with a clinician prior to undergoing the actual exam
649 would provide a greater level of comfort.

650

651 **IMPLEMENTATION ISSUES**

652 This section addressed the following Research Question:

653

654 Research Question 7: What are the issues associated with implementing the optimal use of
655 diagnostic strategies, including imaging, for acute PE in adults in urban, rural, and remote
656 settings?
657

658 **Methods**

659 **Data Collection**

660

661 **Survey**

662 A survey was developed to provide information and context on this topic, and conducted as part
663 of a CADTH Environmental Scan.²⁸¹ The objectives of the Environmental Scan were to: identify
664 current practice related to diagnostic strategies for PE in Canada; identify which tests, scans
665 and tools are available across Canadian jurisdictions and settings (i.e., urban, rural, and remote
666 health care centres) to diagnose PE; and identify challenges and enablers to the diagnosis of
667 PE, including relevant implementation issues in Canada. The survey (Appendix 27) consisted of
668 13 questions that were close-ended (single or multiple responses) or open-ended in nature. The
669 final survey was distributed via email to potential respondents.

670 Potential survey respondents (e.g., clinicians, directors of diagnostic imaging, medical directors,
671 hospital department heads) were identified by CADTH Liaison Officers, through professional
672 and clinical networks, or referred through other respondents. The survey was pilot tested by a
673 clinical expert on the project, and was administered to potential respondents in January 2017.
674

675 **Expert interview**

676 To supplement the findings of the survey and the literature search, an interview with a clinical
677 expert (one of the clinical experts engaged for the larger project) in the field of emergency
678 medicine was conducted. This interview centred on the expert views of the approach to
679 diagnosing pulmonary embolism, including challenges to diagnosis and the Canadian context. A
680 semi-structured interview approach was used. Interview questions related to the general
681 approach to diagnosing PE, challenges and supports to the diagnosis of PE, and gaps in the
682 literature.
683

684 **Literature Search**

685 A targeted literature search was conducted to identify information on issues relevant to
686 implementation of diagnostic strategies for pulmonary embolism in Canada.
687

688 *Search Strategy*

689 The literature search was performed by an information specialist, using a search strategy peer-
690 reviewed according to the PRESS checklist - an evidence-based checklist for the peer review of
691 electronic search strategies.⁷⁵

692 Implementation issues information was identified through targeted literature searches of the
693 following bibliographic databases: MEDLINE (1946-), with in-process records and daily updates,
694 via Ovid; Embase (1974-) via Ovid; CINAHL (1981-) via EBSCO; Scopus; and PubMed. The
695 search strategy comprised both controlled vocabulary, such as the National Library of

696 Medicine's MeSH terms, and keywords. The main search concepts were medical imaging,
697 pulmonary embolism, and Canada, and key terms for implementation issues. No methodological
698 filters were applied to limit retrieval by study design. Retrieval was limited to documents
699 published since January 1, 2006. Results were limited to English- and French-language
700 publications. The detailed strategy can be found in Appendix 1.

701 The search was completed on October 7, 2016. Regular alerts were established to update the
702 search until the publication of the final report. Regular search updates were performed on
703 databases that do not provide alert services.

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

709
710

711 *Screening and selecting articles for inclusion*

712 One reviewer included English- and French-language reports that described implementation
713 and context issues, including barriers (or challenges) and facilitators (or enablers), associated
714 with tests, tools or scans used for the diagnosis of PE. Titles and abstracts from the literature
715 were screened by the reviewer for information related to implementation issues. The full text of
716 all potentially relevant reports was retrieved for determination of eligibility by the same reviewer.
717 Articles were deemed relevant and included for summary if they reported information on the
718 implementation and context domains as per the INTEGRATE-HTA model.²⁸²

719

720 *Data extraction*

721 From each relevant article, the bibliographic details (i.e., author, date of publication),
722 implementation issue under review, and other relevant study information pertaining to barriers or
723 facilitators (e.g., clinical setting, geographical setting) were captured by one reviewer. The
724 information from the literature was used to supplement and augment the information provided
725 by the survey, and address any potential information gaps around implementation.

726

727 **Data analysis**

728 For the survey, quantitative responses that were dichotomous (for example, Yes/No) and
729 nominal (for example, a list of options) were summarized descriptively (see Environmental
730 Scan²⁸¹). Open-ended qualitative responses were categorized by theme and summarized
731 narratively by one reviewer.

732

733 Survey data, interview data, and findings from the literature were coded into categories based
734 on the domains of implementation and the domains of context identified by the *Guidance for the*
735 *Assessment of Context and Implementation in Health Technology Assessments (HTA) and*
736 *Systematic Reviews of Complex Interventions: The Context and Implementation of Complex*
737 *Interventions (CICI) Framework* (INTEGRATE-HTA framework).²⁸² Using this framework, four
738 domains of implementation, i.e., “provider,” “organization and structure,” “policy,” and “funding,”
739 as well as the additional domain of “patient” were used to further guide the categorization of
740 identified strategies, barriers, or supports as they relate to the implementation of diagnostic
741 strategies across the various levels of health care service delivery. The domains of context, i.e.,

742 “socio-economic,” “socio-cultural,” “setting,” “political,” “legal,” “geographical,” “ethical,” and
743 “epidemiological,” were also used to guide the categorization of information.
744 Survey data and the literature were read through for initial familiarization before coding. Data
745 was coded by one researcher. Data could be coded to more than one domain, if relevant. The
746 information from all sources was summarized narratively and presented by domain. The
747 summary includes a brief description of the domain and how the identified issues relate to the
748 implementation of PE diagnosis.

749 **Results**

750 Twelve survey responses (clinicians, directors of diagnostic imaging, a medical director, a
751 department head) were received from five jurisdictions. One or more survey respondents from
752 each province and territory, with the exception of the Northwest Territories where no potential
753 respondent was identified, were contacted to complete the survey. Seventy people were initially
754 sent the survey, and survey recipients were asked to further distribute the survey to their
755 colleagues, as appropriate. Four responses were received from Manitoba, three from New
756 Brunswick, two from Prince Edward Island (PEI), two from Saskatchewan, and one from
757 Ontario. No responses were received from the remaining Canadian jurisdictions. Appendix 28
758 provides additional information on the survey respondents.

759
760 Nine English-language primary studies^{34,283-290} were included in the summary of the literature.
761 Appendix 27 presents the study characteristics for the articles included in this review. Year of
762 publication ranged from 2008³⁴ to 2015.^{286,288} Five studies were retrospective chart
763 reviews,^{34,284,285,287,290} one was a survey,²⁸⁸ one was a survey and retrospective chart review,²⁸³
764 one was a retrospective chart review and review of physician characteristics,²⁸⁶ and one was a
765 survey, with interviews and global information systems mapping components.²⁸⁹ Regarding
766 geographical location of study sites, one study was pan-Canadian,²⁸⁹ one study was Canadian
767 but did not specify which provinces and territories information was from,²⁸⁸ while the remainder
768 were from Ontario.^{34,283-287,290} For clinical setting, one study specifically reported on the
769 experiences of a rural emergency department.²⁸⁵ Six studies were conducted in an academic,
770 tertiary care centre.^{34,283,284,286,287,290} One study²⁸⁸ looked at practices in 48 nuclear medicine
771 departments, while one study²⁸⁹ surveyed 658 acute care hospitals. Five studies^{283,285,286,288,290}
772 reported solely on patients with suspected or confirmed PE, while the remainder^{34,284,287,289}
773 reported on patients with suspected or confirmed VTE (but reported PE specific information).

775 **Domains of implementation**

777 **Provider**

778 At the provider level, both the included studies and survey respondents identified provider
779 knowledge and choice as relevant to the diagnosis of PE.

781 *Risk Stratification and Pretest Probability*

782 Provider factors may influence the assessment of patients as they present with PE-like
783 symptoms. Emergent issues related to physician factors and the risk stratification and pretest
784 probability assessment (PTP) for the diagnosis of PE were: familiarity and knowledge of PTP
785 (including documentation of PTP testing), the consideration of PE as a diagnosis, and the
786 concern of missing a PE diagnosis. These factors may influence the use of these tests.
787 Some survey respondents, when asked what clinical prediction tests (e.g., Wells Criteria,
788 Geneva, etc.) are used to diagnosis PE, indicated that the choice is driven by physician choice,
789 with some providers choosing whichever is more familiar to them. The study by Smith et al.³⁴

790 listed reasons why physicians do not apply clinical prediction rules including: medicolegal
791 concerns (not specified further); challenges with memorizing and applying the rule; perception
792 that clinical gestalt is better; perception that none of the rules have been validated to the
793 physician's standards.³⁴ Provider knowledge and familiarity may be a support if the
794 implementation of a particular PTP tool is the one the provider uses. A barrier could be the
795 implementation of an unfamiliar PTP tool that may require additional provider education.
796 In the interview with a clinical expert, challenges to PTP testing were discussed (Dr. Eddy Lang,
797 Academic Department Head and Professor at the University of Calgary Cumming School of
798 Medicine, Calgary, AB: personal communication, 2017 April 21). The issue was raised that PTP
799 is typically not memorized by physicians, and it can be difficult to incorporate into a busy
800 emergency department; this is a barrier to the implementation of PTP assessment. Findings
801 from several of the studies suggest that PTP, if done, is poorly documented in patient
802 charts.^{34,284,285,287} This appears to be the case for large, academic, tertiary care hospitals^{34,284} as
803 well as a small, rural hospital.²⁸⁵ Additionally, it was noted that there is not much literature
804 regarding clinical gestalt to diagnosis PE compared to a structured approach of PTP.
805

806 In addition to PTP choice and documentation, the survey respondents and the clinical expert
807 indicated that the main challenge is in considering PE as a diagnosis. A diagnosis of PE may be
808 overlooked when patients experience chest complaints, which may then be attributed to other
809 conditions. In the interview, the clinical expert discussed general challenges to diagnosing PE,
810 specifically that most patients with PE present atypically, and that it can be hard to diagnose. It
811 was suggested that most patients with PE do not get diagnosed on their first visit to their doctor
812 or the emergency department. Failure to consider PE as a diagnosis is a challenge; this lack of
813 consideration could result in near misses or potential fatalities when patients fail to be
814 appropriately diagnosed with PE. This fear of missing PE may also cause physicians to start
815 treating patients with anticoagulants, as a bleed complication from being treated is thought by
816 some to be preferable to having PE (Dr. Eddy Lang: personal communication, 2017 April).
817

818 *Rule-Out and Ancillary Testing*

819 Provider factors may also influence the use of rule-out and ancillary testing. This may include
820 knowledge of D-dimer testing, including how it should be used and interpreted. Based on the
821 survey responses and the literature identified in the review, D-dimer may be used as a
822 screening tool, and changing this behaviour may be challenging for the implementation of
823 judicious D-dimer use. A barrier may also be provider education regarding the interpretation and
824 appropriate use of D-dimer.
825

826 Regarding rule-out and ancillary testing, a few studies focused on the use of D-dimer testing, or
827 more specifically, the overuse of D-dimer testing. In the study by Smith et al.,³⁴ the study
828 authors determined that D-dimer was not being used as recommended by their facility, or was
829 being misinterpreted by emergency clinicians. The study by Ingber et al.²⁸⁷ also evaluated the
830 use of D-dimer testing, and suggested that clinicians may have inaccurately filled out PTP forms
831 to gain access to the test. Additionally, the study by Arnason et al.²⁸⁴ regarded the use of
832 appropriate diagnostic strategies for VTE and reviewed 863 charts of patients for whom D-dimer
833 had been ordered. The authors reviewed diagnostic imaging for patients that had D-dimer
834 testing, and suspected that D-dimer was being used as an initial screening tool for patients with
835 chest pains, regardless of their clinical presentation.²⁸⁴ The study authors noted that the
836 prevalence of PE was lower than expected, and thought this may have been due to the use of
837 D-dimer in patients before PE had been considered a possible diagnosis.²⁸⁴
838 From the survey, one participant indicated that D-dimer may be used as a screening tool. Other
839 participants more generally indicated that D-dimer may be required if clinically indicated, as a
840 rule-out test, based on the initial clinical suspicion of PE.

841

842 *Diagnostic Imaging*

843 As with the clinical prediction rules and rule-out testing, provider factors may influence the
844 choice and use of diagnostic imaging modalities. Much of the literature related to clinician
845 utilization or preference for certain modalities; though choice of imaging test could be related to
846 contextual issues such as access, not just provider knowledge. Depending on the diagnostic
847 strategy, provider knowledge or preference for one imaging modality may be either a barrier or a
848 support.

849

850 Limited information was provided by survey participants about provider factors influencing
851 diagnostic imaging; one participant stated that there was an over-reliance on imaging for PE
852 diagnosis. However, over-testing may not always be the case, as the study by Aranson et al.²⁸⁴
853 found that testing strategies for VTE (PE included) are more likely to be classified as
854 inappropriate due to a provider failing to perform imaging than the overuse of diagnostic
855 imaging; in their study, they found that 220 of 230 PE patients had inappropriate testing
856 strategies (based on the Wells Criteria) due to the under use of diagnostic imaging.
857 In the study by Ahn et al., emergency physicians (n = 43) had a general knowledge that a V/Q
858 scan exposed patients to less radiation than CTPA, and they preferentially chose V/Q scans for
859 younger patients (< 50 years old), females, or if they had a history of recent, multiple CT
860 scans.²⁸³ However, physicians had limited knowledge of precise radiation doses, and the study
861 authors did not explore whether radiation risk had been discussed with the patients.²⁸³ The
862 study by Ballantine et al. noted that physicians seemed to prefer CT to diagnose PE, however,
863 they were not certain whether this was because of the perceived ease of access to CT.²⁸⁵

864

865 One study examined CTPA utilization rate among 26 emergency physicians of different genders
866 and ages, with training in either a three year Canadian College of Family Physicians Certificate
867 of Special Competence in Emergency Medicine or a five year Fellowship of the Royal College of
868 Physicians in Emergency Medicine.²⁸⁶ Physician gender, years of practice, and training
869 certification was not correlated with CTPA utilization rate or with PE positivity rate.²⁸⁶ However,
870 CTPA utilization rates differed amongst physicians, with a range of 0.21 to 0.77 scans per 100
871 patient visits (average of 0.48 scans per 100 patient visits).²⁸⁶ The authors of this study listed
872 several factors that may influence how often CTPA is used, including, physicians' knowledge of
873 guidelines, risk tolerance, prior training, prior experiences, and the "need to know".²⁸⁶ While the
874 authors did not specifically look at appropriate use of CTPA and the source of the inter-
875 physician variation in use rates, there were some speculated differences in adherence to
876 guidelines; they suggest future efforts be focused on physician education.²⁸⁶

877 In the study looking at the use of SPECT in Australia, France and Canada the study authors
878 noted some resistance to the adoption of SPECT technology (not specific to Canada but a trend
879 in the overall study) which they suspected was because of several reasons, including:
880 reluctance to change, more experience and familiarity with planar imaging, possible concerns
881 related to time for SPECT, lack of appropriate imaging agents, or resistance from other
882 colleagues.²⁸⁸ These are barriers to using SPECT technology.

883

884 **Policy**

885 At the policy level, survey participants and the literature identified policies, or potential policies,
886 which would support the implementation of diagnostic strategies for PE.

887

888 Though it appears that PTP is rarely documented, if done, it is possible to establish mandatory
889 PTP assessment. This would require collaboration across hospital departments, and while once
890 in place it could be a support to providers, the initial implementation could be challenging. The
891 study by Ballantine et al.²⁸⁵ stated that there was a lack of documented PTP and suggested

892 implementing a protocol that required the use of Wells scores before any further testing or
893 imaging was ordered. In the study by Ingber et al.,²⁸⁷ the study authors investigated the initiation
894 of mandatory PTP algorithms (based on Wells Criteria). The authors were primarily interested in
895 the use of D-dimer and imaging tests in the pre- and post-intervention periods, but they also
896 demonstrated that the initiation of mandatory PTP testing was feasible given a high degree of
897 compliance. This required collaboration with the emergency department and with their
898 laboratory; D-dimer samples had to have a PTP score sheet in order to be tested, and those
899 without would not be tested.²⁸⁷

900
901 The study by Le Roux et al.²⁸⁸ explored the use of SPECT or SPECT/CT instead of planar
902 scintigraphy for the diagnosis of PE at 48 Canadian sites (no provinces or territories specified).
903 Compared to France and Australia where 58% and 42%, respectively, of facilities using V/Q
904 SPECT also acquired CT images, only 11% of Canadian facilities did this. The study authors
905 hypothesized several reasons for this, including different cost and reimbursement policies, but
906 this was not explored further. This same study examined the way V/Q planar was interpreted
907 and found that it was primarily interpreted using the European Association of Nuclear Medicine
908 criteria (60%), followed by binary one sub-segment (17%), probabilistic Prospective
909 Investigation of PE Diagnosis study criteria (17%), or no standardized criteria (7%).²⁸⁸ Existing
910 guidance for the interpretation of SPECT is a potential support for implementation of its use.

911
912 From the survey one participant stated that clear protocols for diagnosing PE are needed for
913 small and medium sized communities. Another mentioned the use of American College of Chest
914 Physician guidelines (no further details provided). No other participants stated the use of
915 guidelines for PE diagnosis, though this may only be reflective of the facility or particular
916 respondent and not of their jurisdiction. There may be a need for consistent protocols, and these
917 may vary depending on the resources available to the facility.

918 The lack of clarity around guidelines or protocols for diagnosing PE was also noted in the
919 literature. Chen et al. indicated that though there have been guidelines developed regarding
920 when to use CTPA, the implementation of these guidelines has been inconsistent, and
921 suggested overuse in some settings (not specified) while being underused in others.²⁸⁶ The
922 study by Southern et al. found that there was considerable variation in the use of decision
923 support tools (e.g., diagnostic critical pathways or computer prompts); it was noted that most
924 provinces had at least some hospitals that used such tools, but PEI and the northern territories
925 did not have decision support tools for the diagnose of VTE at the time of their survey.²⁸⁹

926

927 **Patient**

928 Diagnostic approaches may differ depending on characteristics of and factors related to the
929 patient (e.g., contrast allergy, pregnancy, morbid obesity).

930 The clinical expert also mentioned that D-dimer may have high false positives in certain
931 populations (e.g., the elderly, patients with auto-immune or inflammatory disease) (Dr. Eddy
932 Lang: personal communication, 2017 April). The literature also notes the difficulty in using D-
933 dimer in critically ill patients.²⁸⁷ Use of D-dimer in these populations may be challenging. While
934 our survey attempted to address what type of D-dimer was being used (e.g., age-adjusted), the
935 response rate was too low to determine what is being used across Canada; this is an
936 information gap.

937
938 Survey participants were asked if the diagnostic approach may differ based on particular patient
939 populations. Seven participants indicated that CT imaging may be difficult if patients have renal
940 dysfunction, or an allergy or contraindication to the contrast used. Two participants mentioned
941 V/Q scan, echocardiography, or leg ultrasounds are available in this case. One participant
942 mentioned that if patients are not able to have contrast CT, and are presumed to be high risk for

943 PE, they may be treated if treatment is deemed less risky than investigation. As well, one
944 participant stated that patients are sometimes too unstable to get a CT scan if needed. Two
945 participants indicated that pregnant women are a special population, though alternative
946 diagnostic strategies were not specified. One participant indicated that patients with morbid
947 obesity may be beyond the weight limit of imaging scanners; no alternative diagnostic method
948 was specified. In the literature, it was specified that patients with poor renal function (defined as
949 an estimated glomerular flow rate of 60 ml/min), contrast allergies, asthma, other malignancies,
950 a previous DVT or previous PE were more likely to have a V/Q scan.²⁸³

951
952 It is uncertain the extent to which imaging modalities differs by patient gender. The study by
953 Chen et al.²⁸⁶ examined CTPA utilization rates by patient gender and age. CTPA utilization was
954 higher for females compared to males, and CTPA utilization rates increased with increasing
955 patient age; the increase in CTPA use in females and older patients did not correspond to an
956 increase in PE positivity rate for gender or age cohorts.²⁸⁶ The authors suspected there was a
957 gender-related bias in the use of CTPA.²⁸⁶ For older patients, the authors suspected the
958 increased imaging was related to more ambiguous clinical exams.²⁸⁶ However, in the study by
959 Ahn et al.,²⁸³ females were more likely to receive V/Q scans than CT. This was also noted in the
960 provider factors, and the extent to which the patient or the physician influences this choice was
961 not explored.

962
963 There may also be unintended consequences of imaging in certain patient populations. Spencer
964 Netto et al.,²⁹⁰ assessed at the use of contrast-enhanced chest CT as part of trauma
965 assessment. The increased use of CT for imaging of trauma patients increased the diagnosis of
966 asymptomatic PE.²⁹⁰ Management of coincidental PE may be different than the assessment and
967 management in patients with suspected PE.

968 **Organization and Structure**

969 Issues of organization and structure from the survey dealt with staffing and afterhours access to
970 resources. One respondent indicated that nuclear scans are a limiting step, as only one
971 radiologist is available to read them and that having more staff after hours may enable them to
972 do more nuclear scans. One respondent stated that they are generally satisfied with their tools
973 to diagnose PE, but that access to V/Q scans is limited after hours. Adequate staffing may be a
974 barrier to implementing interventions for the diagnosis of PE.

975
976
977 In the literature, issues of organization and structure were related to referral of patients outside
978 of centres for diagnostic imaging, physician education, the documentation of PTP in patient
979 charts, and regional programs.

980
981 The study by Ballantine et al.²⁸⁵ describes the referral patterns for patients with suspected PE to
982 be transferred out of their facility, if they need CT or V/Q scans. Patients can be sent up to 55
983 km away to receive diagnostic imaging, as there is no CT or V/Q scan available in the small,
984 rural facility. One survey participant indicated that V/Q scans are not available “afterhours” in the
985 province, but that if patients need this, it is a 45 minute transfer away. Establishing when
986 patients need to transfer, and which facility they will be transferred to, requires coordination
987 between facilities and clear protocols in place. This also ties into the section on setting and
988 geographical influences for diagnostic strategies for PE.

989
990 The study by Chen et al.²⁸⁶ explored the differences in CTPA usage among physicians who
991 have completed either the five year emergency medicine (EM) Fellowship of the Royal College
992 of Physicians, or the two-year family EM program of the Canadian College of Family Physicians.
993 CTPA usage for the diagnosis of PE was not different between physicians with either training.

994 On average, it had been 15 years since the completion of their residency for the physicians in
995 the study, and the authors suspected that the effects of training had waned, while other
996 organizational factors may be more influential, like interaction with patients, work environment,
997 the emergency physician's practice pattern, and continuing education.²⁸⁶

998
999 As was previously mentioned in the section on provider factors for implementation, PTP was
1000 seen to be poorly documented in patient charts, and the clinical expert had stated the difficulty
1001 in using formal PTP in busy clinical settings. The study by Ingber et al.²⁸⁷ explored the
1002 establishment of mandatory PTP assessment before D-dimer testing. To implement mandatory
1003 PTP assessment and documentation before D-dimer testing would require system wide
1004 changes and direction from the organization to facilitate the change, in addition to any provider
1005 or policy changes.

1006
1007 There was some exploration into regional resources and clinics, such as outpatient clinics and
1008 home monitoring for VTE (PE specific programs not specified, detail regarding the programs
1009 was also lacking).²⁸⁹ Southern et al. found that Alberta, Saskatchewan, Manitoba, Quebec, New
1010 Brunswick and Nova Scotia had early outpatient clinics for VTE (and not every region within the
1011 jurisdiction had these services). At least one region in Alberta, Saskatchewan, Manitoba,
1012 Quebec, New Brunswick and Nova Scotia had long-term outpatient clinics. For home programs,
1013 Alberta, New Brunswick and Nova Scotia had programs in at least one region. One region in
1014 Saskatchewan had a home monitoring program.²⁸⁹ Though this was not PE specific, it does
1015 provide some insight into the limited availability of additional support services and clinics.

1016 1017 **Funding**

1018 Little information was identified explicitly related to funding or lack of funding for the
1019 implementation of strategies to diagnose PE. Again, the study by Le Roux et al.²⁸⁸ suspected
1020 that a difference in cost and reimbursement policies may have contributed to differential use of
1021 SPECT vs. SPECT/CT in Australia, France and Canada, but this was not explored further. One
1022 survey participant indicated that if patients with suspected PE needed to be transferred from
1023 one health care facility to another that the costs are covered by the province. Intuitively,
1024 adequate funding for interventions is a support; however, lack of funding for diagnostic
1025 strategies is a barrier.

1026
1027 A detailed economic model is explored in a separate chapter of this HTA.

1028 1029 **Domains of Context**

1030 1031 **Socio-economic**

1032 None of the identified relevant articles, survey participants or clinical expert identified issues
1033 explicitly related to socio-economic factors for the implementation of strategies to diagnose PE.

1034 1035 **Socio-cultural**

1036 Socio-cultural factors, such as language and communication, as well as lifestyle and social
1037 resources, may influence the approaches to the diagnosis of PE. Patient related factors,
1038 including knowledge and perceptions, are explored in this HTA in a separate chapter. The
1039 following explores the relevant socio-cultural factors as identified in the literature found during
1040 the implementation search.

1041
1042 For clinicians, the choice of diagnostic imaging for PE may depend, in part, on the surrounding
1043 socio-cultural context. The study by Chen et al.²⁸⁶ found that CTPA was disproportionately used
1044 in females at their tertiary, academic hospital emergency department. The authors suspected

1045 that this may be due to patient histories of oral contraceptive use (which is a risk factor for PE),
1046 but they also stated that this risk factor may be overestimated by clinicians.²⁸⁶ Use and trends in
1047 oral contraceptive use may influence approaches to the diagnosis of PE.
1048 Perceptions of imaging modalities within the clinical community can change over time. The
1049 study by Le Roux²⁸⁸ discusses the change in perception of V/Q SPECT. The author observed
1050 that V/Q SPECT had largely replaced traditional planar imaging at facilities in Australia, France
1051 and Canada; they suspected that the changing perceptions of the nuclear medicine community,
1052 with a more favourable view of SPECT, was a factor in this change.²⁸⁸ For the facilities still using
1053 planar V/Q scintigraphy as opposed to SPECT, the authors proposed that clinician resistance to
1054 change, a greater familiarity with planar imaging, and concerns with the technology and lack of
1055 suitable ventilation agent were barriers to use.²⁸⁸ While SPECT is one example, the perception
1056 of different PTP, ancillary and rule-out tests, and imaging modalities may influence their use
1057 amongst clinicians.

1058 **Setting and Geographical**

1059 Issues of setting (according to INTEGRATE-HTA²⁸²) refer to region, country (e.g., urban and
1060 rural), type of facility, etc. while issues of geography refer to infrastructure (e.g., transport),
1061 access to health care, geographical isolation, etc. The questions of this HTA also combine the
1062 issues of setting and geography as the diagnostic strategies are considered in urban, rural and
1063 remote settings.

1064
1065
1066 Regarding modalities for diagnostic imaging, CADTH's Canadian Medical Imaging Inventory
1067 (CMII)³⁹ provides recent data on the number of CT, MRI, PET, and SPECT units across the
1068 country (with information on the number of hours these units are available per day and per
1069 week), however, whether these are indicated for use in patients with suspected PE is not
1070 known. As of the 2015 data, there are 538 CT units, 340 MRIs, 264 SPECT, 47 PET or hybrid
1071 PET-CT, and 214 SPECT-CT units across Canada; for all of these imaging modalities, the most
1072 units were found in Ontario and Quebec. There are also two PET-MRI units in Canada, both of
1073 which are found in Ontario and operate for research purposes only.

1074
1075 Patient location may influence the appropriateness of the diagnostic strategy; patients with
1076 suspected PE presenting to the emergency department were more likely than inpatients to
1077 undergo appropriate diagnostic testing in one study.²⁸⁴ Regarding treatment, from the interview
1078 with a clinical expert, patients in the North or from remote areas may be treated with
1079 anticoagulants in the interim, before they are able to be transported for further work-up (Dr.
1080 Eddy Lang: personal communication, 2017 April). Survey participants also indicated that high
1081 risk patients may be started on treatment while investigations are still being done.
1082 The Environmental Scan²⁸¹ related to this project reports in more detail the availability of tests
1083 and diagnostic imaging across Canada. As a general trend, provinces with small populations
1084 were more likely to collect samples for D-dimer testing and send them to centralized facilities to
1085 be analyzed, whereas provinces with large populations had more hospitals with on-site D-dimer
1086 testing. CT appeared to be more common than other imaging modalities, like MRI and V/Q, in
1087 smaller centres²⁸⁹ though may still be limited in rural or remote centres.^{39,285}
1088 In the survey, participants were asked if they were aware of instances when their diagnostic
1089 strategy may differ depending on location within their jurisdiction (e.g., urban, rural, remote
1090 hospitals). Seven respondents indicated that how a diagnosis is made may change depending
1091 on the availability of tools and tests within their jurisdictions. Some stated the diagnostic strategy
1092 may differ depending on availability of D-dimer, V/Q and CT scans or nuclear medicine. One
1093 respondent suspected that larger facilities may have different approaches, and another
1094 respondent stated that some facilities do not have CT scans or nuclear medicine departments.
1095 Respondents were aware that rural hospitals may not have the same tools and tests as urban

1096 hospitals; this may require transportation of patients. Two respondents indicated that patients
1097 seen in rural sites requiring CT scans would need to be transferred to a hospital with CT scans.
1098 Similarly, one respondent mentioned that rural sites do not have CT or V/Q available.
1099 Survey respondents were also asked about the availability of rule-out and ancillary tests in their
1100 jurisdiction, including: arterial blood gas, capnography, chest X-ray, D-dimer testing,
1101 echocardiography, electrocardiography, and leg compression ultrasound. All provinces that
1102 provided responses had access to at least some of these tests. New Brunswick and
1103 Saskatchewan, based on responses from survey respondents, did not have capnography;
1104 though this may be a reflection of the facilities where the respondents were located and not for
1105 the provinces as a whole.

1106
1107 Survey respondents were asked about the availability of imaging tests in their jurisdiction,
1108 including: V/Q scintigraphy, V/Q SPECT, V/Q SPECT-CT, CT, thoracic ultrasound, MRI, and
1109 PET. All jurisdictions had access to at least some of these tests. Only the hospital in Ontario
1110 had access to all of the imaging modalities. New Brunswick was the jurisdiction with responses
1111 from both an urban teaching hospital and a rural hospital; only CT and MRI were available at the
1112 rural hospital, while the urban, teaching hospital had the V/Q modalities, CT, and MRI.

1113 1114 **Political**

1115 None of the identified relevant articles, survey participants or clinical expert identified issues
1116 explicitly related to political factors for the implementation of strategies to diagnose PE.

1117 1118 **Legal**

1119 Few sources identified relevant legal issues regarding strategies for the diagnosis of PE. When
1120 exploring imaging test ordering and imaging utilization, the study by Chen et al.²⁸⁶ cited
1121 physician concerns over litigation (presumably due to a missed PE diagnosis), as an influencing
1122 factor.

1123
1124 Related to the section on ethical issues, informing patients of radiation risk (from imaging
1125 modalities such as CT) is a potential legal issue. One study²⁸³ surveyed 31 physicians and
1126 found that 58% of them informed all patients about the radiation risks of diagnostic imaging
1127 tests, 35% informed only high risk patients (“pregnant patients and females of childbearing
1128 age”), one physician stated they told patients there was a risk but that the degree of risk is
1129 uncertain, and another physician never informed patients about radiation risks. One survey
1130 respondent also addressed the issue of consent; they indicated that pregnant women are asked
1131 to give consent after being informed of their risk. There is a possibility that patients who feel
1132 they were not properly informed of risks related to the modalities used to diagnose PE may raise
1133 a legal suit.

1134 1135 **Ethical**

1136 While ethics is one of the INTEGRATE-HTA domains, this HTA also contains a chapter on
1137 ethical issues that provides a more detailed exploration of this topic area. For the
1138 implementation review, relevant ethical issues were related to the issues of informed consent
1139 around, and exposure to, radiation (specifically for CTPA).^{283,286,287} The section on legal issues,
1140 in this HTA chapter, provides more detailed study findings of physician disclosure of radiation
1141 risks.

1142 1143 **Epidemiological**

1144 Relevant epidemiological factors (e.g., subgroups of interest) related to the diagnosis of PE are
1145 explored in more detail in the clinical section of the report, however, few epidemiological issues

1146 were found for this component of the HTA. Patient factors are also explored in a previous
1147 section of this report (e.g., special populations like pregnant women, females, older persons).
1148 The establishment and use of local cut-off values for D-dimer may aid in the appropriate
1149 diagnostic work-up of patients with suspected PE and support further implementation strategies.
1150 The study by Ingber et al.²⁸⁷ explored other findings related to D-dimer use (latex immunoassay
1151 – HemosIL D-dimer, Instrumentation Laboratory Company, Bedford, MA) after mandatory PTP
1152 assessment. Despite efforts to curb inappropriate test usage, the use of diagnostic imaging for
1153 VTE did not decrease in this study, even though PTP was now required for D-dimer testing.²⁸⁷
1154 The authors suspected that this might be partly due to the high false positive rates of the test
1155 they were using, and further emphasized using a local cut-off value (rather than the
1156 manufacturer cut-off), as well as an age-adjusted cut-off.²⁸⁷ Use of more appropriate cut-offs
1157 may have resulted in more low PTP patients in whom VTE might have been ruled-out.²⁸⁷

1158 **Summary of results**

1159 This section of the HTA reported on issues related to the implementation of diagnostic
1160 strategies for PE, based on a survey of stakeholders, a literature review, and an interview with
1161 an expert clinician. The following summarizes the main findings as identified through the
1162 analysis of the information from all sources.

1163
1164 *Provider knowledge and choice, as well as patient factors, may influence the initial assessment,*
1165 *and subsequent investigation, of suspected PE.* Clinicians play a large role in carrying out the
1166 diagnostic strategies for PE, including recognition of PE as a possible diagnosis during the initial
1167 patient assessment. Depending on knowledge and familiarity, a physician may use certain PTP
1168 tests over others. It was found that PTP is poorly documented in patient charts, possibly
1169 because PTP is not typically memorized by physicians and because it is hard to integrate into a
1170 busy work environment like the emergency department.

1171
1172 Provider knowledge of D-dimer may influence how it is used and interpreted. Additionally, D-
1173 dimer may have high false positives in certain populations, such as the elderly, the critically ill,
1174 or patients with auto-immune or inflammatory disease. The need for local cut-off values for D-
1175 dimer tests was also expressed, as high false positive rates did not decrease unnecessary
1176 diagnostic imaging.

1177
1178 Choice of diagnostic imaging was also related to provider knowledge and patient factors. For
1179 example, a physician's knowledge of radiation risk may influence whether they order V/Q or CT
1180 for certain populations; women, younger patients, and those with a recent history of multiple CT
1181 scans were more likely to receive V/Q scans than CT. Physician knowledge and perception of
1182 SPECT also influenced whether it was used.

1183
1184 *Policies and protocols can be used to support the diagnostic strategies for PE.* It could be
1185 possible to establish policies and protocols to implement a particular diagnostic strategy for PE.
1186 For example, mandatory PTP assessment before D-dimer testing was feasible, as evidenced by
1187 one study, though this required collaboration from those involved, such as the laboratory and
1188 the emergency department. There is also the possibility for additional support for PE diagnosis,
1189 such as clinical guidelines and protocols and tools like computer prompts. However, these
1190 policies and protocols may not be the same in every facility, as a need was expressed for tools
1191 specific to small and medium sized centres. This may also relate to the need for protocols for
1192 the transportation of patients out of a facility for further testing. Policies and protocols to aid PE
1193 diagnosis are possible but require clarity on their use and collaboration from those involved.

1194 *Resources, including staffing, access to tests, scans and imaging are differentially located*
1195 *across the country.* As evidenced in the literature, and from the survey and interview, access to
1196 tools and tests used to diagnosis PE varies across Canada and differs depending on whether a
1197 site is located in an urban centre, is rural, or is remote. Urban centres tended to have more
1198 availability and access to tests and imaging modalities than rural or remote centres. Northern
1199 jurisdictions also had less access to certain tests (e.g., one CT for Nunavut). Access also
1200 related to whether certain services were available afterhours or on a 24/7 basis and whether
1201 staff were available to provide these services.

DRAFT

1202 **ENVIRONMENTAL IMPACT**

1203

1204 **Objective**

1205 To assess the potential environmental effects associated with the use of diagnostic strategies
1206 for suspected pulmonary embolism.

1207 **Literature Search**

1208 The literature search was performed by an information specialist, using a search strategy peer-
1209 reviewed according to the PRESS checklist - an evidence-based checklist for the peer review of
1210 electronic search strategies.⁷⁵

1211 Implementation issues information was identified through targeted literature searches of the
1212 following bibliographic databases: MEDLINE (1946-), with in-process records and daily updates,
1213 via Ovid; Embase (1974-) via Ovid; CINAHL (1981-) via EBSCO; Scopus; and PubMed. The
1214 search strategy comprised both controlled vocabulary, such as the National Library of
1215 Medicine's MeSH terms, and keywords. The main search concepts were medical imaging, and
1216 key terms for environmental impact. No methodological filters were applied to limit retrieval by
1217 study design. Retrieval was limited to documents published since January 1, 2007. Results
1218 were limited to English- and French-language publications. The detailed strategy can be found
1219 in Appendix 1.

1220 The search was completed on April 7, 2017. Regular alerts were established to update the
1221 search until the publication of the final report. Regular search updates were performed on
1222 databases that do not provide alert services.

1223 Grey literature (literature that is not commercially published) was identified by searching sources
1224 identified in the Grey Matters checklist (<https://www.cadth.ca/grey-matters>), which includes the
1225 websites of clinical trial registries, regulatory agencies, HTA agencies, clinical guideline
1226 repositories, and professional associations. Google and other Internet search engines were
1227 used to search for additional Web-based materials.

1228

1229 **Study Selection Criteria**

1230

1231 Two reviewers screened the titles and abstracts of all citations retrieved from the literature
1232 search for relevant studies and reports. Full-text articles were retrieved and assessed for
1233 inclusion by the two reviewers if either of them considered a citation potentially relevant to the
1234 research question. Articles and reports were considered eligible if they published from 2007
1235 onwards, provide insights into the potential environmental impact associated with diagnostic
1236 imaging modality for PE. Papers reporting on the effects of ionizing radiation from imaging
1237 devices on patients undergoing imaging studies or clinical staff operating the equipment and
1238 articles that were not published in English or French were excluded.

1239 **Data Extraction**

1240
1241 It was intended that the reviewers will extract from each relevant article the bibliographic details
1242 (i.e., authors, year of publication, and country of origin), population and intervention information,
1243 and identify issues related to the environmental impact. The environmental factors were to be
1244 classified as follows:

- 1245 a) source media (e.g., air, water, soil);
- 1246 b) receptor-macro (e.g., flora, fauna);
- 1247 c) receptor-micro (e.g., fish, wildlife, vegetation);
- 1248 d) receptor-specific (list name);
- 1249 e) impact-macro (e.g., contamination, effect); and
- 1250 f) impact-specific (describe)

1251 **Content Analysis**

1252
1253 Two phases of analysis were planned. Firstly, it was required one reviewer to conduct a content
1254 analysis to identify issues related to the environmental impact from the use of diagnostic
1255 imaging modalities for PE. After review of extracted data, a list of codes was to be developed,
1256 tested for appropriateness and expanded or merged into themes. A constant comparative
1257 technique will be applied to identify all instances and appropriateness of the coding framework,
1258 and to determine how to expand or merge the codes into themes. A sample text passage to
1259 illustrate their application the codes and a narrative summary of the themes were to be
1260 provided. Second, the extracted information was to be organized into the key steps of an
1261 ecological risk assessment, namely hazard identification, exposure assessment, toxicology, and
1262 risk characterization.

1263 **Results**

1264
1265 **Quantity of Research Available**

1266 A total of 3,317 citations were identified, 3237 from the main literature search and 77 from
1267 alerts. Following screening of titles and abstracts, 3,310 citations were excluded and seven
1268 potentially relevant reports from the electronic search were retrieved for full-text review. No
1269 potentially relevant publication was retrieved from the grey literature search. None of these
1270 seven potentially relevant articles met the inclusion criteria for this report. Six of the articles did
1271 not have environmental impact outcomes. The remaining article was published in a language
1272 other than English or French. Appendix 29 describes the PRISMA flowchart of the study
1273 selection.

1274
1275 **Summary of Findings**

1276 The literature search did not find any studies or reports that evaluated the environmental impact
1277 of imaging modalities for PE.
1278

1279 **ETHICS REVIEW**

1280 This ethics section identifies key ethical considerations in relation to the diagnosis of PE for
1281 patients presenting in the emergency department in urban, rural, and remote settings in
1282 Canada. It provides a framework for the ethical development, implementation, and provision of
1283 practices related to the diagnosis of PE. Necessarily, the ethical issues presented in this section
1284 go beyond narrowly defined ethical concerns in the clinical context to also encompass broader
1285 legal and social considerations. It is common in the ethics literature, across a broad range of
1286 health-related issues, to refer to ethical, legal, and social issues when addressing broader
1287 values-related considerations. While the primary emphasis here will be on ethical
1288 considerations, legal and social issues may also be relevant to ethics analyses.
1289

1290 The relevant perspectives that are considered in identifying and addressing the ethical issues
1291 associated with the various strategies for diagnosing acute PE include those of patients, family
1292 members or informal care-givers, health care providers, and the health system, more generally.
1293

1294 **Research Question**

1295
1296 The ethical question explored in this section has developed since the creation of this PE
1297 protocol. In this section, we ask:
1298

1299 *What are the key ethical considerations related to the diagnosis of acute pulmonary embolism*
1300 *within the emergency department in remote, rural, and urban settings in Canada?*
1301

1302 The report aims to identify and analyze explicit and implicit ethical issues present within
1303 literature concerning the diagnosis of PE within emergency departments.
1304

1305 **Methods**

1306
1307 **SEARCH STRATEGY**

1308 The literature search was performed by an information specialist, using a search strategy peer-
1309 reviewed according to the PRESS checklist - an evidence-based checklist for the peer review of
1310 electronic search strategies.⁷⁵
1311

1312 Ethics-related information was identified through targeted literature searches of the following
1313 bibliographic databases: MEDLINE (1946-), with in-process records and daily updates, via Ovid;
1314 Embase (1974-) via Ovid; PsycINFO (1967-) via Ovid; CINAHL (1981-) via EBSCO; and
1315 PubMed. The search strategy comprised both controlled vocabulary, such as the National
1316 Library of Medicine's MeSH terms, and keywords. The main search concepts were medical
1317 imaging and pulmonary embolism, and key terms for ethics concepts. No methodological filters
1318 were applied to limit retrieval by study design. Retrieval was limited to documents published
1319 since January 1, 2006. Results were limited to English- and French-language publications.
1320 Conference abstracts were excluded from the search results. The detailed strategy can be
1321 found in Appendix 1.
1322

1323 The search was completed on October 12, 2016. Regular alerts were established to update the
1324 search until the publication of the final report. Regular search updates were performed on
1325 databases that do not provide alert services.
1326

1327 Grey literature (literature that is not commercially published) was identified by searching sources
1328 identified in the Grey Matters checklist (<https://www.cadth.ca/grey-matters>), which includes the

1329 websites of clinical trial registries, regulatory agencies, HTA agencies, clinical guideline
1330 repositories, and professional associations. Google and other Internet search engines were
1331 used to search for additional Web-based materials.

1332
1333 A review of the empirical and bioethics literature was conducted to identify potential ethical
1334 issues related to the diagnosis of acute PE in the ED context. This includes an analysis of
1335 literature that explicitly and specifically raises ethical issues, as well as literature that provides
1336 data related to PE that, when read through an ethics lens, implicitly raises or point to potential
1337 ethical issues. The relevant literature includes issues related to diagnostic strategies for PE, and
1338 diagnostic testing for other conditions that may be present possible analogies for the ethical
1339 issues related to the diagnosis of PE.

1340 **Search Results**

1341
1342
1343 In the first level of screening, titles and abstracts were reviewed and the full text of potentially
1344 relevant articles were retrieved and assessed for inclusion by the same reviewer. Articles were
1345 be categorized as “retrieve” or “do not retrieve” according to whether they meet the following
1346 inclusion criteria:

- 1347 • Provides information (explicit) on or is relevant to identification (implicit) of an ethical
1348 issue related to diagnosing PE.

1349 In the second stage of screening, two reviewers independently assessed the relevance of the
1350 full-text reports for all citations classified as “retrieve” in the first stage of screening. The
1351 relevance of the full-text reports was assessed according to the following criteria:

- 1352 • On a relevant diagnostic strategy for PE
- 1353 • Explicitly or implicit mention ethical issues

1354 Reports meeting all criteria were included in the analysis. Reports that did not meet these
1355 criteria will be excluded from analysis. The results of the study selection process is presented in
1356 a flow chart (Appendix 30).

1357
1358 The database search results yielded 590 records. Ethics experts also identified an additional 14
1359 articles from a Google search for ethical issues related to radiology and DVT, more generally.
1360 After reviewing record titles and abstracts, 422 articles were removed and the remaining 182 full
1361 text articles were reviewed. These full text articles were assessed based on the inclusion
1362 criteria. Articles that did not meet these inclusion criteria were excluded. A total of 42 articles
1363 were included in this study. Of these 42 articles, two articles explicitly acknowledge “ethics”
1364 related to the diagnosis of PE^{291,292} Gosner and Nau (2013) consider the ethical implications
1365 related to the care of elderly patients with suspected PE, while Amaro et al 2012 explore the
1366 ethical related to over utilization of diagnostic imaging for PE and healthcare reform
1367 responsibilities. In addition, four articles, which were identified by the ethics experts, explicitly
1368 considered ethical issues related to radiology, more broadly (Appendix 31). Thus, a total of six
1369 articles included in this study make explicit mention of ethical issues which are relevant to the
1370 diagnosis of PE. The remaining 36 articles included in this study contain implicit information
1371 which bears ethical relevance to the diagnosis of PE. No articles included in this study
1372 answered our research question. Furthermore, no articles compared the ethical risks and
1373 benefits of the various diagnostic pathways for PE.

1374

1375 Ethically relevant issues mentioned earlier in this report in the clinical, economic, patient
1376 experience, and implementation sections were also included in our ethical analysis. In addition,
1377 we identified and drew upon additional articles that consider analogous medical contexts that
1378 are relevant to understanding the ethical issues surrounding the diagnosis of PE in the ED.
1379

1380 In this report, we do not provide normative arguments in favour or against any specific
1381 diagnostic pathway or imaging modality. Rather, we offer an ethical framework for considering
1382 the various ethical implications related to the use or non-use of various diagnostic pathways for
1383 PE within the ED. This framework can be used to support the ethical provision of diagnostic
1384 imaging for PE.
1385

1386 **Summary of Findings and Ethics Analysis**

1387
1388 Several key themes emerged from our analysis of the implicit and explicit ethical issues in the
1389 literature related to use or non-use of the various diagnostic pathways for PE within the ED
1390 context. We found the ethical considerations related to the following basic ethical principles:

- 1391 • beneficence and maleficence which are related to benefits and risks of diagnosis,
1392 misdiagnosis, or treatment;
- 1393 • autonomy which are related to informed consent and clinical decision-making;
- 1394 • system efficiency and professional responsibilities;
- 1395 • Issues of justice related to costs and economic implications of treatment or non-
1396 treatment, and issues that are unique to certain sub-populations and public health.
1397

1398 Our ethics analysis organizes our findings by presenting the relevant ethical interests of and
1399 implications for, the key stakeholder groups, including patients, clinicians, healthcare
1400 organizations, and society, more generally. Below, we describe 1) patient-related issues, 2)
1401 clinician-related issues, and 3) organization-related issues, and 4) systemic and social issues.
1402 There is some overlap of the ethical considerations discussed both within and between each of
1403 these categories. For example, concerns related to risks to patients will have implications not
1404 only for individual patients, but also for clinicians, and the organization. Such overlap is to be
1405 expected given the relational nature of healthcare practices. Nevertheless, the demarcation of
1406 ethical issues within these four categories encourages shifts in perspectives when considering
1407 the ethics of diagnostic pathways for PE. It prompts one to ask: What are the ethical concerns
1408 for patients, for clinicians, for the organization, or for the healthcare system and society, more
1409 generally?
1410

1411 **a) Patient-related Issues**

1412
1413 *How might patients benefit from the diagnosis of PE?*

1414 Patients who present to the ED with PE or suspected PE, they have an interest in receiving
1415 timely and appropriate care. These patients benefit from the diagnosis of PE, in which case they
1416 may receive potentially life-saving treatment. The use of risk stratification tools can help ensure
1417 that only patients who require diagnostic imaging, receive it. Further, the use of imaging
1418 modalities can confirm the presence PE, with some degree of confidence, prior to initiating
1419 anticoagulant therapy. Similarly, the use of diagnostic imaging to rule out PE helps to ensure
1420 that patients are not given anticoagulant medications unnecessarily. Patients benefit from
1421 receiving the treatment that they need and from not receiving unnecessary treatment.

1422 Patients may also benefit from the use of diagnostic imaging modalities that result, incidental
1423 findings, that is, images that help to detect and diagnose other health concerns. For example, a
1424 CT scan for PE may inadvertently reveal other medical concerns, such as lung cancer.

1425 Finally, the use of clinical prediction rules and diagnostic imaging may be reassuring to patients
1426 who are presenting in the emergency department with unspecified symptoms. For example,
1427 patients who have a CT scan that is negative for PE may feel more confident in a physician's
1428 determination that they do not have PE than if PE was ruled out using clinical prediction rules
1429 and/or D-dimer testing. The Patient Perspectives and Experience Section in this report found
1430 several perceived benefits of diagnostic imaging techniques, more generally. For example, in
1431 one study where patients credited imaging with saving their lives and in most cases, benefits
1432 were articulated in terms of "the technology's non-invasive potential to peer within and deliver
1433 images capable of mapping out current or prospective health concerns." (page 6 of PEP report).
1434 The ability "to know" was often valued by patients.

1435 *How might patients be harmed from the diagnosis of PE?*

1436
1437 First, patients with PE who are not diagnosed will go untreated and can lead to pulmonary
1438 hypertension, post-thrombotic syndrome, right ventricular failure, or death. As mentioned in the
1439 Clinical Section of this report, approximately 30% of untreated PE cases are fatal.¹³ With
1440 treatment, the mortality rate is reduced to 10%.²²³ In addition, patients who have an obstructed
1441 blood vessel in the lungs are at risk of having their lung tissue damaged because of lack of
1442 oxygen.

1443
1444 In addition, false positives can cause patients to worry. According to the Patient Perspectives
1445 and Experience section of this report, some patients saw the use of diagnostic imaging at a
1446 threat to their self-control, and ability to manage the situation, and concern about isolation,
1447 confinement and dependence on others, particularly with the MRI context.

1448
1449 Second, there are also risks associated with the diagnostic testing for PE. The risks will be
1450 different for different modalities. For example, there are risks associated with the use of CTPA.
1451 Although, most patients complete CTPA with no adverse events, there are risks, such as those
1452 related to radiation and to the contrast material used. Radiation is absorbed by the body during
1453 CTPA. The liver, skin, esophagus, heart, breast, and lungs absorb the highest radiation dose.
1454 This kind of radiation exposure has been linked to an increased risk cancer, especially in
1455 younger ages.²⁹³ Patients who undergo CTPA are also at risk of allergic reaction to the
1456 iodinated contrast media used in CTPA. The mortality rate for adverse reactions to the contrast
1457 media is of 1–3 per 100,000 cases of use.²⁹³ Other reactions to the contrast media include
1458 urticaria, nausea, vomiting, bronchospasm, dyspnea, angioedema and anaphylactic shock.²⁹³
1459 Patients with kidney problems are at risk of kidney damage from the iodinated contrast material
1460 used in CTPA.²⁹⁴ There is also a risk that the contrast material will leak from the vein in which it
1461 is being injected, thereby causing damage to the surrounding skin, blood vessels and nerves
1462 (Ibid). This often leads to repeating CTPA and requires exposing patients to additional
1463 radiation.²⁹³ If CTPA is overused for the diagnosis of PE, some patients may be at risk of
1464 receiving unnecessary radiation.²⁹⁵

1465
1466 Some patient populations face increased or unique risks in the diagnosis of PE. For example,
1467 PE is the leading cause of death among pregnant women.²⁹⁶ Pregnant and lactating women
1468 who undergo CTPA or other diagnostic imaging tests, such as V/Q scintigraphy face additional
1469 risks related to radiation. Many argue that the risks to women and the fetus must be considered

1470 in the context of diagnostic imaging.^{207,296} Some suggest that preference should be given to the
1471 mother over the fetus when considering options for diagnostic imaging to detect for PE.²⁹⁷
1472

1473 The imaging of elderly patients presents unique risks for this group.²⁹² For example, imaging
1474 strategies may have to be adjusted to meet the needs of elderly frail patients with respect “to
1475 mobility, and breath holds.” In addition, some older patients may need supervision while waiting
1476 in radiology, more time for positioning, and additional help during testing.²⁹²

1477 Other patient groups may be at high risk for PE, but fail to be diagnosed for PE upon presenting
1478 to the ED. These patients are at a higher risk of not receiving necessary anti-coagulant
1479 treatment. For example, patients with chronic obstructive pulmonary disease (COPD) presenting
1480 to the emergency department with chest pain may be not be considered for PE if their
1481 symptoms are attributed to their chronic disease.

1482 Given the sensitivity of CTPA, as described in the Clinical Section of this report, there is a high
1483 rate of false positives.²⁹⁸ As a result, some patients may be misdiagnosed with PE and this
1484 misdiagnosis may cause them unnecessary concern and anxiety. Furthermore, patients who are
1485 misdiagnosed with PE may then undergo unnecessary anticoagulant treatment for PE. It has
1486 been found that nearly a third of patients with suspected PE who have a low likelihood of PE
1487 and a normal D-dimer test may have anticoagulant therapy be safely withheld.²⁰
1488

1489 *What are the concerns related to patient decision-making in the context of PE diagnosis?*
1490

1491 At a minimum, Informed consent requires that patients understand the risks and benefits of the
1492 proposed treatment or intervention and also appreciate the consequences of receiving or not
1493 receiving the treatment or intervention. Patients must provide consent to all medical
1494 interventions and healthcare treatments, except in emergencies. Obtaining informed consent
1495 can be challenging to obtain for urgent testing or interventions proposed in the ED. Often, in this
1496 context, consent to testing is taken as implied. In some provinces, such as Alberta, (non-
1497 emergent) patients presenting to the ED sign a general waiver in which they give their consent
1498 to the evaluation and treatment within the ED (Correspondence with Dr. Lang). This may also
1499 include consent to receiving care by trainees. Although general consent to diagnosis or
1500 treatment is often given (or implied upon admission), some interventions may require additional/
1501 explicit consent. In the context of diagnostic pathway for PE, patients need not consent to the
1502 use of risks stratification and clinical prediction rules. However, consent (explicit or implied) is
1503 required for diagnostic imaging.
1504

1505 For consent to be informed, patients need an understanding of the risks and benefits of the
1506 medical intervention. Consent, as a dialectic process, also give clinicians opportunities to
1507 address patients’ questions and concerns and counsel them on the risks and benefits of
1508 imaging.²⁹⁹ Patients’ understanding should be confirmed by asking them to acknowledge the
1509 key points as they are explained and, if appropriate, by asking them to explain the risks and
1510 benefits in their own words.²⁹⁹ The consent process could give patients an opportunity to choose
1511 their imaging modality, if the physician were to propose more than one option. For example, this
1512 may be a factor if there are different risks and benefits (increased sensitivity but increased risk)
1513

1514 Pregnant patients will need additional information during the informed consent process. There
1515 are concerns related to whether breast feeding should be temporarily halted after intravenous
1516 administration of the iodizing contrast material used in CTPA.²⁹⁹ It is recommended that
1517 radiologists inquire about the possibility of pregnancy for any reproductive aged females and
1518 conduct a verbal screening and obtain consent prior to diagnostic imaging.²⁹⁹ When feasible and

1519 medically indicated, modalities that do not use ionizing radiation, such as MRI, may be
1520 preferable for pregnant or lactating patients.²⁹⁹ It has also been suggested that radiologists
1521 should strive to minimize risks of radiation and facilitate shared decision-making with patient and
1522 her family. Matthews (2006) describe the difficulties related to the diagnosis and imaging
1523 pulmonary embolism, pointing to the lack of guidelines concerning imaging protocols for
1524 pregnant women. The absence of policies, consensus on level of risk, etc. can make
1525 discussions of informed consent challenging. The authors describe a 2003 survey of members
1526 of the Society of Thoracic Radiology which found that 53% of responding radiologists would use
1527 CTPA as a first line investigation for excluding PE in pregnant patients, but only 60% of
1528 radiologists obtained informed consent from any pregnant patient undergoing CTPA.³⁰⁰

1529
1530 Diagnostic imaging is typically seen as a routine intervention. In practice, it is rare for someone
1531 to refuse diagnostic imaging. When someone presents to the emergency department, they have
1532 either been referred by their family doctor or have come because they are concerned about their
1533 symptoms. Emergency wait times are often long and patients are usually happy and relieved to
1534 receive imaging results to confirm or rule out their diagnosis. If a patient were to refuse a
1535 particular diagnostic imaging modality, physicians could document their refusal and perhaps
1536 suggest another testing modality or intervention. It is possible that some patients with suspected
1537 PE may choose to leave the hospital against medical advice, but this is extremely unlikely.

1538
1539 The process of informed choice is connected to patient medical literacy. For example, within the
1540 context of consent to CTPA, patients may have assumptions or misconceptions related to
1541 “radioactivity”.³⁰¹ The noncritical reading of patient advocacy literature can pose tremendous
1542 ethical challenges. There may also be risks from reading other biased information available to
1543 patients, we see this in the context of vaccines. It is unclear whether such information informs
1544 decisions related to PE diagnosis. It could, however, influence patient’s beliefs about other
1545 aspects of care in the ED. As mentioned in the Patient Perspectives and Experience Section in
1546 relation to some patients’ experiences with cardiac SPECT-CT, perceptions of risks emanated
1547 from an association of terms like “nuclear” with “atom bombs.” As such, literacy and social
1548 privilege are entangled with informed consent.³⁰¹ This can make decision-making around
1549 diagnostic imaging challenging in some cases. Further, informed consent can be compromised
1550 when patients fail to fully understand or appreciate the proposed diagnostic or treatment
1551 intervention due to time constraints and the urgency of PE diagnosis.

1552
1553 *What are the concerns related to patients’ access to testing for PE?*

1554 The geographical size of Canada and the distribution of its population has resulted in some
1555 challenges in accessing timely diagnostic imaging for some rural or remote patients. In larger
1556 urban hospitals, CTPA is available 24/7, but patients visiting a smaller rural or remote hospital
1557 may need to wait for diagnostic imaging or need to travel to a larger hospital. Patients, such as
1558 pregnant patients, who require a VQ scan, may need to return the next day if they present after
1559 hours and VQ testing is not available. These patients may be given a single-dose anti-coagulant
1560 treatment if PE is suspected. Issues of access to diagnostic imaging may influence what is
1561 considered optimal for different populations. For instance, provision of timely diagnosis may be
1562 less feasible in rural and remote facilities due to lack of access to certain testing and imaging
1563 modalities and specialist expertise, as well as geographical barriers to care. Inability to access
1564 optimal diagnostic testing in a timely manner could increase the risk for missed diagnoses, as
1565 well as unnecessary anticoagulation due to either false-positives or long wait times to receive
1566 assessment.⁷

1567 In addition, although cost is not typically an issue for individual patients who have provincial or
1568 territorial healthcare insurance because they do not need to pay out-of-pocket for diagnosis or
1569 treatment of PE, it may be an issue for uninsured patients, such as those visiting from outside of
1570 Canada who are billed for their visit to the ED. In these cases, the cost of various diagnostic
1571 pathways may factor into decision-making.

1572 As mentioned in the Clinical Section above, an accurate estimate of PE incidence is difficult to
1573 obtain, because a large proportion of pulmonary emboli are detected on autopsy. Approximately
1574 80% of patients identified with PE at autopsy are unsuspected or undiagnosed before death.⁷

1575 **b) Clinician-related ethical considerations**

1576

1577 *What are clinician's obligations in relation to the diagnosis of PE?*

1578

1579 The clinician duty to do no harm is arguably one of the most fundamental principles of medical
1580 ethics. In the context of diagnosing PE, there are concerns about the possibility of harming
1581 patients with testing modalities or unnecessary treatments, as discussed above. Some worry
1582 about the iatrogenic harm from the overtreatment of PE.³⁰² A commitment to the duty to do no
1583 harm, a fear of missing a PE and concerns about the professional repercussion for clinicians
1584 can contribute to the practice of “defensive medicine” which causes excessive/ overuse of
1585 diagnostic imaging and other tests.^{295,303,304} Factors like “request from the patient or his/her
1586 relatives” or “fear of being sued” played a minor role within the United States.³⁰⁴ The practice of
1587 defensive medicine is common in the U.S. healthcare contexts where clinicians fear lawsuits if
1588 PE is missed or misdiagnosed.³⁰³ This may not be as common in Canada, given the difference
1589 in health care systems and social and medical cultures. Nevertheless, it may be indicative of
1590 clinicians' concerns relating to the professional repercussions of making a diagnostic error
1591 related to PE. “Defensive behavior” is frequent and associated with decreased odds of positive
1592 CTPA results.³⁰⁴ In other words, many patients are subjected to unnecessary diagnostic
1593 imaging because of the practice of defensive medicine.

1594

1595 Some literature suggests that radiologists have a unique duty to notify patients of any diagnostic
1596 errors, however current disclosure rates are low.³⁰⁵ For example, if a radiologist missed a PE
1597 diagnosis, or another incidental finding from imaging, for that matter, they should notify the
1598 patient or the most responsible physician of this error. The disclosure of errors by radiologists,
1599 or other clinicians, can help ensure that patients ultimately receive accurate diagnostic
1600 information and supports a healthcare culture of trust and transparency.

1601

1602 There are also ethical concerns related to the challenges surrounding the accurate
1603 documentation of the testing and diagnosis of PE. The economic section of this report found
1604 that there is poor documentation of PE in patient charts. Inadequate reporting and poor
1605 communication among healthcare providers can put patients at risk. Failure to accurately
1606 document PE raises concerns about clinicians' transparency and accountability.

1607

1608 *What are the concerns related to clinician's decision-making in the context of PE?*

1609

1610 As discussed in the Clinical Section above, the non-specific nature of common PE symptoms
1611 can make the consideration of a PE diagnosis challenging for physicians. As professionals,
1612 physicians often exercise their clinical judgement in the diagnosis of PE. This may be in tension
1613 with a commitment to evidence-based medicine. According to the Implementation section of this
1614 report, clinicians may order the imaging modality with which they are most comfortable, despite
1615 what the evidence indicates. In a 2002 Poll of American physicians, 79% of respondents

1616 indicated that they order more tests than they otherwise would, “based *only* on professional
1617 judgment of what is medically needed” (my emphasis) It has been found that intuition alone is
1618 unreliable for evaluating the utility of policies in complex diagnostic scenarios.²²³ Duriseti and
1619 colleagues (2006) suggest that experienced clinicians can use clinical judgement (“gestalt”) to
1620 assign a clinical pretest probability for the diagnosis of PE with “reasonable accuracy.” They
1621 suggest that structured clinical prediction rules perform equally well, but have an advantage
1622 because they can be used by less experienced clinicians.⁹⁸

1623
1624 Of note, in exercising clinical judgment, clinicians may exhibit personal biases with respect to
1625 patients in different patient populations groups that influence the likelihood of receiving
1626 diagnostic imaging or testing.

1627
1628 Yan and colleagues (2016) examined the overuse of CTPA for PE in the ED. The odds of
1629 finding an acute PE nearly doubled when providers adhered to evidence presented in clinical
1630 decision-making tools. Most clinician overrides were due to the lack of d-dimer testing in
1631 patients unlikely to have PE. Similarly, Alhassan and colleague (2016) found that suboptimal
1632 implementation of assessment tools can result in the overuse of CTPA. It has also been found
1633 that clinicians seldom use all nine data elements of the PERC rule in patients they deem PERC
1634 negative. These data suggest the need for paper or electronic aids to support use of the PERC
1635 rule.³⁰⁶

1636
1637 Several barriers to improving the utilization of CTPA in the ED have been identified, including
1638 litigation and defensive medicine; pressure for quick turnover; and, patient demands.²⁹⁵ There
1639 is pressure from access and flow that might lead to demand for rapid patient turnover in the ED,
1640 which can lead to “blanket ordering” to obtain a diagnosis as quickly as possible.²⁹⁵ As
1641 individuals, physicians’ tolerance of risk may vary and this can result in differences in ordering
1642 tests and diagnostic pathway for PE. The fundamental issue for physicians in the diagnosis of
1643 PE is often not wanting to miss PE and diagnosing PE can be extremely difficult because it
1644 presents with non-specific symptoms. Some physicians may also worry about the legal
1645 implications of having missed a PE diagnosis. In some jurisdictions, campaigns, such as the
1646 *Choosing Wisely Campaign* have been implemented to support clinicians to choose the
1647 appropriate use of diagnostic imaging. The clinical review in this PE report found that combining
1648 a clinical decision tool with d-dimer testing is a good rule out strategy for PE.

1649
1650 Variations have been found in the diagnostic pathway for PE based on physician specialty.³⁰⁷
1651 For example, cardiologists are more likely to use echocardiography and cardiac perfusion
1652 imaging in the diagnosis of PE, while pulmonologists are more likely to use CT.
1653 It has been shown that physicians who disclose their biases, with respect to their specialty and
1654 their preferred treatment, are able to increase patient trust in their recommended treatment plan.
1655 Moreover, physicians who disclose their bias have increased confidence in their treatment
1656 recommendations to patients and during the disclosure of bias physicians afforded patients with
1657 the opportunity to seek a consultation with a physician from a different specialty.³⁰⁸ This could
1658 be challenging in the ED setting. This finding suggests that physician disclosure of biases with
1659 respect to the pathway for diagnostic testing for PE may be able to increase patient trust in the
1660 proposed testing pathway.

1661
1662 Survey respondents and the clinical expert indicated that the main challenge is in considering
1663 PE as a diagnosis. A diagnosis of PE may be overlooked when patients experience chest
1664 complaints, which may then be attributed to other conditions. In the interview, the clinical expert
1665 discussed general challenges to diagnosing PE, specifically that most patients with PE present
1666 atypically, and that it can be hard to diagnose. It was suggested that most patients with PE do

1667 not get diagnosed on their first visit to their doctor or the emergency department. Failure to
1668 consider PE as a diagnosis is a challenge; this lack of consideration could result in near misses
1669 or potential fatalities when patients fail to be appropriately diagnosed with PE. This fear of
1670 missing PE may also cause physicians to start treating patients with anticoagulants, as a bleed
1671 complication from being treated is thought by some to be preferable to having PE (Dr. Eddy
1672 Lang: personal communication, 2017 April).

1673

1674 *What are the risks to clinicians in the diagnosis of PE?*

1675

1676 There may be some health risks to clinicians related to the administration of radiology imaging
1677 testing A study by Vano and colleagues (2013) found posterior subcapsular lens changes
1678 characteristic of ionizing radiation exposure in 50% of interventional cardiologists and 41% of
1679 nurses and technicians. They suggest that most lens injuries are the result of several years of
1680 work in radiology without eye protection.³⁰⁹

1681

1682 **c) Organization-related Issues**

1683

1684 *How is the diagnosis of PE related to quality care?*

1685

1686 At the hospital level, there are serious concerns about (over)crowded emergency departments.
1687 Lee-Lawandrowski and colleagues (2009) found that the use of a rapid D-dimer test for patients
1688 in the ED was associated with a shorted ED length of stay and few hospital admissions.³¹⁰
1689 Mourad and Adler (2011) found that care for PE on the weekends or nights is less aggressive
1690 and there is variation in the quality of patient care.³¹¹ This means that patients presenting to the
1691 ED with PE during this off-peak hours may not undergo diagnostic imaging and as such, a PE
1692 may be missed and these patients may not receive the necessary treatment. Further, the quality
1693 of care can be compromised during off-peak hours because of the lack of radiologists or other
1694 clinicians needed to interpret diagnostic images for PE testing.

1695

1696 The Implementation section of this report found that provider factors may influence the
1697 assessment of patients as they present with PE-like symptoms. Emergent issues related to
1698 physician factors and the risk stratification and pretest probability assessment (PTP) for the
1699 diagnosis of PE were: familiarity and knowledge of PTP (including documentation of PTP
1700 testing), the consideration of PE as a diagnosis, and the concern of missing a PE diagnosis.
1701 These factors may influence the use of these tests. For example, the implementation of an
1702 unfamiliar PTP tool that may require additional provider education could be a barrier to quality
1703 care. As with the clinical prediction rules and rule-out testing, provider factors may influence the
1704 choice and use of diagnostic imaging modalities. Much of the literature related to clinician
1705 utilization or preference for certain modalities; though choice of imaging test could be related to
1706 contextual issues such as access, not just provider knowledge. Depending on the diagnostic
1707 strategy, provider knowledge or preference for one imaging modality may be either a barrier or a
1708 support.

1709

1710 One proposed solution is the use of an iPad as a mobile device for CT display and interpretation
1711 in identifying PE.³¹² The use of this mobile device would allow for remote image interpretation
1712 and consults during off-peak hours when the radiologist, for example, is not on duty. This use of
1713 technology could help to reduce the waiting time for diagnostic imaging results and speed up
1714 the diagnosis of PE. It could also help to reduce the need to call patients back after a revised
1715 interpretation of results by a specialist.³¹² Although the use of such a technology may be
1716 beneficial and increase accessibility, it may also raise ethical concerns with respect to patient
1717 privacy. The implementation of this new technology may also have practical and ethical

1718 implications for the operation of the ED and coordination and communicating between health
1719 care professionals.

1720
1721 Itri and colleagues (2015) give suggestions for humanizing the patient care environment within
1722 radiology, by using certain lighting, colours, etc. They maintain that a patient's experience of
1723 illness includes the emotional and psychologic consequences of being ill. They argue that health
1724 care providers must adequately address these subjective aspects of illness to provide the most
1725 effective care.³¹³

1726
1727 *What are the ethical issues related to interprofessional collaborations and clinician education?*
1728 *Say more here?*

1729
1730 Clinicians' awareness of PE (or VTE) diagnosis adherence to associated best practices within
1731 the emergency department can help ensure quality patient care and reduce healthcare costs.
1732 Nurse education can be effective at increasing compliance with VTE awareness- and could lead
1733 to reductions in associated health care costs.³¹⁴

1734
1735 **d) Healthcare System and Social Issues**

1736
1737 The diagnosis of PE also has implications for systems-level and population-level ethics. For
1738 systems-level ethics, instead of asking, "Does this technology benefit the patient?" and "Does
1739 this technology disadvantage vulnerable individuals?", we ask, "Does this technology create
1740 overall benefit for the population?" and "Does this technology disadvantage marginalized
1741 groups?"

1742
1743 *What are the financial burdens on the healthcare system?*

1744
1745 As mentioned earlier in this report, of the total population of patients who are evaluated for
1746 suspected PE, few are confirmed to have the condition, indicating a low diagnostic yield of
1747 current evaluation methods. High-cost imaging modalities are over-utilized.^{291,295,303} Further, the
1748 overuse of diagnostic imaging modalities can place a heavy economic burden on healthcare
1749 system.³¹⁵ The costs associated with the diagnosis and treatment of PE may include nursing,
1750 pharmacy, radiology, ER lab, blood bank, and practice fees. The Economic Section of this
1751 report found that CT provides the best 'value' for imaging modalities. It was also found that it is
1752 most cost effective to treat a patient that does not have PE than not treat a patient who does
1753 have PE, given the increased risks of recurring PE and mortality.

1754
1755 Given regional variation in infrastructure for the diagnosis and treatment of PE, there is
1756 sometimes a need to move samples or images between facilities for testing. Similarly, there
1757 may be a need to transfer patients to another hospital for testing or treatment. This need for
1758 transfers increases the financial burden of PE on the healthcare system. At the systemic level,
1759 there is also a concern about the practice of "imaging up," that is, ordering a more advanced,
1760 risky, and costly testing modality when a lesser intervention may be sufficient or more
1761 appropriate. This practice has been associated with the healthcare system costs related to
1762 PE.³¹⁶

1763
1764 The optimal diagnostic strategy for suspected PE can differ based on factors related to the
1765 healthcare setting (i.e., urban, rural, or remote) because there are variations in the availability of
1766 imaging technologies and the relevant clinical expertise across the country. According to the
1767 Economic section of this report, diagnostic strategy with the lowest costs was revised
1768 Geneva>PERC> d-dimer>CTPA. Clinically, this strategy involves providing revised Geneva to

1769 all patients suspected of PE to classify their risk. In those considered of low-to-intermediate risk,
1770 PERC followed by d-dimer was used to rule out PE and, of those who could not be ruled out or
1771 in patients with high probability of PE according to revised Geneva, CT is offered. Eight
1772 strategies provided better clinical outcomes but at greater costs (balancing needs of individual
1773 patients and the system as a whole). Greater cost in this area may limit availability of other
1774 healthcare services within a publicly funded healthcare model. Further, a trade-off was observed
1775 between false positives and false negative findings. Diagnostic strategies with higher ICERs had
1776 fewer false negatives but more false positives findings (REF). These findings reflect the
1777 implications of incorrectly missing a PE diagnosis (i.e., false negative) as patients with PE that
1778 have treatment withheld are associated with considerable morbidity and mortality
1779 consequences.

1780

1781 *What are the concerns related to equity in access for diagnosing PE?*

1782

1783 There was considerable variation across Canada in the availability of key infrastructure for the
1784 diagnosis and management of VTE disease, in general, and PE, in particular.^{289,307} Provinces
1785 with higher populations tended to have a large proportion of hospitals with capability to measure
1786 d-dimer levels. In contrast, less populated provinces were more likely to send samples to
1787 centralized analysis facilities for d-dimer testing. All provinces and territories have some facilities
1788 offering advanced diagnostic imaging, however there are variations in the availability of
1789 diagnostic imaging equipment and specialists across the country. Typically, access to testing
1790 modalities is limited in some rural and remote hospitals. Patients with suspected PE should be
1791 assessed using appropriate diagnostic tests in a timely manner and the timing of access to
1792 diagnostic test results may impact the management of the condition and the effective use of
1793 health care resources (CADTH 2012).

1794

1795 In Canada, CT is the most prevalent imaging modality. As of 2015, across the country there
1796 were 538 CT machines, 340 MRI machines, 264 SPECT, 214 SPECT-CT machines, 47 PET-
1797 CT and 2 PET-MRI machines. Most imaging machines are in large urban hospitals, with the
1798 greatest number in Ontario, Quebec, British Columbia, and Alberta. Nova Scotia, Manitoba,
1799 Saskatchewan, Newfoundland and Labrador, and New Brunswick have a relatively moderate
1800 number of machines, while the less populated jurisdictions have a relatively low number of
1801 machines. Less populated jurisdictions in Canada often have limited imaging modalities. Some
1802 of the less populated jurisdictions have a greater number of some modalities (CT and MRI) per
1803 population, but the population is spread out so the machines may still be difficult for patients to
1804 access. The Northwest Territories have only CT, Yukon has only CT and MRI, and Nunavut has
1805 only CT (CADTH 2016). For this reason, the diagnosis of PE and availability of testing varies
1806 greatly across Canada.

1807

1808 *What are the public health considerations in relation to PE?*

1809

1810 Estimates suggest that PE afflicts 0.1%-1% of the Canadian population⁷. Certain
1811 subpopulations, such as pregnant women and older adults are disproportionately affected by PE
1812 due to a higher risk. Indeed, PE rarely occurs in the absence of risk factors and the likelihood of
1813 occurrence increases progressively where multiple risk factors are present. As mentioned in the
1814 Clinical Section above, factors associated with the development of PE can be inherited or
1815 acquired and include malignancies, immobilization, surgery, extremity paresis, hormone
1816 replacement therapy and oral contraception, and factor V Leiden mutation or other acquired
1817 thrombophilia conditions, the presence of DVT, pregnancy, and the use of medications that alter
1818 coagulation of the blood. There are public health concerns related to the increasing cumulative
1819 radiation exposure of population because of medical imaging tests.³¹⁷ Although the risk of PE

1820 increase with age, it has been found that the prevention of PE in young adults may be a
1821 worthwhile.³¹⁸ The prevention of PE begins with the prevention of DVT. For patients who are at
1822 risk of DVT or PE, their risk can be reduced by exercising or moving after extended periods of
1823 sitting, surgery, or illness. Certain prescription medications (anticoagulants) can help to reduce
1824 the risk of clotting. In addition, leg elevation, compression stockings, or pneumatic compression
1825 may help to prevent swelling in the legs and improve circulation.³¹⁹ The promotion of healthy
1826 lifestyles aimed at reducing risk factors related to PE or a public health campaign aimed at
1827 making at risk populations aware of the symptoms of PE so that they seek the appropriate
1828 medical care. A public health approach which aims to reduce the preventable risk factors
1829 associated with PE may be appropriate. However, some individuals who develop PE will have
1830 no risk factors.

1831
1832 *Summary*

1834 The diagnosis of acute PE in the ED setting raises several ethical issues related to patients,
1835 clinicians, healthcare organizations, the healthcare system and society, more generally. These
1836 ethical issues are grounding in several principles, including, but not limited to beneficence, non-
1837 maleficence, autonomy, and justice. Our findings suggest that there is variation on the clinically
1838 and ethically appropriate diagnostic pathway for individual patients, given their unique histories,
1839 location, and medical needs. The ethical considerations related to the diagnosis of PE will vary
1840 to some degree for clinicians across different specialties. There are likely to be similar ethical
1841 considerations for different healthcare organization, but the ways to address these ethical
1842 challenges may vary across organizations. At a systems level, there appears to be greater
1843 ethical difference between the various diagnostic pathways and imaging modalities for the
1844 diagnosis of PE. According to the economic models and clinical sections described above, the
1845 use of CT seems to be the most likely candidate for the ethical provision of PE diagnosis.

1846
1847
1848

1849 DISCUSSION

1850 Overall Summary of Findings

1851 This report assessed the optimal diagnostic strategy for acute PE with different imaging
1852 modalities that included the clinical and cost-effectiveness analyses, the patient perspectives
1853 and experience, implementation issues, and ethical considerations.

1854
1855 The results of the overview of systematic reviews indicated that the Wells rule for predicting PE
1856 probability, regardless of cut-off (<2 or ≤4), showed greater specificity than both the Geneva
1857 score and the revised Geneva score. There were not enough data or consistency in trend to
1858 allow a conclusive statement about which CPR had the best sensitivity. Strategies combining
1859 CPRs and D-dimer testing were effective and safe to rule out PE in patients presenting with
1860 suspected PE symptoms.

1861
1862 Sufficient data were available for meta-analysis of diagnostic test accuracy for the following
1863 modalities: CT, MRI, thoracic US, VQ, and VQ-SPECT. Our results indicated that CT had both
1864 the highest estimates of sensitivity and specificity, and the least statistical heterogeneity. There
1865 was greater uncertainty in the estimates for the other modalities than for CT, and the results for
1866 thoracic US, in particular, varied widely according to the choice of the statistical model. We were
1867 unable to explain the heterogeneity with the available patient and study covariate data.

1868
1869 Failure rate was available for CT, MRI, Q-SPECT, VQ, and VQ-SPECT, and was low for all
1870 modalities, below the accepted failure rate of 4% over 3 months.¹⁸³ Moreover, failure rate from
1871 diagnostic pathways consisting of combinations of CPR, D-dimer, CT, and VQ, were below 4%
1872 for all studies except one. The low failure rates of diagnostic algorithms that incorporate the d-
1873 Dimer help support current practice and argue for its inclusion in the work-up of patients who
1874 may even be at intermediate risk of PE whose imaging is positive or who are at high risk but
1875 have false negative or indeterminate findings on imaging. The CT results were not viable in the
1876 pregnant population, but this may be balanced to some extent by the requirement for further
1877 imaging which results from indeterminate, but technically viable VQ scans. The role of other
1878 imaging modalities in pregnancy is unclear.

1879
1880 The included SRs^{26,97,100} in the clinical overview of reviews did not show a consistent diagnostic
1881 advantage of one of CPRs over the others with respect to the dichotomized Wells rule, the
1882 Geneva score or the revised Geneva score. This is in agreement with a publication by the
1883 American Academy of Family Physicians which states that no single CPR has been proven to
1884 be superior.⁷²

1885
1886 The economic analysis found that, in patients suspected of PE, CT should be offered so long as
1887 there are no contra-indications as this imaging modality was found to have the highest
1888 diagnostic test accuracy, lowest proportion of nondiagnostic findings and was associated with
1889 the lowest costs to perform. If willingness-to-pay is greater than \$33,016/QALY, leg US should
1890 be part of the diagnostic algorithm as an ancillary test before diagnostic imaging as, despite its
1891 increased costs to perform, leg US reduces the number of false negative cases. In terms of rule-
1892 out test predicated on low pre-test PE risk based on CPR, if willingness-to-pay is below
1893 \$15,734/QALY, the rule-out test should consist of PERC followed by d-dimer whereas, if
1894 willingness-to-pay is between \$15,734/QALY to \$196,369/QALY, d-dimer should be the rule-out
1895 test employed. The CPR followed less of a clear trend although Gestalt-based assessment was
1896 most commonly associated with higher ICER values. In total, nine strategies formed the
1897 efficiency frontier (i.e., the set of strategies that, for varying costs, produces the highest health
1898 benefits). The economic model was robust to most sensitivity analyses including scenarios that

1899 explored different approaches to clinical management of test findings and alternative parameter
1900 inputs for diagnostic tests accuracy. Analyses that impacted the model involved those that had a
1901 more pronounced impact in shifting the cost-benefit ratio such as the analyzed time horizon, the
1902 prevalence of PE and the treatment duration for an index PE event.

1903
1904 In our economic model, external validation was conducted both separately for each sub-model
1905 and together in evaluating the three-month PE risk in individuals with a negative diagnosis of
1906 PE. The external validation exercise provided confidence towards the model's predictions and
1907 therefore, the costs and health benefits predicted. Where possible, Canadian data were used as
1908 inputs to the model.

1909
1910 While the initial research question was set out to understand patient experiences with diagnostic
1911 pathways and imaging technologies for PE, due to a lack of relevant literature on PE this report
1912 also included patient experiences with diagnostic imaging for any condition in any setting. This,
1913 paired with an absence of any studies conducted in Canada, it is possible that the synthesis
1914 reported here does not adequately capture the diversity in perspectives regarding diagnostic
1915 pathways for PE.

1916
1917 There remains a need to understand how surreal an experience diagnostic imaging can be for
1918 individuals unfamiliar with the technologies or settings. While the potential benefits of a scan
1919 may be well understood and at times serve as a calming mechanism throughout the imaging
1920 process, reminders of human presence throughout the exam could help ground the patient in
1921 reality and clear conversations prior to the exams could allow for greater levels of
1922 comprehension. In addition to patient factors, provider knowledge and choice may influence the
1923 initial assessment, and subsequent investigation, of suspected PE.

1924
1925 The implementation issues review found that access to tools and tests used to diagnosis PE
1926 varies across Canada and differs depending on whether a site is located in an urban centre, is
1927 rural, or is remote; this may influence the diagnosis of PE. However, it could be possible to
1928 establish policies and protocols to implement a particular diagnostic strategy for PE, though this
1929 may require clarity on their use and collaboration from those involved. The selected studies,
1930 survey responses and expert interview are all from a Canadian point of view. This was
1931 intentional so that the perspectives offered would be specific to the Canadian context. However,
1932 these findings may not be generalizable to rural and remote settings.

1933
1934 Ethical tensions necessarily arise when different values are given to available choices or
1935 alternatives. In the context of PE there are several diagnostic pathways, each with its own set of
1936 benefits and risks, for the various stakeholders. The diagnosis of PE is further complicated by
1937 the diversity in the patient populations, treating clinicians, and healthcare organizations across
1938 Canada. Conflicting values within the diagnosis of PE can occur within and between each of the
1939 relevant stakeholder groups. For example, while an individual patient may benefit from the relief
1940 associated with the use of CTPA to rule out PE, they may also experience harm from the
1941 iodizing contrast used in this test, while the healthcare organization and healthcare system,
1942 more generally, incur the financial cost of this testing modality. The diagnosis of PE, like many
1943 healthcare interventions, also requires a balancing of the ethical considerations for relevant
1944 stakeholders. The weight of these ethical considerations, in part, relies on the availability of
1945 empirical evidence and on the value to which we ascribe the interests of the relevant
1946 stakeholders. As technological advancements are in the context of PE diagnosis and the
1947 broader healthcare and social environments change, the ethics of various PE diagnostic
1948 pathways will also evolve. In determining the optimal diagnostic pathway for diagnosing PE,

1949 clinicians, healthcare organizations and the relevant policy makers must take the various
1950 stakeholder's values/ interests and the ethical considerations into account.

1951
1952 **Strengths**

1953 To our understanding, this is the most comprehensive evaluation on the clinical and cost-
1954 effectiveness of diagnostic strategies for PE. Further, this is the first report aimed at
1955 understanding more about the patient experience, implementation issues, and ethical
1956 considerations associated with PE diagnostic imaging.

1957
1958 The review was not focused simply on comparing diagnostic imaging modality but evaluated the
1959 full diagnostic pathway consisting of risk stratification, ancillary testing and diagnostic imaging.
1960 Our analysis was based on publicly available evidence. In particular, for the diagnostic tests
1961 accuracy parameters for imaging modalities, the approach taken by the clinical review
1962 addresses many of the methodological concerns with past meta-analyses in this discipline.
1963 Compared with previous DTA meta-analyses,^{24,25,84,101,320-323} the sensitivity of MRI tended to be
1964 lower in the published meta-analyses than in our meta-analysis, although the specificity is
1965 comparable, while both specificity and sensitivity of ultrasound are lower. The published meta-
1966 analyses used a bivariate model that assumed a perfect reference standard, even when they
1967 pooled data across reference standards, and included reference standards that might be
1968 expected to have lower anatomic resolution than the index test (e.g., VQ used as a reference for
1969 CT). It was this issue that we sought to address by using a model that allowed for an imperfect
1970 or variable reference standard.

1971
1972 When concerns were present with the diagnostic data (e.g., inputs for clinical prediction rules),
1973 extensive sensitivity analyses were conducted in the economic model to explore its robustness
1974 by testing alternative values.

1975
1976 **Limitations**

1977 No eligible studies reported on imaging for PE in geographically remote or rural settings, and no
1978 information was captured on what information might be used in the decision to transfer a patient
1979 with suspected PE for further investigation and care in these settings. This is an important
1980 limitation, given the policy question, which reflects the geographical spread of Canada.

1981
1982 A number of subgroups that were of particular interest were not well described. Age was
1983 represented by the covariate of mean age, which did not appear to be associated with
1984 diagnostic test performance, and by three studies that described stratified results. One study
1985 reported results stratified by gender. Other subgroups were excluded from studies for reasons
1986 of safety and feasibility, including elderly patients, obese patients, patients with pre-existing
1987 renal disease, or patients who were hemodynamically unstable at the time of presentation.

1988
1989 For D-dimer and most CPR, the correlation between sensitivity and specificity could not be
1990 derived from the hsROC curve given a lack of primary studies or in difficulties in deriving the 2x2
1991 tables.(Appendix 22: Risk Stratification: Parameters for the Economic Evaluation) A separate
1992 analysis was conducted on diagnostic strategies with 3-tier Wells to compare the expected
1993 costs and outcomes when either the deterministic estimates or the probabilistic inputs were
1994 employed. The expected costs and outcomes were similar for each diagnostic strategy
1995 regardless of whether the deterministic or probabilistic values were used. This highlights that, by
1996 using the deterministic input for the majority of risk stratification inputs and for d-dimer, the
1997 impact is expected to be less on the overall ordering of the diagnostic strategy on the efficiency
1998 frontier but more on the quantification of uncertainty.

1999

2000 Safety was sparsely reported, although the immediate procedures were not associated with
2001 serious adverse events. There was no information on long-term adverse effects, such as cancer
2002 risks associated with radiation dose. It is important to note, given the scope of this project, the
2003 economic model ignored the indirect effects such as the potential clinical benefit of prophylactic
2004 anticoagulation in false positive patients (to prevent VTE) or the impact of incidental findings
2005 emerging from imaging to diagnose other conditions. In addition, the relationship between
2006 radiation exposure to cancer induction was limited in literature and, therefore, not modelled.

2007
2008 To date, few studies addressed patient perspectives, implementation issues, and ethical
2009 considerations related to the diagnosis of PE. For the implementation issues review, the
2010 literature was based on a search strategy with limitations. For example, Canadian studies only
2011 were searched and included, and while this was done to increase relevancy and generalizability,
2012 it is possible that studies from other countries may have been applicable to the Canadian
2013 setting. It, therefore, is possible that relevant information was not captured or retrieved. As well,
2014 twelve survey responses were received from five provinces. This offers limited perspectives
2015 from persons involved in the diagnosis of PE, as the respondents answers cannot speak for all
2016 health care providers. These responses cannot be further generalized to the whole province,
2017 and are specific to the facility the respondent represents.

2018
2019 Finally, we unable to identify relevant literature on the potential environmental impact of PE
2020 diagnostic imaging, such as nuclear waste, based on the literature search conducted.

2021 2022 **Directions for Future Research**

2023 There are insufficient data to evaluate whether the clinical and cost-effectiveness differs by
2024 subgroups, such as patients in rural or remote settings, the pregnant population or patients with
2025 cancer. This may emerge to be an important issue if evidence suggests clinical heterogeneity in
2026 the diagnostic test accuracy of different diagnostic tests and imaging modalities. It has been
2027 suggested that d-dimer tests performs differently in pregnant patients as pregnancy is known to
2028 increase d-dimer concentration above the conventional thresholds leading to higher false
2029 positives tests. However, as there was limited clinical data to support differences in model
2030 inputs for this subgroup, a cost-effectiveness analysis specifically on pregnant patients could not
2031 be conducted. On a related note, the diagnostic test accuracy inputs for d-dimer were based on
2032 the pooled analyses from two different publications.^{32,239} However, emerging data suggest
2033 differences may exist between the type of assay used for d-dimer tests and increasingly, there
2034 is interests in employing age-adjusted d-dimer given that d-dimer levels increase with age.
2035 Greater research in this area and appropriate meta-analyses would permit analysis to evaluate
2036 whether the clinical and cost-effectiveness differs according to the assay type or the patient's
2037 age for d-Dimer testing.

2038
2039 The use of clinical decision support tools and computer assisted diagnosis was out of the scope
2040 for this HTA. As these tools may play a role in diagnosis and may influence the outcome of
2041 screening, additional research may be warranted. Moreover, the clinical review focused on
2042 patients suspected of acute PE. While it is acknowledged that PE is part of the spectrum of
2043 VTE, evidence that focused on patients suspected of DVT or that focused on patients suspected
2044 of broader VTE without PE specific outcomes available was not included. Some of this evidence
2045 may be relevant to the general clinical area, so further research is required

2046
2047 As little has been done to explore experiences or perspectives of individuals undergoing
2048 diagnostic imaging for PE, it would be interesting to see how PE specific experiences align with
2049 those included within this report. While there is value in understanding the perceived benefits,
2050 harms and experiences outlined in this report, a more diverse representation may be possible

2051 with further research. Similarly, as all of these studies were conducted outside of Canada, to
2052 gain a greater understanding of PE imaging within the Canadian context and its range of urban,
2053 semi-urban and rural populations further research should be conducted in Canada.
2054 The Canadian Medical Imaging Inventory update will provide current information regarding
2055 where medical imaging units are located across the country. This report will provide updated
2056 information on access to imaging modalities in the provinces and territories, especially as it
2057 relates to type and placement of imaging units. It may also provide insight on access to these
2058 units for those in rural or remote settings. In addition to this, future research efforts could focus
2059 on hospital or provincial wide policies and procedures for the diagnosis of PE (e.g., travel
2060 policies for patients transported out of centre), and the supports and barriers to the
2061 implementation of these practices.
2062

2063 It remains that there is a need for more research concerning the impact of PE diagnostic
2064 pathways on both the environment and population health. Furthermore, there are opportunities
2065 for deeper exploration of the ethical analyses related to certain patient populations and
2066 comparison of the implementation and provision of the various diagnostic pathways and imaging
2067 modalities within different jurisdictions in Canada.
2068

2069 **Conclusions**

2070 The findings in the overview of reviews indicate that while similar, the clinical decision rules
2071 differ in their ability to identify a low-risk group of patients. When applied to patients at low risk
2072 for PE, the PERC rule can identify a subset of patients that will gain optimal benefit in terms of
2073 imaging decisions from the d-dimer. Similarly, it can identify the ultra low-risk group who do not
2074 require a need for d-Dimer testing. In patients with suspected PE, CT had the highest diagnostic
2075 test accuracy and was the most cost-effective imaging modality. The economic model can help
2076 to inform a clinician's understanding of the clinical outcomes and predicted costs associated
2077 with each diagnostic strategy. Patient factors and provider knowledge and choice can influence
2078 the initial assessment, followed by the investigation of suspected PE. As well, the variability of
2079 access to PE diagnostic tools and tests used across Canada and in urban, rural, and remote
2080 settings may influence PE diagnosis. Ethical considerations and stakeholder's values and
2081 interests must also be taken into account to determine the optimal PE diagnostic pathway.
2082

2083 Data on various subgroups, including patients in rural or remote settings, the pregnant
2084 population, or patients with cancer, were insufficient. Studies on the patient perspectives and
2085 experience, implementation issues, and ethical considerations were also limited, and our
2086 literature search did not identify any relevant studies on the environmental impact of the
2087 different imaging modalities. Future research can provide important insights on the impact of
2088 different diagnostic tests and imaging modalities across these populations from clinical,
2089 economic, patient experience, implementation, ethical, and environmental perspectives.
2090

2091 **REFERENCES**

2092
2093

2094 1. Sadigh G, Kelly A, Cronin P. Challenges, controversies, and hot topics in pulmonary
2095 embolism imaging. *AJR Am J Roentgenol* [Internet]. 2011 [cited 2016 Jul
2096 19];196(3):497-515. Available from:
2097 <http://www.ajronline.org/doi/full/10.2214/AJR.10.5830>

2098 2. Ma Y, Yan S, Zhou L, Yuan DT. Competitive assessments of pulmonary embolism:
2099 noninvasiveness versus the gold standard. *Vascular*. 2016;24(2):217-24.

2100 3. Thompson B. Patient education: pulmonary embolism (beyond the basics). In: Post
2101 TW, editor. *UpToDate* [Internet]. Waltham (MA): UpToDate; 2016 [cited 2016 Sep 9].
2102 Available from: [http://www.uptodate.com/contents/pulmonary-embolism-beyond-the-](http://www.uptodate.com/contents/pulmonary-embolism-beyond-the-basics)
2103 [basics](http://www.uptodate.com/contents/pulmonary-embolism-beyond-the-basics) Subscription required.

2104 4. Tapson VF. Acute pulmonary embolism. *N Engl J Med*. 2008 Mar 6;358(10):1037-52.

2105 5. Moser KM, Fedullo PF, LitleJohn JK, Crawford R. Frequent asymptomatic pulmonary
2106 embolism in patients with deep venous thrombosis. *JAMA*. 1994 Jan 19;271(3):223-5.

2107 6. Sweet PH, III, Armstrong T, Chen J, Masliah E, Witucki P. Fatal pulmonary embolism
2108 update: 10 years of autopsy experience at an academic medical center. *JRSM Short*
2109 *Rep* [Internet]. 2013 [cited 2016 Aug 17];4(9). Available from:
2110 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3767072>

2111 7. Canadian Agency for Drugs and Technologies in Health. Detection of pulmonary
2112 embolism [Internet]. Ottawa: CADTH; 2012. [cited 2016 Jul 19]. Available from:
2113 <https://www.cadth.ca/resources/detection-pulmonary-embolism>

2114 8. Masotti L, Ray P, Righini M, Le GG, Antonelli F, Landini G, et al. Pulmonary embolism
2115 in the elderly: a review on clinical, instrumental and laboratory presentation. *Vasc*
2116 *Health Risk Manag* [Internet]. 2008 [cited 2016 Sep 9];4(3):629-36. Available from:
2117 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2515422>

2118 9. Squizzato A, Galli L, Gerdes V. Point-of-care ultrasound in the diagnosis of pulmonary
2119 embolism [Internet]. *Crit Ultrasound J*. 2016 [cited 2016 Jul 20];7(7). Available from:
2120 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4447771/pdf/13089_2015_Article_25.pdf

2121 10. Kline JA, Hernandez-Nino J, Jones AE, Rose GA, Norton HJ, Camargo CA, Jr.
2122 Prospective study of the clinical features and outcomes of emergency department
2123 patients with delayed diagnosis of pulmonary embolism. *Acad Emerg Med*. 2007
2124 Jul;14(7):592-8.

2125 11. Goldhaber SZ, Visani L, De RM. Acute pulmonary embolism: clinical outcomes in the
2126 International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet*. 1999 Apr
2127 24;353(9162):1386-9.

2128 12. Laporte S, Mismetti P, Decousus H, Uresandi F, Otero R, Lobo JL, et al. Clinical
2129 predictors for fatal pulmonary embolism in 15,520 patients with venous

- 2130 thromboembolism: findings from the Registro Informatizado de la Enfermedad
2131 TromboEmbolica venosa (RIETE) Registry. *Circulation*. 2008 Apr 1;117(13):1711-6.
- 2132 13. Thaler J, Pabinger I, Ay C. Anticoagulant Treatment of Deep Vein Thrombosis and
2133 Pulmonary Embolism: The Present State of the Art. *Front Cardiovasc Med* [Internet].
2134 2015 [cited 2016 Aug 8];2:30. Available from:
2135 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4671349>
- 2136 14. Pollack CV, Schreiber D, Goldhaber SZ, Slattery D, Fanikos J, O'Neil BJ, et al. Clinical
2137 characteristics, management, and outcomes of patients diagnosed with acute
2138 pulmonary embolism in the emergency department: initial report of EMPEROR
2139 (Multicenter Emergency Medicine Pulmonary Embolism in the Real World Registry). *J*
2140 *Am Coll Cardiol*. 2011 Feb 8;57(6):700-6.
- 2141 15. Konstantinides SV. 2014 ESC Guidelines on the diagnosis and management of acute
2142 pulmonary embolism. *Eur Heart J* [Internet]. 2014 Dec 1 [cited 2016 Aug
2143 9];35(45):3145-6. Available from:
2144 <http://eurheartj.oxfordjournals.org/content/ehj/35/45/3145.full.pdf>
- 2145 16. White RH. The epidemiology of venous thromboembolism. *Circulation*. 2003 Jun
2146 17;107(23 Suppl 1):I4-I8.
- 2147 17. Skinner S. Pulmonary embolism: assessment and imaging. *Aust Fam Physician*
2148 [Internet]. 2013;42(9):628-32. Available from:
2149 <http://www.racgp.org.au/download/Documents/AFP/2013/Sep/201309skinner.pdf>
- 2150 18. Kearon C. Natural history of venous thromboembolism. *Circulation*. 2003 Jun
2151 17;107(23 Suppl 1):I22-I30.
- 2152 19. Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton LJ, III. Trends in
2153 the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year
2154 population-based study. *Ann Intern Med*. 2005 Nov 15;143(10):697-706.
- 2155 20. Pasha SM, Klok FA, Snoep JD, Mos IC, Goekoop RJ, Rodger MA, et al. Safety of
2156 excluding acute pulmonary embolism based on an unlikely clinical probability by the
2157 Wells rule and normal D-dimer concentration: a meta-analysis. *Thromb Res*. 2010
2158 Apr;125(4):e123-e127.
- 2159 21. Boka K. Pulmonary embolism clinical scoring systems [Internet]. New York: Medscape;
2160 2015. [cited 2016 Jul 20]. Available from:
2161 <http://emedicine.medscape.com/article/1918940-overview>
- 2162 22. Raja AS, Greenberg JO, Qaseem A, Denberg TD, Fitterman N, Schuur JD, et al.
2163 Evaluation of Patients With Suspected Acute Pulmonary Embolism: Best Practice
2164 Advice From the Clinical Guidelines Committee of the American College of Physicians.
2165 *Ann Intern Med*. 2015 Nov 3;163(9):701-11.
- 2166 23. Thompson BT. Clinical presentation, evaluation, and diagnosis of the adult with
2167 suspected acute pulmonary embolism. In: Post TW, editor. *UpToDate* [Internet].
2168 Waltham (MA): UpToDate; 2016 Aug 8 [cited 2016 Nov 23]. Available from:
2169 www.uptodate.com Subscription required.

- 2170 24. Shen JH, Chen HL, Chen JR, Xing JL, Gu P, Zhu BF. Comparison of the Wells score
2171 with the revised Geneva score for assessing suspected pulmonary embolism: a
2172 systematic review and meta-analysis. *J Thromb Thrombolysis*. 2016 Apr;41(3):482-92.
- 2173 25. Wang RC, Bent S, Weber E, Neilson J, Smith-Bindman R, Fahimi J. The Impact of
2174 Clinical Decision Rules on Computed Tomography Use and Yield for Pulmonary
2175 Embolism: A Systematic Review and Meta-analysis. *Ann Emerg Med*. 2016
2176 Jun;67(6):693-701.
- 2177 26. Lucassen W, Geersing GJ, Erkens PM, Reitsma JB, Moons KG, Büller H, et al. Clinical
2178 decision rules for excluding pulmonary embolism: a meta-analysis. *Ann Intern Med*.
2179 2011 Oct 4;155(7):448-60.
- 2180 27. Screatton NJ, Karia S. Commentary on " Ten years of imaging for pulmonary
2181 embolism: too many scans or the tip of an iceberg?". *Clin Radiol*. 2016;70:1355-6.
- 2182 28. Riley RS, Gilbert AR, Dalton JB, Pai S, McPherson RA. Widely Used Types and
2183 Clinical Applications of D-Dimer Assay. *Lab Med*. 2016 May;47(2):90-102.
- 2184 29. Geersing GJ, Janssen KJ, Oudega R, Bax L, Hoes AW, Reitsma JB, et al. Excluding
2185 venous thromboembolism using point of care D-dimer tests in outpatients: a diagnostic
2186 meta-analysis. *Bmj [Internet]*. 2009 [cited 2016 Jul 8];339:b2990. Available from:
2187 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2727580>
- 2188 30. Lucassen WA, Erkens PM, Geersing GJ, Buller HR, Moons KG, Stoffers HE, et al.
2189 Qualitative point-of-care D-dimer testing compared with quantitative D-dimer testing in
2190 excluding pulmonary embolism in primary care. *J Thromb Haemost*. 2015
2191 Jun;13(6):1004-9.
- 2192 31. Kline JA, Mitchell AM, Kabrhel C, Richman PB, Courtney DM. Clinical criteria to
2193 prevent unnecessary diagnostic testing in emergency department patients with
2194 suspected pulmonary embolism. *J Thromb Haemost [Internet]*. 2004 Aug [cited 2017
2195 Jun 1];2(8):1247-55. Available from: [http://onlinelibrary.wiley.com/doi/10.1111/j.1538-
2196 7836.2004.00790.x/abstract](http://onlinelibrary.wiley.com/doi/10.1111/j.1538-7836.2004.00790.x/abstract)
- 2197 32. Da Costa Rodrigues J, Alzuphar S, Combescure C, Le Gal G, Perrier A. Diagnostic
2198 characteristics of lower limb venous compression ultrasonography in suspected
2199 pulmonary embolism: a metaanalysis. *J Thromb Haemost*. 2016 Jul 5.
- 2200 33. Van der Pol LM, Mairuhu ATA, Tromeur C, Couturaud F, Huisman MV, Klok FA. Use
2201 of clinical prediction rules and D-dimer tests in the diagnostic management of pregnant
2202 patients with suspected acute pulmonary embolism. *Blood Rev*. 2016.
- 2203 34. Smith C, Mensah A, Mal S, Worster A. Is pretest probability assessment on
2204 emergency department patients with suspected venous thromboembolism
2205 documented before SimpliRED D-dimer testing? *CJEM*. 2008 Nov;10(6):519-23.
- 2206 35. Corwin MT, Donohoo JH, Partridge R, Egglin TK, Mayo-Smith WW. Do emergency
2207 physicians use serum D-dimer effectively to determine the need for CT when
2208 evaluating patients for pulmonary embolism? Review of 5,344 consecutive patients.
2209 *AJR Am J Roentgenol*. 2009 May;192(5):1319-23.

- 2210 36. Choosing Wisely. [Internet]. Philadelphia (PA): ABIM Foundation. Avoid CT pulmonary
2211 angiography in emergency department patients with a low-pretest probability of
2212 pulmonary embolism and either a negative Pulmonary Embolism Rule-Out Criteria
2213 (PERC) or a negative D-dimer; 2014 Oct 27 [cited 2016 Jul 27]. Available from:
2214 [http://www.choosingwisely.org/clinician-lists/acep-ct-pulmonary-angiography-in-ed-](http://www.choosingwisely.org/clinician-lists/acep-ct-pulmonary-angiography-in-ed-patients/)
2215 [patients/](http://www.choosingwisely.org/clinician-lists/acep-ct-pulmonary-angiography-in-ed-patients/)
- 2216 37. Dogan H, DE RA, Geleijns J, Huisman MV, Kroft LJ. The role of computed
2217 tomography in the diagnosis of acute and chronic pulmonary embolism. *Diagn Interv*
2218 *Radiol* [Internet]. 2015 Jul [cited 2016 Aug 8];21(4):307-16. Available from:
2219 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4498425>
- 2220 38. van Beek EJ, Brouwerst EM, Song B, Stein PD, Oudkerk M. Clinical validity of a
2221 normal pulmonary angiogram in patients with suspected pulmonary embolism--a
2222 critical review. *Clin Radiol*. 2001 Oct;56(10):838-42.
- 2223 39. Canadian medical imaging inventory [Internet]. Ottawa (ON): CADTH; 2016 Mar 31.
2224 [cited 2017 Jul 27]. Available from: <https://www.cadth.ca/imaginginventory>
- 2225 40. Computed tomography [Internet]. Geneva (CH): World Health Organization (WHO);
2226 2017. [cited 2017 Jul 27]. Available from:
2227 http://www.who.int/diagnostic_imaging/imaging_modalities/dim_comptomography/en/
- 2228 41. Ionizing radiation in pregnant women: a review of the safety and guidelines [Internet].
2229 Ottawa (ON): CADTH; 2015 Jun 9. [cited 2017 Jul 27]. (CADTH rapid response report:
2230 summary with critical appraisal). Available from:
2231 [https://www.cadth.ca/sites/default/files/pdf/htis/june-2015/RC0665-IonizingRadiation-](https://www.cadth.ca/sites/default/files/pdf/htis/june-2015/RC0665-IonizingRadiation-Pregnancy-Final.pdf)
2232 [Pregnancy-Final.pdf](https://www.cadth.ca/sites/default/files/pdf/htis/june-2015/RC0665-IonizingRadiation-Pregnancy-Final.pdf)
- 2233 42. Radiation emissions from computed tomography: a review of the risk of cancer and
2234 guidelines [Internet]. Ottawa (ON): CADTH; 2014 Jun 4. [cited 2017 Jul 27]. (CADTH
2235 rapid response report: summary with critical appraisal). Available from:
2236 [https://www.cadth.ca/sites/default/files/pdf/htis/jul-](https://www.cadth.ca/sites/default/files/pdf/htis/jul-2014/RC0558%20CT%20Radiation%20Emission%20Final.pdf)
2237 [2014/RC0558%20CT%20Radiation%20Emission%20Final.pdf](https://www.cadth.ca/sites/default/files/pdf/htis/jul-2014/RC0558%20CT%20Radiation%20Emission%20Final.pdf)
- 2238 43. Magnetic resonance imaging [Internet]. Geneva (CH): World Health Organization
2239 (WHO); 2017. [cited 2017 Jul 27]. Available from:
2240 http://www.who.int/diagnostic_imaging/imaging_modalities/dim_magresimaging/en/
- 2241 44. Consiglio N. MRI and patient safety. *J Med Imaging Radiat Sci*. 2006;37(2):5-9.
- 2242 45. Sherlock FG. MRIsafety.com [Internet]. [Playa Del Ray (CA)]: Sherlock R & D Services,
2243 Inc.; 2017. [cited 2017 Jul 27]. Available from:
2244 <http://www.mrisafety.com/SafetyInfo.asp>
- 2245 46. Sherlock FG, Crues JV, Karacozoff AM. MRI bioeffects, safety, and patient
2246 management. Los Angeles (CA): Biomedical Research Publishing Group; [2014].
- 2247 47. Nuclear medicine [Internet]. Geneva (CH): World Health Organization (WHO); 2017.
2248 [cited 2017 Jul 27]. Available from:
2249 http://www.who.int/diagnostic_imaging/imaging_modalities/dim_nuclearmed/en/

- 2250 48. Wongwaisayawan S, Suwannanon R, Sawatmongkorngul S, Kaewlai R. Emergency
2251 Thoracic US: The Essentials. *Radiographics*. 2016 May;36(3):640-59.
- 2252 49. Hunsaker AR, Lu MT, Goldhaber SZ, Rybicki FJ. Imaging in acute pulmonary
2253 embolism with special clinical scenarios. *Circ Cardiovasc Imaging*. 2010 Jul;3(4):491-
2254 500.
- 2255 50. Schiebler ML, Nagle SK, Francois CJ, Repplinger MD, Hamedani AG, Vigen KK, et al.
2256 Effectiveness of MR angiography for the primary diagnosis of acute pulmonary
2257 embolism: clinical outcomes at 3 months and 1 year. *J Magn Reson Imaging [Internet]*.
2258 2013 Oct [cited 2016 Oct 7];38(4):914-25. Available from:
2259 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3970266>
- 2260 51. Le Roux PY, Robin P, Delluc A, Abgral R, Duc-Pennec AL, Nowak E, et al. V/Q
2261 SPECT interpretation for pulmonary embolism diagnosis: Which criteria to use? *J Nucl
2262 Med [Internet]*. 2013 [cited 2016 Oct 7];54(7):1077-81. Available from:
2263 <http://jnm.snmjournals.org/content/54/7/1077.full.pdf+html>
- 2264 52. Sheh S, Bellin E, Freeman K, Haramati L. Pulmonary embolism diagnosis and
2265 mortality with pulmonary CT angiography versus ventilation-perfusion scintigraphy:
2266 evidence of overdiagnosis with CT? *AJR Am J Roentgenol [Internet]*. 2012 [cited 2016
2267 Nov 17];198:1340-5. Available from:
2268 <http://www.ajronline.org/doi/pdf/10.2214/AJR.11.6426>
- 2269 53. Anderson DR, Kahn SR, Rodger MA, Kovacs MJ, Morris T, Hirsch A, et al. Computed
2270 tomographic pulmonary angiography vs ventilation-perfusion lung scanning in patients
2271 with suspected pulmonary embolism: a randomized controlled trial. *JAMA*. 2007 Dec
2272 19;298(23):2743-53.
- 2273 54. Smith-Bindman R, Lipson J, Marcus R, Kim KP, Mahesh M, Gould R, et al. Radiation
2274 dose associated with common computed tomography examinations and the
2275 associated lifetime attributable risk of cancer. *Arch Intern Med [Internet]*. 2009 Dec 14
2276 [cited 2016 Jul 27];169(22):2078-86. Available from:
2277 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4635397>
- 2278 55. Kocher KE, Meurer WJ, Fazel R, Scott PA, Krumholz HM, Nallamothu BK. National
2279 trends in use of computed tomography in the emergency department. *Ann Emerg Med*.
2280 2011 Nov;58(5):452-62.
- 2281 56. Feng LB, Pines JM, Yusuf HR, Grosse SD. U.S. trends in computed tomography use
2282 and diagnoses in emergency department visits by patients with symptoms suggestive
2283 of pulmonary embolism, 2001-2009. *Acad Emerg Med [Internet]*. 2013 Oct [cited 2016
2284 Jul 27];20(10):1033-40. Available from:
2285 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4453868>
- 2286 57. Smith-Bindman R, Miglioretti DL, Larson EB. Rising use of diagnostic medical imaging
2287 in a large integrated health system. *Health Aff (Millwood) [Internet]*. 2008 Nov [cited
2288 2016 Jul 27];27(6):1491-502. Available from:
2289 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2765780>

- 2290 58. Robert-Ebadi H, Le Gal G, Righini M. Evolving imaging techniques in diagnostic
2291 strategies of pulmonary embolism. *Exp Rev Cardiovasc Therapy*. 2016;14(4):495-503.
- 2292 59. Le Gal G, Bounameaux H. Diagnosing pulmonary embolism: running after the
2293 decreasing prevalence of cases among suspected patients. *J Thromb Haemost*. 2004
2294 Aug;2(8):1244-6.
- 2295 60. Schissler AJ, Rozenshtein A, Kulon ME, Pearson GD, Green RA, Stetson PD, et al.
2296 CT pulmonary angiography: increasingly diagnosing less severe pulmonary emboli.
2297 PLoS ONE [Internet]. 2013 [cited 2016 Nov 17];8(6):e65669. Available from:
2298 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3680477>
- 2299 61. Walen S, Leijstra MA, Uil SM, Boomsma MF, van den Berg JW. Diagnostic yield of CT
2300 thorax angiography in patients suspected of pulmonary embolism: independent
2301 predictors and protocol adherence. *Insights Imaging* [Internet]. 2014 Apr [cited 2016
2302 Oct 12];5(2):231-6. Available from:
2303 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3999363>
- 2304 62. Mamlouk MD, vanSonnenberg E, Gosalia R, Drachman D, Gridley D, Zamora JG, et
2305 al. Pulmonary embolism at CT angiography: implications for appropriateness, cost,
2306 and radiation exposure in 2003 patients. *Radiology*. 2010 Aug;256(2):625-32.
- 2307 63. Shankar S, Gour A, Khanijao S, Taha O, Kitchloo K, Gorukanti P, et al. The diagnostic
2308 yield of computed tomographic pulmonary angiography (CTPA) for pulmonary
2309 diseases [abstract]. *Chest* [Internet]. 2016 [cited 2016 Aug 30];149(4 Suppl):A521.
2310 Available from: <http://journal.publications.chestnet.org/article.aspx?articleid=2511929>
- 2311 64. Stein PD, Fowler SE, Goodman LR, Gottschalk A, Hales CA, Hull RD, et al.
2312 Multidetector computed tomography for acute pulmonary embolism. *N Engl J Med*.
2313 2006 Jun 1;354(22):2317-27.
- 2314 65. Miller WT, Marinari LA, Mahne A. Frequency and causes of false-positive CTPA
2315 exams in community hospitals [abstract]. *Chest* [Internet]. 2009 [cited 2016 Aug
2316 30];136(4 Suppl):14S. Available from:
2317 <http://journal.publications.chestnet.org/article.aspx?articleid=1095863>
- 2318 66. Hutchinson B, Navin P, Marom E, Truong M, Bruzzi J. Overdiagnosis of pulmonary
2319 embolism by pulmonary CT angiography. *AJR Am J Roentgenol* [Internet].
2320 2015;205:271-7.
- 2321 67. Hogg K, Brown G, Dunning J, Wright J, Carley S, Foex B, et al. Diagnosis of
2322 pulmonary embolism with CT pulmonary angiography: a systematic review. *Emerg*
2323 *Med J*. 2006 Mar [cited 2016 Oct 13];23(3):172-8. Available from:
2324 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2464412>
- 2325 68. Stein PD, Goodman LR, Hull RD, Dalen JE, Matta F. Diagnosis and management of
2326 isolated subsegmental pulmonary embolism: review and assessment of the options.
2327 *Clin Appl Thromb Hemost*. 2012 Jan;18(1):20-6.

- 2328 69. Wiener RS, Schwartz LM, Woloshin S. Time trends in pulmonary embolism in the
2329 United States: evidence of overdiagnosis. *Arch Intern Med*. 2011 May 9;171(9):831-7.
2330 Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3140219>
- 2331 70. Glassroth J. Imaging of pulmonary embolism: too much of a good thing? *JAMA*. 2007
2332 Dec 19;298(23):2788-9.
- 2333 71. Burge AJ, Freeman KD, Klapper PJ, Haramati LB. Increased diagnosis of pulmonary
2334 embolism without a corresponding decline in mortality during the CT era. *Clin Radiol*.
2335 2008 Apr;63(4):381-6.
- 2336 72. Wilbur J, Shian B. Diagnosis of deep venous thrombosis and pulmonary embolism. *Am*
2337 *Fam Physician* [Internet]. 2012 [cited 2016 Jul 19];86(10):913-9. Available from:
2338 <http://www.aafp.org/afp/2012/1115/p913.pdf>
- 2339 73. Stein P, Sostman D, Dalen J, Bailey D, Bajc M, Goldhaber S, et al. Controversies in
2340 diagnosis of pulmonary embolism. *Clin Appl Thromb Hemost*. 2011;17(2):140-9.
- 2341 74. Tapson VF. Overview of the treatment, prognosis, and follow-up of acute pulmonary
2342 embolism in adults. In: Post TW, editor. *UpToDate* [Internet]. Waltham (MA):
2343 UpToDate; 2016 Jul 19 [cited 2016 Jul 27]. Available from:
2344 [http://www.uptodate.com/contents/overview-of-the-treatment-prognosis-and-follow-up-](http://www.uptodate.com/contents/overview-of-the-treatment-prognosis-and-follow-up-of-acute-pulmonary-embolism-in-adults)
2345 [of-acute-pulmonary-embolism-in-adults](http://www.uptodate.com/contents/overview-of-the-treatment-prognosis-and-follow-up-of-acute-pulmonary-embolism-in-adults)
- 2346 75. PRESS peer review electronic search strategies: 2015 guideline explanation and
2347 elaboration (PRESS E&E) [Internet]. Ottawa: CADTH; 2016 Jan. [cited 2016 Sep 13].
2348 (CADTH methods and guidelines). Available from:
2349 https://www.cadth.ca/sites/default/files/pdf/CP0015_PRESS_Update_Report_2016.pdf
- 2350 76. Whiting P, Savovic J, Higgins JP, Caldwell DM, Reeves BC, Shea B, et al. ROBIS: A
2351 new tool to assess risk of bias in systematic reviews was developed. *J Clin Epidemiol*
2352 [Internet]. 2016 Jan [cited 2016 Jul 27];69:225-34. Available from:
2353 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4687950>
- 2354 77. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al.
2355 QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies.
2356 *Ann Intern Med*. 2011 Oct 18;155(8):529-36.
- 2357 78. Higgins JPT, Green S, editors. *Cochrane handbook for systematic reviews of*
2358 *interventions* [Internet]. Version 5.1.0. London (England): The Cochrane Collaboration;
2359 2011 Mar. 8: Assessing risk of bias in included studies. [cited 2016 Jul 27]. Available
2360 from:
2361 http://handbook.cochrane.org/chapter_8/8_assessing_risk_of_bias_in_included_studies.htm
2362
- 2363 79. Sterne JAC, Higgins JPT, Reeves BC, on behalf of the development group. The
2364 ROBINS-I tool (Risk of bias in non-randomized studies - of Interventions) [Internet].
2365 [Oxford, United Kingdom]: The Cochrane Collaboration. 2016 Mar [cited 2016 Jul 27].
2366 Available from: <http://www.riskofbias.info>

- 2367 80. Moga C, Guo B, Schopflocher D, Harstall C. Development of a quality appraisal tool
2368 for case series studies using a modified Delphi technique [Internet]. Edmonton (AB):
2369 Institute of Health Economics; 2012 Mar 7. [cited 2017 Aug 29]. Available from:
2370 [https://www.ihe.ca/publications/development-of-a-quality-appraisal-tool-for-case-](https://www.ihe.ca/publications/development-of-a-quality-appraisal-tool-for-case-series-studies-using-a-modified-delphi-technique)
2371 [series-studies-using-a-modified-delphi-technique](https://www.ihe.ca/publications/development-of-a-quality-appraisal-tool-for-case-series-studies-using-a-modified-delphi-technique)
- 2372 81. Macaskill P, Gatsonis C, Deeks J, Harbord R, Takwoingi Y. Cochrane handbook for
2373 systematic reviews of diagnostic test accuracy [Internet]. Version 1.0. London: The
2374 Cochrane Collaboration; 2010. Chapter 10. Analysing and presenting results. [cited
2375 2016 Aug 9]. Available from:
2376 [http://methods.cochrane.org/sdt/sites/methods.cochrane.org/sdt/files/uploads/Chapter](http://methods.cochrane.org/sdt/sites/methods.cochrane.org/sdt/files/uploads/Chapter%2010%20-%20Version%201.0.pdf)
2377 [%2010%20-%20Version%201.0.pdf](http://methods.cochrane.org/sdt/sites/methods.cochrane.org/sdt/files/uploads/Chapter%2010%20-%20Version%201.0.pdf)
- 2378 82. Dendukuri N, Schiller I, Joseph L, Pai M. Bayesian meta-analysis of the accuracy of a
2379 test for tuberculous pleuritis in the absence of a gold standard reference. Biometrics
2380 [Internet]. 2012 Dec [cited 2016 Jul 27];68(4):1285-93. Available from:
2381 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3728030>
- 2382 83. Spiegelhalter DJ, Best NG, Carlin BP, van der Linde A. Bayesian measures of model
2383 complexity and fit (with discussion). J R Statist Soc B. 2002;64(Part 4):583-639.
- 2384 84. Zhou M, Hu Y, Long X, Liu D, Liu L, Dong C, et al. Diagnostic performance of
2385 magnetic resonance imaging for acute pulmonary embolism: a systematic review and
2386 meta-analysis. J Thromb Haemost. 2015 Sep;13(9):1623-34.
- 2387 85. Squizzato A, Pomero F, Allione A, Priotto R, Riva N, Huisman MV, et al. Diagnostic
2388 accuracy of magnetic resonance imaging in patients with suspected pulmonary
2389 embolism: a bivariate meta-analysis. Thromb Res. 2017 Apr 7;154:64-72.
- 2390 86. Squizzato A, Rancan E, Dentali F, Bonzini M, Guasti L, Steidl L, et al. Diagnostic
2391 accuracy of lung ultrasound for pulmonary embolism: a systematic review and meta-
2392 analysis. J Thromb Haemost. 2013 Jul;11(7):1269-78.
- 2393 87. Rutter CM, Gatsonis CA. A hierarchical regression approach to meta-analysis of
2394 diagnostic test accuracy evaluations. Stat Med. 2001 Oct 15;20(19):2865-84.
- 2395 88. Sinclair A, Xie X, Teltscher M, Dendukuri N. Systematic review and meta-analysis of a
2396 urine-based pneumococcal antigen test for diagnosis of community-acquired
2397 pneumonia caused by Streptococcus pneumoniae. J Clin Microbiol [Internet]. 2013 Jul
2398 [cited 2016 Jul 27];51(7):2303-10. Available from:
2399 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3697702>
- 2400 89. Novielli N, Sutton AJ, Cooper NJ. Meta-analysis of the accuracy of two diagnostic tests
2401 used in combination: application to the ddimer test and the wells score for the
2402 diagnosis of deep vein thrombosis. Value Health. 2013 Jun;16(4):619-28.
- 2403 90. Novielli N, Cooper NJ, Sutton AJ. Evaluating the cost-effectiveness of diagnostic tests
2404 in combination: is it important to allow for performance dependency? Value Health.
2405 2013 Jun;16(4):536-41.

- 2406 91. The R project for statistical computing [Internet]. Vienna: R Foundation; 2016. [cited
2407 2016 Aug 9]. Available from: <https://www.r-project.org/>
- 2408 92. Lunn DJ, Thomas A, Best N, Spiegelhalter D. WinBUGS - A Bayesian modelling
2409 framework: concepts, structure, and extensibility. *Statistics and Computing*. 2000
2410 Oct;10(4):325-37.
- 2411 93. Doebler P. Mada: meta-analysis of diagnostic accuracy [Internet]. Version 0.5.7. [place
2412 unknown]: Comprehensive R Archive Network; 2015. [cited 2016 Aug 9]. Available from:
2413 <https://cran.r-project.org/web/packages/mada/index.html>
- 2414 94. Optimal strategies for the diagnosis of acute pulmonary embolism: a health technology
2415 assessment - project protocol [Internet]. Ottawa: CADTH; 2016 Sep 29. [cited 2017
2416 Jun 28]. (CADTH optimal use, vol. 6, no. 3a). Available from:
2417 [https://www.cadth.ca/optimal-strategies-diagnosis-acute-pulmonary-embolism-health-
2418 technology-assessment-project-protocol](https://www.cadth.ca/optimal-strategies-diagnosis-acute-pulmonary-embolism-health-technology-assessment-project-protocol)
- 2419 95. Higgins JP. *Cochrane handbook for systematic reviews of interventions* [Internet].
2420 Version 5.1.0. London (England): The Cochrane Collaboration; 2011. [cited 2016 Aug
2421 9]. Available from: <http://handbook.cochrane.org/>
- 2422 96. Conducting meta-analyses in R with the metafor package. *Journal of Statistical
2423 Software* [Internet]. 2010 [cited 2016 Aug 8];36(3). Available from:
2424 <https://www.jstatsoft.org/article/view/v036i03>
- 2425 97. Siccama RN, Janssen KJ, Verheijden NA, Oudega R, Bax L, van Delden JJ, et al.
2426 Systematic review: diagnostic accuracy of clinical decision rules for venous
2427 thromboembolism in elderly. *Ageing Res Rev*. 2011 Apr;10(2):304-13.
- 2428 98. van Es N, van der Hulle T, van Es J, den Exter PL, Douma RA, Goekoop RJ, et al.
2429 Wells Rule and d-Dimer testing to rule out pulmonary embolism: a systematic review
2430 and individual-patient data meta-analysis. *Ann Intern Med*. 2016 May 17.
- 2431 99. Sanders S, Doust J, Glasziou P. A systematic review of studies comparing diagnostic
2432 clinical prediction rules with clinical judgment. *PLoS ONE* [Internet].
2433 2015;10(6):e0128233. Available from:
2434 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4454557>
- 2435 100. Pernod G, Maignan M, Marlu R. Questioning the use of an age-adjusted D-dimer
2436 threshold to exclude venous thromboembolism: analysis of individual patient data from
2437 two diagnostic studies: comment. *J Thromb Haemost*. 2016;14(12):2553-4.
- 2438 101. Barnes GD, Izzo B, Conte ML, Chopra V, Holbrook A, Fagerlin A. Use of decision aids
2439 for shared decision making in venous thromboembolism: A systematic review. *Thromb
2440 Res*. 2016 Jul;143:71-5.
- 2441 102. Lu GM, Luo S, Meinel FG, McQuiston AD, Zhou CS, Kong X, et al. High-pitch
2442 computed tomography pulmonary angiography with iterative reconstruction at 80 kVp
2443 and 20 mL contrast agent volume. *Eur Radiol*. 2014 Dec;24(12):3260-8.

- 2444 103. Thieme SF, Graute V, Nikolaou K, Maxien D, Reiser MF, Hacker M, et al. Dual Energy
2445 CT lung perfusion imaging - correlation with SPECT/CT. *Eur J Radiol.* 2012;81(2):360-
2446 5.
- 2447 104. Wang F, Fang W, Lv B, Lu JG, Xiong CM, Ni XH, et al. Comparison of lung
2448 scintigraphy with multi-slice spiral computed tomography in the diagnosis of pulmonary
2449 embolism. *Clin Nucl Med.* 2009 Jul;34(7):424-7.
- 2450 105. Reinartz P, Wildberger JE, Schaefer W, Nowak B, Mahnken AH, Buell U. Tomographic
2451 imaging in the diagnosis of pulmonary embolism: a comparison between V/Q lung
2452 scintigraphy in SPECT technique and multislice spiral CT. *J Nucl Med [Internet].* 2004
2453 Sep [cited 2016 Dec 1];45(9):1501-8. Available from:
2454 <http://iv.iarjournals.org/content/19/5/873.long>
- 2455 106. Winer-Muram HT, Rydberg J, Johnson MS, Tarver RD, Williams MD, Shah H, et al.
2456 Suspected acute pulmonary embolism: evaluation with multi-detector row CT versus
2457 digital subtraction pulmonary arteriography. *Radiology [Internet].* 2004 Dec [cited 2016
2458 Dec 1];233(3):806-15. Available from:
2459 <http://pubs.rsna.org/doi/pdf/10.1148/radiol.2333031744>
- 2460 107. Nilsson T, Soderberg M, Lundqvist G, Cederlund K, Larsen F, Rasmussen E, et al. A
2461 comparison of spiral computed tomography and latex agglutination D-dimer assay in
2462 acute pulmonary embolism using pulmonary arteriography as gold standard. *Scand
2463 Cardiovasc J.* 2002 Dec;36(6):373-7.
- 2464 108. Qanadli SD, Hajjam ME, Mesurole B, Barre O, Bruckert F, Joseph T, et al. Pulmonary
2465 embolism detection: prospective evaluation of dual-section helical CT versus selective
2466 pulmonary arteriography in 157 patients. *Radiology [Internet].* 2000 Nov [cited 2016
2467 Dec 1];217(2):447-55. Available from:
2468 <http://pubs.rsna.org/doi/pdf/10.1148/radiology.217.2.r00nv01447>
- 2469 109. Coche E, Verschuren F, Keyeux A, Goffette P, Goncette L, Hainaut P, et al. Diagnosis
2470 of acute pulmonary embolism in outpatients: comparison of thin-collimation multi-
2471 detector row spiral CT and planar ventilation-perfusion scintigraphy. *Radiology
2472 [Internet].* 2003 Dec [cited 2016 Dec 1];229(3):757-65. Available from:
2473 <http://pubs.rsna.org/doi/pdf/10.1148/radiol.2293020889>
- 2474 110. Mahdavi R, Caronia J, Fayyaz J, Panagopoulos G, Lessnau KD, Scharf SC, et al.
2475 Agreement between SPECT V/Q scan and CT angiography in patients with high
2476 clinical suspicion of PE. *Ann Nucl Med.* 2013 Nov;27(9):834-8.
- 2477 111. Gutte H, Mortensen J, Jensen CV, Johnbeck CB, von der RP, Petersen CL, et al.
2478 Detection of pulmonary embolism with combined ventilation-perfusion SPECT and low-
2479 dose CT: head-to-head comparison with multidetector CT angiography. *J Nucl Med
2480 [Internet].* 2009 Dec [cited 2016 Oct 12];50(12):1987-92. Available from:
2481 <http://jnm.snmjournals.org/content/50/12/1987.full.pdf+html>
- 2482 112. Okada M, Kunihiro Y, Nakashima Y, Nomura T, Kudomi S, Yonezawa T, et al. Added
2483 value of lung perfused blood volume images using dual-energy CT for assessment of
2484 acute pulmonary embolism. *Eur J Radiol.* 2015 Jan;84(1):172-7.

- 2485 113. Megyeri B, Christe A, Schindera ST, Horkay E, Sikula J, Cullmann JL, et al. Accuracy
2486 of computed tomography angiography in the detection of pulmonary embolism in
2487 patients with high body weight. *Eur J Intern Med.* 2014 Oct;25(8):724-30.
- 2488 114. He J, Wang F, Dai HJ, Li M, Wang Q, Yao Z, et al. Chinese multi-center study of lung
2489 scintigraphy and CT pulmonary angiography for the diagnosis of pulmonary embolism.
2490 *Int J Cardiovasc Imaging.* 2012 Oct;28(7):1799-805.
- 2491 115. Blachere H, Latrabe V, Montaudon M, Valli N, Couffinhal T, Raheerisson C, et al.
2492 Pulmonary embolism revealed on helical CT angiography: comparison with ventilation-
2493 perfusion radionuclide lung scanning. *AJR Am J Roentgenol* [Internet]. 2000 Apr [cited
2494 2017 Jan 16];174(4):1041-7. Available from:
2495 <http://www.ajronline.org/doi/pdf/10.2214/ajr.174.4.1741041>
- 2496 116. Stein PD, Beemath A, Quinn DA, Olson RE, Goodman LR, Gottschalk A, et al.
2497 Usefulness of multidetector spiral computed tomography according to age and gender
2498 for diagnosis of acute pulmonary embolism. *Am J Cardiol.* 2007 May 1;99(9):1303-5.
- 2499 117. Gupta A, Raja AS, Khorasani R. Examining clinical decision support integrity: is
2500 clinician self-reported data entry accurate? *J Am Med Inform Assoc* [Internet]. 2014
2501 Jan [cited 2016 Oct 4];21(1):23-6. Available from:
2502 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3912709>
- 2503 118. Kearon C, Ginsberg JS, Douketis J, Turpie AG, Bates SM, Lee AY, et al. An evaluation
2504 of D-dimer in the diagnosis of pulmonary embolism: a randomized trial. *Ann Intern
2505 Med.* 2006 Jun 6;144(11):812-21.
- 2506 119. Li H, Cheng Y, Liu B, Lv Y, Guo Y, Wang G, et al. Diagnostic value of three-
2507 dimensional contrast-enhanced MR pulmonary angiography with liver acquisition
2508 volume acceleration sequence on a 3-T MR system for acute pulmonary embolism.
2509 *International Journal of Clinical and Experimental Medicine* [Internet]. 2017 [cited 2017
2510 Feb 16];10(1):872-80. Available from: <http://www.ijcem.com/files/ijcem0038614.pdf>
- 2511 120. Pasin L, Zanon M, Moreira J, Moreira AL, Watte G, Marchiori E, et al. Magnetic
2512 resonance imaging of pulmonary embolism: diagnostic accuracy of unenhanced MR
2513 and influence in mortality rates. *Lung.* 2017 Jan 23.
- 2514 121. Nyrén S, Nordgren Rogberg A, Vargas Paris R, Bengtsson B, Westerlund E, Lindholm
2515 P. Detection of pulmonary embolism using repeated MRI acquisitions without
2516 respiratory gating: a preliminary study. *Acta Radiol.* 2016 Jun 6.
- 2517 122. Zhang LJ, Luo S, Yeh BM, Zhou CS, Tang CX, Zhao Y, et al. Diagnostic accuracy of
2518 three-dimensional contrast-enhanced MR angiography at 3-T for acute pulmonary
2519 embolism detection: comparison with multidetector CT angiography. *Int J Cardiol.*
2520 2013 Oct 12;168(5):4775-83.
- 2521 123. Revel MP, Sanchez O, Lefort C, Meyer G, Couchon S, Hernigou A, et al. Diagnostic
2522 accuracy of unenhanced, contrast-enhanced perfusion and angiographic MRI
2523 sequences for pulmonary embolism diagnosis: results of independent sequence
2524 readings. *Eur Radiol.* 2013 Sep;23(9):2374-82.

- 2525 124. Revel MP, Sanchez O, Couchon S, Planquette B, Hernigou A, Niarra R, et al.
2526 Diagnostic accuracy of magnetic resonance imaging for an acute pulmonary
2527 embolism: results of the 'IRM-EP' study. *J Thromb Haemost* [Internet]. 2012 May [cited
2528 2017 Feb 8];10(5):743-50. Available from:
2529 <http://onlinelibrary.wiley.com/doi/10.1111/j.1538-7836.2012.04652.x/epdf>
- 2530 125. Kluge A, Luboldt W, Bachmann G. Acute pulmonary embolism to the subsegmental
2531 level: diagnostic accuracy of three MRI techniques compared with 16-MDCT. *AJR Am*
2532 *J Roentgenol* [Internet]. 2006 Jul [cited 2016 Oct 31];187(1):W7-14. Available from:
2533 <http://www.ajronline.org/doi/pdf/10.2214/AJR.04.1814>
- 2534 126. Grist TM, Sostman HD, MacFall JR, Foo TK, Spritzer CE, Witty L, et al. Pulmonary
2535 angiography with MR imaging: preliminary clinical experience. *Radiology*. 1993
2536 Nov;189(2):523-30.
- 2537 127. Oudkerk M, van Beek EJ, Wielopolski P, van Ooijen PM, Brouwers-Kuyper EM,
2538 Bongaerts AH, et al. Comparison of contrast-enhanced magnetic resonance
2539 angiography and conventional pulmonary angiography for the diagnosis of pulmonary
2540 embolism: a prospective study. *Lancet*. 2002 May 11;359(9318):1643-7.
- 2541 128. Gupta A, Frazer CK, Ferguson JM, Kumar AB, Davis SJ, Fallon MJ, et al. Acute
2542 pulmonary embolism: diagnosis with MR angiography. *Radiology*. 1999
2543 Feb;210(2):353-9.
- 2544 129. Meaney JF, Weg JG, Chenevert TL, Stafford-Johnson D, Hamilton BH, Prince MR.
2545 Diagnosis of pulmonary embolism with magnetic resonance angiography. Abstract
2546 presented at: 1997 May 15. Department of Internal Medicine, University of Michigan
2547 Hospitals, Ann Arbor 48109, USA.
- 2548 130. Stein PD, Chenevert TL, Fowler SE, Goodman LR, Gottschalk A, Hales CA, et al.
2549 Gadolinium-enhanced magnetic resonance angiography for pulmonary embolism: a
2550 multicenter prospective study (PIOPED III). *Ann Intern Med* [Internet]. 2010 Apr 6
2551 [cited 2016 Oct 4];152(7):434-43. Available from:
2552 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3138428>
- 2553 131. Ohno Y, Higashino T, Takenaka D, Sugimoto K, Yoshikawa T, Kawai H, et al. MR
2554 angiography with sensitivity encoding (SENSE) for suspected pulmonary embolism:
2555 comparison with MDCT and ventilation-perfusion scintigraphy. *AJR Am J Roentgenol*
2556 [Internet]. 2004 Jul [cited 2016 Dec 1];183(1):91-8. Available from:
2557 <http://www.ajronline.org/doi/pdf/10.2214/ajr.183.1.1830091>
- 2558 132. Erdman WA, Peshock RM, Redman HC, Bonte F, Meyerson M, Jayson HT, et al.
2559 Pulmonary embolism: comparison of MR images with radionuclide and angiographic
2560 studies. *Radiology*. 1994 Feb;190(2):499-508.
- 2561 133. Pleszewski B, Chartrand-Lefebvre C, Qanadli SD, Déry R, Perreault P, Oliva VL, et al.
2562 Gadolinium-enhanced pulmonary magnetic resonance angiography in the diagnosis of
2563 acute pulmonary embolism: a prospective study on 48 patients. *Clin Imaging*. 2006
2564 May;30(3):166-72.

- 2565 134. Abootalebi A, Golshani K, Karami M, Masoumi B, Aliasgharlou M. Diagnostic validity of
2566 ultrasonography in evaluation of pulmonary thromboembolism. *Adv Biomed Res*
2567 [Internet]. 2016 [cited 2016 Oct 4];5:4. Available from:
2568 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4763566>
- 2569 135. Nazerian P, Vanni S, Volpicelli G, Gigli C, Zanobetti M, Bartolucci M, et al. Accuracy of
2570 point-of-care multiorgan ultrasonography for the diagnosis of pulmonary embolism.
2571 *Chest*. 2014 May;145(5):950-7.
- 2572 136. Comert SS, Caglayan B, Akturk U, Fidan A, Kiral N, Parmaksiz E, et al. The role of
2573 thoracic ultrasonography in the diagnosis of pulmonary embolism. *Ann Thorac Med*
2574 [Internet]. 2013 Apr [cited 2016 Oct 4];8(2):99-104. Available from:
2575 http://www.thoracicmedicine.org/temp/AnnThoracMed8299-5029393_135813.pdf
- 2576 137. Pfeil A, Reissig A, Heyne JP, Wolf G, Kaiser WA, Kroegel C, et al. Transthoracic
2577 sonography in comparison to multislice computed tomography in detection of
2578 peripheral pulmonary embolism. *Lung*. 2010 Jan;188(1):43-50.
- 2579 138. Reißig A, Heyne JP, Kroegel C. Ancillary lung parenchymal findings at spiral CT
2580 scanning in pulmonary embolism. Relationship to chest sonography. *Eur J Radiol*.
2581 2004 Mar;49(3):250-7.
- 2582 139. Mohn K, Quiot JJ, Nonent M, Lacut K, Le Gall G, Couturaud F, et al. Transthoracic
2583 sonography of the lung and pleura in view of a suspected pulmonary embolism: a pilot
2584 study. *J Ultrasound Med* [Internet]. 2003 Jul [cited 2016 Dec 1];22(7):673-8. Available
2585 from: <http://www.jultrasoundmed.org/content/22/7/673.full.pdf+html>
- 2586 140. Lechleitner P, Riedl B, Raneburger W, Gamper G, Theurl A, Lederer A. Chest
2587 sonography in the diagnosis of pulmonary embolism: a comparison with MRI
2588 angiography and ventilation perfusion scintigraphy. *Ultraschall Med*. 2002
2589 Dec;23(6):373-8.
- 2590 141. Reissig A, Heyne JP, Kroegel C. Sonography of lung and pleura in pulmonary
2591 embolism: sonomorphologic characterization and comparison with spiral CT scanning.
2592 *Chest*. 2001 Dec;120(6):1977-83.
- 2593 142. Mathis G, Metzler J, Fussenegger D, Sutterlutti G, Feurstein M, Fritzsche H.
2594 Sonographic observation of pulmonary infarction and early infarctions by pulmonary
2595 embolism. *Eur Heart J*. 1993 Jun [cited 2016 Dec 1];14(6):804-8.
- 2596 143. Lechleitner P, Raneburger W, Gamper G, Riedl B, Benedikt E, Theurl A. Lung
2597 sonographic findings in patients with suspected pulmonary embolism. *Ultraschall Med*.
2598 1998 Apr;19(2):78-82.
- 2599 144. Kim PS, Gasparis AP, Probeck K, Elitharp D, Tassiopoulos A, Labropoulos N.
2600 Accuracy of venous thromboembolism assessment and compliance to prophylaxis in a
2601 tertiary care center. *Phlebology*. 2016;31(8):541-5.
- 2602 145. Watanabe N, Fettich J, Kucuk NO, Kraft O, Mut F, Choudhury P, et al. Modified
2603 PISAPED criteria in combination with ventilation scintigraphic finding for predicting
2604 acute pulmonary embolism. *World J Nucl Med* [Internet]. 2015 Sep [cited 2016 Oct

- 2605 4];14(3):178-83. Available from: http://www.wjnm.org/temp/WorldJNuclMed143178-4442071_122020.pdf
2606
- 2607 146. Skarlovnik A, Hrastnik D, Fettich J, Grmek M. Lung scintigraphy in the diagnosis of
2608 pulmonary embolism: Current methods and interpretation criteria in clinical practice.
2609 Radiol Oncol [Internet]. 2014 [cited 2016 Oct 7];48(2):113-9. Available from:
2610 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4078029/pdf/rado-48-02-113.pdf>
- 2611 147. Tondeur MC, Mols PG, Ham HR. Is the perfusion lung-scan still useful for the
2612 diagnosis approach towards lung embolism suspicion in the emergency department?
2613 JEUR. 2007;20(4):153-7.
- 2614 148. Lu Y, Lorenzoni A, Fox JJ, Rademaker J, Vander Els N, Grewal RK, et al. Noncontrast
2615 perfusion single-photon emission CT/CT scanning: a new test for the expedited, high-
2616 accuracy diagnosis of acute pulmonary embolism. Chest. 2014 May;145(5):1079-88.
- 2617 149. Sostman HD, Miniati M, Gottschalk A, Matta F, Stein PD, Pistolesi M. Sensitivity and
2618 specificity of perfusion scintigraphy combined with chest radiography for acute
2619 pulmonary embolism in PIOPED II. J Nucl Med [Internet]. 2008 Nov [cited 2016 Oct
2620 7];49(11):1741-8. Available from:
2621 <http://jnm.snmiournals.org/content/49/11/1741.full.pdf+html>
- 2622 150. Rubini G, Niccoli AA, Stabile Ianora AA, Rubini D, Gaudio A, Angelelli G, et al.
2623 Acute pulmonary embolism: comparison and integration of perfusion lung scintigraphy
2624 with multislice spiral CT. Radiol Med (Torino). 2007 Mar;112(2):174-84.
- 2625 151. Mazurek A, Dziuk M, Witkowska-Patena E, Piszczek S, Gizewska A. The Utility of
2626 Hybrid SPECT/CT Lung Perfusion Scintigraphy in Pulmonary Embolism Diagnosis.
2627 Respiration. 2015;90(5):393-401.
- 2628 152. van Es J, Douma RA, Hezemans REL, Penaloza A, Motte S, Erkens PGM, et al.
2629 Accuracy of X-ray with perfusion scan in young patients with suspected pulmonary
2630 embolism. Thromb Res. 2015;136(2):221-4.
- 2631 153. Miniati M, Pistolesi M, Marini C, Di Ricco G, Formichi B, Prediletto R, et al. Value of
2632 perfusion lung scan in the diagnosis of pulmonary embolism: results of the Prospective
2633 Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA-PED). Am J Respir
2634 Crit Care Med. 1996 Nov;154(5):1387-93.
- 2635 154. Casals-Sole J, Bernaudo D, Camp J, Lozano N, Ballester E, Escolar G. A normal D-
2636 Dimer value, measured by a high sensitivity assay, rule out a suspected Venous
2637 Thromboembolism episode independently of pretest clinical probability [abstract].
2638 Haematologica. 2009;94:408-9. (Presented at 14th Congress of the European
2639 Hematology Association; 2009 Jun 4-7; Berlin, Germany).
- 2640 155. Bajc M, Miniati M, Jogi J, Stein PD. Perfusion SPECT in patients with suspected
2641 pulmonary embolism. European Journal of Nuclear Medicine and Molecular Imaging.
2642 2013;40(9):1432-7.
- 2643 156. Le Roux PY, Robin P, Delluc A, Abgral R, Palard X, Tissot V, et al. Additional value of
2644 combining low-dose computed tomography to V/Q SPECT on a hybrid SPECT-CT

- 2645 camera for pulmonary embolism diagnosis. Nucl Med Commun. 2015 Sep;36(9):922-
2646 30.
- 2647 157. Kumar N, Xie K, Mar W, Anderson TM, Carney B, Mehta N, et al. Software-based
2648 hybrid perfusion SPECT/CT provides diagnostic accuracy when other pulmonary
2649 embolism imaging is indeterminate. Nucl Med Mol Imaging. 2015 Dec;49(4):303-11.
- 2650 158. Gutte H, Mortensen J, Jensen CV, von der Recke P, Petersen CL, Kristoffersen US, et
2651 al. Comparison of V/Q SPECT and planar V/Q lung scintigraphy in diagnosing acute
2652 pulmonary embolism. Nucl Med Commun. 2010 Jan;31(1):82-6.
- 2653 159. PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary
2654 embolism. Results of the prospective investigation of pulmonary embolism diagnosis
2655 (PIOPED). JAMA. 1990 May 23;263(20):2753-9.
- 2656 160. Collart JP, Roelants V, Vanpee D, Lacrosse M, Trigaux JP, Delaunois L, et al. Is a
2657 lung perfusion scan obtained by using single photon emission computed tomography
2658 able to improve the radionuclide diagnosis of pulmonary embolism? Nucl Med
2659 Commun. 2002 Nov;23(11):1107-13.
- 2660 161. Gray HW, McKillop JH, Bessent RG, Fogelman I, Smith ML, Moran F. Lung scanning
2661 for pulmonary embolism: clinical and pulmonary angiographic correlations. Poster
2662 presented at: 1990 Nov. Department of Nuclear Medicine, Royal Infirmary, Glasgow.
- 2663 162. Woods ER, Iles S, Jackson S. Comparison of scintigraphic diagnostic criteria in
2664 suspected pulmonary embolism. Can Assoc Radiol J. 1989 Aug;40(4):194-7.
- 2665 163. Sostman HD, Stein PD, Gottschalk A, Matta F, Hull R, Goodman L. Acute pulmonary
2666 embolism: sensitivity and specificity of ventilation-perfusion scintigraphy in PIOPED II
2667 study. Radiology [Internet]. 2008 Mar [cited 2016 Nov 16];246(3):941-6. Available
2668 from: <http://pubs.rsna.org/doi/pdf/10.1148/radiol.2463070270>
- 2669 164. Stein PD, Terrin ML, Gottschalk A, Alavi A, Henry JW. Value of ventilation/perfusion
2670 scans versus perfusion scans alone in acute pulmonary embolism. Am J Cardiol. 1992
2671 May 1;69(14):1239-41.
- 2672 165. Quirce R, Ibanez-Bravo S, Jimenez-Bonilla J, Martinez-Rodriguez I, Martinez-Amador
2673 N, Ortega-Nava F, et al. Contribution of V/Q SPECT to planar scintigraphy in the
2674 diagnosis of pulmonary embolism. Rev Esp Med Nucl Imagen Mol [Internet]. 2014 May
2675 [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>
- 2676
2677
- 2678 166. Le Duc-Pennec A, Le Roux PY, Cornily JC, Jaffrelot M, Delluc A, de Saint-Martin L, et
2679 al. Diagnostic accuracy of single-photon emission tomography ventilation/perfusion
2680 lung scan in the diagnosis of pulmonary embolism. Chest. 2012 Feb;141(2):381-7.
- 2681 167. Miles S, Rogers KM, Thomas P, Soans B, Attia J, Abel C, et al. A comparison of
2682 single-photon emission CT lung scintigraphy and CT pulmonary angiography for the
2683 diagnosis of pulmonary embolism. Chest. 2009 Dec;136(6):1546-53.

- 2684 168. Bajc M, Olsson B, Palmer J, Jonson B. Ventilation/Perfusion SPECT for diagnostics of
2685 pulmonary embolism in clinical practice. *J Intern Med.* 2008 Oct;264(4):379-87.
- 2686 169. Harris B, Bailey D, Miles S, Bailey E, Rogers K, Roach P, et al. Objective analysis of
2687 tomographic ventilation-perfusion scintigraphy in pulmonary embolism. *Am J Respir
2688 Crit Care Med.* 2007 Jun 1;175(11):1173-80.
- 2689 170. Reinartz P, Kaiser HJ, Wildberger JE, Gordji C, Nowak B, Buell U. SPECT imaging in
2690 the diagnosis of pulmonary embolism: automated detection of match and mismatch
2691 defects by means of image-processing techniques. *J Nucl Med [Internet].* 2006 Jun
2692 [cited 2016 Oct 13];47(6):968-73. Available from:
2693 <http://jnm.snmjournals.org/content/47/6/968.full.pdf+html>
- 2694 171. Weinmann P, Moretti JL, Brauner MW. Usefulness of tomographic versus planar lung
2695 scintigraphy in suspected pulmonary embolism in a daily practice. *The Open Medical
2696 Imaging Journal [Internet].* 2008 [cited 2016 Oct 21];9(2):49-55. Available from:
2697 <http://benthamopen.com/contents/pdf/TOMIJ/TOMIJ-2-49.pdf>
- 2698 172. Ibáñez-Bravo S, Banzo I, Quirce R, Martínez-Rodríguez I, Jiménez-Bonilla J,
2699 Martínez-Amador N, et al. Ventilation/Perfusion SPECT lung scintigraphy and
2700 computed tomography pulmonary angiography in patients with clinical suspicion of
2701 pulmonary embolism. *Revista Espanola de Medicina Nuclear e Imagen Molecular.*
2702 2016;35(4):215-20.
- 2703 173. Bajc M, Olsson CG, Olsson B, Palmer J, Jonson B. Diagnostic evaluation of planar
2704 and tomographic ventilation/perfusion lung images in patients with suspected
2705 pulmonary emboli. *Clin Physiol Funct Imaging.* 2004 Sep;24(5):249-56.
- 2706 174. Bhatia KD, Ambati C, Dhaliwal R, Paschkewitz R, Hsu E, Ho B, et al. SPECT-CT/VQ
2707 versus CTPA for diagnosing pulmonary embolus and other lung pathology: Pre-
2708 existing lung disease should not be a contraindication. *J Med Imaging Radiat Oncol.*
2709 2016 Aug;60(4):492-7.
- 2710 175. Ling IT, Naqvi HA, Siew TK, Loh NK, Ryan GF. SPECT ventilation perfusion scanning
2711 with the addition of low-dose CT for the investigation of suspected pulmonary
2712 embolism. *Intern Med J.* 2012 Nov;42(11):1257-61.
- 2713 176. Bosson JL, Pernod G, Joubin E, Hamidfar R, Bricault I, Hugon V, et al. Non-conform
2714 diagnostic management of pulmonary embolism suspected patients is responsible for
2715 a higher risk of thrombotic event occurrence. *J Mal Vasc.* 2007;32(1):15-22.
- 2716 177. Galipienzo J, Garcia de Tena J, Flores J, Alvarez C, Garcia-Avello A, Arribas I.
2717 Effectiveness of a diagnostic algorithm combining clinical probability, D-dimer testing,
2718 and computed tomography in patients with suspected pulmonary embolism in an
2719 emergency department. *Rom J Intern Med.* 2012 Jul;50(3):195-202.
- 2720 178. Ghanima W, Almaas V, Aballi S, Dorje C, Nielssen BE, Holmen LO, et al.
2721 Management of suspected pulmonary embolism (PE) by D-dimer and multi-slice
2722 computed tomography in outpatients: an outcome study. *J Thromb Haemost.* 2005
2723 Sep;3(9):1926-32.

- 2724 179. Hogg K, Dawson D, kway-Jones K. Outpatient diagnosis of pulmonary embolism: the
2725 MIOPED (Manchester Investigation Of Pulmonary Embolism Diagnosis) study. *Emerg*
2726 *Med J* [Internet]. 2006 Feb [cited 2016 Oct 13];23(2):123-7. Available from:
2727 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2564034>
- 2728 180. Jouveshomme S, Bohn I, Cazaban A. Diagnosis of pulmonary embolism in
2729 hospitalised patients: retrospective survey of an institutional standard. *Eur Respir J*
2730 [Internet]. 2007 Dec [cited 2016 Oct 6];30(6):1117-23. Available from:
2731 <http://erj.ersjournals.com/content/erj/30/6/1117.full.pdf>
- 2732 181. Miniati M, Monti S, Bauleo C, Scoscia E, Tonelli L, Dainelli A, et al. A diagnostic
2733 strategy for pulmonary embolism based on standardised pretest probability and
2734 perfusion lung scanning: a management study. *Eur J Nucl Med Mol Imaging*. 2003
2735 Nov;30(11):1450-6.
- 2736 182. Miron MJ, Perrier A, Bounameaux H, de Moerloose P, Slosman DO, Didier D, et al.
2737 Contribution of noninvasive evaluation to the diagnosis of pulmonary embolism in
2738 hospitalized patients. *Eur Respir J* [Internet]. 1999 Jun [cited 2016 Dec 6];13(6):1365-
2739 70. Available from: <http://erj.ersjournals.com/content/erj/13/6/1365.full.pdf>
- 2740 183. Perrier A, Roy PM, Sanchez O, Le Gal G, Meyer G, Gourcier AL, et al. Multidetector-
2741 row computed tomography in suspected pulmonary embolism. *N Engl J Med* [Internet].
2742 2005 Apr 28;352(17):1760-8. Available from:
2743 <http://www.nejm.org/doi/pdf/10.1056/NEJMoa042905>
- 2744 184. Vigo M, Pesavento R, Bova C, Porro F, Ghirarduzzi A, Bazzan M, et al. The value of
2745 four-detector row spiral computed tomography for the diagnosis of pulmonary
2746 embolism. *Semin Thromb Hemost*. 2006 Nov;32(8):831-7.
- 2747 185. Righini M, Le Gal G, Aujesky D, Roy PM, Sanchez O, Verschuren F, et al. Diagnosis
2748 of pulmonary embolism by multidetector CT alone or combined with venous
2749 ultrasonography of the leg: a randomised non-inferiority trial. *Lancet*. 2008 Apr
2750 19;371(9621):1343-52.
- 2751 186. Galipienzo J, Garcia de Tena J, Flores J, Álvarez C, Alonso-Viteri S, Ruiz A. Safety of
2752 withholding anticoagulant therapy in patients with suspected pulmonary embolism with
2753 a negative multislice computed tomography pulmonary angiography. *Eur J Intern Med*.
2754 2010 Aug;21(4):283-8.
- 2755 187. Bourriot K, Couffinhal T, Bernard V, Montaudon M, Bonnet J, Laurent F. Clinical
2756 outcome after a negative spiral CT pulmonary angiographic finding in an inpatient
2757 population from cardiology and pneumology wards. *Chest*. 2003 Feb;123(2):359-65.
- 2758 188. Donato AA, Scheirer JJ, Atwell MS, Gramp J, Duszak R. Clinical outcomes in patients
2759 with suspected acute pulmonary embolism and negative helical computed tomographic
2760 results in whom anticoagulation was withheld. *Arch Intern Med*. 2003 Sep
2761 22;163(17):2033-8.
- 2762 189. Gimber LH, Travis RI, Takahashi JM, Goodman TL, Yoon HC. Computed tomography
2763 angiography in patients evaluated for acute pulmonary embolism with low serum D-

- 2764 dimer levels: a prospective study. *Perm J* [Internet]. 2009 [cited 2016 Oct 6];13(4):4-
2765 10. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2911823>
- 2766 190. Hantous-Zannad S, Esseghaier S, Ridène I, Zidi A, Ben Romdhane K, Baccouche I, et
2767 al. Acute pulmonary embolism: epidemiologic and tomodensitometric study. *Tunis*
2768 *Med*. 2010 Dec;88(12):880-4.
- 2769 191. Huisman MV. Effectiveness of managing suspected pulmonary embolism using an
2770 algorithm combining clinical probability, D-dimer testing, and computed tomography.
2771 *JAMA*. 2006;295(2):172-9.
- 2772 192. Meier A, Higashigaito K, Martini K, Wurnig M, Seifert B, Keller D, et al. Dual energy CT
2773 pulmonary angiography with 6g iodine-A propensity score-matched study. *PLoS ONE*
2774 [Internet]. 2016 [cited 2016 Jan 4];11(12):e0167214. Available from:
2775 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5132396/pdf/pone.0167214.pdf>
- 2776 193. Moores L, Kline J, Portillo AK, Resano S, Vicente A, Arrieta P, et al. Multidetector
2777 computed tomographic pulmonary angiography in patients with a high clinical
2778 probability of pulmonary embolism. *J Thromb Haemost*. 2016;14(1):114-20.
- 2779 194. Ost D, Rozenshtein A, Saffran L, Snider A. The negative predictive value of spiral
2780 computed tomography for the diagnosis of pulmonary embolism in patients with
2781 nondiagnostic ventilation-perfusion scans. *Am J Med*. 2001 Jan;110(1):16-21.
- 2782 195. Pérez De Llano LA, Veres Racamonde A, Ortiz Piquer M, López Diaz MJ, Janeiro
2783 Amela M, Méndez Maroto L, et al. Safety of withholding anticoagulant therapy in
2784 patients who have clinically suspected pulmonary embolism and negative results on
2785 helical computed tomography. *Respiration*. 2006;73(4):514-9.
- 2786 196. Pesavento R, De Conti G, Minotto I, Filippi L, Mongiat M, de Faveri D, et al. The value
2787 of 64-detector row computed tomography for the exclusion of pulmonary embolism.
2788 *Thromb Haemost*. 2011 May;105(5):901-7.
- 2789 197. Revel MP, Petrover D, Hernigou A, Lefort C, Meyer G, Frija G. Diagnosing pulmonary
2790 embolism with four-detector row helical CT: prospective evaluation of 216 outpatients
2791 and inpatients¹. *Radiology* [Internet]. 2005 Jan [cited 2016 Dec 8];234(1):265-73.
2792 Available from: <http://pubs.rsna.org/doi/pdf/10.1148/radiol.2341031880>
- 2793 198. Sodhi KS, Gulati M, Aggarwal R, Kalra N, Mittal BR, Jindal SK, et al. Computed
2794 tomographic pulmonary angiography: utility in acute pulmonary embolism in providing
2795 additional information and making alternative clinical diagnosis. *Indian J Med Sci*. 2010
2796 Jan;64(1):26-32.
- 2797 199. Woo JK, Chiu RY, Thakur Y, Mayo JR. Risk-benefit analysis of pulmonary CT
2798 angiography in patients with suspected pulmonary embolus. *AJR Am J Roentgenol*.
2799 2012 Jun;198(6):1332-9.
- 2800 200. Mitchell AM, Kline JA. Contrast nephropathy following computed tomography
2801 angiography of the chest for pulmonary embolism in the emergency department. *J*
2802 *Thromb Haemost*. 2007 Jan;5(1):50-4.

- 2803 201. Yazici S, Kiris T, Emre A, Ceylan US, Akyuz S, Uzun AO, et al. Relation of contrast
2804 nephropathy to adverse events in pulmonary emboli patients diagnosed with contrast
2805 CT. *Am J Emerg Med.* 2016 Jul;34(7):1247-50.
- 2806 202. Kaul D, Grupp U, Kahn J, Ghadjar P, Wiener E, Hamm B, et al. Reducing radiation
2807 dose in the diagnosis of pulmonary embolism using adaptive statistical iterative
2808 reconstruction and lower tube potential in computed tomography. *Eur Radiol.* 2014
2809 Nov;24(11):2685-91.
- 2810 203. Kluge A, Mueller C, Strunk J, Lange U, Bachmann G. Experience in 207 combined
2811 MRI examinations for acute pulmonary embolism and deep vein thrombosis. *AJR Am J*
2812 *Roentgenol* [Internet]. 2006 Jun [cited 2016 Oct 13];186(6):1686-96. Available from:
2813 <http://pubs.rsna.org/doi/pdf/10.1148/radiol.2392050118>
- 2814 204. Kyrtatos PG, Navalkisoor S, Burniston M, Wagner T. Planar images reprojected from
2815 SPECT V/Q data perform similarly to traditional planar V/Q scans in the diagnosis of
2816 pulmonary embolism. *Nucl Med Commun.* 2013 May;34(5):445-50.
- 2817 205. Leblanc M, Leveillé F, Turcotte E. Prospective evaluation of the negative predictive
2818 value of V/Q SPECT using ^{99m}Tc-Technegas. *Nucl Med Commun.* 2007
2819 Aug;28(8):667-72.
- 2820 206. Rhee KH, Iyer RS, Cha S, Naidich DP, Rusinek H, Jacobowitz GR, et al. Benefit of CT
2821 venography for the diagnosis of thromboembolic disease. *Clin Imaging.* 2007
2822 Jul;31(4):253-8.
- 2823 207. Shahir K, Goodman LR, Tali A, Thorsen KM, Hellman RS. Pulmonary embolism in
2824 pregnancy: CT pulmonary angiography versus perfusion scanning. *AJR Am J*
2825 *Roentgenol.* 2010 Sep;195(3):W214-W220.
- 2826 208. Cahill AG, Stout MJ, Macones GA, Bhalla S. Diagnosing pulmonary embolism in
2827 pregnancy using computed-tomographic angiography or ventilation-perfusion. *Obstet*
2828 *Gynecol.* 2009 Jul;114(1):124-9.
- 2829 209. Ridge CA, Mcdermott S, Freyne BJ, Brennan DJ, Collins CD, Skehan SJ. Pulmonary
2830 embolism in pregnancy: comparison of pulmonary CT angiography and lung
2831 scintigraphy. *AJR Am J Roentgenol.* 2009 Nov;193(5):1223-7.
- 2832 210. Chan WS, Ray JG, Murray S, Coady GE, Coates G, Ginsberg JS. Suspected
2833 pulmonary embolism in pregnancy: clinical presentation, results of lung scanning, and
2834 subsequent maternal and pediatric outcomes. *Arch Intern Med.* 2002 May
2835 27;162(10):1170-5.
- 2836 211. Bajc M, Olsson B, Gottsater A, Hindorf C, Jogi J. V/P SPECT as a diagnostic tool for
2837 pregnant women with suspected pulmonary embolism. *Eur J Nucl Med Mol Imaging*
2838 [Internet]. 2015 Jul [cited 2017 Mar 6];42(8):1325-30. Available from:
2839 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4480826>
- 2840 212. Browne AM, Cronin CG, NiMhuirheartaigh J, Donagh C, Morrison JJ, Lohan DG, et
2841 al. Evaluation of imaging quality of pulmonary 64-MDCT angiography in pregnancy

- 2842 and puerperium. *AJR Am J Roentgenol* [Internet]. 2014 Jan [cited 2017 Mar
2843 6];202(1):60-4. Available from: <http://www.ajronline.org/doi/pdf/10.2214/AJR.12.9917>
- 2844 213. Grüning T, Mingo RE, Gosling MG, Farrell SL, Drake BE, Loader RJ, et al. Diagnosing
2845 venous thromboembolism in pregnancy. *Br J Radiol*. 2016 Jun;89(1062):20160021.
- 2846 214. Scarsbrook AF, Bradley KM, Gleeson FV. Perfusion scintigraphy: diagnostic utility in
2847 pregnant women with suspected pulmonary embolic disease. *Eur Radiol*. 2007
2848 Oct;17(10):2554-60.
- 2849 215. Bourjeily G, Khalil H, Raker C, Martin S, Auger P, Chalhoub M, et al. Outcomes of
2850 negative multidetector computed tomography with pulmonary angiography in pregnant
2851 women suspected of pulmonary embolism. *Lung*. 2012 Feb;190(1):105-11.
- 2852 216. van Mens TE, Scheres LJ, de Jong PG, Leeflang MM, Nijkeuter M, Middeldorp S.
2853 Imaging for the exclusion of pulmonary embolism in pregnancy. *Cochrane Database*
2854 *Syst Rev*. 2017 Jan 26;1:CD011053.
- 2855 217. Mila M, Bechini J, Vazquez A, Vallejos V, Tenesa M, Espinal A, et al. Acute pulmonary
2856 embolism detection with ventilation/perfusion SPECT combined with full dose CT:
2857 What is the best option? *Revista Espanola de Medicina Nuclear e Imagen Molecular*.
2858 2017;36(3):139-45.
- 2859 218. van der HT, van EN, den EP, van EJ, Mos ICM, Douma RA, et al. Is a normal
2860 computed tomography pulmonary angiography safe to rule out acute pulmonary
2861 embolism in patients with a likely clinical probability? A patient-level meta-analysis.
2862 *Thromb Haemost*. 2017 Jun 1;117(8).
- 2863 219. Pelletier-Galarneau M, Zannier E, Zuckier LS, Le GG. Referral Patterns and
2864 Diagnostic Yield of Lung Scintigraphy in the Diagnosis of Acute Pulmonary Embolism.
2865 *Thrombosis* [Internet]. 2017 [cited 2017 Jun 12]. Available from:
2866 [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5405392/pdf/THROMBOSIS2017-
2867 1623868.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5405392/pdf/THROMBOSIS2017-1623868.pdf)
- 2868 220. Raymakers AJ, Mayo J, Marra CA, FitzGerald M. Diagnostic strategies incorporating
2869 computed tomography angiography for pulmonary embolism: a systematic review of
2870 cost-effectiveness analyses. *J Thorac Imaging*. 2014 Jul;29(4):209-16.
- 2871 221. Gospodarevskaya E, V, Goergen SK, Harris AH, Chan T, de Campo JF, Wolfe R, et al.
2872 Economic evaluation of a clinical protocol for diagnosing emergency patients with
2873 suspected pulmonary embolism. *Cost Effectiveness and Resource Allocation*
2874 [Internet]. 2006 Jun 27 [cited 2016 Jul 14];4(12). Available from:
2875 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1550258/pdf/1478-7547-4-12.pdf>
- 2876 222. Hull RD, Pineo GF, Stein PD, Mah AF, Butcher MS. Cost-effectiveness of currently
2877 accepted strategies for pulmonary embolism diagnosis. *Semin Thromb Hemost*.
2878 2001;27(1):15-23.
- 2879 223. Duriseti RS, Shachter RD, Brandeau ML. Value of quantitative D-dimer assays in
2880 identifying pulmonary embolism: implications from a sequential decision model. *Acad*

- 2881 Emerg Med [Internet]. 2006 [cited 2016 Nov 17];13(7):755-66. Available from:
2882 <http://onlinelibrary.wiley.com/doi/10.1197/j.aem.2006.02.011/abstract>
- 2883 224. Duriseti RS, Brandeau ML. Cost-effectiveness of strategies for diagnosing pulmonary
2884 embolism among emergency department patients presenting with undifferentiated
2885 symptoms. Ann Emerg Med [Internet]. 2010 Oct [cited 2016 Oct 5];56(4):321-32.
2886 Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3699695>
- 2887 225. van Erkel AR, Pattynama PM. Cost-effective diagnostic algorithms in pulmonary
2888 embolism: an updated analysis. Acad Radiol. 1998 Sep;5 Suppl 2:S321-S327.
- 2889 226. van Erkel AR, van Rossum AB, Bloem JL, Kievit J, Pattynama PM. Spiral CT
2890 angiography for suspected pulmonary embolism: a cost-effectiveness analysis.
2891 Radiology. 1996 Oct;201(1):29-36.
- 2892 227. Lee JA, Zierler BK, Liu CF, Chapko MK. Cost-effective diagnostic strategies in patients
2893 with a high, intermediate, or low clinical probability of pulmonary embolism. Vasc
2894 Endovascular Surg. 2011;45(2):113-21.
- 2895 228. Righini M, Nendaz M, Gal G, Bounameaux H, Perrier A. Influence of age on the cost-
2896 effectiveness of diagnostic strategies for suspected pulmonary embolism. J Thromb
2897 Haemost [Internet]. 2007 [cited 2016 Oct 5];5(9):1869-77. Available from:
2898 <http://onlinelibrary.wiley.com/doi/10.1111/j.1538-7836.2007.02667.x/epdf>
- 2899 229. Paterson DI, Schwartzman K. Strategies incorporating spiral CT for the diagnosis of
2900 acute pulmonary embolism: a cost-effectiveness analysis. Chest. 2001
2901 Jun;119(6):1791-800.
- 2902 230. Elias A, Molinier L, Bauvin E, Elias M, Duru G, Colin C. Integrating complete lower limb
2903 venous ultrasound into diagnostic strategies for pulmonary embolism: a cost-
2904 effectiveness analysis. Thromb Haemost. 2004 Jan;91(1):205-7.
- 2905 231. Perrier A, Nendaz MR, Sarasin FP, Howarth N, Bounameaux H. Cost-effectiveness
2906 analysis of diagnostic strategies for suspected pulmonary embolism including helical
2907 computed tomography. Am J Respir Crit Care Med. 2003 Jan 1;167(1):39-44.
- 2908 232. Guidelines for the economic evaluation of health technologies: Canada [Internet]. 4th
2909 ed. Ottawa: CADTH; 2017. [cited 2017 Jun 28]. Available from:
2910 [https://www.cadth.ca/guidelines-economic-evaluation-health-technologies-canada-4th-
2911 edition](https://www.cadth.ca/guidelines-economic-evaluation-health-technologies-canada-4th-edition)
- 2912 233. Guidelines for the economic evaluation of health technologies: Canada [Internet].
2913 Ottawa: CADTH; 2006. [cited 2016 Aug 2]. Available from:
2914 https://www.cadth.ca/media/pdf/186_EconomicGuidelines_e.pdf
- 2915 234. Huisman MV, Klok FA. Diagnostic management of clinically suspected acute
2916 pulmonary embolism. J Thromb Haemost [Internet]. 2009 Jul [cited 2017 Jun 28];7
2917 Suppl 1:312-7. Available from: [http://onlinelibrary.wiley.com/doi/10.1111/j.1538-
2918 7836.2009.03386.x/pdf](http://onlinelibrary.wiley.com/doi/10.1111/j.1538-7836.2009.03386.x/pdf)

- 2919 235. Pulmonary embolism: diagnosis and management [Internet]. Hamilton (ON):
 2920 Thrombosis Canada; 2013. [cited 2017 Jun 28]. Available from:
 2921 <http://thrombosiscanada.ca/guides/pdfs/PE.pdf>
- 2922 236. Direct oral anticoagulants for the treatment of venous thromboembolic events:
 2923 economic evaluation [Internet]. Ottawa: CADTH; 2016 Mar. [cited 2016 Aug 2].
 2924 (CADTH Technology review; no. 3). Available from:
 2925 https://www.cadth.ca/sites/default/files/pdf/TR0005_DOACS_for_DVT_and_PE_Report.pdf
 2926
- 2927 237. Kabrhel C, McAfee AT, Goldhaber SZ. The contribution of the subjective component of
 2928 the Canadian Pulmonary Embolism Score to the overall score in emergency
 2929 department patients. Acad Emerg Med [Internet]. 2005 Oct [cited 2017 Jun
 2930 1];12(10):915-20. Available from:
 2931 <http://onlinelibrary.wiley.com/doi/10.1197/j.aem.2005.05.030/abstract>
- 2932 238. Chagnon I, Bounameaux H, Aujesky D, Roy PM, Gourdi er AL, Cornuz J, et al.
 2933 Comparison of two clinical prediction rules and implicit assessment among patients
 2934 with suspected pulmonary embolism. Am J Med. 2002 Sep;113(4):269-75.
- 2935 239. Carrier M, Righini M, Djurabi RK, Huisman MV, Perrier A, Wells PS, et al. VIDAS D-
 2936 dimer in combination with clinical pre-test probability to rule out pulmonary embolism.
 2937 A systematic review of management outcome studies. Thromb Haemost. 2009
 2938 May;101(5):886-92.
- 2939 240. Singh B, Mommer SK, Erwin PJ, Mascarenhas SS, Parsaik AK. Pulmonary embolism
 2940 rule-out criteria (PERC) in pulmonary embolism--revisited: a systematic review and
 2941 meta-analysis. Emerg Med J [Internet]. 2013 Sep [cited 2016 Nov 17];30(9):701-6.
 2942 Available from: <http://emj.bmj.com/content/30/9/701.full.pdf+html>
- 2943 241. Kanal KM, Butler PF, Sengupta D, Bhargavan-Chatfield M, Coombs LP, Morin RL.
 2944 U.S. Diagnostic Reference Levels and Achievable Doses for 10 Adult CT
 2945 Examinations. Radiology. 2017 Jul;284(1):120-33.
- 2946 242. Jones JG, Mills CN, Mogensen MA, Lee CI. Radiation dose from medical imaging: a
 2947 primer for emergency physicians. West J Emerg Med [Internet]. 2012 May [cited 2017
 2948 Jul 26];13(2):202-10. Available from:
 2949 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3415811>
- 2950 243. Janbabanezhad TA, Shabestani-Monfared A, Deevband MR, Abdi R, Nabahati M.
 2951 Dose Assessment in Computed Tomography Examination and Establishment of Local
 2952 Diagnostic Reference Levels in Mazandaran, Iran. J Biomed Phys Eng [Internet]. 2015
 2953 Dec [cited 2017 Aug 25];5(4):177-84. Available from:
 2954 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4681462>
- 2955 244. Leung AN, Bull TM, Jaeschke R, Lockwood CJ, Boiselle PM, Hurwitz LM, et al. An
 2956 official American Thoracic Society/Society of Thoracic Radiology clinical practice
 2957 guideline: evaluation of suspected pulmonary embolism in pregnancy. Am J Respir Crit
 2958 Care Med [Internet]. 2011 Nov 15 [cited 2017 Aug 25];184(10):1200-8. Available from:
 2959 <http://www.atsjournals.org/doi/pdf/10.1164/rccm.201108-1575ST>

- 2960 245. Life tables, Canada, provinces and territories 2009 to 2011 [Internet]. Ottawa:
2961 Statistics Canada; 2015. [cited 2017 Jun 28]. Available from:
2962 <http://www.statcan.gc.ca/pub/84-537-x/84-537-x2013005-eng.htm>
- 2963 246. Quinlan DJ, McQuillan A, Eikelboom JW. Low-molecular-weight heparin compared
2964 with intravenous unfractionated heparin for treatment of pulmonary embolism: a meta-
2965 analysis of randomized, controlled trials. *Ann Intern Med.* 2004 Feb 3;140(3):175-83.
- 2966 247. Agnelli G, Prandoni P, Becattini C, Silingardi M, Taliani MR, Miccio M, et al. Extended
2967 oral anticoagulant therapy after a first episode of pulmonary embolism. *Ann Intern*
2968 *Med.* 2003 Jul 1;139(1):19-25.
- 2969 248. BARRITT DW, JORDAN SC. Anticoagulant drugs in the treatment of pulmonary
2970 embolism. A controlled trial. *Lancet.* 1960 Jun 18;1(7138):1309-12.
- 2971 249. Aujesky D, Smith KJ, Cornuz J, Roberts MS. Cost-effectiveness of low-molecular-
2972 weight heparin for treatment of pulmonary embolism. *Chest.* 2005 Sep;128(3):1601-
2973 10.
- 2974 250. Stein PD, Matta F, Alrifai A, Rahman A. Trends in case fatality rate in pulmonary
2975 embolism according to stability and treatment. *Thromb Res.* 2012 Dec;130(6):841-6.
- 2976 251. Wells GA, Kelly S, Elliott J, Carrier M, Hsieh S, Chen L. Direct oral anticoagulants for
2977 the treatment of venous thromboembolic events: a systematic review and network
2978 meta-analysis [Internet]. Ottawa: University of Ottawa Heart Institute; 2016. [cited 2017
2979 Jun 28]. Available from:
2980 [https://www.ottawaheart.ca/sites/default/files/uploads/documents/Researchers/gwells-
2981 doac-vte-scientific-report-2015-2016.pdf](https://www.ottawaheart.ca/sites/default/files/uploads/documents/Researchers/gwells-doac-vte-scientific-report-2015-2016.pdf)
- 2982 252. Roman A, Barbera JA, Castillo MJ, Munoz R, Escribano P. Health-related quality of life
2983 in a national cohort of patients with pulmonary arterial hypertension or chronic
2984 thromboembolic pulmonary hypertension. *Arch Bronconeumol.* 2013 May;49(5):181-8.
- 2985 253. Johnson JA, Pickard AS. Comparison of the EQ-5D and SF-12 health surveys in a
2986 general population survey in Alberta, Canada. *Med Care.* 2000 Jan;38(1):115-21.
- 2987 254. Hogg K, Kimpton M, Carrier M, Coyle D, Forgie M, Wells P. Estimating quality of life in
2988 acute venous thrombosis. *JAMA Intern Med.* 2013 Jun 24;173(12):1067-72.
- 2989 255. Rivero-Arias O, Ouellet M, Gray A, Wolstenholme J, Rothwell PM, Luengo-Fernandez
2990 R. Mapping the modified Rankin scale (mRS) measurement into the generic EuroQol
2991 (EQ-5D) health outcome. *Med Decis Making.* 2010 May;30(3):341-54.
- 2992 256. Consumer price index, health and personal care, by province (Canada) [Internet].
2993 Ottawa: Statistics Canada; 2017. [cited 2017 Jun 28]. Available from:
2994 <http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/econ161a-eng.htm>
- 2995 257. Exchange rates [Internet]. Ottawa: Bank of Canada; 2017. [cited 2017 Jun 28].
2996 Available from: http://www.bankofcanada.ca/rates/exchange/?page_moved=1

- 2997 258. Ontario Ministry of Health and Long-term Care OCCl costing analysis tool. In: Health
2998 data branch web portal [Internet]. Toronto: Ontario Ministry of Health and Long-Term
2999 Care; 2015 [cited 2017 Jun 28]. Available from:
3000 <https://hsim.health.gov.on.ca/hdbportal/> Registration required.
- 3001 259. Wilbur K, Lynd LD, Sadatsafavi M. Low-molecular-weight heparin versus
3002 unfractionated heparin for prophylaxis of venous thromboembolism in medicine
3003 patients--a pharmacoeconomic analysis. Clin Appl Thromb Hemost. 2011
3004 Oct;17(5):454-65.
- 3005 260. Schedule of benefits: physician services under the Health Insurance Act (December
3006 22, 2015 (effective Mar 1, 2016)) [Internet]. Toronto: Ontario Ministry of Health and
3007 Long-Term Care; 2015. [cited 2017 Jun 28]. Available from:
3008 [http://www.health.gov.on.ca/en/pro/programs/ohip/sob/physserv/sob_master20160401](http://www.health.gov.on.ca/en/pro/programs/ohip/sob/physserv/sob_master20160401.pdf)
3009 [.pdf](http://www.health.gov.on.ca/en/pro/programs/ohip/sob/physserv/sob_master20160401.pdf)
- 3010 261. Ontario drug benefit formulary/comparative drug index. effective from May 31, 2017
3011 [Internet]. Toronto: Ontario Ministry of Health and Long-Term Care; 2017 [cited 2017
3012 Jun 28].
- 3013 262. Wu O, Robertson L, Twaddle S, Lowe GD, Clark P, Greaves M, et al. Screening for
3014 thrombophilia in high-risk situations: systematic review and cost-effectiveness
3015 analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia
3016 Screening (TREATS) study. Health Technol Assess. 2006 Apr;10(11):1-110.
- 3017 263. Pengo V, Lensing AW, Prins MH, Marchiori A, Davidson BL, Tiozzo F, et al. Incidence
3018 of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Engl
3019 J Med. 2004 May 27;350(22):2257-64.
- 3020 264. Lobo JL, Zorrilla V, Aizpuru F, Uresandi F, Garcia-Bragado F, Conget F, et al. Clinical
3021 syndromes and clinical outcome in patients with pulmonary embolism: findings from
3022 the RIETE registry. Chest. 2006 Dec;130(6):1817-22.
- 3023 265. van Erkel AR, Pattynama PM. Cost-effective diagnostic algorithms in pulmonary
3024 embolism: an updated analysis. Acad Radiol. 1998 Sep;5 Suppl 2:S321-S327.
- 3025 266. Wilts IT, Le GG, den Exter PL, van EJ, Carrier M, Planquette B, et al. Performance of
3026 the age-adjusted cut-off for D-dimer in patients with cancer and suspected pulmonary
3027 embolism. Thromb Res. 2017;152:49-51.
- 3028 267. Righini M, Le GG, Perrier A, Bounameaux H. More on: clinical criteria to prevent
3029 unnecessary diagnostic testing in emergency department patients with suspected
3030 pulmonary embolism. J Thromb Haemost [Internet]. 2005 Jan [cited 2017 Jun
3031 1];3(1):188-9. Available from: [http://onlinelibrary.wiley.com/doi/10.1111/j.1538-](http://onlinelibrary.wiley.com/doi/10.1111/j.1538-7836.2004.01097.x/epdf)
3032 [7836.2004.01097.x/epdf](http://onlinelibrary.wiley.com/doi/10.1111/j.1538-7836.2004.01097.x/epdf)
- 3033 268. Hendriksen JM, Lucassen WA, Erkens PM, Stoffers HE, van Weert HC, Buller HR, et
3034 al. Ruling Out Pulmonary Embolism in Primary Care: Comparison of the Diagnostic
3035 Performance of "Gestalt" and the Wells Rule. Ann Fam Med [Internet]. 2016 May [cited
3036 2017 Jun 28];14(3):227-34. Available from:
3037 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4868561>

- 3038 269. Di MS, Cilia C, Campagna A, D'Arrigo G, Abd ES, Tripepi G, et al. Comparison of
3039 Wells and Revised Geneva Rule to Assess Pretest Probability of Pulmonary Embolism
3040 in High-Risk Hospitalized Elderly Adults. *J Am Geriatr Soc.* 2015 Jun;63(6):1091-7.
- 3041 270. Klok FA, Kruisman E, Spaan J, Nijkeuter M, Righini M, Aujesky D, et al. Comparison of
3042 the revised Geneva score with the Wells rule for assessing clinical probability of
3043 pulmonary embolism. *J Thromb Haemost.* 2008 Jan;6(1):40-4.
- 3044 271. Meyer G, Planquette B, Sanchez O. Long-term outcome of pulmonary embolism. *Curr
3045 Opin Hematol.* 2008 Sep;15(5):499-503.
- 3046 272. Carrier M, Wells PS, Rodger MA. Excluding pulmonary embolism at the bedside with
3047 low pre-test probability and D-dimer: safety and clinical utility of 4 methods to assign
3048 pre-test probability. *Thromb Res.* 2006;117(4):469-74.
- 3049 273. Stein PD, Huang H, Afzal A, Noor HA. Incidence of acute pulmonary embolism in a
3050 general hospital: relation to age, sex, and race. *Chest.* 1999 Oct;116(4):909-13.
- 3051 274. Strand T, Tornqvist E, Rask M, Roxberg A. The experience of patients with neoplasm
3052 metastasis in the spine during a magnetic resonance imaging examination. *J RADIOL
3053 NURS.* 2014;33(4):191-8.
- 3054 275. Nightingale JM, Murphy FJ, Blakeley C. 'I thought it was just an x-ray': a qualitative
3055 investigation of patient experiences in cardiac SPECT-CT imaging. *Nucl Med
3056 Commun.* 2012 Mar;33(3):246-54.
- 3057 276. Hinton L, Locock L, Knight M. Partner experiences of "near-miss" events in pregnancy
3058 and childbirth in the UK: a qualitative study. *PLoS ONE [Internet].* 2014 [cited 2017
3059 Feb 8];9(4):e91735. Available from:
3060 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3981658>
- 3061 277. Carlsson S, Carlsson E. 'The situation and the uncertainty about the coming result
3062 scared me but interaction with the radiographers helped me through': a qualitative
3063 study on patients' experiences of magnetic resonance imaging examinations. *J Clin
3064 Nurs.* 2013 Nov;22(21-22):3225-34.
- 3065 278. Thornton RH, Dauer LT, Shuk E, Bylund CL, Banerjee SC, Maloney E, et al. Patient
3066 perspectives and preferences for communication of medical imaging risks in a cancer
3067 care setting. *Radiology [Internet].* 2015 [cited 2017 Feb 2];275(2):545-52. Available
3068 from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4976442/pdf/nihms804378.pdf>
- 3069 279. Munn Z, Jordan Z. The patient experience of high technology medical imaging: a
3070 systematic review of the qualitative evidence. *Radiography.* 2011;17(4):323-31.
- 3071 280. Törnqvist E, Mansson A, Larsson EM, Hallstrom I. It's like being in another world--
3072 patients' lived experience of magnetic resonance imaging. *J Clin Nurs.* 2006
3073 Aug;15(8):954-61.
- 3074 281. Garland S, Severn M. Approaches to diagnosing acute pulmonary embolism in
3075 Canada: current practice, challenges, and availability of testing. [Internet]. Ottawa:
3076 CADTH. Forthcoming 2017. [cited 2017 Jul 28]. Available from:

- 3077 <https://www.cadth.ca/approaches-diagnosing-acute-pulmonary-embolism-canada-current-practice-challenges-and-availability>
3078
- 3079 282. Pfadenhauer L, Rohwer A, Burns J, Booth A, Bakke Lysdahl K, HJofmann B, et al.
3080 Guidance for the assessment of context and implementation in Health Technology
3081 Assessments (HTA) and systematic reviews of complex interventions: the Context and
3082 Implementation of Complex Interventions (CICI) Framework [Internet]. place unknown:
3083 Integrated Health Technology Assessment for Evaluating Complex Technologies
3084 (INTEGRATE-HTA); 2016. [cited 2017 Jan 19]. Available from: [http://www.integrate-
3085 hta.eu/wp-content/uploads/2016/02/Guidance-for-the-Assessment-of-Context-and-
3086 Implementation-in-HTA-and-Systematic-Reviews-of-Complex-Interventions-The-
3087 Co.pdf](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)
- 3088 283. Ahn JS, Edmonds ML, McLeod SL, Dreyer JF. Familiarity with radiation exposure dose
3089 from diagnostic imaging for acute pulmonary embolism and current patterns of
3090 practice. CJEM Can J Emerg Med [Internet]. 2014 Sep [cited 2016 Nov 30];16(5):393-
3091 404. Available from: [https://www.cambridge.org/core/services/aop-cambridge-
3092 core/content/view/S1481803500003079](https://www.cambridge.org/core/services/aop-cambridge-core/content/view/S1481803500003079)
- 3093 284. Arnason T, Wells PS, Forster AJ. Appropriateness of diagnostic strategies for
3094 evaluating suspected venous thromboembolism. Thromb Haemost. 2007
3095 Feb;97(2):195-201.
- 3096 285. Ballantine M, Bhimani M, Milne WK. Diagnostic approach to pulmonary embolism in a
3097 rural emergency department. Can j rural med [Internet]. 2012 [cited 2016 Nov
3098 15];17(1):17-20. Available from: <http://www.srpc.ca/PDF/cjrm/vol17n1/pg17.pdf>
- 3099 286. Chen YA, Gray BG, Bandiera G, MacKinnon D, Deva DP. Variation in the utilization
3100 and positivity rates of CT pulmonary angiography among emergency physicians at a
3101 tertiary academic emergency department. Emerg Radiology. 2015 Jun;22(3):221-9.
- 3102 287. Ingber S, Selby R, Lee J, Geerts W, Brnjac E. Combination pretest probability
3103 assessment and D-dimer did not reduce outpatient imaging for venous
3104 thromboembolism in a tertiary care hospital emergency department. CJEM Can J
3105 Emerg Med [Internet]. 2014 Jan [cited 2016 Dec 1];16(1):53-62. Available from:
3106 [https://www.cambridge.org/core/services/aop-cambridge-
3107 core/content/view/E554192410CD97381E3D0F418682EB1A/S1481803500003328a.p
3108 df/comboination-pretest-probability-assessment-and-d-dimer-did-not-reduce-outpatient-
3109 imaging-for-venous-thromboembolism-in-a-tertiary-care-hospital-emergency-
3110 department.pdf](https://www.cambridge.org/core/services/aop-cambridge-core/content/view/E554192410CD97381E3D0F418682EB1A/S1481803500003328a.pdf/comboination-pretest-probability-assessment-and-d-dimer-did-not-reduce-outpatient-imaging-for-venous-thromboembolism-in-a-tertiary-care-hospital-emergency-department.pdf)
- 3111 288. Le Roux PY, Pelletier-Galarneau M, De Laroche R, Hofman MS, Zuckier LS, Roach P,
3112 et al. Pulmonary scintigraphy for the diagnosis of acute pulmonary embolism: a survey
3113 of current practices in Australia, Canada, and France. J Nucl Med [Internet]. 2015 Aug
3114 [cited 2016 Dec 2];56(8):1212-7. Available from:
3115 <http://jnm.snmjournals.org/content/56/8/1212.full.pdf+html>
- 3116 289. Southern DA, Poole J, Patel A, Waters N, Pilote L, Hull RD, et al. Health system
3117 capacity and infrastructure for adopting innovations to care for patients with venous
3118 thromboembolic disease. Open medicine : a peer-reviewed, independent, open-access

- 3119 journal [Internet]. 2014 [cited 2016 Nov 15];8(2):e46-e53. Available from:
3120 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4085085/pdf/OpenMed-08-46.pdf>
- 3121 290. Spencer Netto F, Tien H, Ng J, Ortega S, Scarpelini S, Rizoli SB, et al. Pulmonary
3122 emboli after blunt trauma: timing, clinical characteristics and natural history. *Injury*.
3123 2012 Sep;43(9):1502-6.
- 3124 291. Armao D, Semelka RC, Elias J. Radiology's ethical responsibility for healthcare reform:
3125 tempering the overutilization of medical imaging and trimming down a heavyweight.
3126 *Journal of Magnetic Resonance Imaging*. 2012;35(3):512-7.
- 3127 292. Gossner J, Nau R. Geriatric chest imaging: When and how to image the elderly lung,
3128 age-related changes, and common pathologies. *Radiology Research and Practice*
3129 [Internet]. 2013 [cited 2016 Nov 15]. Available from:
3130 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3713368/pdf/RRP2013-584793.pdf>
- 3131 293. Alhassan S, Sayf A, Arsene C, Krayem H. Suboptimal implementation of diagnostic
3132 algorithms and overuse of computed tomography-pulmonary angiography in patients
3133 with suspected pulmonary embolism. *Annals of Thoracic Medicine* [Internet]. 2016
3134 [cited 2017 Feb 1];11(4):254-60. Available from:
3135 http://www.thoracicmedicine.org/temp/AnnThoracMed114254-4993048_135210.pdf
- 3136 294. Browne AM, Cronin CG, English C, NiMhuircheartaigh J, Murphy JM, Bruzzi JF.
3137 Unsuspected pulmonary emboli in oncology patients undergoing routine computed
3138 tomography imaging. *J Thorac Oncol* [Internet]. 2010 Jun [cited 2016 Oct 7];5(6):798-
3139 803. Available from: http://ac.els-cdn.com/S1556086415305062/1-s2.0-S1556086415305062-main.pdf?tid=3f376638-8cc1-11e6-bef2-00000aab0f6b&acdnat=1475867409_ff68ac277eb054c81cab4c1450043bab
- 3142 295. Booker MT, Johnson JO. Optimizing CT Pulmonary Angiogram Utilization in a
3143 Community Emergency Department: A Pre- and Postintervention Study. *J am coll*
3144 *radiol*. 2016 Oct 4.
- 3145 296. Goodacre S, Nelson-Piercy C, Hunt B, Chan WS. When should we use diagnostic
3146 imaging to investigate for pulmonary embolism in pregnant and postpartum women?
3147 *Emerg Med J*. 2015;32(1):78-82.
- 3148 297. Groves AM, Yates SJ, Win T, Kayani I, Gallagher FA, Syed R, et al. CT pulmonary
3149 angiography versus ventilation-perfusion scintigraphy in pregnancy: implications from
3150 a UK survey of doctors' knowledge of radiation exposure. *Radiology* [Internet]. 2006
3151 Sep;240(3):765-70. Available from:
3152 <http://pubs.rsna.org/doi/pdf/10.1148/radiol.2403050910>
- 3153 298. Adams DM, Stevens SM, Woller SC, Evans RS, Lloyd JF, Snow GL, et al. Adherence
3154 to PLOPED II investigators' recommendations for computed tomography pulmonary
3155 angiography. *Am J Med*. 2013 Jan;126(1):36-42.
- 3156 299. Tirada N, Dreizin D, Khati NJ, Akin EA, Zeman RK. Imaging pregnant and lactating
3157 patients. *Radiographics*. 2015 Oct;35(6):1751-65.

- 3158 300. Schuster ME, Fishman JE, Copeland JF, Hatabu H, Boiselle PM. Pulmonary embolism
3159 in pregnant patients: a survey of practices and policies for CT pulmonary angiography.
3160 AJR Am J Roentgenol. 2003 Dec;181(6):1495-8.
- 3161 301. Rosenthal MS. Patient misconceptions and ethical challenges in radioactive iodine
3162 scanning and therapy. J Nucl Med Technol. 2006 Sep;34(3):143-50.
- 3163 302. D'Apuzzo MR, Keller TC, Novicoff WM, Browne JA. CT pulmonary angiography after
3164 total joint arthroplasty: overdiagnosis and iatrogenic harm? Clin Orthop [Internet]. 2013
3165 Sep [cited 2016 Nov 15];471(9):2737-42. Available from:
3166 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3734436>
- 3167 303. Bozarth AL, Bajaj N, Wessling MR, Keffer D, Jallu S, Salzman GA. Evaluation of the
3168 pulmonary embolism rule-out criteria in a retrospective cohort at an urban academic
3169 hospital. Am J Emerg Med. 2015 Apr;33(4):483-7.
- 3170 304. Rohacek M, Buatsi J, Szucs-Farkas Z, Kleim B, Zimmermann H, Exadaktylos A, et al.
3171 Ordering CT pulmonary angiography to exclude pulmonary embolism: defense versus
3172 evidence in the emergency room. Intensive Care Med. 2012 Aug;38(8):1345-51.
- 3173 305. Berlin L, Murphy DR, Singh H. Breakdowns in communication of radiological findings:
3174 an ethical and medico-legal conundrum. Diagnosis (Berl). 2014 Dec;1(4):263-8.
3175 Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4799785>
- 3176 306. Kline JA, Peterson CE, Steuerwald MT. Prospective evaluation of real-time use of the
3177 pulmonary embolism rule-out criteria in an academic emergency department. Acad
3178 Emerg Med [Internet]. 2010 Sep [cited 2017 Jun 1];17(9):1016-9. Available from:
3179 <http://onlinelibrary.wiley.com/doi/10.1111/j.1553-2712.2010.00826.x/epdf>
- 3180 307. Bhargavan M, Sunshine JH, Lewis RS, Jha S, Owen JB, Vializ J. Frequency of use of
3181 imaging tests in the diagnosis of pulmonary embolism: Effects of physician specialty,
3182 patient characteristics and region. Am J Roentgenol [Internet]. 2010 [cited 2016 Nov
3183 14];194(4):1018-26. Available from:
3184 <http://www.ajronline.org/doi/pdf/10.2214/AJR.09.3215>
- 3185 308. Sah S, Fagerlin A, Ubel P. Effect of physician disclosure of specialty bias on patient
3186 trust and treatment choice. Proc Natl Acad Sci U S A. 2016 Jul 5;113(27):7465-9.
3187 Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4941435>
- 3188 309. Vano E, Kleiman NJ, Duran A, Romano-Miller M, Rehani MM. Radiation-associated
3189 lens opacities in catheterization personnel: results of a survey and direct assessments.
3190 J Vasc Interv Radiol. 2013 Feb;24(2):197-204.
- 3191 310. Lee-Lewandrowski E, Nichols J, Van CE, Grisson R, Louissaint A, Benzer T, et al.
3192 Implementation of a rapid whole blood D-dimer test in the emergency department of an
3193 urban academic medical center: impact on ED length of stay and ancillary test
3194 utilization. Am J Clin Pathol [Internet]. 2009 Sep [cited 2016 Nov 14];132(3):326-31.
3195 Available from: <http://ajcp.oxfordjournals.org/content/ajcpath/132/3/326.full.pdf>
- 3196 311. Brockbank J, Wolowacz S. Economic evaluations of new oral anticoagulants for the
3197 prevention of venous thromboembolism after total hip or total knee replacement

- 3198 [abstract]. Value in Health Conference. 2015;18(7):A392. (Presented at ISPOR 18th
3199 Annual European Congress; 2015 Nov 7-11; Milan, Italy).
- 3200 312. Johnson PT, Zimmerman SL, Heath D, Eng J, Horton KM, Scott WW, et al. The iPad
3201 as a mobile device for CT display and interpretation: diagnostic accuracy for
3202 identification of pulmonary embolism. *Emerg Radiol*. 2012 Aug;19(4):323-7.
- 3203 313. Itri JN. Patient-centered Radiology. *Radiographics*. 2015 Oct;35(6):1835-46.
- 3204 314. Gaston S, White S. Venous thromboembolism (VTE) risk assessment: rural nurses'
3205 knowledge and use in a rural acute care hospital. *Int J Nurs Pract*. 2013;19(1):60-4.
- 3206 315. Fanikos J, Rao A, Seger AC, Carter D, Piazza G, Goldhaber SZ. Hospital costs of
3207 acute pulmonary embolism. *Am J Med*. 2013;126(2):127-32.
- 3208 316. Keefer R. Ethical dilemmas in radiology and the vow to do no harm. *ACR Radiology*
3209 [Internet]. 2012 Mar 9 [cited 2017 Aug 22]. Available from: [https://www.acr.org/News-](https://www.acr.org/News-Publications/News/News-Articles/2012/ACR-Bulletin/201203-Do-No-Harm)
3210 [Publications/News/News-Articles/2012/ACR-Bulletin/201203-Do-No-Harm](https://www.acr.org/News-Publications/News/News-Articles/2012/ACR-Bulletin/201203-Do-No-Harm)
- 3211 317. Albrecht MH, Bickford MW, Nance JW, Jr., Zhang L, De Cecco CN, Wichmann JL, et
3212 al. State-of-the-Art Pulmonary CT Angiography for Acute Pulmonary Embolism. *AJR*
3213 *Am J Roentgenol*. 2017 Mar;208(3):495-504.
- 3214 318. Chenaghlou M, Parizad R, Jafarabadi MA. Risk factors and prevention of pulmonary
3215 embolism in young adults. *Crescent Journal of Medical and Biological Sciences*. 2017
3216 Jan;4(1):7-12.
- 3217 319. Goldhaber SZ, Fanikos J. Prevention of deep vein thrombosis and pulmonary
3218 embolism. *Circulation*. 2004;110:e445-7.
- 3219 320. van Es N, van der Hulle T, van Es J, den Exter PL, Douma RA, Goekoop RJ, et al.
3220 Excluding pulmonary embolism in cancer patients using the Wells rule and age-
3221 adjusted D-dimer testing: an individual patient data meta-analysis. *Thromb Res*. 2016
3222 Apr;140 Suppl 1:S179.
- 3223 321. McDonald H, Diamantopoulos A, Wells P, Lees M, Folkerts K, Forster F, et al. Cost-
3224 effectiveness of rivaroxaban in the prevention of venous thromboembolism: A
3225 Canadian analysis using the Ontario Ministry of Health Perspective. *J Med Econ*.
3226 2012;15(5):817-28.
- 3227 322. Sud S, Mittmann N, Cook DJ, Geerts W, Chan B, Dodek P, et al. Screening and
3228 prevention of venous thromboembolism in critically ill patients: a decision analysis and
3229 economic evaluation. *Am J Respir Crit Care Med* [Internet]. 2011 Dec 1 [cited 2016 Jul
3230 6];184(11):1289-98. Available from:
3231 [http://www.atsjournals.org/doi/abs/10.1164/rccm.201106-1059OC?url_ver=Z39.88-](http://www.atsjournals.org/doi/abs/10.1164/rccm.201106-1059OC?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed&#readcube-epdf)
3232 [2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed&#readcube-epdf](http://www.atsjournals.org/doi/abs/10.1164/rccm.201106-1059OC?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed&#readcube-epdf)
- 3233 323. Lynd LD, Goeree R, Crowther MA, O'Brien BJ. A probabilistic cost-effectiveness
3234 analysis of enoxaparin versus unfractionated heparin for the prophylaxis of deep-vein
3235 thrombosis following major trauma. *Can J Clin Pharmacol*. 2007;14(2):e215-e226.

- 3236 324. van Es N, van der Hulle T, Büller H, Klok FA, Huisman MV, Galapienzo J, et al. Stand-
3237 alone D-dimer testing to rule out acute pulmonary embolism. *J Thromb Haemost.* 2016
3238 Nov 22.
- 3239 325. Adams D, Welch JL, Kline JA. Clinical utility of an age-adjusted D-dimer in the
3240 diagnosis of venous thromboembolism. *Ann Emerg Med.* 2014;64(3):232-4.
- 3241 326. Akgul O, Uyarel H. D-dimer: a novel predictive marker for cardiovascular disease. *Int J*
3242 *Cardiol.* 2013;168(5):4930-1.
- 3243 327. Ayaram D, Bellolio MF, Murad MH, Laack TA, Sadosty AT, Erwin PJ, et al. Triple rule-
3244 out computed tomographic angiography for chest pain: a diagnostic systematic review
3245 and meta-analysis. *Acad Emerg Med.* 2013 Sep;20(9):861-71.
- 3246 328. Becattini C, Lignani A, Masotti L, Forte MB, Agnelli G. D-dimer for risk stratification in
3247 patients with acute pulmonary embolism. *J Thromb Thrombolysis.* 2012 Jan;33(1):48-
3248 57.
- 3249 329. Ceriani E, Combescure C, Le GG, Nendaz M, Perneger T, Bounameaux H, et al.
3250 Clinical prediction rules for pulmonary embolism: a systematic review and meta-
3251 analysis. *J Thromb Haemost.* 2010 May;8(5):957-70.
- 3252 330. Carrier M, Righini M, Wells PS, Perrier A, Anderson DR, Rodger MA, et al.
3253 Subsegmental pulmonary embolism diagnosed by computed tomography: incidence
3254 and clinical implications. A systematic review and meta-analysis of the management
3255 outcome studies. *J Thromb Haemost.* 2010 Aug;8(8):1716-22.
- 3256 331. Challen K, Goodacre SW. Predictive scoring in non-trauma emergency patients: a
3257 scoping review. *Emerg Med J.* 2011;28(10):827-37.
- 3258 332. Crawford F, Andras A, Welch K, Sheares K, Keeling D, Chappell FM. D-dimer test for
3259 excluding the diagnosis of pulmonary embolism. *Cochrane Database Syst Rev.*
3260 2016;8:CD010864.
- 3261 333. Douketis J. Review: Positive D-dimer results predict recurrence after first unprovoked
3262 VTE regardless of test timing or cutpoint, or patient age. *Ann Intern Med.*
3263 2011;154(2):JC1-JC5.
- 3264 334. Current evidence does not support the use of a negative d-dimer to rule out suspected
3265 pulmonary embolism in pregnancy. *Emerg Med J.* 2011;28(3):245-6.
- 3266 335. Graham SM, Mwilu R, Liles WC. Clinical utility of biomarkers of endothelial activation
3267 and coagulation for prognosis in HIV infection: a systematic review. *Virulence.* 2013
3268 Aug 15;4(6):564-71.
- 3269 336. Hallifax RJ, Talwar A, Rahman NM. The role of computed tomography in assessing
3270 pleural malignancy prior to thoracoscopy. *Curr Opin Pulm Med.* 2015 Jul;21(4):368-71.
- 3271 337. Hendriksen JM, Geersing GJ, Lucassen WA, Erkens PM, Stoffers HE, van Weert HC,
3272 et al. Diagnostic prediction models for suspected pulmonary embolism: systematic
3273 review and independent external validation in primary care. *Bmj [Internet].* 2015 [cited

- 3274 2016 Oct 14];351:h4438. Available from:
3275 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4561760>
- 3276 338. Corrigendum to prognostic clinical prediction rules to identify a low-risk pulmonary
3277 embolism: a systematic review and meta-analysis. *J Thromb Haemost.*
3278 2013;11(1):218-20.
- 3279 339. Klok FA, Mos IC, Huisman M, V. Brain-type natriuretic peptide levels in the prediction
3280 of adverse outcome in patients with pulmonary embolism: a systematic review and
3281 meta-analysis. *Am J Respir Crit Care Med.* 2008;178(4):425-30.
- 3282 340. Kohn CG, Mearns ES, Parker MW, Hernandez AV, Coleman CI. Prognostic accuracy
3283 of clinical prediction rules for early post-pulmonary embolism all-cause mortality: a
3284 bivariate meta-analysis. *Chest.* 2015 Apr;147(4):1043-62.
- 3285 341. Manara A, D'hoore W, Thys F. Capnography as a diagnostic tool for pulmonary
3286 embolism: a meta-analysis. *Ann Emerg Med.* 2013 Dec;62(6):584-91.
- 3287 342. Mos IC, Klok FA, Kroft LJ, DE RA, Dekkers OM, Huisman MV. Safety of ruling out
3288 acute pulmonary embolism by normal computed tomography pulmonary angiography
3289 in patients with an indication for computed tomography: systematic review and meta-
3290 analysis. *J Thromb Haemost.* 2009 Sep;7(9):1491-8.
- 3291 343. Mos IC, Douma RA, Erkens PM, Kruij MJ, Hovens MM, van Houten AA, et al.
3292 Diagnostic outcome management study in patients with clinically suspected recurrent
3293 acute pulmonary embolism with a structured algorithm. *Thromb Res.* 2014
3294 Jun;133(6):1039-44.
- 3295 344. Ouatu A, Tanase DM, Ionescu SD, Rezus C, Ambarus V, Arsenescu-Georgescu C.
3296 The importance of clinical prediction models in non-fatal pulmonary embolism: an
3297 analysis of the best known clinical scores. *Rev Med Chir Soc Med Nat Iasi.* 2014
3298 Oct;118(4):932-41.
- 3299 345. Pulivarthi S, Gurram MK. Effectiveness of D-Dimer as a screening test for venous
3300 thromboembolism: an update. *N A J Med Sci (Hamilt) [Internet].* 2014 Oct [cited 2016
3301 Oct 4];6(10):491-9. Available from:
3302 http://www.najms.org/temp/NorthAmJMedSci610491-4195742_113917.pdf
- 3303 346. Rehnberg JV, Vondy A. Towards evidence-based emergency medicine: Best BETs
3304 from the Manchester Royal Infirmary. BET 3: Pulmonary embolism rule-out criteria
3305 (PERC) for excluding pulmonary embolism. *Emerg Med J.* 2014 Jan;31(1):81-2.
- 3306 347. Schouten HJ, Geersing GJ, Koek HL, Zuithoff NP, Janssen KJ, Douma RA, et al.
3307 Diagnostic accuracy of conventional or age adjusted D-dimer cut-off values in older
3308 patients with suspected venous thromboembolism: systematic review and meta-
3309 analysis. *Bmj [Internet].* 2013;346:f2492. Available from:
3310 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3643284>
- 3311 348. Self WH, Barrett TW. *Annals of Emergency Medicine journal club.* Is "PERC negative"
3312 adequate to rule out pulmonary embolism in the emergency department? Evaluating

- 3313 meta-analysis for studies of clinical prediction models. *Ann Emerg Med.* 2012
3314 Jul;60(1):129-31.
- 3315 349. Self WH, Barrett TW. Is "PERC negative" adequate to rule out pulmonary embolism in
3316 the emergency department? Evaluating meta-analysis for studies of clinical prediction
3317 models. *Ann Emerg Med.* 2012;60(1):129-31.
- 3318 350. Sharma A, Chatterjee S, Lichstein E, Mukherjee D. Extended thromboprophylaxis for
3319 medically ill patients with decreased mobility: does it improve outcomes? *J Thromb*
3320 *Haemost.* 2012;10(10):2053-60.
- 3321 351. Singh B, Parsaik AK, Agarwal D, Surana A, Mascarenhas SS, Chandra S. Diagnostic
3322 accuracy of pulmonary embolism rule-out criteria: a systematic review and meta-
3323 analysis. *Ann Emerg Med.* 2012 Jun;59(6):517-20.
- 3324 352. Squizzato A, Donadini MP, Galli L, Dentali F, Aujesky D, Ageno W. Prognostic clinical
3325 prediction rules to identify a low-risk pulmonary embolism: a systematic review and
3326 meta-analysis. *J Thromb Haemost.* 2012 Jul;10(7):1276-90.
- 3327 353. Stevens SM. 2011 - Review: Gestalt or clinical decision rules have limited sensitivity
3328 and specificity for detecting acute PE [Philadelphia, Pennsylvania]. *ACP J Club.* 2012
3329 Jan 17;156(1):1. Available from:
3330 <http://search.ebscohost.com/login.aspx?direct=true&db=cin20&AN=104527902&site=ehost-live>
3331
- 3332 354. Tafur A. Systematic review: a low wells score and a negative D-dimer was not safe in
3333 patients with cancer for ruling out DVT. *Evid Based Med.* 2014;19(5):188.
- 3334 355. van Es N, Kraaijpoel N, Klok FA, Huisman MV, den Exter PL, Mos IC, et al. The
3335 original and simplified Wells rules and age-adjusted D-dimer testing to rule out
3336 pulmonary embolism: an individual patient data meta-analysis. *J Thromb Haemost.*
3337 2017 Jan 20.
- 3338 356. van Leent MW, Stevanovic J, Jansman FG, Beinema MJ, Brouwers JR, Postma MJ.
3339 Cost-Effectiveness of Dabigatran Compared to Vitamin-K Antagonists for the
3340 Treatment of Deep Venous Thrombosis in the Netherlands Using Real-World Data.
3341 *PLoS ONE* [Internet]. 2015 [cited 2016 Oct 4];10(8):e0135054. Available from:
3342 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4524689>
- 3343 357. Wessler BS, Lai YL, Kramer W, Cangelosi M, Raman G, Lutz JS, et al. Clinical
3344 prediction models for cardiovascular disease: The Tufts PACE CPM database. *Circ*
3345 *Cardiovasc Qual Outcomes* [Internet]. 2015 Jul [cited 2016 Oct 4];8(4):368-75.
3346 Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4512876/pdf/nihms-692018.pdf>
3347
- 3348 358. Witt DM. Review: Positive D-dimer results predict recurrence after first unprovoked
3349 VTE regardless of test timing or cutpoint, or patient age [Philadelphia, Pennsylvania].
3350 *ACP J Club.* 2011 Jan 18;154(1):4.

- 3351 359. Zhou XY, Ben SQ, Chen HL, Ni SS. The prognostic value of pulmonary embolism
3352 severity index in acute pulmonary embolism: a meta-analysis. *Respir Res* [Internet].
3353 2012;13:111. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3571977>
- 3354 360. Abujudeh HH, Kaewlai R, Farsad K, Orr E, Gilman M, Shepard JA. Computed
3355 tomography pulmonary angiography. An assessment of the radiology report. *Acad*
3356 *Radiol*. 2009;16(11):1309-15.
- 3357 361. Alhadad A, Miniati M, Alhadad H, Gottsater A, Bajc M. The value of tomographic
3358 ventilation/perfusion scintigraphy (V/PSPECT) for follow-up and prediction of
3359 recurrence in pulmonary embolism. *Thromb Res*. 2012 Dec;130(6):877-81.
- 3360 362. Summaries for patients. Evaluation of patients with suspected acute pulmonary
3361 embolism: best practice advice from the Clinical Guidelines Committee of the
3362 American College of Physicians. *Ann Intern Med*. 2015 Nov 3;163(9):134.
- 3363 363. Summaries for patients. Diagnosis of pulmonary embolism with magnetic resonance
3364 angiography. *Ann Intern Med*. 2010 Apr 6;152(7):144.
- 3365 364. Arnason T, Wells PS, Forster AJ. Appropriateness of diagnostic strategies for
3366 evaluating suspected venous thromboembolism. *Thromb Haemost*. 2007;97(2):195-
3367 201.
- 3368 365. Astani SA, Davis LC, Harkness BA, Supanich MP, Dalal I. Detection of pulmonary
3369 embolism during pregnancy: comparing radiation doses of CTPA and pulmonary
3370 scintigraphy. *Nucl Med Commun*. 2014 Jul;35(7):704-11.
- 3371 366. Bajc M. Potential of hybrid V/P SPECT-low-dose CT in lung diagnostics. *Breathe*
3372 [Internet]. 2012 [cited 2016 Oct 12];9(1):49-60. Available from:
3373 <http://breathe.ersjournals.com/content/breathe/9/1/48.full.pdf>
- 3374 367. Baliga RR. Diagnosis of pulmonary embolism by multidetector CT alone or combined
3375 with venous ultrasonography of the leg. *ACC Cardiosource Rev J*. 2008;17(6):31-2.
- 3376 368. Bannas P, Schiebler ML, Motosugi U, Francois CJ, Reeder SB, Nagle SK. Pulmonary
3377 MRA: differentiation of pulmonary embolism from truncation artefact. *Eur Radiol*
3378 [Internet]. 2014 Aug [cited 2016 Oct 4];24(8):1942-9. Available from:
3379 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4362685>
- 3380 369. Bates DD, Tkacz JN, LeBedis CA, Holalkere N. Suboptimal CT pulmonary
3381 angiography in the emergency department: a retrospective analysis of outcomes in a
3382 large academic medical center. *Emerg Radiol*. 2016 Jul 27.
- 3383 370. Begic A, Opankovic E, Cukic V, Rustempasic M, Basic A, Miniati M, et al. Impact of
3384 ventilation/perfusion single-photon emission computed tomography on treatment
3385 duration of pulmonary embolism. *Nucl Med Commun* [Internet]. 2015 Feb [cited 2016
3386 Oct 4];36(2):162-7. Available from:
3387 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4280272>
- 3388 371. Blackmore CC. Evidence-based imaging and cost-effectiveness analysis in
3389 cardiopulmonary imaging. *J Thorac Imaging*. 2012;27(5):272-6.

- 3390 372. Boldt BM, Cox CW, Dedekam EA, Tsytsik B, Mysliwiec V. Pulmonary embolism at
3391 follow-up outpatient CT pulmonary angiography: implications on patient risk
3392 stratification. *Blood Coagul Fibrinolysis*. 2013 Sep;24(6):633-7.
- 3393 373. Stawicki SP, Seamon MJ, Kim PK, Meredith DM, Chovanes J, Schwab CW, et al.
3394 Transthoracic echocardiography for pulmonary embolism in the ICU: finding the "right"
3395 findings. *J Am Coll Surg*. 2008 Jan;206(1):42-7.
- 3396 374. Branch KR, Strote J, Shuman WP, Mitsumori LM, Busey JM, Rue T, et al. Diagnostic
3397 accuracy and clinical outcomes of ECG-gated, whole chest CT in the emergency
3398 department. *PLoS ONE* [Internet]. 2013 [cited 2016 Oct 4];8(4). Available from:
3399 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3629052/pdf/pone.0061121.pdf>
- 3400 375. Callejas MF, Errazuriz JI, Castillo F, Otarola C, Riquelme C, Ortega C, et al. Incidental
3401 venous thromboembolism detected by PET-CT in patients with cancer: prevalence and
3402 impact on survival rate. *Thromb Res*. 2014 May;133(5):750-5.
- 3403 376. Darze ES, Braghiroli JF, Almeida RV, Araujo EP, Toscano SM, Araujo-Neto CA.
3404 Clinical outcomes after investigation for pulmonary embolism using CT angiography
3405 and venography. *Arq Bras Cardiol* [Internet]. 2012 Aug [cited 2016 Oct 4];99(2):740-6.
3406 Available from: http://www.scielo.br/pdf/abc/v99n2/en_aop05512.pdf
- 3407 377. Douma RA, Hofstee HM, Schaefer-Prokop C, van Waesberghe JH, Lely RJ,
3408 Kamphuisen PW, et al. Comparison of 4- and 64-slice CT scanning in the diagnosis of
3409 pulmonary embolism. *Thromb Haemost*. 2010 Jan;103(1):242-6.
- 3410 378. Duralde XA, McClelland WB, Jr. The clinical results of arthroscopic transtendinous
3411 repair of grade III partial articular-sided supraspinatus tendon tears. *Arthroscopy*. 2012
3412 Feb;28(2):160-8.
- 3413 379. Easter S, Langdana F, Beasley R, Maharaj D, Entwisle J, Abels P. The diagnostic
3414 role of ventilation/perfusion scans versus computed tomography pulmonary
3415 angiography in obstetric patients investigated for pulmonary embolism at Wellington
3416 Hospital from 2010 to 2012. *N Z Med J*. 2016;129(1433):62-8.
- 3417 380. Engelke C, Rummeny EJ, Marten K. Pulmonary embolism at multi-detector row CT of
3418 chest: one-year survival of treated and untreated patients. *Radiology* [Internet]. 2006
3419 May [cited 2016 Oct 13];239(2):563-75. Available from:
3420 <http://pubs.rsna.org/doi/pdf/10.1148/radiol.2392050118>
- 3421 381. Ersoy H, Goldhaber SZ, Cai T, Luu T, Rosebrook J, Mulkern R, et al. Time-resolved
3422 MR angiography: a primary screening examination of patients with suspected
3423 pulmonary embolism and contraindications to administration of iodinated contrast
3424 material. *AJR Am J Roentgenol* [Internet]. 2007 May [cited 2016 Oct 6];188(5):1246-
3425 54. Available from: <http://www.ajronline.org/doi/pdf/10.2214/AJR.06.0901>
- 3426 382. Fabiá Valls MJ, van der Hulle T, den Exter PL, Mos IC, Huisman MV, Klok FA.
3427 Performance of a diagnostic algorithm based on a prediction rule, D-dimer and CT-
3428 scan for pulmonary embolism in patients with previous venous thromboembolism. A
3429 systematic review and meta-analysis. *Thromb Haemost*. 2015 Feb;113(2):406-13.

- 3430 383. Feragalli B, Galluzzo M, Scaglione M. MDCT venography in patients with suspected
3431 pulmonary embolism: diagnostic impact of pelvic vein evaluation in thromboembolic
3432 disease detection. *Panminerva Med.* 2012 Dec;54(1 Suppl 4):67-72.
- 3433 384. Ferreira EV, Gazzana MB, Sarmiento MB, Guazzelli PA, Hoffmeister MC, Guerra VA,
3434 et al. Alternative diagnoses based on CT angiography of the chest in patients with
3435 suspected pulmonary thromboembolism. *J Bras Pneumol [Internet].* 2016
3436 Jan;42(1):35-41. Available from:
3437 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4805385>
- 3438 385. Flavell RR, Behr SC, Brunsing RL, Naeger DM, Pampaloni MH. The incidence of
3439 pulmonary embolism and associated FDG-PET findings in IV contrast-enhanced
3440 PET/CT. *Acad Radiol.* 2014 Jun;21(6):718-25.
- 3441 386. Garg KC, Das KM. 64-slice CT diagnosis of pulmonary embolism. *Journal of*
3442 *Emergency Medicine, Trauma and Acute Care.* 2008;8(1):38-41.
- 3443 387. Ghazvinian R, Gottsater A, Elf J. Is it safe to withhold long-term anticoagulation
3444 therapy in patients with small pulmonary emboli diagnosed by SPECT scintigraphy?
3445 *Thrombosis Journal [Internet].* 2016 [cited 2016 Oct 7];14:12. Available from:
3446 [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4886445/pdf/12959_2016_Article_86.p](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4886445/pdf/12959_2016_Article_86.pdf)
3447 [df](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4886445/pdf/12959_2016_Article_86.pdf)
- 3448 388. Glaser JE, Chamarthy M, Haramati LB, Esses D, Freeman LM. Successful and safe
3449 implementation of a trinary interpretation and reporting strategy for V/Q lung
3450 scintigraphy. *J Nucl Med [Internet].* 2011 [cited 2016 Oct 7];52(10):1508-12. Available
3451 from: <http://jnm.snmjournals.org/content/52/10/1508.full.pdf+html>
- 3452 389. Grimm LJ, Coleman RE. Assessing the utility of the ventilation phase in ventilation-
3453 perfusion imaging for acute pulmonary embolism. *Nucl Med Commun.* 2013
3454 Jan;34(1):1-4.
- 3455 390. Gruettner J, Fink C, Walter T, Meyer M, Apfalter P, Schoepf UJ, et al. Coronary
3456 computed tomography and triple rule out CT in patients with acute chest pain and an
3457 intermediate cardiac risk profile. Part 1: Impact on patient management. *Eur J Radiol.*
3458 2013;82(1):100-5.
- 3459 391. Gruettner J, Walter T, Bolte M, Haghi D, Sudarski S, Henzler T. Incidence of
3460 pulmonary embolism in an emergency department cohort evaluated with a simple
3461 symptom-based diagnostic algorithm. *In Vivo.* 2013 Mar;27(2):215-20.
- 3462 392. Hansch A, Betge S, Poehlmann G, Neumann S, Baltzer P, Pfeil A, et al. Combined
3463 magnetic resonance imaging of deep venous thrombosis and pulmonary arteries after
3464 a single injection of a blood pool contrast agent. *Eur Radiol.* 2011;21(2):318-25.
- 3465 393. Hata T, Ikeda M, Nakamori S, Suzuki R, Kim T, Yasui M, et al. Single-photon emission
3466 computed tomography in the screening for postoperative pulmonary embolism. *Dig Dis*
3467 *Sci.* 2006 Nov;51(11):2073-80.
- 3468 394. Hayes SA, Soff GA, Zabor EC, Moskowitz CS, Liu CC, Ginsberg MS. Clinical
3469 consequences of an indeterminate CT pulmonary angiogram in cancer patients. *Clin*

- 3470 Imaging [Internet]. 2014 Sep [cited 2016 Oct 4];38(5):637-40. Available from:
3471 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4431545>
- 3472 395. Hirsch AM, Kahn SR, Morris T, Wells PS, Rodger M, Kovacs MJ, et al. PEDS
3473 (pulmonary embolism diagnosis study) a randomized controlled trial of CT pulmonary
3474 angiography and V/Q scanning in patients with suspected pulmonary embolism. Proc
3475 Am Thorac Soc. 2006;A783p.
- 3476 396. Hochuli M, Duewell S, Frauchiger B. Quantitative d-dimer levels and the extent of
3477 venous thromboembolism in CT angiography and lower limb ultrasonography. VASA.
3478 2007 Nov;36(4):267-74.
- 3479 397. Hofman MS, Beauregard JM, Barber TW, Neels OC, Eu P, Hicks RJ. ⁶⁸Ga PET/CT
3480 ventilation-perfusion imaging for pulmonary embolism: a pilot study with comparison to
3481 conventional scintigraphy. J Nucl Med [Internet]. 2011 Oct [cited 2016 Oct
3482 7];52(10):1513-9. Available from:
3483 <http://jnm.snmjournals.org/content/52/10/1513.full.pdf+html>
- 3484 398. Holmquist F, Hansson K, Pasquariello F, Bjork J, Nyman U. Minimizing contrast
3485 medium doses to diagnose pulmonary embolism with 80-kVp multidetector computed
3486 tomography in azotemic patients. Acta Radiol. 2009 Mar;50(2):181-93.
- 3487 399. Howarth DM, Booker JA, Voutnis DD. Diagnosis of pulmonary embolus using
3488 ventilation/perfusion lung scintigraphy: more than 0.5 segment of ventilation/perfusion
3489 mismatch is sufficient. Intern Med J. 2006 May;36(5):281-8.
- 3490 400. Hsiao SH, Lee CY, Chang SM, Yang SH, Lin SK, Chiou KR. Usefulness of pulmonary
3491 arterial flow discordance to identify pulmonary embolism. Am J Cardiol. 2007 Feb
3492 15;99(4):579-83.
- 3493 401. Hunsaker AR, Zou KH, Poh AC, Trotman-Dickenson B, Jacobson FL, Gill RR, et al.
3494 Routine pelvic and lower extremity CT venography in patients undergoing pulmonary
3495 CT angiography. AJR Am J Roentgenol [Internet]. 2008 Feb [cited 2016 Oct
3496 7];190(2):322-6. Available from: <http://www.ajronline.org/doi/pdf/10.2214/AJR.07.2568>
- 3497 402. Hussein W, Dalouk KA, O'Brien A. Negative predictive value of CTPA in pulmonary
3498 embolism in an Irish population. Ir Med J. 2008 Mar;101(3):92-3.
- 3499 403. Ingrisich M, Maxien D, Meinel FG, Reiser MF, Nikolaou K, Dietrich O. Detection of
3500 pulmonary embolism with free-breathing dynamic contrast-enhanced MRI. Journal of
3501 Magnetic Resonance Imaging. 2016;43(4):887-93.
- 3502 404. Inonu H, Acu B, Pazarli AC, Doruk S, Erkorkmaz U, Altunkas A. The value of the
3503 computed tomographic obstruction index in the identification of massive pulmonary
3504 thromboembolism. Diagn Interv Radiol [Internet]. 2012 May [cited 2016 Oct
3505 4];18(3):255-60. Available from:
3506 [http://www.dirjournal.org/sayilar/43/buyuk/pdf DIR 433.pdf](http://www.dirjournal.org/sayilar/43/buyuk/pdf_DIR_433.pdf)
- 3507 405. Ishiyama M, Matsusako M, Oikado K, Nishi Y, Ohi K, Hirano M, et al. Three-
3508 dimensional T2-weighted imaging using the dark blood method for detecting

- 3509 pulmonary embolisms: comparison with computed tomography angiography. *Jpn J*
3510 *Radiol.* 2011 Nov;29(9):667-72.
- 3511 406. Jia CF, Li YX, Yang ZQ, Zhang ZH, Sun XX, Wang ZQ. Prospective evaluation of
3512 unsuspected pulmonary embolism on coronary computed tomographic angiography. *J*
3513 *Comput Assist Tomogr.* 2012 Mar;36(2):187-90.
- 3514 407. Jögi J, Jonson B, Ekberg M, Bajc M. Ventilation-perfusion SPECT with 99mTc-DTPA
3515 versus Technegas: a head-to-head study in obstructive and nonobstructive disease. *J*
3516 *Nucl Med [Internet].* 2010 May [cited 2016 Oct 7];51(5):735-41. Available from:
3517 <http://jnm.snmjournals.org/content/51/5/735.full.pdf+html>
- 3518 408. Jogi J, Markstad H, Tufvesson E, Bjermer L, Bajc M. The added value of hybrid
3519 ventilation/perfusion SPECT/CT in patients with stable COPD or apparently healthy
3520 smokers. Cancer-suspected CT findings in the lungs are common when hybrid
3521 imaging is used. *Int J Chron Obstruct Pulmon Dis [Internet].* 2015 [cited 2016 Oct
3522 4];10:25-30. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4279608>
- 3523 409. Jones C, Teixeira PG, Inaba K, Keesara SR, Rhee P, Brown C, et al. Combined CT
3524 venography and CT pulmonary angiography for the detection of deep venous
3525 thrombosis in injured patients. *Am Surg.* 2008 Oct;74(10):935-8.
- 3526 410. Jordan EJ, Godelman A, Levsky JM, Zalta B, Haramati LB. CT pulmonary angiography
3527 in pregnant and postpartum women: low yield, high dose. *Clin Imaging.* 2015
3528 Mar;39(2):251-3.
- 3529 411. Junger M, Diehm C, Storiko H, Hach-Wunderle V, Heidrich H, Karasch T, et al.
3530 Mobilization versus immobilization in the treatment of acute proximal deep venous
3531 thrombosis: a prospective, randomized, open, multicentre trial. *Curr Med Res Opin.*
3532 2006 Mar;22(3):593-602.
- 3533 412. Kado R, Siegwald E, Lewis E, Goodsitt MM, Christodoulou E, Kazerooni E, et al. Utility
3534 and associated risk of pulmonary embolism computed tomography scans in the
3535 Michigan lupus cohort. *Arthritis Care Res (Hoboken).* 2016 Mar;68(3):406-11.
- 3536 413. Kamel EM, Schmidt S, Doenz F, Adler-Etehami G, Schnyder P, Qanadli SD.
3537 Computed tomographic angiography in acute pulmonary embolism: do we need
3538 multiplanar reconstructions to evaluate the right ventricular dysfunction? *J Comput*
3539 *Assist Tomogr.* 2008 May;32(3):438-43.
- 3540 414. Kiley CA, Lowry KJ, Mysliwiec V. Examination of hospital referral practices for CT
3541 pulmonary angiography. *J Hosp Med.* 2007 Jul;2(4):253-7.
- 3542 415. Kim HJ, Walcott-Sapp S, Leggett K, Bass A, Adler RS, Pavlov H, et al. The Use of
3543 spiral computed tomography scans for the detection of pulmonary embolism. *J*
3544 *Arthroplasty.* 2008;23(6 Suppl):31-5.
- 3545 416. Kligerman S, Lahiji K, Weihe E, Lin CT, Terpenning S, Jeudy J, et al. Detection of
3546 pulmonary embolism on computed tomography: improvement using a model-based
3547 iterative reconstruction algorithm compared with filtered back projection and iterative
3548 reconstruction algorithms. *J Thorac Imaging.* 2015 Jan;30(1):60-8.

- 3549 417. Koch C, Schramm R, Roller FC, Hecker A, Henrich M, Schneck E, et al. Impact of
3550 unsuspected subsegmental pulmonary embolism in ICU patients. *Anaesthesist*. 2016
3551 Feb;65(2):122-8.
- 3552 418. Konstantinides SV, Torbicki A. Management of pulmonary embolism: recent evidence
3553 and the new European guidelines. *Eur Respir J* [Internet]. 2014 Dec [cited 2016 Aug
3554 16];44(6):1385-90. Available from:
3555 <http://erj.ersjournals.com/content/erj/44/6/1385.full.pdf>
- 3556 419. Kooiman J, Klok FA, Mos IC, van der MA, DE RA, Sijpkens YW, et al. Incidence and
3557 predictors of contrast-induced nephropathy following CT-angiography for clinically
3558 suspected acute pulmonary embolism. *J Thromb Haemost* [Internet]. 2010 Feb [cited
3559 2016 Oct 7];8(2):409-11. Available from:
3560 <http://onlinelibrary.wiley.com/doi/10.1111/j.1538-7836.2009.03698.x/epdf>
- 3561 420. Korkeila PJ, Saraste MK, Nyman KM, Koistinen J, Lund J, Juhani Airaksinen KE.
3562 Transesophageal echocardiography in the diagnosis of thrombosis associated with
3563 permanent transvenous pacemaker electrodes. *Pacing Clin Electrophysiol*. 2006
3564 Nov;29(11):1245-50.
- 3565 421. Krishan S, Panditaratne N, Verma R, Robertson R. Incremental value of CT
3566 venography combined with pulmonary CT angiography for the detection of
3567 thromboembolic disease: systematic review and meta-analysis. *AJR Am J Roentgenol*.
3568 2011 May;196(5):1065-72.
- 3569 422. Kumamaru KK, Kumamaru H, Bateman BT, Gronsbell J, Cai T, Liu J, et al. Limited
3570 hospital variation in the use and yield of CT for pulmonary embolism in patients
3571 undergoing total hip or total knee replacement surgery. *Radiology*. 2016 May
3572 26;152765.
- 3573 423. Kwon WJ, Jeong YJ, Kim KI, Lee IS, Jeon UB, Lee SH, et al. Computed tomographic
3574 features of pulmonary septic emboli: comparison of causative microorganisms. *J*
3575 *Comput Assist Tomogr*. 2007 May;31(3):390-4.
- 3576 424. Lang O, Balon HR, Píichová R, Krizova H, Kuníková I. Lung tissue density measured
3577 by low-dose CT during pulmonary perfusion SPECT/CT as a tool for differentiation
3578 pulmonary embolism from chronic obstructive pulmonary disease - A pilot study. *Cor et*
3579 *Vasa*. 2013 [cited 2016 Oct 12];55(6):e492-e496.
- 3580 425. Lapergue B, Decroix JP, Evrard S, Wang A, Bendetowicz D, Offroy MA, et al.
3581 Diagnostic yield of venous thrombosis and pulmonary embolism by combined CT
3582 venography and pulmonary angiography in patients with cryptogenic stroke and patent
3583 foramen ovale. *Eur Neurol*. 2015;74(1-2):69-72.
- 3584 426. Le Roux P-Y, Delluc A, Abgral R, Reffad A, Cornily JC, Querellou S, et al. Positron
3585 emission tomography with ¹⁸F-fluorodeoxyglucose of venous thromboembolism.
3586 *Medecine Nucleaire*. 2011;35(4):179-85. in French.
- 3587 427. Le Roux PY, Robin P, Delluc A, Tardy B, Abgral R, Couturaud F, et al. Performance of
3588 ¹⁸F fluoro-2-desoxy-D-glucose positron emission tomography/computed tomography
3589 for the diagnosis of venous thromboembolism. *Thromb Res*. 2015 Jan;135(1):31-5.

- 3590 428. Lee EY, Khong PL. The value of ¹⁸F-FDG PET/contrast-enhanced CT in detection of
3591 tumor thrombus. *Clin Nucl Med*. 2013 Feb;38(2):e60-e65.
- 3592 429. Lessler AL, Isserman JA, Agarwal R, Palevsky HI, Pines JM. Testing low-risk patients
3593 for suspected pulmonary embolism: a decision analysis. *Ann Emerg Med*. 2010
3594 Apr;55(4):316-26.
- 3595 430. Lim KY, Kligerman SJ, Lin CT, White CS. Missed pulmonary embolism on abdominal
3596 CT. *Am J Roentgenol* [Internet]. 2014 [cited 2016 Oct 7];202(4):738-43. Available from:
3597 <http://www.ajronline.org/doi/pdf/10.2214/AJR.13.11436>
- 3598 431. Lucassen WA, Beenen LF, Buller HR, Erkens PM, Schaefer-Prokop CM, van den Berk
3599 I, et al. Concerns in using multi-detector computed tomography for diagnosing
3600 pulmonary embolism in daily practice. A cross-sectional analysis using expert opinion
3601 as reference standard. *Thromb Res* [Internet]. 2013 Feb [cited 2016 Oct 7];131(2):145-
3602 9. Available from:
3603 <http://www.sciencedirect.com/science/article/pii/S0049384812008481>
- 3604 432. Mao X, Wang S, Jiang X, Zhang L, Xu W. Diagnostic value of dual-source
3605 computerized tomography combined with perfusion imaging for peripheral pulmonary
3606 embolism. *Iranian Journal of Radiology*. 2016;13(2).
- 3607 433. Meinel FG, Nance JW, Schoepf UJ, Hoffmann VS, Thierfelder KM, Costello P, et al.
3608 Predictive Value of Computed Tomography in Acute Pulmonary Embolism: Systematic
3609 Review and Meta-analysis. *Am J Med*. 2015 Jul;128(7):747-59.
- 3610 434. Meysman M, Everaert H, Buls N, Nieboer K, de MJ. Comparison of ventilation-
3611 perfusion single-photon emission computed tomography (V/Q SPECT) versus dual-
3612 energy CT perfusion and angiography (DECT) after 6 months of pulmonary embolism
3613 (PE) treatment. *Eur J Radiol*. 2015 Sep;84(9):1816-9.
- 3614 435. Minshall CT, Doben AR, Leon SM, Fakhry SM, Eriksson EA. Computed tomography
3615 pulmonary angiography: more than a screening tool for pulmonary embolus. *J Crit
3616 Care*. 2015 Feb;30(1):196-200.
- 3617 436. Moon KT. SPECT V/Q scintigraphy is an option for diagnosing pulmonary embolism.
3618 *Am Fam Physician*. 2010;82(5):531-2.
- 3619 437. Morris TA, Gerometta M, Smart RC, Eisenberg P, Roach PJ, Tsui WW, et al.
3620 Pulmonary Emboli Imaging with ^{99m}Tc-labelled Anti-D-dimer (DI-80B3) Fab' Followed
3621 by SPECT. *Heart Lung and Circulation*. 2011;20(8):503-11.
- 3622 438. Morris TA, Gerometta M, Yusen RD, White RH, Douketis JD, Kaatz S, et al. Detection
3623 of pulmonary emboli with ^{99m}Tc-labeled anti-D-dimer (DI-80B3)Fab' fragments
3624 (ThromboView). *Am J Respir Crit Care Med*. 2011 Sep 15;184(6):708-14.
- 3625 439. Mortensen J, Gutte H. SPECT/CT and pulmonary embolism. *European Journal of
3626 Nuclear Medicine and Molecular Imaging*. 2014;41(Suppl 1):S81-S90.

- 3627 440. Muangman N, Totanarungroj K. Cost effectiveness of combined CT pulmonary
3628 angiography (CTPA) and indirect CTV in patient with intermediate to high probability
3629 for pulmonary embolism. *J Med Assoc Thai*. 2012 Oct;95(10):1321-6.
- 3630 441. Nazaroglu H, Ozmen CA, Akay HO, Kilinc I, Bilici A. 64-MDCT pulmonary angiography
3631 and CT venography in the diagnosis of thromboembolic disease. *AJR Am J*
3632 *Roentgenol*. 2009 Mar;192(3):654-61.
- 3633 442. Nobre C, Thomas B. Ultrasound in suspected pulmonary embolism. *Chest*.
3634 2014;146(3):e109.
- 3635 443. Palla A, Marconi L, Bigazzi F, Pistolesi M. Lung scintigraphy in the diagnosis of
3636 pulmonary embolism: pathophysiological and practical evidence. *Clinical and*
3637 *Translational Imaging*. 2014;2(5):363-7.
- 3638 444. Precious BJ, Raju R, Leipsic J. Recent advances in thoracic x-ray computed
3639 tomography for pulmonary imaging. *Can Respir J [Internet]*. 2014 [cited 2016 Oct
3640 7];21(5):307-9. Available from:
3641 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4198234/pdf/crj-21-307.pdf>
- 3642 445. Reagle Z, Tringali S, Gill N, Peterson MW. Diagnostic yield and renal complications
3643 after computed tomography pulmonary angiograms performed in a community-based
3644 academic hospital. *J Community Hosp Intern Med Perspect [Internet]*. 2012 [cited
3645 2016 Oct 4];2. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3714054>
- 3646 446. Phillips JJ, Straiton J, Staff RT. Planar and SPECT ventilation/perfusion imaging and
3647 computed tomography for the diagnosis of pulmonary embolism: A systematic review
3648 and meta-analysis of the literature, and cost and dose comparison. *Eur J Radiol*. 2015
3649 Jul;84(7):1392-400.
- 3650 447. Richard MC, Lambert R, Rey E, Turpin S. Is perfusion scintigraphy sufficient in
3651 pregnant or post-partum women? *Medecine Nucleaire*. 2015;39(6):479-85. French.
- 3652 448. Ritchie G, McGurk S, McCreath C, Graham C, Murchison JT. Prospective evaluation
3653 of unsuspected pulmonary embolism on contrast enhanced multidetector CT (MDCT)
3654 scanning. *Thorax [Internet]*. 2007 Jun [cited 2016 Oct 6];62(6):536-40. Available from:
3655 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2117210>
- 3656 449. Rodger MA, Bredeson CN, Jones G, Rasuli P, Raymond F, Clement AM, et al. The
3657 bedside investigation of pulmonary embolism diagnosis study: a double-blind
3658 randomized controlled trial comparing combinations of 3 bedside tests vs ventilation-
3659 perfusion scan for the initial investigation of suspected pulmonary embolism. *Arch*
3660 *Intern Med*. 2006 Jan 23;166(2):181-7.
- 3661 450. Rubins JB. The current approach to the diagnosis of pulmonary embolism: lessons
3662 from PIOPED II. *Postgrad Med*. 2008 Apr;120(1):1-7.
- 3663 451. Sakuma M, Nakamura M, Nakanishi N, Miyahara Y, Tanabe N, Yamada N, et al.
3664 Diagnostic and therapeutic strategy for acute pulmonary thromboembolism. *Intern Med*
3665 [Internet]. 2006 [cited 2016 Oct 13];45(12):749-58. Available from:
3666 https://www.jstage.jst.go.jp/article/internalmedicine/45/12/45_12_749/pdf

- 3667 452. Salaun PY, Le Duc-Pennec A, Le Gal G, Couturaud F, Guillo P, Mottier D, et al.
3668 Management of suspected pulmonary embolism patients with low clinical and low V/Q
3669 probability. *Thromb Res.* 2008;122(4):450-4.
- 3670 453. Sampson FC, Goodacre SW, Thomas SM, van Beek EJ. The accuracy of MRI in
3671 diagnosis of suspected deep vein thrombosis: systematic review and meta-analysis.
3672 *Eur Radiol.* 2007 Jan;17(1):175-81.
- 3673 454. Sangwaiya MJ, Kalra MK, Sharma A, Halpern EF, Shepard JA, Digumarthy SR. Dual-
3674 energy computed tomographic pulmonary angiography: a pilot study to assess the
3675 effect on image quality and diagnostic confidence. *J Comput Assist Tomogr.* 2010
3676 Jan;34(1):46-51.
- 3677 455. Sasbou T, Tachinante R, Tazi Saoud A, Ksayr R, Ben Rais Aouad N. Place of
3678 scintigraphy in the diagnosis of pulmonary embolism in pregnant women-About 17
3679 cases. *Medecine Nucleaire.* 2013;37(10-11):439-45. French.
- 3680 456. Sawyer KN, Shah P, Qu L, Kurz MC, Clark CL, Swor RA. Triple rule ot versus CT
3681 angiogram plus stress test for evaluation of chest pain in the emergency department.
3682 *West J Emerg Med [Internet].* 2015 Sep [cited 2016 Oct 4];16(5):677-82. Available
3683 from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4644034>
- 3684 457. Schiebler ML, Ahuja J, Repplinger MD, Francois CJ, Vigen KK, Grist TM, et al.
3685 Incidence of actionable findings on contrast enhanced magnetic resonance
3686 angiography ordered for pulmonary embolism evaluation. *Eur J Radiol.* 2016
3687 Aug;85(8):1383-9.
- 3688 458. Schonfeld C, Cebotari S, Voskrebenezv A, Gutberlet M, Hinrichs J, Renne J, et al.
3689 Performance of perfusion-weighted Fourier decomposition MRI for detection of chronic
3690 pulmonary emboli. *J Magn Reson Imaging.* 2015 Jul;42(1):72-9.
- 3691 459. Scialpi M, Rebonato A, Cagini L, Brunese L, Pisciole I, Pierotti L, et al. Split-bolus
3692 single-pass multidetector-row CT protocol for diagnosis of acute pulmonary embolism.
3693 *Iranian Journal of Radiology [Internet].* 2016 [cited 2016 Oct 7];13(1):e19844. Available
3694 from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4837285/pdf/iranjradiol-13-01-19844.pdf>
3695 [19844.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4837285/pdf/iranjradiol-13-01-19844.pdf)
- 3696 460. Scott K, Rutherford N, Fagermo N, Lust K. Use of imaging for investigation of
3697 suspected pulmonary embolism during pregnancy and the postpartum period. *Obstet*
3698 *Med [Internet].* 2011 Mar [cited 2016 Oct 6];4(1):20-3. Available from:
3699 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4989656>
- 3700 461. Sellem A, Elajmi W, Mahjoub Y, Hammami H. Diagnosis pulmonary embolism in
3701 pregnancy: contribution of lung scintigraphy. Retrospective study about 116cases.
3702 *Medecine Nucleaire.* 2013;37(10-11):432-8. in French.
- 3703 462. Serra W, Crisafulli E, Sverzellati N, Ugolotti PT, Tzani P, Marangio E, et al.
3704 Transthoracic echocardiography and chest computed tomography arteriography in
3705 patients with acute pulmonary embolism: a two-year follow-up study. *Respiration.* 2016
3706 Sep 8.

- 3707 463. Shahir K, Goodman LR, Lam CA, Midia EC. Dose reduction of 69% for computed
3708 tomography pulmonary angiography: reduced z-axis computed tomography pulmonary
3709 angiography retains accuracy in those younger than 40 years. *J Comput Assist*
3710 *Tomogr.* 2013 Sep;37(5):765-9.
- 3711 464. Shao W, Zhang F, Zuo S, Wang X, Song J. Lower limb deep vein thrombosis in
3712 patients with suspected pulmonary embolism detected with ^{99m}Tc-MAA simultaneously
3713 with lung perfusion scan. *Hell J Nucl Med.* 2012;15(3):220-3+270.
- 3714 465. Silva S, Biendel C, Ruiz J, Olivier M, Bataille B, Geeraerts T, et al. Usefulness of
3715 cardiothoracic chest ultrasound in the management of acute respiratory failure in
3716 critical care practice. *Chest.* 2013 Sep;144(3):859-65.
- 3717 466. Sinzinger H, Berent R, Kummer F. Value of ventilation/perfusion SPECT for diagnosis
3718 of pulmonary embolism. *European Journal of Nuclear Medicine and Molecular*
3719 *Imaging.* 2015;42(6):977-8.
- 3720 467. Slater S, Oswal D, Bhartia B. A retrospective study of the value of indirect CT
3721 venography: a British perspective. *Br J Radiol [Internet].* 2012 Jul [cited 2016 Oct
3722 4];85(1015):917-20. Available from:
3723 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3474055>
- 3724 468. Stein PD, Woodard PK, Weg JG, Wakefield TW, Tapson VF, Sostman HD, et al.
3725 Diagnostic pathways in acute pulmonary embolism: recommendations of the PIOPED
3726 II investigators. *Am J Med.* 2006 Dec;119(12):1048-55.
- 3727 469. Stein PD, Gottschalk A, Sostman HD, Chenevert TL, Fowler SE, Goodman LR, et al.
3728 Methods of prospective investigation of pulmonary embolism diagnosis III (PIOPED
3729 III). *Semin Nucl Med [Internet].* 2008 Nov [cited 2016 Oct 7];38(6):462-70. Available
3730 from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2605689>
- 3731 470. Su J, Zhai RY, Jiang T, Ma ZH, Liu M. Suspected pulmonary thromboembolism and
3732 deep venous thrombosis: a comprehensive 64-slice multidetector computed
3733 tomography diagnosis in gynecologic patients. *Chin Med J [Internet].* 2015 Jun 5 [cited
3734 2016 Oct 4];128(11):1549-51. Available from:
3735 http://www.cmj.org/temp/ChinMedJ128111549-4431971_121839.pdf
- 3736 471. Subedi D, Bell D, Lewinski MJB, Aslam S, Murchison JT. Use of SimpliRED D-dimer
3737 assay and computerised tomography in the diagnosis of acute pulmonary embolism.
3738 *Acute Med.* 2009;8(2):84-6.
- 3739 472. Sun S, Semionov A, Xie X, Kosiuk J, Mesurole B. Detection of central pulmonary
3740 embolism on non-contrast computed tomography: a case control study. *Int J*
3741 *Cardiovasc Imaging.* 2014 Mar;30(3):639-46.
- 3742 473. Szucs-Farkas Z, Schaller C, Bensler S, Patak MA, Vock P, Schindera ST. Detection of
3743 pulmonary emboli with CT angiography at reduced radiation exposure and contrast
3744 material volume: comparison of 80 kVp and 120 kVp protocols in a matched cohort.
3745 *Invest Radiol.* 2009 Dec;44(12):793-9.

- 3746 474. Szucs-Farkas Z, Christe A, Megyeri B, Rohacek M, Vock P, Nagy EV, et al. Diagnostic
3747 accuracy of computed tomography pulmonary angiography with reduced radiation and
3748 contrast material dose: a prospective randomized clinical trial. *Invest Radiol*. 2014
3749 Apr;49(4):201-8.
- 3750 475. Takagi H, Umemoto T. An algorithm for managing suspected pulmonary embolism.
3751 *JAMA*. 2006;295(22):2603-4.
- 3752 476. Tarr GP, Modahl L, Jones P. Wells score, D-dimer testing and computer tomographic
3753 pulmonary angiography appropriateness in the Auckland Hospital Adult Emergency
3754 Department. *N Z Med J [Internet]*. 2015 [cited 2016 Oct 14];128(1413):81-3. Available
3755 from: [https://www.nzma.org.nz/ data/assets/pdf file/0015/42171/Tarr.pdf](https://www.nzma.org.nz/data/assets/pdf_file/0015/42171/Tarr.pdf)
- 3756 477. Thomeer MG, Pattynama PM, Hartmann IJ, Kieft GJ, Van Strijen MJ. High incidence of
3757 isolated subsegmental pulmonary emboli on multi-slice spiral CT: a comparative
3758 clinical study. *Thromb Haemost*. 2006 May;95(5):914-5.
- 3759 478. Tunariu N, Gibbs SJ, Win Z, Gin-Sing W, Graham A, Gishen P, et al. Ventilation-
3760 perfusion scintigraphy is more sensitive than multidetector CTPA in detecting chronic
3761 thromboembolic pulmonary disease as a treatable cause of pulmonary hypertension. *J*
3762 *Nucl Med [Internet]*. 2007 May [cited 2016 Oct 6];48(5):680-4. Available from:
3763 <http://jnm.snmjournals.org/content/48/5/680.full.pdf+html>
- 3764 479. Viau P, Franken P, Padovani B, Koulibaly PM, Benoliel J, Razzouk M, et al. Hybrid
3765 imaging for the diagnosis of acute pulmonary embolism: contribution of CT combined
3766 to V/P SPECT. *Med Nucl*. 2011;35(3):117-25. in French.
- 3767 480. Vongchaiudomchoke T, Boonyasirinant T. Positive Pulmonary Computed Tomography
3768 Angiography in Patients with Suspected Acute Pulmonary Embolism: Clinical
3769 Prediction Rules, Thromboembolic Risk Factors, and Implications for Appropriate Use.
3770 *J Med Assoc Thai*. 2016 Jan;99(1):25-33.
- 3771 481. Wu L, Yao Y, Chen G, Fan X, Zheng L, Ding L, et al. Intracardiac thrombosis in
3772 patients with arrhythmogenic right ventricular cardiomyopathy. *J Cardiovasc*
3773 *Electrophysiol*. 2014 Dec;25(12):1359-62.
- 3774 482. Zhu L, Wang C, Yang Y, Wu Y, Zhai Z, Dai H, et al. Value of transthoracic
3775 echocardiography in therapy regimens evaluation in pulmonary embolism. *J Thromb*
3776 *Thrombolysis*. 2008 Dec;26(3):251-6.
- 3777 483. Le Roux PY, Abgral R, Jaffrelot M, Delluc A, Gut-Gobert C, Querellou S, et al.
3778 Diagnosis of pulmonary embolism: planar images generated from V/Q SPECT are not
3779 a reliable substitute for traditional planar V/Q scan. *Nucl Med Commun*. 2012
3780 Jul;33(7):695-700.
- 3781 484. Doyle NM, Ramirez MM, Mastrobattista JM, Monga M, Wagner LK, Gardner MO.
3782 Diagnosis of pulmonary embolism: a cost-effectiveness analysis. *Am J Obstet*
3783 *Gynecol*. 2004 Sep;191(3):1019-23.
- 3784 485. Larcos G, Chi KK, Shiell A, Berry G. Suspected acute pulmonary emboli: cost-
3785 effectiveness of chest helical computed tomography versus a standard diagnostic

3786 algorithm incorporating ventilation-perfusion scintigraphy. Aust N Z J Med. 2000
3787 Apr;30(2):195-201.

3788 486. Ward MJ, Sodickson A, Diercks DB, Raja AS. Cost-effectiveness of lower extremity
3789 compression ultrasound in emergency department patients with a high risk of
3790 hemodynamically stable pulmonary embolism. Acad Emerg Med. 2011;18(1):22-31.

3791

3792

3793

DRAFT

3794 **Appendices**

3795 **Appendix 1: Literature search strategy**

3796 **Clinical Database Search**

3797

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
oemzd	Ovid database code; Embase 1974 to present, updated daily

3798
3799

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/

(magnetic resonance imag* or MR imag* or MRI* or fMRI* or magnetic resonance tomograph* or MR tomograph* or magnetization transfer contrast imag* or magnetisation

13 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/

(radionuclide imag* or gamma camera imag* or perfusion imaging or lung perfusion or

16 scintigraph* or scintigram* or scintiphograph* 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/
(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.

105

106 104 or 105
exp scintigraphy/ or single photon emission computer tomography/ or exp scintiscanning/

107 lung scintiscanning/
(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.

108

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/
(ultrasound or sonogra* or ultrasonic or ultrasonogra* or echotomogra* or echogra* or doppler).ti,ab,kw.

119

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

(cardiac echo* or heart echo* or echocardiogra* or echo-cardiogra* or cardiac echogra* or

125 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 oomezd

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

3800
3801

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	Searched to capture records not indexed in MEDLINE. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used.

Reviews (CDSR)	
Database of Abstracts of Reviews of Effects (DARE)	
Cochrane Central Register of Controlled Trials	
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.

3802

3803 **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
oemzd	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.
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
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-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

	<p>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.</p>
95	<p>((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.</p>
96	<p>((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</p>
97	<p>((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</p>

	complan* or noncomplan* 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
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 oemez
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

3805
3806
3807
3808

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.

3809
3810
3811

3812 **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
oomezd	Ovid database code; Embase 1974 to present, updated daily

3813
3814

MULTI-STRATEGY SEARCH	
#	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 scintiphograph* 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.
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 scintiphograph* 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 oemez
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 oemez
113	112 not conference abstract.pt.
114	39 or 79 or 95 or 113
115	exp Ethics/
116	exp Privacy/
117	exp Sociology/
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/
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

3816

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.

3817
3818

DRAFT

3819 **Implementation Issues Database Search**
 3820

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
 omezd Ovid database code; Embase 1974 to present, updated daily

3821
 3822

MULTI-STRATEGY SEARCH

#	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 scintiphograph* 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.
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 scintiphograph* 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 oomezd
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 oomezd
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
141	limit 140 to yr="2006 -Current"
142	limit 141 to (english or french)
143	remove duplicates from 142

3824

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 &	Searched to capture records not indexed in MEDLINE. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate

Humanities) syntax used.

3825
3826
3827
3828

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
oomezd Ovid database code; Embase 1974 to present, updated daily

3829
3830

MULTI-STRATEGY SEARCH

#	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 oomezd
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.
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/
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

3832
3833
3834

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 (Environmental Science subject area)	Searched to capture records not indexed in MEDLINE. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used.

3835
3836
3837
3838

Grey Literature

Dates for Search:	Sept 2016
Keywords:	Pulmonary embolism, venous thromboembolism
Limits:	Publication years 2006 – Sept 2016

3839
3840
3841
3842
3843
3844
3845
3846
3847
3848
3849
3850

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

3851 **Appendix 2: Clinical Full-Text Screening Checklist**

3852
 3853 Reviewer: _____ Date: _____
 3854

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 1)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2) The interventions of interest:			
Risk Stratification Strategies			
• Wells or Geneva rules			
• PERC			
• D-Dimer			
• Biochemical or imaging studies	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Imaging			
• CT-based studies			
• MRI-based studies			
• V/Q-based studies			
• PET-based studies			
• Thoracic ultrasound			
3) 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)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
• Direct patient harms			
5) The study designs of interest:			
• SR	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
• MA			

- HTA
- RCT
- NRS
- CS

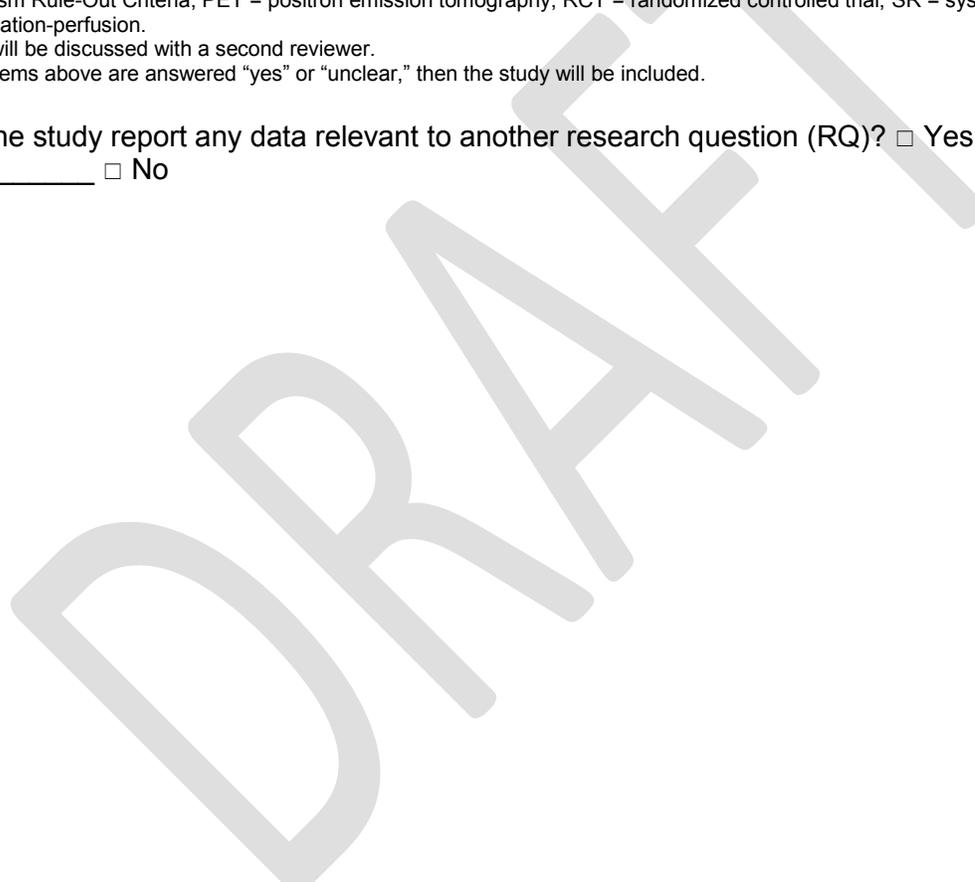
Decision to include the study: ^b	Yes <input type="checkbox"/>	No <input type="checkbox"/>
Reason(s) for exclusion:	<input type="checkbox"/> Inappropriate study population <input type="checkbox"/> No intervention of interest <input type="checkbox"/> No or inappropriate comparator <input type="checkbox"/> No relevant outcomes <input type="checkbox"/> Irrelevant study design <input type="checkbox"/> Study description only <input type="checkbox"/> Other: _____	

3855 CS = case series; CT = computed tomography; DTA = diagnostic test accuracy; HTA = health technology assessment; MA = meta-
 3856 analysis; MRI = magnetic resonance imaging; NRS = non-randomized study; PE = pulmonary embolism; PERC = Pulmonary
 3857 Embolism Rule-Out Criteria; PET = positron emission tomography; RCT = randomized controlled trial; SR = systematic review; V/Q
 3858 = ventilation-perfusion.

3859 ^aThis will be discussed with a second reviewer.

3860 ^bIf all items above are answered "yes" or "unclear," then the study will be included.

3861
 3862 Did the study report any data relevant to another research question (RQ)? Yes: RQ#
 3863 _____ No
 3864



3865 **Appendix 3: Clinical Data Extraction Form for Primary Studies**

3866
3867 Reviewer: _____ Date: _____
3868

STUDY CHARACTERISTICS	
Ref ID:	
Author(s):	
Publication title	
Publication year:	
Country (where the study was conducted):	
Funding:	

3869

METHODOLOGY	
Study design:	<input type="checkbox"/> RCT <input type="checkbox"/> NRS <input type="checkbox"/> CS
Details of study design	
Number of included participants:	
Study eligibility criteria:	
Period of conduct:	
Setting of conduct:	<input type="checkbox"/> Emergency room <input type="checkbox"/> Secondary or tertiary in-patient care <input type="checkbox"/> Primary care <input type="checkbox"/> Rural <input type="checkbox"/> Remote <input type="checkbox"/> Urban
Subgroup analyses	
Multivariate analyses	

3870 CS = case series; NRS = non-randomized study; RCT = randomized controlled trial.
3871

POPULATION	
Age	
Clinical condition or subgroup	<input type="checkbox"/> Trauma or ICU <input type="checkbox"/> Pregnancy <input type="checkbox"/> Cancer <input type="checkbox"/> Hemodynamically unstable <input type="checkbox"/> Oral contraceptive or HRT <input type="checkbox"/> Obesity <input type="checkbox"/> Renal insufficiency <input type="checkbox"/> Allergy to contrast dye <input type="checkbox"/> Patients with COPD or pneumonia <input type="checkbox"/> Elderly patients <input type="checkbox"/> Patients with inherited or acquired thrombophilias
Sex	

3872 COPD = chronic obstructive pulmonary disease; HRT = hormone replacement therapy; ICU = intensive care unit.
3873

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	

3874 ^a Including any information about age-specific cut-offs (e.g., for D-dimer)

3875

REPORTED OUTCOMES	
Primary (including definition):	
Secondary (including definition):	
Length of follow-up:	

3876

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:	

3877

3878 Did the study report any data relevant to another research question (RQ)? Yes: RQ#

3879 _____ No

3880

3881 **Appendix 4: Clinical Data Extraction Form for Systematic Reviews**

3882
3883 Reviewer: _____ Date: _____
3884

STUDY CHARACTERISTICS	
Ref ID:	
Author(s):	
Publication title	
Publication year:	
Country (where the study was conducted):	
Funding:	

3885

METHODOLOGY	
Study design:	<input type="checkbox"/> SR <input type="checkbox"/> MA <input type="checkbox"/> 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:	

3886 HTA = health technology assessment; MA = meta-analysis; SR = systematic review.
3887

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:	

3888

REPORTED OUTCOMES	
Primary (including definition):	
Secondary (including definition):	
Length of follow-up:	

3889

RESULTS (TO BE COMPLETED FOR EACH COMPARISON AND OUTCOME)	
Comparison	
Intervention:	
Comparator:	

Outcome	
Study (1 st 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)	
<i>P</i> value for effect	
<i>I</i> ² statistics	
NMA	
DTA (95% CI)	
<i>P</i> value for effect	
Subgroups	
Subgroup 1:	
Number of included studies	
DTA or effect estimate (95% CI)	
<i>P</i> value for effect	
<i>I</i> ² statistics	
Subgroup 2:	
Number of included studies	
DTA or effect estimate (95% CI)	
<i>P</i> value for effect	
<i>I</i> ² statistics	
(Add subgroups as needed)	
Meta-regression	
Variables	
Variable 1:	
Variable 2:	
(Add variables as needed)	
Main conclusions:	

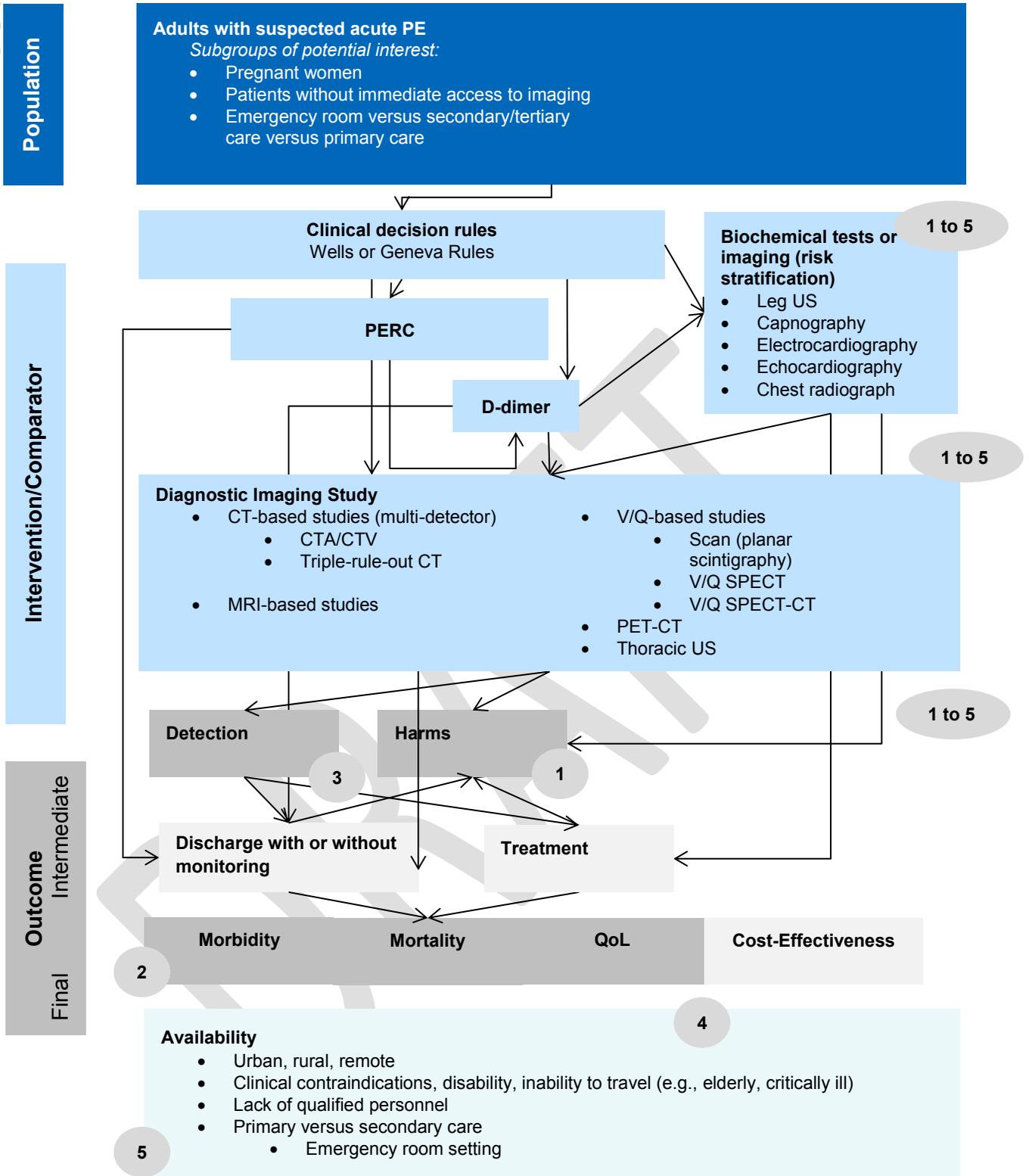
CI = confidence interval; DTA = diagnostic test accuracy; MA = meta-analysis; NMA = network meta-analysis.

3890
3891
3892
3893
3894

Did the systematic review report any data relevant to another research question (RQ)? Yes:
RQ# _____ No

3895 **Appendix 5: Pulmonary Embolism Diagnosis and Management**
 3896 **Strategies and Subsequent Outcomes**

3897
 3898
 3899
 3900



1	Clinical effectiveness (safety)
2	Clinical utility
3	Diagnostic accuracy
4	Cost-effectiveness
5	Factors influencing modality implementation and use

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; V/Q = ventilation-perfusion.

3901 **Appendix 6: Selection Criteria for Network Meta-Analysis**

3902

Table A1: Selection Criteria for Network Meta-Analysis

Population	
Q2 and 3: Adult patients undergoing testing for acute PE^a <u>Patient subgroups of interest:</u> <ul style="list-style-type: none"> • 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 (\pm clinical decision rule \pm biochemical or imaging-based risk stratification strategies ^b) <ul style="list-style-type: none"> • CT technologies^c • MRI technologies • V/Q-based technologies^d • PET-CT • Thoracic ultrasound (+ echocardiography) 	Q2 and 3A: <ul style="list-style-type: none"> • 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 (\pm clinical decision rule \pm biochemical or imaging-based risk stratification strategies)
Outcomes ^e	
Q2 and 3: <ul style="list-style-type: none"> 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 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	
<ul style="list-style-type: none"> 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)	

3903 \pm = with or without; AUROC = area under the receiver operating curve; CT = computed tomography; CTV/CTA = computed tomographic angiography in combination with venous-
 3904 phase imaging; DOR = diagnostic odds ratio; DVT = deep vein thrombosis; MRI = magnetic resonance imaging; NLR = negative likelihood ratio; NPV = negative predictive value; PE =
 3905 pulmonary embolism; PET-CT = positron emission tomography – computed tomography; PLR = positive likelihood ratio; PPV = positive predictive value; RCT = randomized controlled
 3906 trial; SPECT = single-photon emission computed tomography; V/Q = ventilation-perfusion; VTE = venous thromboembolism.
 3907 ^a Excluding pediatric patients, patients with recurrent VTE, and patients with suspected DVT.
 3908 ^b Leg compression US, capnography, electrocardiography, echocardiography, chest radiograph.
 3909 ^c Excluding single-detector, including CTA/CTV and triple-rule-out CT.
 3910 ^d Including planar V/Q scan, V/Q SPECT, V/Q SPECT-CT.
 3911 ^e No restriction on length of follow-up.

3912
3913
3914
3915
3916

^f 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).

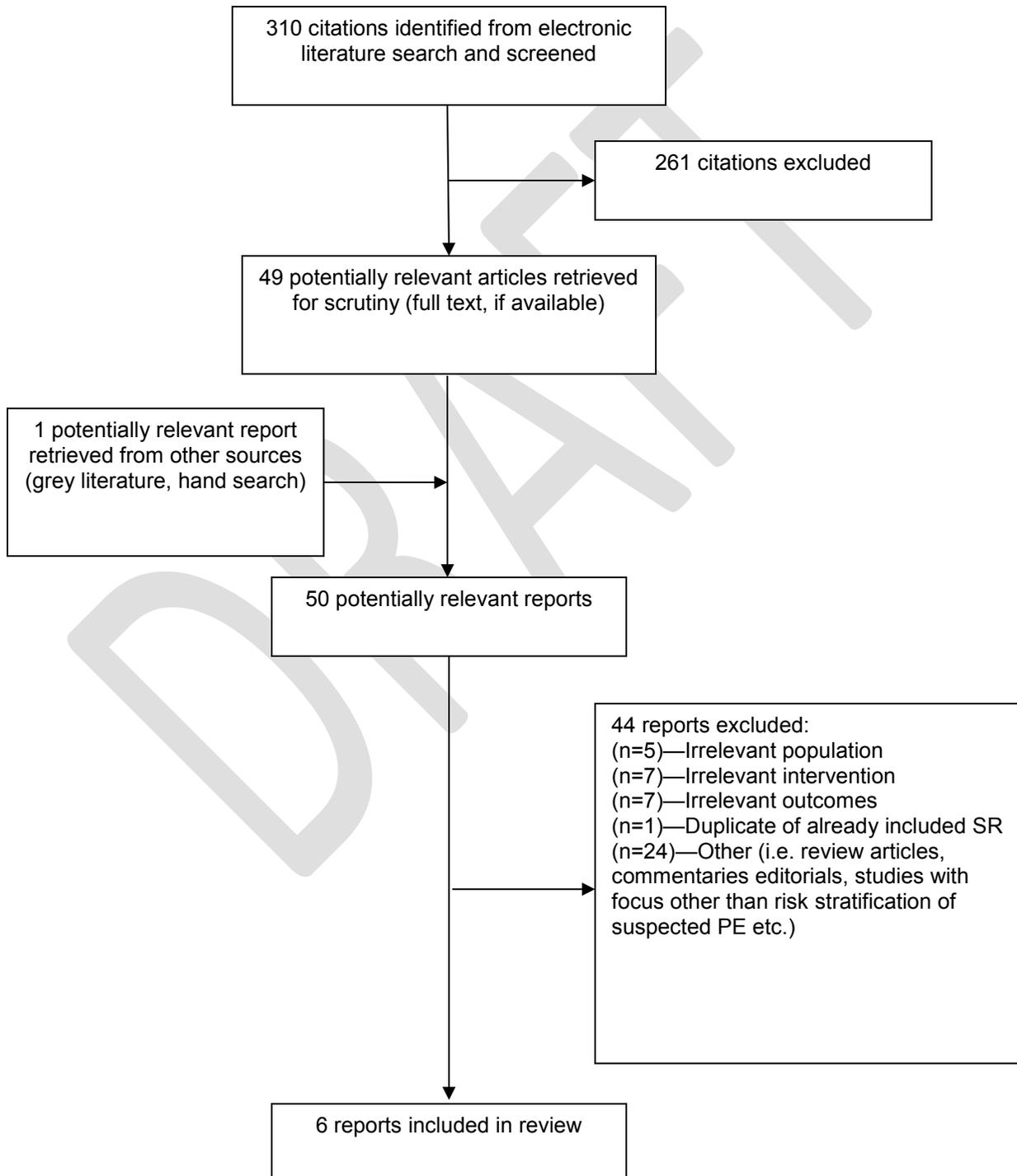
^g The proportion of patients in the study cohort stratified to the group with low predicted probability of PEs (sum of true and false-negatives/total cohort).

DRAFT

3917
3918

3919 Appendix 7: Study Selection Flowchart (PRISMA) for Clinical Review

3920
3921 **FIGURE A1: PRISMA Flowchart for Study Selection for the Overview of Systematic**
3922 **Reviews of Risk Stratification Strategies**
3923



3924

3925

3926

3927

3928

3929

3930

3931

3932

3933

3934

3935

3936

3937

3938

3939

3940

3941

3942

3943

3944

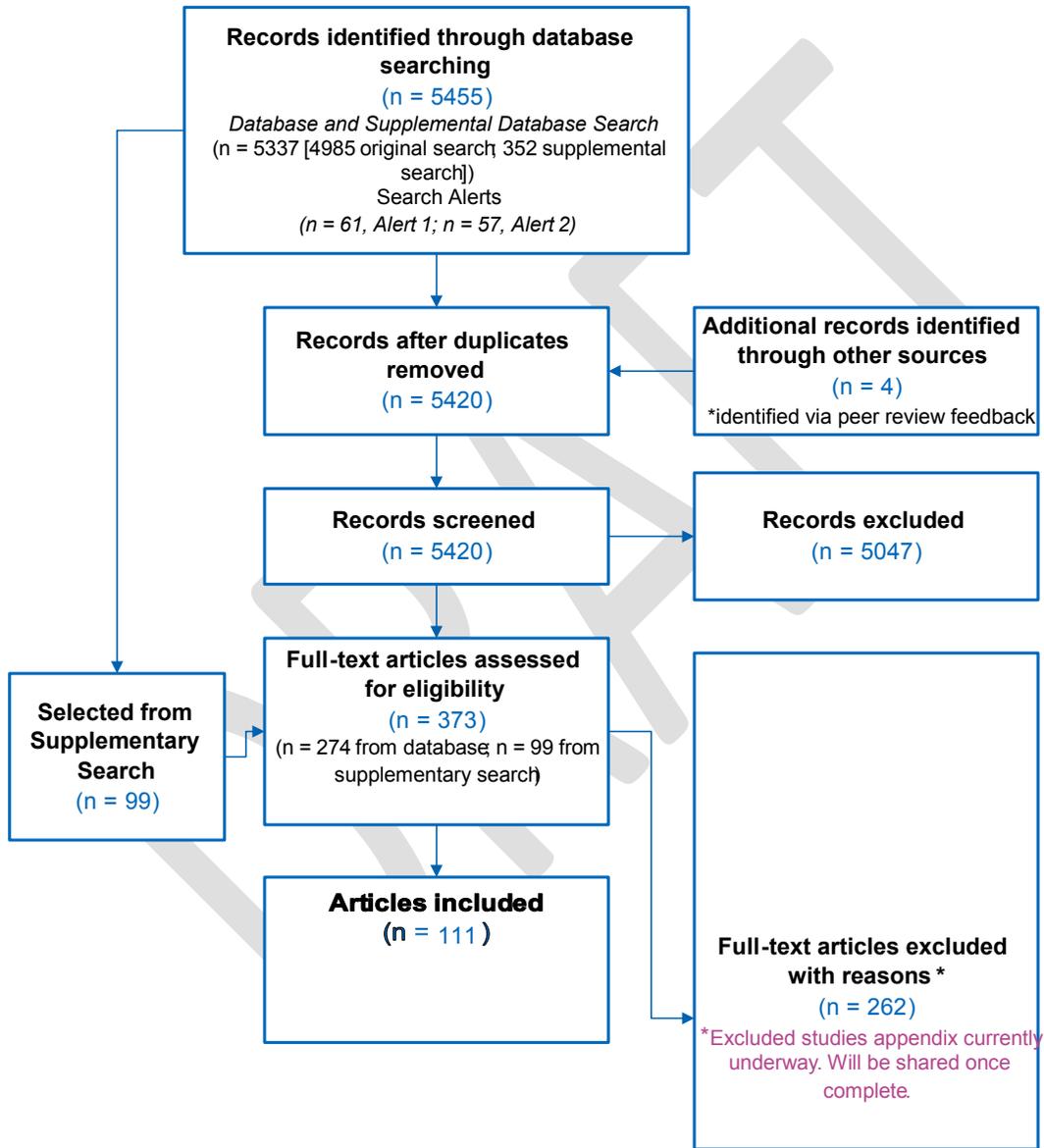
3945

3946

3947

3948

3949 **Figure A 2: PRISMA Flowchart for Diagnostic Imaging and Pathway Studies (Research**
3950 **Questions 2 and 3)**



3951

3952

3953 **Appendix 8: Overlap Among Primary Studies from Included**
 3954 **Systematic Reviews**

3955

	First Author, Publication Year	Lucassen, 2011 ²⁶	Shen, 2016 ²⁴	Siccama, 2011 ⁹⁷	Van Es, 2016 ^{98,324}	Sanders, 2015 ⁹⁹	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						•

	First Author, Publication Year	Lucassen, 2011 ²⁶	Shen, 2016 ²⁴	Siccama, 2011 ⁹⁷	Van Es, 2016 ^{98,324}	Sanders, 2015 ⁹⁹	Wang, 2016 ²⁵
32	Klok, 2008	•	•				
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			•			
67	Sohne, 2006			•			
68	Soo Hoo, 2011						•

	First Author, Publication Year	Lucassen, 2011 ²⁶	Shen, 2016 ²⁴	Siccama, 2011 ⁹⁷	Van Es, 2016 ^{98,324}	Sanders, 2015 ⁹⁹	Wang, 2016 ²⁵
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

3956

3957

DRAFT

3958 **Appendix 9: List of Excluded Studies for Clinical Review (Questions 1,**
 3959 **2, and 3)**

3960
 3961
 3962
 3963

Question 1: Overview of Systematic Reviews

	Author, Year	Reasons for Exclusion
1	Adams, 2014 ³²⁵	Other—Summary of an article without a specified CDR
2	Akgul 2013 ³²⁶	Other—Narrative article
3	Ayaram, 2013 ³²⁷	Other—Insufficient numbers of patients with PE
4	Barnes, 2016 ¹⁰¹	Irrelevant Outcome—No diagnostic accuracy or comparative utility outcome
5	Becattini, 2012 ³²⁸	Other—Association between D-dimer levels and mortality and/or markers of PE severity
6	Ceriani, 2010 ³²⁹	Irrelevant Outcome—Prevalence
7	Carrier, 2010 ³³⁰	Irrelevant outcomes—Single vs. multi-slice CTPA
8	Challen, 2011 ³³¹	Irrelevant study—Scoping Review
9	Crawford, 2016 ³³²	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 ³²	Irrelevant Intervention—Data on CUS alone
11	Douketis, 2011 ³³³	Irrelevant population—Patients with recurrent PE
12	Emerg Med J 2011 ³³⁴	Other—Abstract with insufficient information
13	Geersing, 2009 ²⁹	Other—Out of study selection date range
14	Graham, 2013 ³³⁵	Other—Prognosis of PE in HIV
15	Hallifax 2015 ³³⁶	Irrelevant population—Not suspected PE patients
16	Hendriksen, 2015 ³³⁷	Other—Validation study of all diagnostic prediction models
17	J of Thromb 2013 ³³⁸	Other—A corrigendum to an excluded study
18	Klok, 2008 ³³⁹	Irrelevant intervention—BNP
19	Kohn, 2015 ³⁴⁰	Irrelevant Outcome—All-cause mortality in early post-acute PE
20	Manara, 2013 ³⁴¹	Irrelevant intervention—Data on capnography alone
21	Mos, 2009 ³⁴²	Irrelevant outcome—Not specifically associated with CDRs
22	Mos, 2014 ³⁴³	Irrelevant population—Suspected recurrent PE patients
23	Pasha, 2010 ²⁰	Other—Out of study selection date range
24	Quatu, 2014 ³⁴⁴	Other—Narrative review
25	Pulivarthi, 2014 ³⁴⁵	Other—Narrative review
26	Raymakers, 2014 ²²⁰	Irrelevant outcome—Cost-effectiveness
27	Rehnberg, 2014 ³⁴⁶	Other—Insufficient information for appraisal
28	Schouten, 2013 ³⁴⁷	Other—Findings are not adequately specific to CPRs. Study is not specifically for PE
29	Self, 2012 ³⁴⁸	Other—Editor’s note and discussion points on study/insufficient info
30	Self, 2012 ³⁴⁹	Other—Summary of finding of meta-analysis of PERC alone
31	Sharma, 2012 ³⁵⁰	Irrelevant intervention—Thromboprophylaxis
32	Singh, 2012 ³⁵¹	Irrelevant intervention—Sole focus on PERC
33	Singh, 2014 ²⁴⁰	Irrelevant intervention—Sole focus on PERC
34	Squizzato 2012 ³⁵²	Irrelevant population—Not suspected PE patients
35	Stevens, 2012 ³⁵³	Other—Summary of findings of and commentary on already included study
36	Tafur 2014 ³⁵⁴	Irrelevant population—Not suspected PE patients
37	Van der Pol, 2016 ³³	Other—Only one primary studies with some relevant outcomes
38	van Es 2016 ³²⁰	Other—Abstract with insufficient information
39	van Es 2016 ⁹⁸	Duplicate of already included study
40	Van Es, 2017 ³⁵⁵	Other—Post-hoc analysis of data from already included study.
41	van Leent, 2015 ³⁵⁶	Other—Cost effectiveness of Dabigatran vs. Vit K
42	Wessler, 2015 ³⁵⁷	Other—Non-specific intervention and PE outcomes
43	Witt 2011 ³⁵⁸	Other—Commentary
44	Zhou, 2012 ³⁵⁹	Irrelevant intervention—PESI to evaluate prognosis of PE

3964

3965 Questions 2 and 3: Primary studies

	Author, Year	Comment
1.	Abujideh, 2009 ³⁶⁰	Evaluation of CTPA reporting
2.	Akgul 2013 ³²⁶	Narrative article
3.	Alhadad 2012 ³⁶¹	Not suspected PE patients/irrelevant outcomes
4.	Ann Int Med 2015 ³⁶²	Guideline summary
5.	Ann-In med, 2010 ³⁶³	Summary for patients
6.	Arnason 2007 ³⁶⁴	Primary study for CDR and diagnostic algorithm. Irrelevant outcome – ‘appropriate diagnostic work-up’
7.	Astani, 2014 ³⁶⁵	The focus is on radiation doses not diagnostic ability. The doses of radiation used in each modality were significantly below the thresholds for clinical concern and thus raises questions about the clinical significance of the study findings.
8.	Ayaram, 2013 ³²⁷	Insufficient numbers of patients with PE
9.	Bajc, 2012 ³⁶⁶	Narrative review
10.	Baliga 2008 ³⁶⁷	Incomplete article. <i>Note: I did not see the authors name (Baliga) on the paper</i>
11.	Bannas 2014 ³⁶⁸	Identification of signal drops that were due to truncation artifacts, not PE
12.	Barnes, 2016 ¹⁰¹	Might be useful for patient input purposes
13.	Bates 2016 ³⁶⁹	Irrelevant study
14.	Becattini, 2012 ³²⁸	Association between D-dimer levels and mortality and/or markers of PE severity
15.	Bejic, 2015 ³⁷⁰	Post-diagnosis imaging
16.	Blackmore, 2012 ³⁷¹	Irrelevant outcomes
17.	Boldt, 2013 ³⁷²	Irrelevant outcomes
18.	Brader, 2008 ³⁷³	Paddlewheel reformations
19.	Branch, 2013 ³⁷⁴	CT sensitivity to detect obstructive CAD in ACS patients
20.	Carrier, 2010 ³³⁰	Single vs. multi-slice CTPA
21.	Callejas, 2014 ³⁷⁵	Not suspected PE patients, unclear outcome (VTE) reporting
22.	Challen, 2011 ³³¹	Scoping Review
23.	Corrigan, 2015 ¹⁰¹	Narrative review
24.	Darze, 2012 ³⁷⁶	NPV of re-current VTE
25.	Douketis, 2011 ³³³	Recurrent PE
26.	Douma, 2010 ³⁷⁷	Comparison of 4-slices and 64-slices MCTA devices
27.	Duralde, 2012 ³⁷⁸	Arthroscopic Transtendinous Repair
28.	Easther, 2016 ³⁷⁹	Guideline
29.	Emerg Med J 2011 ³³⁴	Abstract/insufficient information
30.	Engelke 2006 ³⁸⁰	Patients with unsuspected PE
31.	Ersoy, 2007 ³⁸¹	Image quality of MRA scans. Incomplete comparison of MRA to CTA
32.	Fabia Vallis, 2015 ³⁸²	Study in patients with a history of VTE, thus recurrence DVT/PE
33.	Fabia Vallis, 2015 ³⁸² suppl	Supplemental with not additional relevant data or information

34.	Feragalli 2012 ³⁸³	Research question was not about technology/device but scanning of additional body parts
35.	Ferreira, 2016 ³⁸⁴	Study in patients already diagnosed as not having PE
36.	Flaveli, 2014 ³⁸⁵	Incidental diagnoses of PE
37.	Garg 2008 ³⁸⁶	Unsure of suspected PE; irrelevant outcome; and insufficient details
38.	Ghazvinian, 2016 ³⁸⁷	Study in patients already diagnosed with small PE
39.	Glaser, 2011 ³⁸⁸	Interpretation and reporting strategy for V/Q lung scan
40.	Goldhaber, 2010 ⁶²	Abstract/commentary
41.	Graham, 2013 ³³⁵	Prognosis in HIV
42.	Grimm, 2013 ³⁸⁹	Utility of the ventilation phase when the perfusion phase is defective
43.	Gruettner, 2013 ³⁹⁰	Irrelevant P and I
44.	Gruettner, 2013 ³⁹¹	An in-house algorithm for PE diagnosis of a hospital
45.	Gupta, 2014 ¹¹⁷	Study of integrity of data entry
46.	Hallifax 2015 548	Not suspected PE patients
47.	Hansch, 2011 ³⁹²	A feasibility study in patients with no clinical signs of PE (i.e. unsuspected PE)
48.	Harris, 2007 ¹⁶⁹	
49.	Hata 2006 ³⁹³	Uncertain if patients were suspected of PE
50.	Hayes, 2014 ³⁹⁴	
51.	Hirsch 2006 ³⁹⁵	Abstract/insufficient information
52.	Hochuli, 2007 ³⁹⁶	Clot burden
53.	Hofman, 2011 ³⁹⁷	
54.	Holmquist, 2009 ³⁹⁸	
55.	Howarth 2006 ³⁹⁹	Determination of optimal diagnostic cut-off point
56.	Hsiao, 2007 ⁴⁰⁰	Irrelevant intervention
57.	Hunsaker, 2008 ⁴⁰¹	
58.	Hussein 2008 ⁴⁰²	Letter
59.	Ingrisch, 2016 ⁴⁰³	Confirmed PE patients and healthy control
60.	Inonu, 2012 ⁴⁰⁴	
61.	Ishiyama, 2011 ⁴⁰⁵	3-D T2-weighted imaging using the dark blood method
62.	Jia, 2012 ⁴⁰⁶	Patients without or unsuspected of having PE
63.	Jogi, 2010 ⁴⁰⁷	Head-to-head comparison of radioaerosols in V/Q
64.	Jogi, 2015 ⁴⁰⁸	COPD
65.	Jones, 2008 ⁴⁰⁹	Diagnosis of DVT in patients without PE
66.	Jordan, 2015 ⁴¹⁰	It is unknown is the patients had suspected PE. Doubtful relevance of design and outcome of the study
67.	J of Thromb 2013 ³³⁸	Corrigendum (for error in reported tables) to an already excluded study (see Squizzato 2012³⁵²)
68.	Junger 2006 ⁴¹¹	Information not specific to suspected PE patients. Irrelevant outcome
69.	Kado, 2016 ⁴¹²	Irrelevant - Incidence of PE in Lupus patients
70.	Kamel 2008 ⁴¹³	Not suspected PE patients. Irrelevant outcomes – ventricular dysfunction
71.	Kaul 2014 ²⁰²	Software assisted intervention, irrelevant outcome-image quality
72.	Kiley 2007 ⁴¹⁴	Information not specific to suspected PE patients. Irrelevant

		outcome
73.	Kim, 2008 ⁴¹⁵	Not suspected PE patients
74.	Kim, 2016 ¹⁴⁴	Irrelevant PICO
75.	Kligerman, 2015 ⁴¹⁶	Retrospective reconstruction study
76.	Klok, 2008 ³³⁹	Irrelevant intervention-BNP
77.	Koch, 2016 ⁴¹⁷	Impact study
78.	Kohn, 2015 ³⁴⁰	Early post-acute PE all-cause mortality
79.	Konstantinides 2014 ⁴¹⁸	Guideline summary
80.	Kooiman, 2010 ⁴¹⁹	Incidence of contrast-induced AEs
81.	Korkeila, 2006 ⁴²⁰	Not suspected PE patient
82.	Krishan, 2011 ⁴²¹	Not suspected PE patients at baseline
83.	Kumamaru 2016 ⁴²²	Uncertain if patients were suspected of PE
84.	Kwon, 2007 ⁴²³	Irrelevant study
85.	Kyrtatos, 2013 ²⁰⁴	V/Q planar images compared with planar-like images re-projected from SPECT
86.	Lang, 2013 ⁴²⁴	Irrelevant outcome
87.	Lapergue 2015 ⁴²⁵	Not suspected PE patients. Irrelevant intervention CVPA
88.	Le Roux 2011 ⁴²⁶	Full-text in French. English abstract suggests irrelevant outcomes
89.	Le Roux, 2013 ⁵¹	Criteria for interpretations of outcomes
90.	Le Roux, 2015 ¹⁵⁶	Software aided
91.	Le Roux, 2015 ⁴²⁷	Patients already classified as having idiopathic VTE (not suspected PE)
92.	Lee, 2013 ⁴²⁸	Tumor thrombus
93.	Lessler, 2010 ⁴²⁹	Irrelevant outcome
94.	Lim, 2014 ⁴³⁰	Not suspected PE
95.	Lu, 2014 ¹⁰²	Comparison of contrast dose radiation intensity in CT
96.	Lucassen, 2013 ⁴³¹	Comparison of diagnosis by local radiologist versus experts
97.	Mahdavi, 2013 ¹¹⁰	Unclear design and uncertain interpretation of outcomes
98.	Mao, 2016 ⁴³²	PED software of dual-source CT combined with perfusion imaging
99.	Meinel, 2015 ⁴³³	Predictive value of CT in prognosis of PE
100.	Meysman, 2015 ⁴³⁴	Not suspected PE patients
101.	Minshall, 2015 ⁴³⁵	Not suspected PE patients
102.	Moon 2010 ⁴³⁶	Abstract/insufficient info for CA. <i>Also uncertain if authored by Moon</i>
103.	Morris 2011 ⁴³⁷	Not suspected PE patients
104.	Morris, 2011 ⁴³⁸	Irrelevant intervention
105.	Mortensen, 2014 ⁴³⁹	Narrative review
106.	Mos, 2014 ³⁴³	Suspected recurrent PE
107.	Muangman, 2012 ⁴⁴⁰	Cost-effectiveness study
108.	Nazaroglu, 2009 ⁴⁴¹	Irrelevant outcome – diagnostic quality (DQ)
109.	Nobre, 2014 ⁴⁴²	Letter
110.	Ouatu, 2014 ³⁴⁴	Narrative review
111.	Palla, 2014 ⁴⁴³	Narrative review
112.	Precious, 2014 ⁴⁴⁴	Narrative review
113.	Pulivarthi, 2014 ³⁴⁵	Narrative review
114.	Raymakers, 2014 ²²⁰	Cost-effectiveness
115.	Reagle, 2012 ⁴⁴⁵	Unspecified if suspected PE patients

116.	Rehnberg	Abstract/insufficient information
117.	Rehnberg, 2014 ³⁴⁶	Insufficient information for appraisal
118.	Reinartz, 2006 ¹⁷⁰	Automation of detection of mismatch defects
119.	Rhavar 2012 ⁴⁴⁶	Irrelevant study
120.	Rhee, 2007 ²⁰⁶	No PE specific outcomes
121.	Richard 2015 ⁴⁴⁷	In French
122.	Ritchie, 2007 ⁴⁴⁸	Unsuspected PE
123.	Rodger 2006 ⁴⁴⁹	7-variable clinical model, non-enzyme-linked immunosorbent assay D-dimer test, and alveolar dead-space fraction
124.	Rubins, 2008 ⁴⁵⁰	Narrative review
125.	Sakuma 2006 ⁴⁵¹	Irrelevant study
126.	Salaun, 2008 ⁴⁵²	Irrelevant objective
127.	Sampson, 2007 ⁴⁵³	DVT outcomes only
128.	Sangwaiya, 2010 ⁴⁵⁴	Irrelevant outcome –image quality and diagnostic confidence
129.	Sasbou 2013 ⁴⁵⁵	Full-text in French. English abstract suggests irrelevant outcomes
130.	Sawyer, 2015 ⁴⁵⁶	Nonspecific
131.	Schiebler, 2016 ⁴⁵⁷	Irrelevant outcomes – actionable, non-actionable, and normal
132.	Schonfeld, 2015 ⁴⁵⁸	Chronic PE
133.	Schouten, 2013 ³⁴⁷	No specific info for PE
134.	Scialpi, 2016 ⁴⁵⁹	Irrelevant outcome – image quality of target pulmonary vessels and occurrence and severity of flow-related artifact
135.	Scott, 2011 ⁴⁶⁰	Utilization of imaging in one institution
136.	Self 2012 ³⁴⁸	Editor's note and discussion points on study/insufficient info
137.	Sellem 2013 ⁴⁶¹	Full-text in French. English abstract suggests irrelevant outcomes
138.	Serra 2016 ⁴⁶²	Not suspected PE patients
139.	Shahir 2013 ⁴⁶³	Not suspected PE patients
140.	Shao, 2012 ⁴⁶⁴	Detection and location of DVT in PE patients
141.	Sharma, 2012 ³⁵⁰	Thromboprophylaxis
142.	Shen, 2012 ⁵²	Irrelevant outcomes
143.	Silva, 2013 ⁴⁶⁵	Not suspected PE
144.	Sinzinger 2015 ⁴⁶⁶	Letter
145.	Slater, 2012 ⁴⁶⁷	No PE specific outcomes
146.	Squizzato 2012 ³⁵²	Not suspected PE patients
147.	Stawicki 2008 ³⁷³	Not suspected PE patients
148.	Stein, 2006 ⁴⁶⁸	Recommendations for diagnostic approach
149.	Stein, 2008 ⁴⁶⁹	Protocol
150.	Su, 2015 ⁴⁷⁰	Irrelevant outcome
151.	Subedi, 2009 ⁴⁷¹	Not a systematic review. Only partial article (summary) delivered; full text to be requested if needed
152.	Sun, 2014 ⁴⁷²	Inappropriate design – a case study
153.	Szucs-Farkas, 2009 ⁴⁷³	Lower radiation intensity and contrast dose
154.	Szucs-Farkas, 2014 ⁴⁷⁴	Lower radiation intensity and contrast dose
155.	Tafur 2014 ³⁵⁴	Not suspected PE patients
156.	Takagi, 2006 ⁴⁷⁵	Letter

157.	Takahashi, 2013	Irrelevant outcome
158.	Tarr 2015 ⁴⁷⁶	Letter
159.	Thomeer, 2006 ⁴⁷⁷	Letter
160.	Tiseo	Irrelevant study
161.	Tunariu, 2007 ⁴⁷⁸	Chronic PE
162.	van Es 2016 ³²⁰	Abstract/insufficient information
163.	van Es 2016	Duplicate of Ref id ⁹⁸
164.	van Leent, 2015 ³⁵⁶	Dabigatran vs. vit k; cost effectiveness
165.	Van Mens, 2017 ²¹⁶	Systematic review
166.	Viau 2011 ⁴⁷⁹	Full-text in French. English abstract suggests study could be relevant
167.	Vongchaiudomchoke 2016 ⁴⁸⁰	Irrelevant outcome – prevalence of positive test for PE by pulmonary CTA; No comparator
168.	Watanabe, 2015 ¹⁴⁵	PISAPED Criteria
169.	Wessler, 2015 ³⁵⁷	No specific relevant intervention; no specific PE outcomes
170.	Witt 2011 ³⁵⁸	Commentary
171.	Wu 2014 ⁴⁸¹	Not suspected PE patients
172.	Zhou, 2012 ³⁵⁹	Irrelevant – PESI
173.	Zhu, 2008 ⁴⁸²	Irrelevant I/O
174.	Adams, 2014 ³²⁵	Summary of another article by unnamed authors, and without a specified PTP
175.	Hendriksen, 2015 ³³⁷	In appropriate study – Validation study of all diagnostic prediction models
176.	Self, 2012 ³⁴⁹	Summary of finding of meta-analysis of PERC alone
177.	Stevens, 2012 ³⁵³	Summary of findings of and commentary on already included study
178.	Manara, 2013 ³⁴¹	Irrelevant intervention – Data on capnography alone
179.	Da Costa Rodrigues, 2016 ³²	Irrelevant Intervention – Data on CUS alone
180.	Schouten, 2013 ³⁴⁷	Inadequate reporting – unable to differentiate between the contribution of the individual CPR to reported findings

3966

3967

3968

3969 **Appendix 10: Quality Assessment Questions for Clinical Review**

3970
3971
3972

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

3973

3974 **ROBIS**

3975

3976 1. Domain 1: study eligibility criteria

3977 1.1 Did the review adhere to pre-defined objectives eligibility criteria?

3978 1.2 Were the eligibility criteria appropriate for the review questions?

3979 1.3 Were eligibility criteria unambiguous?

3980 1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g.,
3981 date, study design, sample size, study quality, outcomes measured)?

3982 1.5 Were any restrictions in eligibility criteria based on sources of information appropriate
3983 (e.g., publication status or format, language, availability of data)?

3984 2. Domain 2: identification and selection of studies

- 3985 2.1 Did the search include an appropriate range of databases/electronic sources for
3986 published and unpublished reports?
- 3987 2.2 Were methods additional to database searching used to identify relevant methods?
- 3988 2.3 Were the terms and structure of the search strategy likely to retrieve as many eligibility
3989 studies as possible?
- 3990 2.4 Were restrictions based on date, publication format, or language appropriate?
- 3991 2.5 Were efforts made to minimise error in selection of studies?
- 3992 3. Domain 3: data collection and study appraisal
- 3993 3.1 Were efforts made to minimise error in data collection?
- 3994 3.2 Were sufficient study characteristics available for both review authors and readers to be
3995 able to interpret the results?
- 3996 3.3 Were all relevant study results collected for use in the synthesis?
- 3997 3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?
- 3998 3.5 Were efforts made to minimise error in risk of bias assessment?
- 3999 4. Domain 4: synthesis and findings
- 4000 4.1 Did the synthesis include all studies that it should?
- 4001 4.2 Were all pre-defined analyses reported or departures explained?
- 4002 4.3 Was the synthesis appropriate given the nature and similarity in the research questions,
4003 study designs and outcomes across included studies?
- 4004 4.4 Was between-study variation (heterogeneity) minimal or addressed in the synthesis?
- 4005 4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity
4006 analyses?
- 4007 4.6 Were biases in primary studies minimal or addressed in the synthesis?

4008

4009 **Cochrane Risk of Bias**

- 4010
- 4011 1. Sequence generation: was the allocation sequence adequately generated?
- 4012 2. Allocation concealment: was the sequence generation adequately concealed before group
4013 assignments?
- 4014 3. Blinding of participants and personnel: was knowledge of the allocated interventions
4015 adequately hidden from the participants and personnel after participants were assigned to
4016 respective groups?
- 4017 4. Blinding of outcome assessment: was knowledge of the allocated interventions adequately
4018 hidden from the outcome assessors after participants were assigned to respective groups?
- 4019 5. Incomplete outcome data: were incomplete outcome data adequately addressed?
- 4020 6. Selective outcome reporting: are reports of the study free of suggestion of selective outcome
4021 reporting?

- 4022 7. Other potential threats to validity: was the study apparently free of other problems that could
4023 put it at a risk of bias?
4024

4025

4026

4027

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?

4028

4029

4030

4031

DRAFT

4032

4033 **Appendix 11: Characteristics of Included Systematic Reviews for Clinical Review of Risk**
 4034 **Stratification (Question 1)**

4035

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	Comparator/ Reference	Outcome
Wang, 2016²⁵ 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	CDR-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, 2016²⁴ 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	3-Level Wells and 3-Level Geneva Scores	CTPA; composite of angiography CT and V/Q; V/Q; DSPA; V/Q or PA	Sensitivity, Specificity, and Prevalence.

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	Comparator/ Reference	Outcome
						years. The settings of the primary studies were not reported			
van Es, 2016⁹⁸ 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 patients at secondary care settings.	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 Wells + age-adjusted D-dimer	N/A. Patients were re-evaluated for PE 3 months after the initial tests	Diagnostic efficiency; failure rate, and risk factor assessment
Lucassen, 2011²⁶ 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	CDR (Wells, Geneva, and Gestalt) ± D-dimer	V/Q, CT, PA, or autopsy, diagnosis of DVT as surrogate for diagnosis of PE	Sensitivity, specificity, failure rate, and efficiency

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	Comparator/ Reference	Outcome
						patients, referred patients, or inpatients.			
Siccama, 2011⁹⁷ 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.	CDR (Wells, Geneva, Revised Geneva)	PA, V/Q scanning (50% had either inadequate or unclear reference standards)	Sensitivity, specificity, failure rate, ^a and efficiency.
Sanders, 2015⁹⁹ 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 CDRs using PubMed Clinical Queries	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 performed in a hospital setting and included ED patients, outpatients, or inpatients.	CDR (Wells rule, or Geneva score) clinical judgment (gestalt)	CDR alone or in combination with gestalt	Sensitivity, specificity, proportion of TR, TF, FP, FN

AUC = area under the receiver operating characteristic (ROC) curve, CI = confidence interval; CDR= clinical decision 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

4036

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	Comparator/ Reference	Outcome
in Epidemiology, PA = pulmonary angiography, PE = pulmonary embolism, RCT = randomized controlled trial, TN = true negative, TP = true positive, V/Q = ventilation perfusion scintigraphy,									

DRAFT

4037

4038 **Appendix 12: Diagnostic Accuracy Outcomes Reported by Included Systematic Review**
 4039 **(Question 1)**

4040

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 ⁹⁹	Dichotomized CDRs (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 CDRs (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)
Siccama, 2011 ⁹⁷	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, CDR= Clinical decision rule, NR = not reported, SDC = structured data collection, vs. = versus				

4041
4042
4043

DRAFT

4044 **Appendix 13: Utility Outcomes Reported by Included Systematic Reviews (Question 1)**

4045
4046

Summary of findings for utility of CDRs

Author	Diagnostic Strategy	Population Subgroups	Failure rate, % (95% CI)	Efficiency, % (95% CI)	Yield, % (95% CI)
Van Es, 2016 ⁹⁸	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 CDR (Wells)	NA	0.4 (NR) to 1.2 (NR) ^{c, d}	NR	12 (11–14)
	Imaging without CDR				9 (6–12)
	Increase in Yield due to Wells				3.1 (1.4–4.9)
Sanders, 2015 ⁹⁹	Wells <2	NA	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	NA	0.5 (0.2–0.9)	39 (31–47)	NR
	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, CDR = clinical decision rule, NA = not applicable, NE = not estimated, NR = not reported, R-Geneva = revised Geneva rule, SDC = structured data collection, S-Geneva = simplified Geneva rule					

4047
4048
4049
4050
4051

^a The authors reported outcomes for the overall Wells rule or Geneva scores, not the different probability levels of these CDRs.

^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

DRAFT

4052
4053
4054
4055

Appendix 14: 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 ⁹⁸	Lucassen, 2011 ²⁶	Siccama, 2011 ⁹⁷	Sanders, 2015 ⁹⁹	
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 methods?	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

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 ⁹⁸	Lucassen, 2011 ²⁶	Siccama, 2011 ⁹⁷	Sanders, 2015 ⁹⁹
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
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 (-2), NA = not applicable, NI = no information (0), PN = probably no (-1), PY = probably yes (+1), Y = yes (+2), U = unclear, UC = unclear concern (>3 NI)							

4056
4057

4058

4059 **Appendix 15: Characteristics of Included Primary Studies for Clinical Review (Questions 2 and 3)**

4060

4061 Studies reporting diagnostic test accuracy, utility, and/or safety analyses in non-pregnant patients are included in these tables.

4062 Studies are included under all index tests where they contributed data.

4063 **Table 10-A: Studies in non-pregnant patients with CT as index test**

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
Meier 2016¹⁹² France; Screened during May to October 2015 Single; In and outpatients in secondary care setting	N = 101 (65 after exclusions and indeterminate tests) Non-Pregnant Clinically suspected PE Severely impaired renal function (eGFR	CTPA (low CM and standard protocol) (CT) Interpreted on PACS	CTPA standard protocol (CT) NA	Primary: Objective and subjective 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
Moore 2015¹⁹³ Spain; January 2008	N = 134 Non-Pregnant	CTPA (CT) Positive = contrast material outlined an	Confirmation of PE by V/Q perfusion scan showing high probability, abnormal findings on venous	Primary: Failure rate Secondary: Incidental

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
<p>to December 2013</p> <p>Single; Emergency Room</p>	<p>High pretest probability of PE (based on Wells criteria ? 7)</p> <p>Non-high clinical probability of PE (Wells), treatment with therapeutic doses of anticoagulants >24 hours, life expectancy of</p>	<p>intraluminal defect or if a vessel was totally occluded by low-attenuation material on at least two adjacent slices; Inconclusive = images could not be interpreted because of motion artifacts or insufficient contrast enhancement of the pulmonary arteries</p>	<p>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 clinically severe PE; possibly present in patients who died suddenly or unexpectedly) (CC)</p> <p>NA</p>	<p>findings</p> <p>Follow-up: 3 months</p>
<p>Okada 2015¹¹²</p> <p>Japan; April 1, 2012 and March 31, 2013</p> <p>Single; Unclear</p>	<p>N = 83</p> <p>Non-Pregnant</p> <p>All initial weighted average CTPA using the</p>	<p>CTPA and CTPA with color coded LPBV (CT)</p> <p>CTPA images with and without color-coded LPBV images were evaluated in separate</p>	<p>CTPA / LPBV + clinical and physical findings (CC)</p> <p>When CTPA showed a complete filling defect with a lack of enhancement of the entire lumen of pulmonary</p>	<p>Primary: Number and locations of intra-pulmonary clots (IPCs)</p> <p>Secondary: DTA values</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
	<p>dual-energy technique.</p> <p>Motion artifact caused by insufficient breath-holding or previous history of PE.</p>	<p>session 4-week apart to minimize recall bias.</p> <p>Two interpretation sessions were held for each radiologist to review the CTPA only and CTPA with color-coded LPBV images over a 4-week interval.</p> <p>For each review session, the 2 readers were asked to record the following findings: the locations of IPCs (central, segmental or subsegmental) in each segment on CTPA and the regional iodine perfusion defects with IPCs on LPBV. The iodine perfusion defects were also compared with the lung CT, because the iodine map was also affected by the lung parenchyma. CT obstruction index (CTOI) was also</p>	<p>arteries, a partial filling defect surrounded by areas of contrast enhancement or a peripheral filling defect that formed an acute angle with the pulmonary arterial wall.</p>	<p>Follow-up: 1-month</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
		<p>measured by each reader using Qanadli scoring. The pulmonary arterial tree of each lung was regarded to have 10 segmental pulmonary arteries. The presence of an embolus in a segmental PA was scored as 1 point, and emboli at the most proximal arterial level were scored a value equal to the number of segmental PAs arising distally. To provide additional information on the residual perfusion distal to the embolus, a weighting factor was used for each value (0 = no defect, 1 = partial occlusion, and 2 = complete occlusion). An isolated subsegmental embolus was considered to be a</p>		

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
		partially occluded segmental PA, and was assigned a value of 1, and the maximum CTOI was 40.		
Watanabe 2015¹⁴⁵ Slovenia; Turkey; Czeck Republic; Uruguay; India; October 2004 and September 2008 Multi-International; Hospitals and tertiary care centres (nuclear medicine departments); urban	<p>N = 201 patients included, 129 had no abnormalities on CXR</p> <p>Non-Pregnant</p> <p>Presenting with suspicion of acute PE within 24 h, No abnormalities on CXR.</p> <p>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</p>	<p>1. V/Q Scintigraphy + modified PIOPED, PISAPED, or modified PISAPED criteria. 2. CTPA. After inclusion: Intermediate or high likelihood or positive D-dimer – V/Q scan and CTPA and 24 weeks follow-up; Low likelihood and negative D-dimer – no imaging, followed 24 weeks. (VQ)</p> <p>3 sets of diagnostic criteria applied:: PIOPED (V/Q) (PE present, PE absent or non-diagnostic), PISAPED (Q alone) (PE present, PE absent or</p>	<p>Final clinical assessment at 24 weeks by physician blinded to interpretations of imaging except CXR. Assessment took into account response to anticoagulation. (FU)</p> <p>NA</p>	<p>Primary: Sensitivity and specificity</p> <p>Secondary: AUROC</p> <p>Follow-up: 24 weeks</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
		<p>nondiagnostic), modified PISAPED (V/Q) (PE present, PE absent, nondiagnostic).</p> <p>See Table 2 and 3 in the paper.</p> <p>CTPA: See Reference 12 to 14 PE present: complete arterial occlusion, failure to opacify, artery possibly enlarged. Central filling defect. Peripheral intraluminal 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</p>		

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
		thickening.		
Lu 2014¹⁰² China; May 2013 to December 2013 Single; Imaging unit of a hospital, setting unclear	N = 100 Non-Pregnant Suspected PE. History of allergy to iodinated contrast agent, age 80 kg.	CTPA - group A, 100 kVp, 1.2 pitch, 60 ml of contrast medium and filtered back projection algorithm; CTPA - group B, 80 kVp, 2.2 pitch, 20 ml of contrast medium and sinogram affirmed iterative reconstruction (CT) PEs were defined as luminal filling defects or non-visualisation of segmental pulmonary and subsegmental arteries compared to the contralateral side.	Consensus reading including patient history, clinical data and supplementary imaging modalities (CC) 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
Megyeri 2014¹¹³ Switzerland; September 2007 to April 2011 Single; Emergency unit of a tertiary-	N = 123 (BW > 100kg): 114 (BW Non-Pregnant ?100 kg BW, requiring CTPA to exclude PE;	CT (CT) The diagnosis of PE was established in the case of a complete or partial filling defect in the pulmonary arteries on at least three	Composite reference standard (clinical probability, reference CTPA result, additional imaging (US, VQ) when performed, and 90-day follow-up) (CC)	Primary: Diagnostic accuracy of CTPA in two patient groups Secondary: NA Follow-up: 3 - 12 months

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
care center	None.	contiguous transverse images of 1 mm thickness with no major movement artifacts.	NA	
Mahdavi 2013¹¹⁰ US; January 2007 to December 2008 Single; Secondary/Tertiary Care	N = 100 Non-Pregnant Admitted and underwent both V/Q and CTA within a 3 day period NA	V/Q SPECT (VQ-SPECT) NA	CTPA (CT) NA	Primary: degree of agreement between the two tests Secondary: NA Follow-up: None
He 2012¹¹⁴ China; June 2007 to January 2011 Multi-National or Regional; Secondary care centers (including academic centers)	N = 544 Non-Pregnant Suspected PE (based on signs and symptoms, laboratory findings, medical history and predisposing factors - assessed formally by Wells). Abnormal serum creatinine, unwilling to investigations,	V/Q (VQ) PISAPED and PIOPED II criteria V/Q: PE present, PE absent, or non-diagnostic; Q only: PE present or PE absent CT: PE present, PE absent, or non-diagnostic	Composite Reference Test (clinical data, laboratory recorders (D-dimer and Doppler US available), imaging information (e.g., echocardiography), CTPA, V/Q, 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);	Primary: Sensitivity, specificity, PPV, NPV, proportion of non-diagnostic tests Secondary: NA Follow-up: 6 months

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
	pregnancy, circulatory shock, hypotension, renal failure, hemodynamically unstable, ventilatory support, anticoagulation, history of allergy to contrast media, received thrombolytic therapy before examinations excluded.		Pulmonary contrast angiography (Allura Xper FD10/10 angiographic unit) performed in patients in whom PE not conclusively diagnosed or ruled out by non-invasive tests (CC) Final diagnosis made at consensus meeting	
Thieme 2012¹⁰³ Germany; October 2007 and November 2009 Single; NA	N = 15 Non-Pregnant Suspected PE (9 patients) or suspected pulmonary arterial hypertension (PAH, 10 patients). NA	Dual energy pulmonary CT angiography (DE CTPA) (CT) Comprehensive image reading (CTPA and iodine maps), diagnosis of acute PE with respect to all imaging features	V/Q SPECT-CT (VQ-SPECT-CT) 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
Woo 2012¹⁹⁹ Canada; January 1,	N = 1424 Non-Pregnant	CT angiography (CT) Pulmonary CTA	None (None) NA	Primary: We estimated mortality benefit of pulmonary CTA by

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
<p>2007 to December 31, 2007</p> <p>Multi-National or Regional; Academic teaching hospitals and community hospital within a single urban Canadian center</p>	<p>NA</p> <p>NA</p>	<p>interpretations for PE were categorized as positive, negative, or indeterminate using the impression in the finalized report. In accordance with the literature, radiologists defined CTA findings as positive for PE if one or more low-density filling defects were seen within the contrast-enhanced lumen of central, segmental, or subsegmental pulmonary arteries. If the report impression was negative or was a qualified negative for PE (e.g., no central or segmental PE but subsegmental PE cannot be excluded), the pulmonary CTA interpretation was categorized as negative. If the</p>		<p>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 estimated effective dose and using sex-specific polynomial equations derived from the Biological Effects of Ionizing Radiation VII report. We calculated benefit-risk ratios by dividing the mortality benefit of preventing a fatal PE by the mortality risk of a radiation-induced cancer.</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
		impression stated that the examination was nondiagnostic because of excessive motion artifact or because of inadequate pulmonary arterial contrast density (Secondary: NA Follow-up: one-year
Pesavento 2011¹⁹⁶ Italy; June 2007 to September 2009 Single; Emergency room and internal medicine wards	N = 545 Non-Pregnant Suspected PE, 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	CT (CT) Diagnostic criteria of PE were an intraluminal filling defect outlined by contrast medium or total vessel occlusion by low-attenuation material in at least two adjacent layers. In patients without PE, an attempt was systematically made to identify alternative diagnoses. The radiological evaluation was performed using Siemens SOMATOM Definition 64-detector	3 month follow-up (FU) 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

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
		<p>row CT scanner. CT scanning was considered inconclusive in the presence of 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.</p>		
<p>Galipienzo 2010¹⁸⁶ Spain; January 2007 to July 2008 Single; Emergency room</p>	<p>N = 242 Non-Pregnant Clinically suspected PE and negative MCTPA Exclusion criteria included age > 24 h, logistic reasons (eg, unavailability of CT and patient too ill to undergo CT scanning), or</p>	<p>MCTPA (CT) A CT was positive for PE if contrast material outlined a central intraluminal defect or if a vessel was totally occluded in at least two different projections. Recurrent thromboembolic events were diagnosed according to standard</p>	<p>Follow up of 3 months (FU) NA</p>	<p>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</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
	hemodynamic instability.	criteria: positive Doppler ultrasound findings for deep-vein thrombosis, ventilation perfusion scintigram showing high probability of PE following the PIOPED 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		
Hantous-Zannad 2010¹⁹⁰ Tunisia; June 2006 to March 2007 Single; Imaging unit of a hospital, setting unclear	N = 184 Non-Pregnant Suspected PE based on empiric clinical probability assessment NA	CT (CT) CTPA inconclusive: important artefacts making segmental pulmonary arteries poorly analyzed, high image noise, poor enhancement of pulmonary arteries and	Follow up of 6 months (FU) NA	Primary: recurrent VTE events, prevalence of acute PE, calculate sensitivity and specificity of multidetector CT Secondary: NA Follow-up: 6 months

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
		<p>pulmonary infarction images without embolus in the corresponding pulmonary artery. Acute PE was defined as pulmonary arterial occlusion by a large filling defect, a partial filling defect surrounded by contrast material and a peripheral intraluminal filling defect that forms acute angles with the pulmonary arterial wall.</p>		
<p>Sodhi 2010¹⁹⁸ India; 2-year period Single; Imaging department of academic medical center (tertiary referral level)</p>	<p>N = 50 Non-Pregnant High clinical suspicion of PE: Hemodynamic compromise (systolic BP < 90 mmHg) NA</p>	<p>CT (CT) CT examinations were read and interpreted by two radiologists, independently on a viewing workstation using three window and level settings: Mediastinal (window width 450 HU, window level 35HU) Lung</p>	<p>combination of clinical, imaging, and laboratory analysis, after adequate imaging, laboratory tests (V-P 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</p>	<p>Primary: to evaluate the role of CT pulmonary angiography (CT-PA) in detecting additional information that may help in making an alternative diagnosis, in patients referred to CT for a suspected acute PE</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
		<p>parenchyma (window width 1500 HU, window level -600 HU) Pulmonary vascular (window width 250 HU, window level 40 HU) Overlapping images (reconstructed at 5 mm) were also printed on hard copy film at two standard (mediastinal and lung parenchymal) settings. Evaluation of central, segmental, and subsegmental pulmonary arteries was first done to detect PE. Subsequently, all other abnormalities in the mediastinum, chest wall, lung parenchyma, soft tissues, pleural/pericardial, cardiovascular system were also looked for and recorded. All clinical data was available at the time of</p>	<p>echocardiography (Echo) were done in all patients) (CC) All clinical data was available at the time of interpretation of images. At the end of the entire diagnostic work up, all available imaging, laboratory analysis, and clinical information was used by the radiologists to provide a possible alternative diagnosis in cases with excluded PE on CT PA.</p>	<p>Secondary: NA Follow-up: 3 months</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
		<p>interpretation of images. At the end of the entire diagnostic work up, all available imaging, laboratory analysis, and clinical information was used by the radiologists to provide a possible alternative diagnosis in cases with excluded PE on CT PA.</p>		
<p>Gimber 2009¹⁸⁹ US; February 2005 to January 2006 Single; Emergency Department of a health maintenance organization (HMO) patient population</p>	<p>N = 347</p> <p>Non-Pregnant Suspected PE, underwent pulmonary CTA and had a D-dimer level of ≥ 1.0 $\mu\text{g/mL}$.</p> <p>NA</p>	<p>CTPA (CT)</p> <p>Positive if a filling defect was present in one or more pulmonary arteries. A negative finding resulted if there was no filling defect and if there was normal enhancement of the pulmonary arteries. An indeterminate finding resulted if the pulmonary study findings could not be classified as positive or</p>	<p>Follow up of 3 months (FU)</p> <p>NA</p>	<p>Primary: NA</p> <p>Secondary: NA</p> <p>Follow-up: 3 months</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
		negative.		
Gutte 2009¹¹¹ Denmark; June 2006 to February 2008 Multi-National or Regional; Secondary/Tertiary Care	N = 81 Non-Pregnant 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 Contraindication to CT including allergy to contrast agents, impaired renal function (P-creatinine level >0.120 mmol/L), women	V/Q SPECT (VQ-SPECT) Diagnosed if one or more mismatched perfusion defects with normal ventilation were present	Composite: Side-by-side consensus based on MDCT, V/Q SPECT and all available information (ECG, echo, LUS, D-dimer, clinical data and follow-up of 6 months) (CC) NA	Primary: Diagnostic accuracy (sens/spec) Secondary: NA Follow-up: 6 months
Wang 2009¹⁰⁴ China; October 2005 to February 2007	N = 82 Non-Pregnant Normal creatinine level, willing to undergo VQ	CTPA VQ Perfusion and chest radiography (CR) (Multiple) VQ: The perfusion images were interpreted	Composite reference standard (all imaging modalities, all available laboratory recorders, clinical data, opinions of physicians)	Primary: DTA values Secondary: NA Follow-up: NA

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
Single; NA	<p>scan and CTPA.</p> <p>Pregnan, 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.</p>	<p>in conjunction with ventilation images and/or CR. Diagnosis was based on the refined modified PLOPED (RM-PIOPED) criteria. In brief, high probability which was defined as 2 or more segments of perfusion-ventilation mismatch or perfusion-CR mismatch was classified as PE present, intermediate probability as nondiagnostic, and all others as PE absent.</p> <p>The CTPA scans were assessed by 2 experienced radiologists who were unaware of the results of the V/Q scan (or perfusion scan combined with CR). The main, lobar, segmental, and subsegmental arteries were examined.</p>	<p>responsible for treatment, and outcomes) (CC)</p> <p>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 physicians responsible for treatment and outcomes.</p>	

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
		<p>Complete visualization of a main, lobar, or segmental arteries required that the branch should be followed to its bifurcation. Readers scored their degree of diagnostic certainty by using a 3-point scale (PE present, PE absent, or nondiagnostic).</p>		
<p>Anderson 2007⁵³ Canada; US; May 2001 to April 2005 Multi-International; Outpatient clinics, emergency departments, and inpatient units 5 academic health centers</p>	<p>N = 1417</p> <p>Non-Pregnant</p> <p>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.</p> <p>DVT or PE diagnosed within the previous 3 months, no change in severity of pulmonary</p>	<p>CTPA (CT)</p> <p>PE present: intraluminal filling defect within a pulmonary arterial vessel. PE absent: no filling defect observed</p>	<p>VQ (VQ)</p> <p>Lung scan results were categorized as high probability if there were 1 or more segmental perfusion defect(s) with normal ventilation or 2 or more large subsegmental perfusion defects ($\geq 75\%$ of a segment) with normal ventilation. Lung scans were categorized as normal if there were no perfusion defects. All other combinations of V/Q scan</p>	<p>Primary: subsequent development of symptomatic PE or proximal DVT in patients in whom PE had initially been excluded</p> <p>Secondary: NA</p> <p>Follow-up: 3 months</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
	<p>symptoms within the previous 2 weeks, use of therapeutic doses of parenteral anticoagulants for >48 hours, comorbid condition making life expectancy</p>		<p>results were categorized as non-diagnostic (non-high probability).</p>	
<p>Stein 2007¹¹⁶ Canada; US; September 2001 to July 2003 Multi-National or Regional; NA</p>	<p>N = 824</p> <p>Non-Pregnant</p> <p>As for Stein 2006⁶⁴. At least 18 years of age with clinically suspected acute PE, referred for diagnostic imaging for suspected PE, consultation request for suspected PE.</p> <p>As for Stein 2006⁶⁴. Unable to complete testing within 36 hr abnormal creatinine levels, receiving long-term renal dialysis, history of long-term anticoagulant use,</p>	<p>Refer Stein 2006⁶⁴ (CT or CTCTV)</p> <p>Refer Stein 2006⁶⁴</p>	<p>Composite reference standard (SC)</p> <p>Refer Stein 2006⁶⁴</p>	<p>Primary: DTA values</p> <p>Secondary: NA</p> <p>Follow-up: NA</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
	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 to have thrombolytic therapy within the next 24 hr			
Hogg 2006¹⁷⁹ UK; February 2002 to May 2003 Single; Secondary/Tertiary Care	N = 425 Non-Pregnant Pleuritic chest pain Trauma, pregnancy, pneumothorax, myocardial infarction, cardiac ischemia, pericarditis, hypoxia with	Pathway including Wells, D-dimer, VQ, CT, PA (PW) PIOPED criteria	Follow up of three months (FU) NA	Primary: Safety Secondary: NA Follow-up: 3 months

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
	Pao2140 kg			
Huisman 2006¹⁹¹ Netherlands; November 2002 to December 2004 Multi-National or Regional; Emergency Department	N = 3306 Non-Pregnant Suspected PE (sudden onset of dyspnea, sudden deterioration of existing dyspnea or onset of pleuritic chest pain). 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	Single detector or multidetector row computed tomography (CT) Contrast material outlined an intraluminal defect or if a vessel was totally occluded by low-attenuation material on at least 2 adjacent slices	Follow up of three months (FU) NA	Primary: incidence of symptomatic VTE events during 3 month follow-up (fatal PE, DVT) Secondary: NA Follow-up: 3 months
Perez de Llano 2006¹⁹⁵ Spain; January 2001 to December 2002	N = 87 Non-Pregnant Clinically suspected PE, a negative helical CT,	Helical CT (CT) The pulmonary angiograms were graded as optimal when a high degree of	Follow up of three months (FU) NA	Primary: To determine the safety of withholding anticoagulants in patients with clinically

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
<p>Single; Emergency room and Internal Medicine wards</p>	<p>and no symptoms or signs of DVT were eligible.</p> <p>Contraindications to CT positive helical CT</p>	<p>contrast material enhancement was obtained without motion artifacts. The examination was considered inconclusive when the segmental arterial anatomy of all lobes was inadequate to exclude thrombus based on motion artifacts, poor contrast opacification, or inadequate anatomic visualization on axial reconstructions. The criteria used to diagnose embolism consisted of 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. Indirect</p>		<p>suspected PE (PE) and negative CT results when ultrasonography (US) was performed only in patients with clinical suspicion of DVT (DVT)</p> <p>Secondary: to evaluate the effect of CT findings on the final clinical diagnosis</p> <p>Follow-up: 3 months</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
		<p>signs like wedged shaped pleural based consolidation, linear bands, and dilated central or segmental pulmonary arteries were not considered, by themselves, sufficient for a diagnosis of PE.</p>		
<p>Stein 2006⁶⁴ Canada; US; September 2001 to July 2003 Multi-International; Inpatient or outpatient clinical centers</p>	<p>N = 824</p> <p>Non-Pregnant</p> <p>At least 18 years of age with clinically suspected acute PE, referred for diagnostic imaging for suspected PE, consultation request for suspected PE.</p> <p>Unable to complete testing within 36 hr abnormal creatinine levels, receiving long-term renal dialysis, history of long-term anticoagulant use,</p>	<p>multidetector CTA alone; multidetector CTA combined with venous-phase imaging (CTA-CTV) (CT or CTCTV)</p> <p>PE present on CT: failure of contrast material to fill the entire lumen due to central filling defect (with possibly enlarged artery); a partial filling defect surrounded by contrast material on a cross-sectional image; contrast material</p>	<p>Composite reference standard (VQ scan showing high probability, abnormal DSA, abnormal US) (SC)</p> <p>Diagnosis of PE according to the composite reference standard required one of the following conditions: 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</p>	<p>Primary: diagnosis of PE</p> <p>Secondary: addition of Wells score improved ability to detect or rule out PE</p> <p>Follow-up: 3- and 6-months</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
	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 to have thrombolytic therapy within the next 24 hr	between the central filling defect and the artery wall on an in-plane, longitudinal image; and a peripheral intraluminal filling defect that forms an acute angle with the artery wall. DVT present on CTV: complete or partial central filling defect.	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 DSA, normal findings on ventilationperfusion scanning, ventilationperfusion scanning showing either a low or very low probability of PE, a clinical Wells score of	
Vigo 2006 ¹⁸⁴	N = 702	CT / D-dimer / VQ (PW)	Follow up of 6 months (FU)	Primary: VTE events
Italy; April 2001 to November 2005	Non-Pregnant Clinical suspicion of the	With CT, a PE was considered present if	NA	Secondary: NPV, safety of withholding

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
Multi-National or Regional; Outpatients and inpatients referred to six Italian centers	<p>first episode of PE</p> <p>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</p>	<p>contrast material outlined an intraluminal filling defect or if a vessel was totally occluded by low-attenuation material.</p> <p>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</p>	<p>anticoagulation from patients with negative CT and negative D-dimer (estimated rate of alternative diagnoses on spiral CT in patients free from PE)</p> <p>Follow-up: 6 months</p>	

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
<p>Ghanima 2005¹⁷⁸</p> <p>Norway; February 1, 2002, and December 31, 2003</p> <p>Single; Emergency Department of stfold Hospital Trust in Fredrikstad, Norway</p>	<p>N = 329</p> <p>Non-Pregnant</p> <p>Clinical suspicion of PE de?ned as acute onset of dyspnea, chest pain, palpitation, or syncope, >= 18 years of age.</p> <p>Clinical probability not assessed in patients normal D-dimer, CT not performed, anticoabulation, iodinated contrast medium, pregnancy, expected survival</p>	<p>angiographic findings.</p> <p>Pathway of D-dimer, Multi-slice spiral CT, and bilateral compression US, Q scint, or PA (PW)</p> <p>CT: PE was diagnosed if a ?lling defect or complete occlusion was seen in proximal, segmental or subsegmental arteries. PE was considered absent when the pulmonary vasculature, including subsegmental branches, was visualized and was free of ?lling defects. The diagnosis was considered inconclusive when poor opaci?cation or major motion artefact was observed or due to the ambiguity of ?ndings as irregular</p>	<p>Follow up of 3 months (FU)</p> <p>NA</p>	<p>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</p> <p>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.</p> <p>Deaths were adjudicated by an independent committee on the basis of autopsy</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
		<p>arterial walls or the presence of an adjacent pulmonary abnormality.</p> <p>Ultrasonography Bilateral compression ultrasonography of the lower extremities consisting of B-mode examination of the common femoral and popliteal veins was recommended to be performed on patients with inconclusive CT scan; lack of vein compressibility was considered as the main criterion for the diagnosis of DVT</p> <p>D-dimer test was performed as the initial diagnostic test in all patients. high clinical probability and a normal D-dimer as well as those with elevated D-</p>		<p>reports, death certificates and hospital charts as definitely caused by PE, definitely unrelated to PE, or possibly related to PE if the cause of death could not be clearly established.</p> <p>Follow-up: 3-months</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
		<p>dimer proceeded to MSCT. In case of an incon-clusive MSCT, bilateral compression ultrasonography of the lower extremities to rule out DVT was recommended followed by perfusion scintigraphy and/or pulmonary angiography if no DVT was revealed.</p>		
<p>Revel 2005¹⁹⁷ France; January 2001 to June 2001 Single; Unclear</p>	<p>N = 220 Non-Pregnant Referred to undergo thoracic CT angiography for suspicion of PE Contrast contraindicated, previous PE and prior ventilation-perfusion scanning, young patients free of prior cardiopulmonary disease, low clinical suspicion of PE and</p>	<p>CT Angiography CTA + CT Venography (CT and CTCTV) The diagnosis of acute PE was based on the presence of filling defects within pulmonary arteries, or global hypoattenuation of enlarged arterial sections, on at least two contiguous sections. PE was then classified as either central (up to the</p>	<p>Follow up of 3 months (FU) NA</p>	<p>Primary: Recurrent VTE events Secondary: NA Follow-up: 3 months</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
	normal chest radiographs	<p>first division of a segmental artery) or subsegmental (beyond the first division of a segmental artery) if the two chest radiologists independent readings agreed on the presence and site(s) of subsegmental clots.</p>		
		<p>Thoracic CT angiography was considered non-diagnostic, as in the Evaluation du Scanner Spirale dans l'Embolie Pulmonaire (or ESSEP) study, if enhancement of pulmonary arteries was insufficient compared with that of pulmonary veins or if it was inhomogeneous; if breathing, motion artifacts, or underlying lung disease hindered examination of at least</p>		

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
		<p>one segmental artery; or if an image did not lead to a definite conclusion, whatever its location. CT findings were considered normal when there were no signs of PE on images that were judged technically adequate.</p>		
<p>Reinartz 2004¹⁰⁵ Germany; January 2001 to April 2003 Single; NA</p>	<p>N = 83 Non-Pregnant Had V/Q lung scintigraphy in SPECT technique as well as multislice spiral CT within an interval of 3 d NA</p>	<p>V/Q lung scintigraphy (VQ) PIOPED criteria</p>	<p>Multislice CT (CT) PE was diagnosed if one or more embolic clots were detected in the pulmonary arteries</p>	<p>Primary: NA Secondary: NA Follow-up: at least 5 months (max 10 months)</p>
<p>Winer-Muram 2004¹⁰⁶ US; September 1999 to March 2001 Single; Emergency</p>	<p>N = 93 Non-Pregnant Suspicion of acute PE on the basis of clinical</p>	<p>CTPA (CT) For CT, the presence of acute PE was defined as a low-attenuation filling defect noted after enhancement of</p>	<p>Pulmonary Arteriography (PA) (PA) Since the study was directed toward acute PE, patients who had only chronic PE (eg, organizing</p>	<p>Primary: Presence of PE, CT Sensitivity, CT Specificity Secondary: NA</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
room and inpatient populations of tertiary care center and a public hospital	<p>presentation.</p> <p>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.</p>	pulmonary arteries.	<p>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).</p>	Follow-up: NA
<p>Bourriot 2003¹⁸⁷</p> <p>France; June 1996 to December 1998 (30-month period)</p> <p>Single; Inpatient</p>	<p>N = 117</p> <p>Non-Pregnant</p> <p>Negative spiral CT (SCT) angiographic finding after a suspicion of acute PE</p>	<p>All patients underwent both SCT and color Doppler ultrasound of the legs and d-dimer test. (CT)</p>	<p>Follow up of mean 21 months (FU)</p> <p>NA</p>	<p>Primary: recurrent thromboembolism, mortality, and cause of death</p> <p>Secondary: NA</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
Population From Cardiology and Pneumology Wards	(PE) in a population of inpatients with cardiac and/or respiratory disease NA	<p>CT studies were categorized as follows: (1) positive for PE if a clot was observed, (2) negative for PE if no clot was observed, or (3) indeterminate if poor examination, inadequate enhancement, or motion artifacts precluded confident interpretation of the study. Acute PE was diagnosed if a normal-sized or enlarged pulmonary artery was obstructed completely by an enhancing thrombus, or if nonocclusive filling defects were apparent centrally in the vessel.</p> <p>Dopler Ultrasound: The criterion for deep venous thrombosis was the presence of an intraluminal thrombus or</p>		Follow-up: 6-months

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
		<p>incomplete compressibility of the veins, or both.</p> <p>D-dimer: d-Dimer test results were considered positive at > 500 ng/mL.</p>		
<p>Coche 2003¹⁰⁹</p> <p>Belgium; 21-months (dates not reported)</p> <p>Single; Emergency department of urban teaching hospital with an annual census of 50,000 patients</p>	<p>N = 94</p> <p>Non-Pregnant</p> <p>Clinical suspicion of PE, age >18 years, absence of clinically suspected deep venous thrombosis, and plasma D-dimer levels >500 ng/mL.</p> <p>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</p>	<p>Multi detector Spiral CT angiography, thin collimation (MDCT) (CT)</p> <p>PE were identified when either complete or partial filling defects within the main, lobar, segmental, or subsegmental arteries were identified</p>	<p>Ventilation-perfusion (V-P) scintigraphy, pulmonary digital subtraction angiography when indicated, and chest radiography (SC)</p> <p>VQ: PE excluded if perfusion defects of any kind. PE unlikely (low probability), perfusion defects of any size were matched by equal or larger ventilation defects and were smaller or equal in size and shape to CXR abnormalities. PE present (high probability), single or multiple large, wedge-shaped perfusion defects, coexisted with a normal</p>	<p>Primary: Episodes of recurrent or new deep venous thrombosis or PE were recorded</p> <p>Secondary: Baseline creatinine levels were measured in all patients before the spiral CT examination, and the creatinine level was monitored in hospitalized patients</p> <p>Follow-up: 6 months</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
	transfer, death, and patient refusal or inability to participate.		<p>distribution of ventilation. Pulmonary angiography. Pulmonary angiograms were reviewed at a computer workstation (Integris V3000). The criterion for diagnosis of acute PE was a 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. Any abnormalities that were suspicious for chronic PE were also recorded. Chest radiography. Chest radiographic description included the evaluation and tabulation of abnormalities that could interfere with interpretation of V-P scintigrams, such as parenchymal consolidation, atelectasis, pleural effusion,</p>	

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
			and emphysema	
Donato 2003¹⁸⁸ US; NA Single; Secondary or tertiary center	N = 243 Non-Pregnant Reports using words “PE” and “clot” for the 2 years before the initiation of the study NA	Helical CT scan (CT) NA	Follow up of three months (FU) NA	Primary: NA Secondary: NA Follow-up: 3 months
Nilsson 2002¹⁰⁷ Sweden; March 1999 and May 2001 Multi-National or Regional; Emergency ward	N = 90 Non-Pregnant Hemodynamically stable outpatients with symptoms of acute PE presenting during the daytime Pregnancy, previous adverse reactions to contrast media, renal insufficiency (serum-creatinin >150 mmol/l), treatment with metformine, ongoing	Spiral CTPA (CT) Spiral CTPA: Low-attenuation area that completely or partially filled the lumen of an opacified vessel.	PA (PA) 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, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
	anticoagulation therapy, two or more previous VTE events, severe malnutrition or cachexia, expected survival			
Ost 2001¹⁹⁴ US; 18-month period Single; Unclear	<p>N = 103</p> <p>Non-Pregnant</p> <p>High clinical suspicion of PE, determined by the attending physician and a non-diagnostic ventilation-perfusion scan, defined as an intermediate- or low-probability scan that was discordant with the clinical suspicion.</p> <p>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,</p>	<p>Spiral CT (CT)</p> <p>A study was considered positive for PE if there was an intraluminal filling defect in a pulmonary artery. A radiologist experienced in CT body imaging and a chest radiologist interpreted the scans. Results were recorded as positive, negative, or indeterminate for PE. If both radiologists did not agree on the reading, it was classified as indeterminate. The sizes of pulmonary vessels with documented emboli were recorded.</p>	<p>Conventional PA and clinical FU of 6 months (CC)</p> <p>Conventional digital subtraction pulmonary angiography was performed by selective injection of approximately 35 mL of Omnipaque 350 into each pulmonary artery in two oblique projections for a total of 140 mL per study. All studies were read as positive, negative, or indeterminate. The sizes of the pulmonary vessels with documented emboli were recorded.</p>	<p>Primary: angiographic evidence of PE</p> <p>recurrent thromboembolism events</p> <p>Secondary: NA</p> <p>Follow-up: 6 months</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
were				
Blachere 2000¹¹⁵ France; 18-month period Single; inpatients, outpatient, intensive care unit	N = 179 Non-Pregnant Clinically suspected of having acute PE Contraindication for the use of iodine contrast material (renal failure, history of allergy), unstable hemodynamic status, and pregnancy.	helical CT angiography All patients underwent ventilationperfusion radionuclide lung scanning, contrast-enhanced he-lical CT angiography, and Doppler sonography of the legs (CT) PE if a clot was observed; negative for PE if no clot was observed; and indeterminate if poor examination, inadequate enhancement, or motion artifacts precluded con?dent interpretation of the study. PE positive: normal-sized or enlarged pulmonary obstructed completely by nonenhancing thrombus, or central	Composite (PA positive, CT, VQ, and US concordant, event during clinical follow-up) (CC) After initial interpretation, the need for pulmonary angiography was determined by the referring physician depending on the degree of suspicion of PE, Doppler sonography results, and concordance of the results of helical CT angiography and ventilationperfusion radionuclide lung scanning. The ventilationperfusion scans were interpreted by the nuclear medicine physician on service, and results were tabulated using the original and revised criteria of the Prospective Investigation of PE Diagnosis (PIOPED). As	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

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
		nonocclusive filling defects. Main, lobar, segmental, and subsegmental arteries recorded.	with the initial helical CT angiography, the initial interpretation was used to determine the need for pulmonary angiography.	
<p>Qanadli 2000¹⁰⁸</p> <p>France; September 1996 to August 1998</p> <p>Single; Department of radiology (inpatient and outpatient)</p>	<p>N = 158</p> <p>Non-Pregnant</p> <p>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).</p> <p>Clinical signs of life-threatening PE, renal failure, history of allergy to iodinated contrast media, refused CT.</p>	<p>Dual section Helical CT (CT)</p> <p>For the grading of PE, the pulmonary vascular bed was divided into five anatomic 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) by using a slightly modified Boyden classification (21) to facilitate CT and selective pulmonary arteriographic analysis</p>	<p>Pulmonary Arteriography (PA) (PA)</p> <p>The arteriographic criteria defined by Sagel and Greenspan (22) were used to detect PE. An embolism was diagnosed if an intraluminal filling defect or a vessel cutoff at least 2 mm in diameter was seen. The findings were considered negative if two projections (posteroanterior and oblique) did not show PE.</p>	<p>Primary: Presence of PE, CT Sensitivity, CT Specificity</p> <p>Secondary: NA</p> <p>Follow-up: NA</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
		<p>and comparison. Anatomic segments were graded as positive, negative, or inconclusive. Examination findings were considered positive if at least one anatomic segment was graded as positive; as negative if all anatomic segments were graded as negative; or as inconclusive if at least one segment was graded as inconclusive, without associated positive segments.</p>		

4064 CC = complex composite; CM = contrast medium; CT = computed Tomography; CTPA = computed tomography pulmonary
 4065 angiography; DSA = digital subtraction angiography; DVT = deep vein thrombosis; eGFR = estimated glomerular filtration rate; PE =
 4066 pulmonary embolism; PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis; PISAPED = Prospective Investigative
 4067 Study of Acute Pulmonary Embolism Diagnosis; SC = simple composite; SPECT = single photon emission tomography; VQ =
 4068 ventilation-perfusion; VTE = venous thromboembolism; NA = not available.

4069 **Table 10-B: Studies in non-pregnant patients with CTCTV as index test**

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
<p>Stein 2007¹¹⁶</p> <p>Canada; US; September 2001 to July 2003</p> <p>Multi-National or Regional; NA</p>	<p>N = 824</p> <p>Non-Pregnant</p> <p>As for Stein 2006.⁶⁴ At least 18 years of age with clinically suspected acute PE, referred for diagnostic imaging for suspected PE, consultation request for suspected PE.</p> <p>As for Stein 2006⁶⁴. 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</p>	<p>Refer Stein 2006⁶⁴ (CT or CTCTV)</p> <p>Refer Stein 2006⁶⁴</p>	<p>Composite reference standard (SC)</p> <p>Refer Stein 2006⁶⁴</p>	<p>Primary: DTA values</p> <p>Secondary: NA</p> <p>Follow-up: NA</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
	<p>enrolled in the study VF or sustained VT within 24 hr shock or hypotension Planned to have thrombolytic therapy within the next 24 hr</p>			
<p>Stein 2006⁶⁴ Canada; US; September 2001 to July 2003 Multi-International; Inpatient or outpatient clinical centers</p>	<p>N = 824 Non-Pregnant At least 18 years of age with clinically suspected acute PE, referred for diagnostic imaging for suspected PE, consultation request for suspected PE. 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</p>	<p>multidetector CTA alone; multidetector CTA combined with venous-phase imaging (CTA-CTV) (CT or CTCTV) PE present on CT: failure of contrast material to fill the entire lumen due to central filling defect (with possibly enlarged artery); a partial filling defect surrounded by contrast material on a cross-sectional image; contrast material between the central filling defect and the artery wall on an in-plane, longitudinal image; and a peripheral intraluminal filling defect that forms an acute</p>	<p>Composite reference standard (VQ scan showing high probability, abnormal DSA, abnormal US) (SC) Diagnosis of PE according to the composite reference standard required one of the following conditions: 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</p>	<p>Primary: diagnosis of PE Secondary: addition of Wells score improved ability to detect or rule out PE Follow-up: 3- and 6-months</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
	<p>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 to have thrombolytic therapy within the next 24 hr</p>	<p>angle with the artery wall. DVT present on CTV: complete or partial central filling defect.</p>	<p>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 DSA, normal findings on ventilationperfusion scanning, ventilationperfusion scanning showing either a low or very low probability of PE, a clinical Wells score of</p>	

4070 CT = computed Tomography; DSA = digital subtraction angiography; DVT = deep vein thrombosis; PE = pulmonary embolism; SC =
4071 simple composite; VQ = ventilation-perfusion; NA = not available

4072

4073 **Table 10-C: Studies in non-pregnant patients with MRI as index test**

4074

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
Li 2017¹¹⁹ China; NA Single; Secondary care	N = 32 Non-Pregnant Suspected acute PE based on clinical symptoms and D-dimer 30, dependency on connection to external electrical device or pump	3D Contrast Enhanced MRI (MRI) PE present: Complete arterial occlusion with failure to opacify the entire lumen on >one image in each of two places with or without an artery that was enlarged compared with the pulmonary arteries of the same order of branching; a central arterial filling defect surrounded by IV contrast material; peripheral intraluminal filling defect that made 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	CTPA (CT) Same as index	Primary: Sensitivity, specificity, PPV, NPV Secondary: NA Follow-up: NA

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
		arteries were not assessed within the sequence		
Pasin 2017¹²⁰ Brazil; NA Single; Radiology Department - Secondary Care	N = 93 Non-Pregnant Referred with clinical suspicion of acute PE Contraindications to MRI examinations (e.g., claustrophobia or iodinated contrast media)	Real-time MRI using TrueFISP (MRI) PE present: Concordant results from two planes necessary and one of the following criterion: direct visualization of the thrombus; cutoff of pulmonary vessel, any sudden changes in the signal intensity during the course of the pulmonary artery (graded as central, lobar, segmental, or subsegmental)	Multidetector CT (CT) 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 central, lobar, segmental, subsegmental)	Primary: Sensitivity, specificity, PPV, NPV, Accuracy, NPV Secondary: NA Follow-up: 1 year
Nyren 2016¹²¹ Sweden; February 2012 to January 2014	N = 33 Non-Pregnant Clinically suspected PE, underwent diagnostic CTA,	1.5T MRI (MRI) PE present: filling defect, partial filling defect, and or railway track sign; if embolus detected distal	CTA (CT) NA	Primary: DTA (sensitivity, specificity, PPV, NPV) Secondary: Inter-reader

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
<p>Single; Secondary care hospital</p>	<p>examined by the same two clinicians (primarily patients admitted to hospital)</p> <p>Contraindications to MRI, >48 hrs between exams</p>	<p>vasculature was not studied further</p>		<p>agreement</p> <p>Follow-up: NR/no follow-up?</p>
<p>Revel 2013¹²³</p> <p>France; June 2007 to June 2009</p> <p>Single; Hospital</p>	<p>N = 300 patients included; 277 MRI completed (2 MR images lost; 1 patient with inconclusive CT lost to follow-up)</p> <p>Non-Pregnant</p> <p>High clinical probability of PE or D-dimer >500 ug/L</p> <p>Signs of severe PE (hypotension), curative anticoagulation >=48h, 3 month follow-up not possible, MRI contraindicated (claustrophobia, metallic ocular implant, pacemaker,</p>	<p>MRA (MRI)</p> <p>Unenhanced Inconclusive due artefacts or partial acquisition Positive: signal void within pulmonary artery branch, whatever its division order Negative: no signal void up to subsegmental level, artefact-free</p> <p>Perfusion sequences Inconclusive due artefacts or partial acquisition or poor enhancement PE perfusion defect: defect with sharp borders fitting sub-segmental, segmental,</p>	<p>CTPA (CT)</p> <p>No details. All results considered as confirming CTA.</p>	<p>Primary: Diagnostic accuracy, comparing 3 MRI sequences</p> <p>Secondary: NA</p> <p>Follow-up: NA</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
	<p>allergy to gadolinium-based contrast agents, obesity (weight >130 kg, postero-anterior abdominal diameter >60 cm), contraindications to CTA (GFR</p>	<p>or lobar distribution Inconclusive PE defect: Poorly circumscribed defect not fitting sub-segmental, segmental or lobar distribution. Negative: homogenous enhancement of lung parenchyma Contrast-enhanced sequence Inconclusive due artefacts or partial acquisition or poor enhancement, and no PE detected otherwise Positive: Signal void within pulmonary artery branch, whatever its division order Negative: No signal void on well-enhanced artefact-free pulmonary arteries</p>		
Schiebler 2013⁵⁰	N = 190 with MRA; 167 with 3+ months follow-up; 148	MRA (MRI) Technical adquacy = no	NA (FU)	Primary: VTE or death at 3 months (for all

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
<p>US; September 2007 to December 2009</p> <p>Single; Hospital</p>	<p>with 1 year follow-up</p> <p>Non-Pregnant</p> <p>Possible PE in symptomatic patient; physician selection of imaging modality, but physicians encouraged to use for children, younger women, patients with contraindications to iodinated contrast, and for use during business hours; Both ill and minimally symptomatic patients</p> <p>Contraindications to MRI (metal, pacemakers, non-compatible implants)</p> <p>Outside hours of MRA-PE availability</p>	<p>significant breathing motion and clear visualization of the segmental pulmonary arteries</p>	<p>NA</p>	<p>patients) and 1 year of follow-up (in patients with an initial negative scan)</p> <p>Secondary: NA</p> <p>Follow-up: 1 year</p>
<p>Zhang 2013¹²²</p> <p>China; December 2010</p>	<p>N = 27 patients included (43 assessed, 16 excluded due to time between index and reference, lack of CTPA</p>	<p>3-dimensional contrast-enhanced MR pulmonary angiography (MRI)</p>	<p>CT, on dual-source CT scanner. Somatom Definition, Siemens</p>	<p>Primary: Diagnostic sensitivity, specificity, PPV, NPV, accuracy for MRPA on per-patient,</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
<p>to March 2012</p> <p>Single; Not specified where imaging was done; patients from department of nephrology</p>	<p>data, and non-compliance)</p> <p>Non-Pregnant</p> <p>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 cholesterol ? 10 mmol/L), serum creatinine</p> <p>>3 days between CTPA and MPRA</p>	<p>PE positive: nonenhancing intraluminal filling defect within the specified pulmonary arterial branch resulting in partially or completely occluding pulmonary arteries (see references 16, 20, 24)</p>	<p>Medical Solutions. (CT)</p> <p>PE defined as intraluminal filling defect partially or completely occluding the pulmonary arteries (11-12,16-23 Ref for details)</p>	<p>per-lobe basis, and different pulmonary artery levels.</p> <p>Secondary: Inter-reader agreement</p> <p>Follow-up: NA</p>
<p>Revel 2012¹²⁴</p> <p>France; June 2007 to June 2009</p> <p>Single; University</p>	<p>N = 300 (275 completed; results unavailable for the rest either due to dropout, inability to have MRI, interruption of MRI, extravasation of injected contrast, lost images on PACS; of 275 - 11 tests</p>	<p>1.5 T MRI (MRI)</p> <p>Positive; negative; or inconclusive (if technically inadequate)</p>	<p>CTA (64 detector) including all subsegmental results;</p> <p>Secondary reference standard where all single-subsegmental emboli were considered negative</p>	<p>Primary: Sensitivity, specificity</p> <p>Secondary: NA</p> <p>Follow-up: 3 months</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
Hospital	<p>were inconclusive)</p> <p>Non-Pregnant</p> <p>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)</p> <p>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 abdominal diameter > 60 cm</p>		<p>(considering unclear clinical significance) (CT)</p> <p>See reference 7 for interpretation criteria</p>	

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
	<p>were additional exclusions; patients with inconclusive CT 9(unless normal VQ or uneventful follow-up were excluded); patients who presented out of hours (882/1796 ineligible on this basis)</p>			
<p>Stein 2010¹³⁰ US; April 2006 to September 2008 Multi-National or Regional; Outpatient site, Hospitals, emergency departments; urban</p>	<p>N = 818 enrolled, 371 completed both imaging modalities, 279 had diagnosis on imaging (92 nondiagnostic)</p> <p>Non-Pregnant</p> <p>18 years or older, hospitalized or in ER with diagnosed or excluded PE. (Recruitment during nurse-coordinator's working hours).</p> <p>Implanted ferromagnetic foreign bodies, dependency</p>	<p>Magnetic Resonance Imaging +/- Magnetic Resonance Venography (MRIMRV)</p> <p>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:</p>	<p>Imaging: CT angiogram and venography V/Q lung scan PE excluded only: Normal D-dimer in patient with low (whole blood or latex D-dimer) or intermediate probability. Clinical assessment (CC)</p> <p>CT angiogram: PE positive: PE in main or lobar pulmonary artery PE in segmental or subsegmental artery + high clinical probability (Wells) PE excluded:</p>	<p>Primary: Sensitivity, specificity, likelihood ratio</p> <p>Secondary: Adverse events</p> <p>Follow-up: 3 months. 6 months for patients with reduced renal function.</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
	on external electrical device, claustrophobia, pregnant or nursing, inability to lie still for 30 minutes, renal exclusions (criteria changed multiple times).	Adequate opacification of subsegmental branches; Both MRA and MTV had to be considered technically adequate	<p>Negative + low clinical probability (Wells) Negative angiogram and venogram / US venogram + intermediate probability (Wells)</p> <p>V/Q: High probability V/Q + no previous PE + high/intermediate clinical probability (Wells)</p>	
Kluge 2006²⁰³ Germany; June 2002 and February 2005 Single; Cardiac surgery and cardiology departments within a hospital	N = 221 Non-Pregnant Suspected acute PE (based on clinical symptoms + ECG and echocardiography + D-dimer in a subset) in cardiology and cardiac surgery departments before and after surgery Cardiogenic shock; prolonged low cardiac	Multitechnique thoracic MRI protocol (real-time MRI using true fast imaging with steady-state precession [FISP], perfusion MRI, and MR angiography) + stepping table MR venography (MRI) See reference 17; Interpreted in fixed order of	Alternative MRI modalities (MRI) 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 agreement with duplex

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
	output; implanted device	sequence types; Criteria: direct thrombus visualization or vessel cutoff (real-time - concordant 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 consensus interpretation on all thoracic techniques if discrepancy between techniques evident		sonography Follow-up: NA
Kluge 2006¹²⁵ Germany; NA Single; Departments of	N = 65 Non-Pregnant Symptoms of acute PE (symptoms, ECG, echo,	Stepwise real-time MRI; MR perfusion; MR angiography (MRI) PE present: (1) Real-time MRI. Thrombotic material	16-MDCT (CT-CTA) (CT) Diagnosis made when embolic material was directly visualized or when vessel truncation implied	Primary: DTA Secondary: Incidental diagnoses Follow-up: Median = 4.6

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
cardiology and cardiac surgery in a hospital	<p>pulse oximetry, arterial blood gas, D-dimer)</p> <p>History of adverse reaction to contrast; elevated serum creatinine (CT); cardiogenic shock; prolonged low cardiac output; implanted cardiac pacemaker or cardioverter defibrillator; other implants</p>	<p>directly visualized on >one image in each of two planes, or if vessel 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.</p>	<p>the presence of occlusion (categorized as central, lobar, segmental, subsegmental, or isolated subsegmental)</p>	<p>days (range 1 to 121 days)</p>
Pleszewski	N = 48	Gadolinium enhanced magnetic resonance	Catheter angiography,	Primary: Sensitivity,

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
2006 ¹³³ Canada; NA Single; Hospital (Secondary Care)	Non-Pregnant Clinical suspicion of PE referred from emergency unit, medical unit, or surgical unit NA	angiography (fast gradient echo coronal acquisition) (MRI) Luminal filling defect.	CTA, VQ Luminal filling defect; CT interpretation done at workstation; scintigraphic criteria (see reference 13)	specificity Secondary: NA Follow-up: 6 to 12 months
Ohno 2004 ¹³¹ US; NA Single; NA	N = 48 Non-Pregnant Suspicion of PE due to risk factors, symptoms, signs, or laboratory findings.	MRI (MRI) 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	Composite: Pulmonary angiography + one year of follow-up, and low/normal VQ + uneventful follow-up and no anticoagulation in those without PA (CC) 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
Oudkerk 2002 ¹²⁷ Netherlands; NA	N = 118 Non-Pregnant NA	MRA (MRI) NA	Pulmonary angiography (PA) Emboli were shown by a filling defect or a persistent cut-off of a large artery in spite of	Primary: Sensitivity, specificity, and positive and negative predictive values were assessed and 95% CI calculated

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
Single; NA	NA		highly selective injection.	Secondary: NA Follow-up: NA
Gupta 1999¹²⁸ Australia; 8 month Single; Secondary or tertiary center	N = 36 Non-Pregnant Intermediate-probability V-P scan or a low-probability V-P scan, with a high clinical suspicion for acute PE NA	pulmonary MR angiograms (MRI) PE present: Intravascular filling defect or an abrupt vessel cutoff. Other abnormalities, such as vascular irregularity and zones of hypovascularity, were ignored.	DSA (PA) PE present: intravascular filling defect or an abrupt vessel cutoff. Other abnormalities, such as vascular irregularity and zones of hypovascularity, were ignored.	Primary: Sensitivity and specificity Secondary: NA Follow-up: NA
Meaney 1997¹²⁹ US; Eight month period (dates not reported) Single; Secondary or tertiary center	N = 30 Non-Pregnant Referred to centre for investigation. Contraindication to MRI, mechanical ventilation.	Magnetic Resonance angiography (MRI) PE present: Presence of an intravascular filling defect. Nonvisualization of a vessel alone was considered insufficient evidence for the diagnosis.	Conventional angiography (PA) NA	Primary: sensitivity, specificity, and positive and negative predictive values of magnetic resonance angiography in detecting pulmonary embolism, along with exact two-sided 95 percent confidence intervals for binomial proportions, were

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
				<p>calculated for each reviewer reading and for the final consensus of opinion.</p> <p>Secondary: NA</p> <p>Follow-up: NA</p>
<p>Erdman 1994¹³²</p> <p>US; December 1986 to June 1990</p> <p>Single; Secondary or tertiary center</p>	<p>N = 86</p> <p>Non-Pregnant</p> <p>Referral to department for scintigraphic or angiographic evaluation of possible PE</p> <p>NA</p>	<p>cardiac gated spin-echo MR imaging (MRI)</p> <p>NA</p>	<p>Angiography (PA)</p> <p>NA</p>	<p>Primary: NA</p> <p>Secondary: NA</p> <p>Follow-up: NA</p>
<p>Grist 1993¹²⁶</p> <p>US; NA</p> <p>Single; Secondary or tertiary center</p>	<p>N = 14</p> <p>Non-Pregnant</p> <p>NA</p> <p>NA</p>	<p>MR pulmonary angiogram (MRI)</p> <p>PE present: Intraluminal filling defects, occluded pulmonary artery branches and the presence of</p>	<p>CPA (CT)</p> <p>NA</p>	<p>Primary: NA</p> <p>Secondary: NA</p> <p>Follow-up: NA</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
		hypovascularity manifested by poor blood-flow related enhancements in the pulmonary arteries.		

4075 CC = complex composite; CT = computed Tomography; CTPA = computed tomography pulmonary angiography; DSA = digital
4076 subtraction angiography; GFR = glomerular filtration rate; MRI = magnetic Resonance Imaging; PE = pulmonary embolism; PIOPED
4077 = Prospective Investigation of Pulmonary Embolism Diagnosis; VQ = ventilation-perfusion; VTE = venous thromboembolism; NA =
4078 not available.

4079

4080 **Table 10-D: Studies in non-pregnant patients with MRI-MRV as index test**

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
Stein 2010¹³⁰ US; April 2006 to September 2008 Multi-National or Regional;	N = 818 enrolled, 371 completed both imaging modalities, 279 had diagnosis on imaging (92 nondiagnostic)	Magnetic Resonance Imaging +/- Magnetic Resonance Venography (MRIMRV) PE Positive: Partially occlusive intraluminal filling defect or	Imaging: CT angiogram and venography V/Q lung scan PE excluded only: Normal D-dimer in patient with low (whole blood or latex D-dimer) or intermediate probability. Clinical	Primary: Sensitivity, specificity, likelihood ratio Secondary:

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
Outpatient site, Hospitals, emergency departments; urban	<p>Non-Pregnant</p> <p>18 years or older, hospitalized or in ER with diagnosed or excluded PE. (Recruitment during nurse-coordinator's working hours).</p> <p>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).</p>	<p>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</p>	<p>assessment (CC)</p> <p>CT angiogram: PE positive: PE in main or lobar pulmonary artery PE in segmental or subsegmental artery + high clinical probability (Wells) PE excluded: Negative + low clinical probability (Wells) Negative angiogram and venogram / US venogram + intermediate probability (Wells)</p> <p>V/Q: High probability V/Q + no previous PE + high/intermediate clinical probability (Wells)</p>	<p>Adverse events</p> <p>Follow-up: 3 months. 6 months for patients with reduced renal function.</p>

4081 CC = complex composite; CT = computed tomography.

4082

4083 **Table 10-E: Studies in non-pregnant patients with MRI-VQ as index test**

Study information, country and time	Number of patients, inclusion and	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes,
-------------------------------------	-----------------------------------	--------------------------------	------------------------------------	---------------------------------------

of conduct, setting	exclusion criteria			follow-up
Ohno 2004 ¹³¹	N = 48	MRI (MRI)	Composite: Pulmonary angiography + one year of follow-up, and low/normal VQ + uneventful follow-up and no anticoagulation in those without PA (CC)	Primary: Sensitivity, specificity, positive and negative predictive values, and accuracy of data sets per vascular zone
US; NA	Non-Pregnant	PE present: Vascular signs of PE reported in the literature;	VQ: Revised PIOPED.	Secondary: NA
Single; NA	Suspicion of PE due to risk factors, symptoms, signs, or laboratory findings.	decreased area of perfusion within the lung parenchyma with or without filling defect in the corresponding pulmonary artery		Follow-up: 1 year

4084 CC = complex composite; MRI = magnetic Resonance Imaging; PE = pulmonary embolism; PIOPED = Prospective Investigation of
4085 Pulmonary Embolism Diagnosis; VQ = ventilation-perfusion; NA = not available;

4086 **Table 10-F: Studies in non-pregnant patients with US as index test**

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
Abootalebi 2016 ¹³⁴	N = 77	TUS (US)	MSCT (CT)	Primary: Number of lesions, shape, size and location of lesions
Iran; September 2011 to September	Non-Pregnant Clinical signs, symptoms and risk factors for PE with moderate to high PE	The presence of typical triangular or round hypoechoic pleural-based lesion which are often wedge-shaped and move with respiration and pleural	NA	Secondary: sensitivity, specificity, PPV, NPV and accuracy of

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
2012 Single; Emergency room (University Hospital)	probability (including dyspnea pleuritic, chest pain, hemoptysis, tachypnea, and vertigo or syncope) Wells scoring system (>6 points: High risk; 26 points: Moderate risk; Overweight, pregnant.	effusion (as an indirect sign) were considered as signs of PE.		ultrasonography Follow-up: NA
Nazerian 2014¹³⁵ Italy; June 2012 to November 2012 Multi-National or Regional; Emergency department	N = 357 Non-Pregnant Aged ≥ 18 years suspected of having a PE; Wells score > 4 or D-dimer value ≥ 500 ng/mL (positive D-dimer); Underwent MCTPA. Wells score	Multi-organ ultrasound (US) Multiorgan ultrasonography was considered diagnostic of PE when lung ultrasonography visualized at least one pulmonary subpleural infarct, or heart ultrasonography detected right ventricular dilatation or thrombi in the right cavities, or leg vein ultrasonography detected DVT. In cases	MCTPA (CT) NA	Primary: Number of pulmonary subpleural infarcts Secondary: DTA values Follow-up: NA

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
(2 university hospitals; 1 community hospital)		where multiorgan ultrasonography was negative for PE, the investigator was asked to specify whether an alternative ultrasonography diagnosis among pneumonia, pleural effusion, diffuse interstitial syndrome, pericardial effusion, or aortic dissection could justify the symptoms of presentation.		
Comert 2013¹³⁶ Turkey; January 2010 to July 2011 Single; Department of Pulmonary Diseases of a Training	N = 50 Non-Pregnant Clinical suspicion of PE under consideration of risk factors (malignancy, lower extremity fracture, obesity, congestive heart failure, postpartum period, and history of	TUS (US) Diagnosis of PE was suggested if at least one typical pleural?based/subpleural wedge?shaped or round hypochoic lesion with or without pleural effusion was reported by TUS. Presence of pure pleural effusion or normal sonographic findings	CTPA (CT) The diagnosis of PE was confirmed by the presence of at least one filling defect in the pulmonary artery. The static multidetector row CT scan was analyzed on a Vitrea workstation.	Primary: Number of lesions / sensitivity, specificity, NPV, PPV Secondary: NA Follow-up: NA

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
and Research Hospital	venous thromboembolism, operation, and PE) NA	were accepted as negative TUS for PE.		
Pfeil 2010¹³⁷ Germany; NA Single; NA	N = 33 Non-Pregnant Symptoms of suspected PE were enrolled in the study (including dyspnea, pleuritic chest pain, hemoptysis, vertigo or syncope, and/or tachypnea). NA	Transthoracic sonography (TS) (US) NA	MSCT (CT) A diagnosis of PE was accepted upon direct computed tomographic visualization of an embolism. Images were analyzed for the 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.	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
Reissig 2004¹³⁸	N = 62 Non-Pregnant	TUS (US) Intraluminal filling defects	Spiral CT (CT) NA	Primary: Sensitivity, specificity, and positive and

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
Germany; NA Single; NA	TS as well as sCT performed within 24 h after the onset of symptoms NA	within the central and segmental/subsegmental pulmonary arteries, the dilatation of main pulmonary arteries and a decrease in the size of small branches as well as vessel irregularities.		negative predictive values Secondary: NA Follow-up: NA
Mohn 2003¹³⁹ France; November 2000 to May 2001 Single; Department of internal medicine	N = 74 Non-Pregnant Suspicion of PE. Recent clinical symptoms of PE had to be present (e.g., pleuritic chest pain, unexplained dyspnea, or hemoptysis). Symptoms reported >7 days previously, clinical indication of acute massive PE in the Emergency Department (e.g.,	Transthoracic Sonography CT Pulmonary angiography (US) Transthoracic sonography was interpreted as follows: PE suggestive, consisting of (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; or PE	Composite including VQ, LUS, CT, PA, and clinical follow-up (not all patients received the same tests) (CC) NA	Primary: DTA values Secondary: Other sonographic findings (describe transthoracic abnormalities) Follow-up: 3 months

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
	hemodynamic failure), unavailability of a 3-month follow-up.	nonsuggestive, consisting of unspecific lesions of other shapes that have not been described in connection with PE, or no lesions detected; the presence of an isolated pleural effusion was classified as nonsuggestive.		
Lechleitner 2002¹⁴⁰ Austria; NA Single; Department of Medicine	N = 55 Non-Pregnant Suspected PE Haemodynamically unstable patients, those receiving mechanical ventilation, patients with contraindications to MRI, pregnant women	ventilation perfusion scanning, chest ultra-sound, chest x-ray and D-Dimer blood sampling were carried out in all patients (US or VQ) Ventilation/perfusion scintigraphy: The scans were categorized by applying a 4-grade classification (high, intermediate low/very low and negative probability) according to the PIOPED criteria. Chest sonography: Specific lesions: Echo poor and	MRI angiography (reference method) (MRI) NA	Primary: categorize sonographic lesions (specific lesions, unspecific lesions, no lesion) Secondary: sensitivity, specificity Follow-up: NA

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
		<p>homogenous. rounded and less sharply bordered to the ventilated lung wedge shaped. well demarcated lesions with a hyperechoic reflexion at the center. Possibly corresponding to the bronchioles. Echogenicity was influenced by the presence of a pleural effusion which was present in 10% of patients. Unspecific lesions: All lesions of other shapes. which have never been described in connection with PE. No lesion; Normal pleural reflex.</p>		
<p>Reissig 2001¹⁴¹ Germany; February 1998 to March 2000</p>	<p>N = 69 Non-Pregnant NA NA</p>	<p>TUS (US) Intraluminal filling defects, defects within the central pulmonary srteries, dilatation of the main pulmonary arterires and decreases in</p>	<p>Spiral CT (CT) NA</p>	<p>Primary: Sensitivity, specificity, and positive and negative predictive values Secondary: NA Follow-up: NA</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
Single; NA		the size of the small branches of the lung as well as irregularities of the blood vessels		
Lechleitner 1998¹⁴³ Austria; 15-month period in 1995/1996 NA; NA	N = 119 Non-Pregnant Clinical signs of PE NA	Chest x-ray, chest sonography (US) All intercostal spaces were examined from dorsal and from ventral sites. Started by investigating the intercostal spaces where the patient localised the pain (if any). In the event that a suspicious lesion was discovered, the longitudinal axis was also scanned. Investigators were not aware of the results of the chest x-ray, which was performed shortly before or after chest sonography, usually within a few hours of admission. Specific lesions: Echo poor	since pulmonary angiography was performed only in some selected cases, perfusion/ventilation scintigraphy was the reference method (VQ) The scans were categorized by applying a 5 grade classification in 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

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
		<p>and homogenous. rounded and less sharply bordered to the ventilated lung wedge shaped. well demarcated lesions with a hyperechoic reflexion at the center. Possibly corresponding to the bronchioles. Echogenicity was influenced by the presence of a pleural effusion which was present in 10% of patients. Unspecific lesions: All lesions of other shapes. which have never been described in connection with PE. No lesion; Normal pleural reflex.</p>		
<p>Mathis 1993¹⁴² Austria; October 1989 to August 1991</p>	<p>N = 58 Non-Pregnant Clinical signs of PE / infarction</p>	<p>Ultrasonography Ventilation lung scintigraphy (US) NA</p>	<p>Ventilation-perfusion scintigraphy pulmonary angiography (SC) NA</p>	<p>Primary: diagnostic accuracy of chest sonography Secondary: NA Follow-up: NA</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
Single; NA	NA			

4087 CC = complex composite; CT = computed Tomography; CTPA = computed tomography pulmonary angiography; DVT = deep vein
4088 thrombosis; MRI = magnetic Resonance Imaging; PE = pulmonary embolism; PIOPED = Prospective Investigation of Pulmonary
4089 Embolism Diagnosis; SC = simple composite; VQ = ventilation-perfusion; NA = not available.

4090

4091 **Table 10-G: Studies in non-pregnant patients with perfusion (Q) as index test**

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
Mazurek 2015¹⁵¹ Poland; 2010 to 2011 Single; Secondary or tertiary inpatient care	N = 84 Non-Pregnant Perfusion scintigraphy performed using planar scintigraphy, SPECT, or SPECT/CT Three images could not be recorded due increased dyspnea or absence of observational	SPECT/CT(Q) scintigraphy (Q-SPECT-CT) Positive diagnosis: At least 1 segmental or 2 subsegmental perfusion defects without abnormalities in the lung parenchyma Negative diagnosis: Normal perfusion	Composite reference standard - side-by-side consensus based on clinical presentation, lab test results, other imaging test results, and follow-up data (CC) clinical presentation (dyspnea, chest pain, hemoptysis, syncope, jugular vein distention and DVT symptoms), lab test	Primary: Sensitivity and specificity of planar, SPECT/CT, SPECT Secondary: NA Follow-up: 6 months

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
	data 6 months after the examination	pattern, perfusion defects that were not arranged in accordance with the pulmonary vasculature and perfusion defects caused by abnormalities in the lung parenchyma	(arterial blood gas analysis, troponin and NT-proBNP levels, other imaging test result (check x-ray, echocardiography and lower extremity ultrasound), and follow-up data.	
<p>van Es 2015¹⁵²</p> <p>Netherlands; Belgium; October 2008 and February 2012</p> <p>Multi-International; Urban, academic and non-academic medical centres (hospitals)</p>	<p>N = 76 patients, 74 with definite diagnosis</p> <p>Non-Pregnant</p> <p>In/out patients</p> <p>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</p>	<p>Perfusion scan with CXR (Q)</p> <p>PISAPED criteria</p> <p>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 (details see Table 1). Or defects not wedge shaped; PE</p>	<p>CPTA (CT)</p> <p>PE confirmed if constant intraluminal defect in sub-segmental or more proximal branches of pulmonary artery</p>	<p>Primary: Sensitivity, specificity, PPV, NPV. Inter-observer agreement.</p> <p>Secondary: NA</p> <p>Follow-up: No formal follow up. Retrospective assessment of PE in patients with negative scans. (Discrepancy between CTPA and X/Q scan result)</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
		<p>nondiagnostic = all other cases.</p> <p>Chest X-Ray PISAPED readers considered abnormal if: enlargement of the heart or hilar vessels; elevated diaphragm; pleural effusion; increased lung density; pulmonary edema; consolidation suggestive of infarction; emphysema; or fibrothorax</p>		
<p>Watanabe 2015¹⁴⁵ Slovenia; Turkey; Czech Republic; Uruguay; India; October 2004 and September 2008 Multi-International; Hospitals and tertiary care centres (nuclear medicine)</p>	<p>N = 201 patients included, 129 had no abnormalities on CXR</p> <p>Non-Pregnant</p> <p>Presenting with suspicion of acute PE within 24 h, No abnormalities on CXR.</p> <p>3 days thrombolytic</p>	<p>1. V/Q Scintigraphy + modified PLOPED, PISAPED, or modified PISAPED criteria. 2. CTPA. After inclusion: Intermediate or high likelihood or positive D-dimer – V/Q scan and CTPA and 24 weeks follow-up; Low likelihood and negative</p>	<p>Final clinical assessment at 24 weeks by physician blinded to interpretations of imaging except CXR. Assessment took into account response to anticoagulation. (FU)</p> <p>NA</p>	<p>Primary: Sensitivity and specificity</p> <p>Secondary: AUROC</p> <p>Follow-up: 24 weeks</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
<p>departments); urban</p>	<p>therapy before event, difficult to follow-up for 24 weeks, renal failure, known allergy to iodine, known pulmonary hypertension, abnormalities on CXR</p>	<p>D-dimer – no imaging, followed 24 weeks. (VQ)</p> <p>3 sets of diagnostic criteria applied: PLOPED (V/Q) (PE present, PE absent or non-diagnostic), PISAPED (Q alone) (PE present, PE absent or nondiagnostic), modified PISAPED (V/Q) (PE present, PE absent, nondiagnostic).</p> <p>See Table 2 and 3 in the paper.</p> <p>CTPA: See Reference 12 to 14 PE present: complete arterial occlusion, failure to opacify, artery possibly enlarged. Central filling defect. Peripheral intraluminal defect that makes acute angle with arterial wall. PE absent:</p>		

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
		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.		
<p>Lu 2014¹⁴⁸</p> <p>US; 2006 to 2010</p> <p>Single; Secondary/Tertiary Care</p>	<p>N = 106</p> <p>Non-Pregnant</p> <p>Underwent both planar / and -SPECT/CT imaging on the same day, with at least 3 months of clinical follow-up.</p> <p>NA</p>	<p>Q SPECT-CT (Q-SPECT-CT)</p> <p>PE present indicated at least one wedge-shaped peripheral defect estimated as 50% of a pulmonary segment 27 without corresponding CT image abnormality and clearly seen in all three orthogonal planes</p>	<p>Planar V/Q scan was comparator, final diagnosis was made by by consensus of the pulmonologist and the imaging arbiter who used 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</p>	<p>Primary: NA</p> <p>Secondary: NA</p> <p>Follow-up: 3 months</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
			(CC) Planar scans were analyzed according to modified PIOPED II 24,25 and PISA-PED 16,26 criteria and categorized	
Skarlovnik 2014 ¹⁴⁶ Slovenia; 2010 Multi-National or Regional; Secondary or tertiary inpatient care	N = 147 Non-Pregnant NA Technically inadequate scans,	V/Q SPECT (VQ-SPECT) Criteria from EANM guidelines. Perfusion abnormalities compatible with PE reported in %. Using 0.5 segment mismatch criteria and revised PIOPED II. PE present: ?2 segments of V/Q mismatch or ?3 V/Q mismatch defects >50% of segment.	Composite diagnosis absed on clinical decision and 12 months follow-up where all investigations including CTPA were taken into account (CC) 0.5 segment mismatch criteria; ?2 segments of V/Q mismatch ?3 V/Q mismatch defects >50% of segment	Primary: NA Secondary: NA Follow-up: 12 month
He 2012 ¹¹⁴ China; June 2007 to January 2011 Multi-National or	N = 544 Non-Pregnant Suspected PE (based on signs and symptoms,	V/Q (VQ) PISAPED and PIOPED II criteria V/Q: PE present, PE	Composite Reference Test (clinical data, laboratory recorders (D-dimer and Doppler US available), imaging information (e.g.,	Primary: Sensitivity, specificity, PPV, NPV, proportion of non-diagnostic tests

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
Regional; Secondary care centers (including academic centers)	<p>laboratory findings, medical history and predisposing factors - assessed formally by Wells).</p> <p>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.</p>	<p>absent, or non-diagnostic;</p> <p>Q only: PE present or PE absent</p> <p>CT: PE present, PE absent, or non-diagnostic</p>	<p>echocardiography), CTPA, V/Q, 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);</p> <p>Pulmonary contrast angiography (Allura Xper FD10/10 angiographic unit) performed in patients in whom PE not conclusively diagnosed or ruled out by non-invasive tests (CC)</p> <p>Final diagnosis made at consensus meeting</p>	<p>Secondary: NA</p> <p>Follow-up: 6 months</p>
<p>Wang 2009¹⁰⁴</p> <p>China; October 2005 to February 2007</p> <p>Single; NA</p>	<p>N = 82</p> <p>Non-Pregnant</p> <p>Normal creatinine level, willing to undergo VQ scan and CTPA.</p>	<p>CTPA VQ Perfusion and chest radiography (CR) (Multiple)</p> <p>VQ: The perfusion images were interpreted in conjunction with ventilation images</p>	<p>Composite reference standard (all imaging modalities, all available laboratory recorders, clinical data, opinions of physicians responsible for treatment, and outcomes)</p>	<p>Primary: DTA values</p> <p>Secondary: NA</p> <p>Follow-up: NA</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
	<p>Pregnan, 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.</p>	<p>and/or CR. Diagnosis was based on the refined modified PIOPED (RM-PIOPED) criteria. In brief, high probability which was defined as 2 or more segments of perfusion-ventilation mismatch or perfusion-CR mismatch was classified as PE present, intermediate probability as nondiagnostic, and all others as PE absent.</p> <p>The CTPA scans were assessed by 2 experienced radiologists who were unaware of the results of the V/Q scan (or perfusion scan combined with CR). The main, lobar, segmental, and subsegmental arteries were examined. Complete visualization</p>	<p>(CC)</p> <p>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 physicians responsible for treatment and outcomes.</p>	

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
		<p>of a main, lobar, or segmental arteries required that the branch should be followed to its bifurcation. Readers scored their degree of diagnostic certainty by using a 3-point scale (PE present, PE absent, or nondiagnostic).</p>		
<p>Sostman 2008¹⁴⁹ US; September 2001 to July 2004 Multi-National or Regional; Hospital or ER</p>	<p>N = 910 usable data, 889 complete data (41 excluded due to incomplete data)</p> <p>Non-Pregnant</p> <p>Included in PIOPED II,⁶⁴ had DSA diagnosis or CTA result concordant with Wells score, interpretable perfusion scans.</p> <p>As for PIOPED II,⁶⁴ did not undergo CTA, VQ; does not have CTA diagnosis, or CTA</p>	<p>Q + CXR (Q)</p> <p>PIOPED II, modified for absence of V component, and examining perfusion-chest radiograph match</p> <p>High probability (2 or more segments of perfusion-chest radiograph mismatch)</p> <p>PE absent: Normal, very low probability</p> <p>[[detail in paper]] Not diagnostic: all other findings</p> <p>PISAPED (Prospective</p>	<p>DSA, or if no DSA, CTA results concordant with Wells results (e.g., CTA positive + Wells score >2 or CTA negative + Wells score</p> <p>NA</p>	<p>Primary: Sensitivity and specificity of Q + CXR in patients categorized as PE present or PE absent</p> <p>Secondary: NA</p> <p>Follow-up: NA</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
	discordant with Wells score, intermediate or low probability V/Q scan, perfusion scan not available or interpretable	Investigative Study of PE Diagnosis) PE present: 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		
Rubini 2007¹⁵⁰ Italy; May 2002 to June 2004 NA; Secondary or tertiary inpatient care	N = 107 Non-Pregnant PLS and MSCT examination obtained within 7 days of the clinical-laboratory suspicion of PE, no thrombolytic therapy under way, prior chest radiography. NA	Perfusion lung scintigraphy (Q) PISAPED	Multislice CT (CT) MSCT was considered positive in the presence of 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

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
Tondeur 2007¹⁴⁷ Belgium; One year period Single; Urban ER	<p>N = 53 included and imaged</p> <p>Pregnant</p> <p>Admitted to ER with potential diagnosis of PE (suspicion based on clinical data, radiological data, d-dimers, and inferior legs ultrasound derived pre-test probability), helical CT and 81m-Krypton ventilation scan not available, or contraindicated (renal failure, allergy to contrast media).</p> <p>None: pregnant patients received reduced radioactive dose.</p>	<p>Lung perfusion scan (Q)</p> <p>PISAPED criteria. Separated into normal/near normal (PE unlikely), abnormal and suggesting PE (PE very likely), abnormal and equivocal (PE possible).</p>	<p>Helical lung CT or V/Q or change in perfusion scan with treatment or combination of both tests (SC)</p> <p>NA</p>	<p>Primary: Number of patients diagnosed with/without PE by perfusion scan, compared to final diagnosis. (Allows calculation of S, C, etc)</p> <p>Secondary: Impact on clinical decision making</p> <p>Follow-up: >3 months</p>
Miniati 1996¹⁵³ Italy; November 1991 to April 1995	<p>N = 890</p> <p>Non-Pregnant</p> <p>Suspected PE -</p>	<p>Perfusion scanning (Q)</p> <p>(1) normal; (2) near-normal; (3) abnormal compatible with PE; (4)</p>	<p>Pulmonary angiography (PA)</p> <p>Identification of embolus obstructing the vessel or</p>	<p>Primary: Sensitivity; specificity (adjusted using Bayes theorem)</p> <p>Secondary: NA</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
Single; Unclear	NA	abnormal not compatible with PE (See Table 2 page 1388)	the outline of an embolus within a vessel; consensus sought by two readers simultaneously reexamine angiogram; if still unclear clinical and scintigraphic follow-up used for definitive diagnosis	Follow-up: Clinical, reoentgenographic and scintigraphic follow-up at 1 week, 1 month, and 1 year after enrollment (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

4092 CC = complex composite; CT = computed Tomography; CTPA = computed tomography pulmonary angiography; DSA = digital
4093 subtraction angiography; DVT = deep vein thrombosis; PE = pulmonary embolism; PIOPED = Prospective Investigation of Pulmonary
4094 Embolism Diagnosis; PISAPED = Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis; SC = simple composite;
4095 SPECT = single photon emission tomography; VQ = ventilation-perfusion; NA = not available;

4096

4097 **Table 10-H: Studies in non-pregnant patients with Q-SPECT as index test**

Study information,	Number of patients, inclusion	Index test (as coded), details	Reference test (as coded), details	Primary outcomes,
--------------------	-------------------------------	--------------------------------	------------------------------------	-------------------

country and time of conduct, setting	and exclusion criteria			secondary outcomes, follow-up
Mazurek 2015¹⁵¹ Poland; 2010 to 2011 Single; Secondary or tertiary inpatient care	N = 84 Non-Pregnant Perfusion scintigraphy preformed using planar scintigraphy, SPECT, or SPECT/CT Three images could not be recorded due increased dyspnea or absence of observational data 6 months after the examination	SPECT/CT(Q) scintigraphy (Q-SPECT-CT) Positive diagnosis: At least 1 segmental or 2 subsegmental perfusion defects without abnormalities in the lung parenchyma Negative diagnosis: 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	Composite reference standard - side-by-side consensus based on clinical presentation, lab test results, other imaging test results, and follow-up data (CC) 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 result (check x-ray, echocardiography and lower extremity ultrasound), and follow-up data.	Primary: Sensitivity and specificity of planar, SPECT/CT, SPECT Secondary: NA Follow-up: 6 months
Bajc 2013¹⁵⁵ Sweden; 1.5 years Single; Academic hospital (secondary)	N = 152 Non-Pregnant Clinically suspected PE based on clinical symptoms and ancillary tests.	Q-SPECT (V/Q-SPECT analyzed retrospectively without ventilation component) (Q-SPECT) Negative = No perfusion defects Positive = single or multiple wedge-shaped perfusion defects (EANM)	Combination of clinical findings, V/Q SPECT, 16-detector CT; multidetector CT, and compression ultrasonography (CC) V/Q SPECT - in accordance with European guidelines; CT = identification of a embolus obstructing a vessel or the outline of an embolus	Primary: Failure rate; rate of non-diagnostic tests; specificity; diagnostic accuracy; positive and negative predictive values

care)	NA	criteria) Differential diagnosis categorized as no PE = perfusion defects other than “wedge shaped”	within a vessel	Secondary: NA Follow-up: 3 months
-------	----	---	-----------------	--------------------------------------

4098 CC = complex composite; CT = computed Tomography; DVT = deep vein thrombosis; PE = pulmonary embolism; SPECT = single
4099 photon emission tomography; NA = not available;

4100

4101 **Table 10-I: Studies in non-pregnant patients with Q-SPECT-CT as index test**

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
Kumar (Group I) 2015¹⁵⁷ US; December 2011 to June 2013 Single; NA	N = 49 Non-Pregnant Group I: Scintigraphic perfusion imaging within 7 days of nondiagnostic CTPA study Group II: Perfusion imaging due to contraindication to CTPA or clinician preference NA	Q-SPECT-CT (Q-SPECT-CT) PE is indicated by at least one wedge-shaped peripheral defect estimated as ≥50 % of a pulmonary segment without corresponding CT image abnormality and clearly seen in all three orthogonal planes. Any perfusion defects corresponding to CT abnormalities (Fig. 1) (such as radiation fibrosis, pleural effusion, emphysematous bullae, pneumonia, or solid	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 V/Q, Q-SPECT/CT and CTPA (CC)	Primary: NA Secondary: NA Follow-up: 6 months

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
		tumor mass, etc.) are deemed negative for PE.; MSKCC-Q-SPECT/CT criteria (20, 14, 21 ref)	Planar V/Q images were interpreted in accordance with the modified PIOPED II criteria	
Le Roux 2015¹⁵⁶ France; April 2011 to March 2013 Single; Secondary/Tertiary Care	N = 393 Non-Pregnant >=18 years, symptoms suggestive of PE, high clinical probability of PE or nonhigh clinical probability but abnormal plasma ELISA D-dimer concentration (>500ug/ml). NA	V/Q SPECT-CT (VQ-SPECT-CT) V/Q SPECT was interpreted by the nuclear medicine physician in charge using a diagnostic cutoff of one segmental or two subsegmental mismatched defects	Composite: Final diagnostic conclusion was established by the physician in charge of patient care on the basis of clinical symptoms, laboratory tests, V/Q SPECT and other imaging procedures performed. (CC) NA	Primary: NA Secondary: NA Follow-up: 3 months
Mazurek 2015¹⁵¹ Poland; 2010 to 2011 Single; Secondary or tertiary inpatient	N = 84 Non-Pregnant Perfusion scintigraphy performed using planar scintigraphy,	SPECT/CT(Q) scintigraphy (Q-SPECT-CT) Positive diagnosis: At least 1 segmental or 2 subsegmental perfusion defects without abnormalities in the lung	Composite reference standard - side-by-side consensus based on clinical presentation, lab test results, other imaging test results, and follow-up data (CC) clinical presentation (dyspnea,	Primary: Sensitivity and specificity of planar, SPECT/CT,

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
care	<p>SPECT, or SPECT/CT</p> <p>Three images could not be recorded due increased dyspnea or absence of observational data 6 months after the examination</p>	<p>parenchyma</p> <p>Negative diagnosis: 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</p>	<p>chest pain, hemoptysis, syncope, jugular vein distention and DVT symptoms), lab test (arterial blood gas analysis, troponin and NT-proBNP levels_, other imaging test result (check x-ray, echocardiography and lower extremity ultrasound), and follow-up data.</p>	<p>SPECT</p> <p>Secondary: NA</p> <p>Follow-up: 6 months</p>
<p>Lu 2014¹⁴⁸</p> <p>US; 2006 to 2010</p> <p>Single; Secondary/Tertiary Care</p>	<p>N = 106</p> <p>Non-Pregnant</p> <p>Underwent both planar / and -SPECT/CT imaging on the same day, with at least 3 months of clinical follow-up.</p> <p>NA</p>	<p>Q SPECT-CT (Q-SPECT-CT)</p> <p>PE present indicated at least one wedge-shaped peripheral defect estimated as 50% of a pulmonary segment 27 without corresponding CT image abnormality and clearly seen in all three orthogonal planes</p>	<p>Planar V/Q scan was comparator, final diagnosis was made by by consensus of the pulmonologist and the imaging arbiter who used 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 (CC)</p> <p>Planar scans were analyzed</p>	<p>Primary: NA</p> <p>Secondary: NA</p> <p>Follow-up: 3 months</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
			according to modified PIOPED II 24,25 and PISA-PED 16,26 criteria and categorized	

4102 CC = complex composite; CT = computed Tomography; CTPA = computed tomography pulmonary angiography; DVT = deep vein
4103 thrombosis; PE = pulmonary embolism; PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis; SPECT = single
4104 photon emission tomography; VQ = ventilation-perfusion; NA = not available;

4105

4106 **Table 10-J: Studies in non-pregnant patients with VQ as index test**

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
Watanabe 2015¹⁴⁵ Slovenia; Turkey; Czech Republic; Uruguay; India; October 2004 and September 2008 Multi-International; Hospitals and tertiary care centres (nuclear medicine)	N = 201 patients included, 129 had no abnormalities on CXR Non-Pregnant Presenting with suspicion of acute PE within 24 h, No abnormalities on CXR. 3 days thrombolytic	1. V/Q Scintigraphy + modified PIOPED, PISAPED, or modified PISAPED criteria. 2. CTPA. After inclusion: Intermediate or high likelihood or positive D-dimer – V/Q scan and CTPA and 24 weeks follow-up; Low likelihood and negative D-dimer –	Final clinical assessment at 24 weeks by physician blinded to interpretations of imaging except CXR. Assessment took into account response to anticoagulation. (FU) NA	Primary: Sensitivity and specificity Secondary: AUROC Follow-up: 24 weeks

departments); urban therapy before event, difficult to follow-up for 24 weeks, renal failure, known allergy to iodine, known pulmonary hypertension, abnormalities on CXR

no imaging, followed 24 weeks. (VQ)

3 sets of diagnostic criteria applied:: PIOPED (V/Q) (PE present, PE absent or non-diagnostic), PISAPED (Q alone) (PE present, PE absent or nondiagnostic), modified PISAPED (V/Q) (PE present, PE absent, nondiagnostic).

See Table 2 and 3 in the paper.

CTPA: See Reference 12 to 14 PE present: complete arterial occlusion, failure to opacify, artery possibly enlarged. Central filling defect. Peripheral intraluminal 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.		
Lu 2014 ¹⁴⁸	N = 106	Q SPECT-CT (Q-SPECT-CT)	Planar V/Q scan was comparator, final diagnosis was made by consensus of the pulmonologist and the imaging arbiter who used 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 (CC)	Primary: NA
US; 2006 to 2010	Non-Pregnant	PE present indicated at least one wedge-shaped peripheral defect estimated as 50% of a pulmonary segment 27 without corresponding CT image abnormality and clearly seen in all three orthogonal planes	Planar scans were analyzed according to modified PIOPED II 24,25 and PISA-PED 16,26 criteria and categorized	Secondary: NA
Single; Secondary/Tertiary Care	Underwent both planar / and -SPECT/CT imaging on the same day, with at least 3 months of clinical follow-up. NA			Follow-up: 3 months
Skarlovnik 2014 ¹⁴⁶	N = 147	V/Q SPECT (VQ-SPECT)	Composite diagnosis based on clinical decision and 12 months follow-up where all investigations including	Primary: NA
Slovenia; 2010	Non-Pregnant	Criteria from EANM guidelines. Perfusion		Secondary: NA
Multi-National or				

<p>Regional; Secondary or tertiary inpatient care</p>	<p>NA Technically inadequate scans,</p>	<p>abnormalities compatible with PE reported in %. Using 0.5 segment mismatch criteria and revised PIOPED II. PE present: ?2 segments of V/Q mismatch or ?3 V/Q mismatch defects >50% of segment.</p>	<p>CTPA were taken into account (CC) 0.5 segment mismatch criteria; ?2 segments of V/Q mismatch ?3 V/Q mismatch defects >50% of segment</p>	<p>Follow-up: 12 month</p>
<p>He 2012 ¹¹⁴ China; June 2007 to January 2011 Multi-National or Regional; Secondary care centers (including academic centers)</p>	<p>N = 544 Non-Pregnant Suspected PE (based on signs and symptoms, laboratory findings, medical history and predisposing factors - assessed formally by Wells). Abnormal serum creatinine, unwilling to investigations, pregnancy, circulatory shock, hypotension, renal failure, hemodynamically unstable, ventilatory support, anticoagulation,</p>	<p>V/Q (VQ) PISAPED and PIOPED II criteria V/Q: PE present, PE absent, or non- diagnostic; Q only: PE present or PE absent CT: PE present, PE absent, or non- diagnostic</p>	<p>Composite Reference Test (clinical data, laboratory recorders (D-dimer and Doppler US available), imaging information (e.g., echocardiography), CTPA, V/Q, 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) performed in patients in whom PE not conclusively diagnosed or ruled out by</p>	<p>Primary: Sensitivity, specificity, PPV, NPV, proportion of non- diagnostic tests Secondary: NA Follow-up: 6 months</p>

	history of allergy to contrast media, received thrombolytic therapy before examinations excluded.		non-invasive tests (CC) Final diagnosis made at consensus meeting	
Gutte 2010 ¹⁵⁸ Denmark; June 2006 to February 2008 Single; Secondary/Tertiary Care	N = 36 Non-Pregnant 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 Contraindication to CT including allergy to contrast agents, impaired renal function (P-creatinine level >0.120 mmol/L), women	V/Q SPECT (VQ-SPECT) Diagnosed if one or more perfusion defects (> 0.5 segment) with normal ventilation (mismatch) were present	Planar Lung Scintigraphy (VQ) NA	Primary: sens, spec Secondary: NA Follow-up: 6 months
Miles 2009 ¹⁶⁷	N = 79	V/Q SPECT (VQ-	Final diagnosis made by respiratory physicians who	Primary: NA

<p>Australia; March 18 2004 to May 26 2006</p> <p>Multi-National or Regional; Secondary or tertiary inpatient care</p>	<p>Non-Pregnant</p> <p>NA</p> <p>Patients</p>	<p>SPECT)</p> <p>A SPECT scan was considered to be positive for PE if at least one mismatched defect of > 0.5 of a lung segment was present.</p>	<p>were provided with the planar scintigraphy and CTPA reports and with extensive clinical information, including d-dimer levels, modified Wells score, and patient status at the 3-month follow-up (CC)</p> <p>NA</p>	<p>Secondary: NA</p> <p>Follow-up: 3 months</p>
<p>Wang 2009¹⁰⁴</p> <p>China; October 2005 to February 2007</p> <p>Single; NA</p>	<p>N = 82</p> <p>Non-Pregnant</p> <p>Normal creatinine level, willing to undergo VQ scan and CTPA.</p> <p>Pregnan, currently experiencing circulatory shock or had hypotension or renal failure, hemodynamically unstable, ventilatory support, chronic pulmonary hypertension, receiving anticoagulation, history of allergy to</p>	<p>CTPA VQ Perfusion and chest radiography (CR) (Multiple)</p> <p>VQ: The perfusion images were interpreted in conjunction with ventilation images and/or CR. Diagnosis was based on the refined modified PIOPED (RM-PIOPED) criteria. In brief, high probability which was defined as 2 or more segments of perfusion-ventilation mismatch or perfusion-CR mismatch was classified as PE present, intermediate probability as nondiagnostic, and all</p>	<p>Composite reference standard (all imaging modalities, all available laboratory recorders, clinical data, opinions of physicians responsible for treatment, and outcomes) (CC)</p> <p>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 physicians responsible for treatment and outcomes.</p>	<p>Primary: DTA values</p> <p>Secondary: NA</p> <p>Follow-up: NA</p>

contrast media.

others as PE absent.

The CTPA scans were assessed by 2 experienced radiologists who were unaware of the results of the V/Q scan (or perfusion scan combined with CR). The main, lobar, segmental, and subsegmental arteries were examined. Complete visualization of a main, lobar, or segmental arteries required that the branch should be followed to its bifurcation. Readers scored their degree of diagnostic certainty by using a 3-point scale (PE present, PE absent, or nondiagnostic).

Sostman 2008 ¹⁶³ US; September 2001 to July 2003 Multi-National or Regional; Hospital or ER	N = 951 enrolled, 910 had DSA or concordant CT/Wells scores (41 excluded) Non-Pregnant Included in PIOPED II ⁶⁴ , had DSA	V/Q (VQ) Modified PIOPED II Includes PE present (high probability), PE absent (normal low or vey low), nondiagnostic (all other findings -	DSA, or if no DSA, CTA results concordant with Wells results (e.g., CTA positive + Wells score >2 or CTA negative + Wells score NA	Primary: Sensitivity and specificity of V/Q studies of patients categorized as PE present or PE absent Secondary: NA
---	--	--	---	---

	<p>diagnosis or CTA result concordant with Wells score</p> <p>As for PIOPED II⁶⁴, did not undergo CTA, VQ, does not have CTA diagnosis, or CTA discordant with Wells score, intermediate or low probability V/Q scan</p>	intermediate probability)		Follow-up: NA
<p>Ohno 2004 ¹³¹</p> <p>US; NA</p> <p>Single; NA</p>	<p>N = 48</p> <p>Non-Pregnant</p> <p>Suspicion of PE due to risk factors, symptoms, signs, or laboratory findings.</p>	<p>MRI (MRI)</p> <p>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</p>	<p>Composite: Pulmonary angiography + one year of follow-up, and low/normal VQ + uneventful follow-up and no anticoagulation in those without PA (CC)</p> <p>VQ: Revised PIOPED.</p>	<p>Primary: Sensitivity, specificity, positive and negative predictive values, and accuracy of data sets per vascular zone</p> <p>Secondary: NA</p> <p>Follow-up: 1 year</p>
<p>Reinartz 2004 ¹⁰⁵</p> <p>Germany; January 2001 to April 2003</p> <p>Single; NA</p>	<p>N = 83</p> <p>Non-Pregnant</p> <p>Had V/Q lung scintigraphy in SPECT technique as well as multislice spiral CT</p>	<p>V/Q lung scintigraphy (VQ)</p> <p>PIOPED criteria</p>	<p>Multislice CT (CT)</p> <p>PE was diagnosed if one or more embolic clots were detected in the pulmonary arteries</p>	<p>Primary: NA</p> <p>Secondary: NA</p> <p>Follow-up: at least 5 months (max 10 months)</p>

	within an interval of 3 d			
	NA			
Coche 2003 ¹⁰⁹	N = 94	Multi detector Spiral CT angiography, thin collimation (MDCT) (CT)	Ventilation-perfusion (V-P) scintigraphy, pulmonary digital subtraction angiography when indicated, and chest radiography (SC)	Primary: Episodes of recurrent or new deep venous thrombosis or PE were recorded
Belgium; 21-months (dates not reported)	Non-Pregnant	PE were identified when either complete or partial filling defects within the main, lobar, segmental, or subsegmental arteries were identified	VQ: PE excluded if perfusion defects of any kind. PE unlikely (low probability), perfusion defects of any size were matched by equal or larger ventilation defects and were smaller or equal in size 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. Pulmonary angiograms were reviewed at a computer workstation (Integris V3000). The	Secondary: Baseline creatinine levels were measured in all patients before the spiral CT examination, and the creatinine level was monitored in hospitalized patients
Single; Emergency department of urban teaching hospital with an annual census of 50,000 patients	Clinical suspicion of PE, age >18 years, absence of clinically suspected deep venous thrombosis, and plasma D-dimer levels >500 ng/mL. 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.			Follow-up: 6 months

			<p>criterion for diagnosis of acute PE was a 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. Any abnormalities that were suspicious for chronic PE were also recorded. Chest radiography. Chest radiographic description included the evaluation and tabulation of abnormalities that could interfere with interpretation of V-P scintigrams, such as parenchymal consolidation, atelectasis, pleural effusion, and emphysema</p>	
<p>Collart 2002 ¹⁶⁰ Belgium; November 1997 to September 1998 Single; Secondary or tertiary center</p>	<p>N = 70 Non-Pregnant Clinical suspicion of PE on the basis of history, clinical examination, chest X-ray, electrocardiogram</p>	<p>VQ SPECT and VQ Planar (VQ and VQ-SPECT) Planar perfusion scans used PISA-PED criteria; V/Q used PIOPED; V/Q SPECT - perfusion defects indicated by this</p>	<p>Positive CT, high probability VQ + abnormal D-dimer + positive LUS, high probability VQ + abnormal D-dimer + positive CT (CC) PE was considered to be present in the following situations. . All positive</p>	<p>Primary: NA Secondary: NA Follow-up: 2 months</p>

	and blood gas values were included prospectively NA	technique were considered as evidence of PE when they presented a wedge shaped morphology with the sharp angle oriented towards the corresponding segmental artery with sharp borders and three plane visualization, whatever the degree of photopenia; One or more wedge shaped defect with sharp borders, three-plane visualization whatever the photopenia	chest spiral CT in a central pulmonary region (lobar arteries included), whatever the results of the other investigations. . All high probability V/Q scans associated with Ddimers 4500 ngml71 and positive leg ultrasonography. . All high probability V/Q scans associated with Ddimers 4500 ngml71 and positive chest spiral CT, whatever the localization (central or peripheral).		
Lechleitner 2002 ¹⁴⁰	N = 55 Austria; NA Single; Department of Medicine	Non-Pregnant Suspected PE Haemodynamically unstable patients, those receiving mechanical ventilation, patients with contraindications to MRI, pregnant women	ventilation perfusion scanning, chest ultrasound, chest x-ray and D-Dimer blood sampling were carried out in all patients (US or VQ) Ventilation/perfusion scintigraphy: The scans were categorized by applying a 4-grade classification (high, intermediate low/very low and negative	MRI angiography (reference method) (MRI) NA	Primary: categorize sonographic lesions (specific lesions, unspecific lesions, no lesion) Secondary: sensitivity, specificity Follow-up: NA

probability) according to the PIOPED criteria.

Chest sonography:
 Specific lesions: Echo poor and homogenous. rounded and less sharply bordered to the ventilated lung wedge shaped. well demarcated lesions with a hyperechoic reflexion at the center. Possibly corresponding to the bronchioles.
 Echogenicity was influenced by the presence of a pleural effusion which was present in 10% of patients. Unspecific lesions: All lesions of other shapes. which have never been described in connection with PE. No lesion; Normal pleural reflex.

Blachere 2000 ¹¹⁵	N = 179	helical CT angiography	Composite (PA positive, CT, VQ, and US concordant, event during clinical follow-	Primary: Negative diagnosis of PE were followed up to determine whether a recurrence of
France; 18-month period	Non-Pregnant Clinically suspected of	All patients underwent ventilationperfusion		

Single; inpatients, outpatient, intensive care unit	<p>having acute PE</p> <p>Contraindication for the use of iodine contrast material (renal failure, history of allergy), unstable hemodynamic status, and pregnancy.</p>	<p>radionuclide lung scanning, contrast-enhanced helical CT angiography, and Doppler sonography of the legs (CT)</p> <p>PE if a clot was observed; negative for PE if no clot was observed; and indeterminate if poor examination, inadequate enhancement, or motion artifacts precluded confident interpretation of the study. PE positive: normal-sized or enlarged pulmonary obstructed completely by nonenhancing thrombus, or central nonocclusive filling defects. Main, lobar, segmental, and sub-segmental arteries recorded.</p>	<p>up) (CC)</p> <p>After initial interpretation, the need for pulmonary angiography was determined by the referring physician depending on the degree of suspicion of PE, Doppler sonography results, and concordance of the results of helical CT angiography and ventilation-perfusion radionuclide lung scanning.</p> <p>The ventilation-perfusion scans were interpreted by the nuclear medicine physician on service, and results were tabulated using the original and revised criteria of the Prospective Investigation of PE Diagnosis (PIOPED). As with the initial helical CT angiography, the initial interpretation was used to determine the need for pulmonary angiography.</p>	<p>PE or of a VTE had occurred.</p> <p>Secondary: NA</p> <p>Follow-up: 3-months</p>
Stein 1992¹⁶⁴ US; January 1985 to	<p>N = 98 selected; 67 with definitive</p>	<p>V/Q (VQ)</p>	<p>Perfusion scanning + CXR (Q)</p>	<p>Primary: Sensitivity, specificity and PPV at</p>

<p>September 1986 (PIOPED)</p> <p>Multi-National or Regional; Hospital</p>	<p>diagnosis by CTA</p> <p>Non-Pregnant</p> <p>Included in PIOPED, received V/Q scanning, had definitive diagnosis or exclusion of PE per CTA and adjudicated endpoint (standard in PIOPED)</p> <p>Nondiagnostic CTA</p>	<p>Described in ¹⁵⁹</p>	<p>As for index test (described in ¹⁵⁹) except abnormalities in perfusion scan were related to CXR.</p>	<p>various strata (high, intermediate, low, normal/near normal)</p> <p>Secondary: NA</p> <p>Follow-up: NA</p>
<p>Gray 1990 ¹⁶¹</p> <p>Scotland; 1979 and 1984</p> <p>Single; Not explicitly stated; but involved staff from the Department of Respiratory Medicine, presumably in hospital</p>	<p>N = 101</p> <p>Non-Pregnant</p> <p>Underwent angiography or were to undergo angiography and were referred for lung scanning</p> <p>NA</p>	<p>VQ scintigraphy (lung scanning) (VQ)</p> <p>Highly specific criteria (normal, low probability, indeterminate probability, significant probability, high probability) (see reference 19, 20, 21 - Table 2); Equivalent areas of abnormality in VF/Q were matched; areas of abnormal perfusion with normal ventilation were mismatched; non-diagnostic = abnormality</p>	<p>Pulmonary angiography (PA)</p> <p>intraluminal filling defects or multiple cut-off vessels reported as PE; normal angiography or minor perfusion abnormalities reported as 'no PE'; other abnormalities (e.g., oligoemia or flow asymmetry) reported as indeterminate</p>	<p>Primary: Diagnostic accuracy; failure rate</p> <p>Secondary: NA</p> <p>Follow-up: NA</p>

			on chest X-ray and corresponding matched ventilation and perfusion abnormality	
PIOPED Investigators 1990 ¹⁵⁹ US; January 1985 to September 1986 Multi-National or Regional; Hospital or ER	<p>N = 931 patients included, 755 with DTA comparative data</p> <p>Non-Pregnant</p> <p>>= 18 years, with symptoms of PE within 24 hours of study entry, and request for V/Q scan or pulmonary angiogram</p> <p>Contraindications to CTA, pregnancy, creatinine >260 umol/L, hypersensitivity to contrast medium</p>	<p>V/Q lung scan (VQ)</p> <p>High probability, intermediate probability (indeterminate), low probability, very low probability, normal, per PIOPED criteria (Table 1 in paper)</p>	<p>Pulmonary angiography (PA)</p> <p>PE present: identification of embolus obstructing a vessel, or outline of an embolus (filling defect) in a vessel.</p>	<p>Primary: Sensitivity, specificity of V/Q scans at various strata (high, intermediate, low, etc) or thresholds (high, high/intermediate, high/intermediate/low)</p> <p>Secondary: NA</p> <p>Follow-up: 12 months</p>
Woods 1989 ¹⁶² Canada; February 1985 to September 1987 NA; NA	<p>N = 38</p> <p>Non-Pregnant</p> <p>Suspected PE with PA within 48 hours of V/Q lung scan, and 24 hours of chest</p>	<p>V/Q scan (VQ)</p> <p>Modified Biello; PIOPED criteria with ratings of normal, low, indeterminate, or high probability</p>	<p>PA (PA)</p> <p>The arteriographic diagnosis of PE was made only if an intraluminal filling defect was identified</p>	<p>Primary: Differences between the Biello and PIOPED criteria of interpreting VQ scans with respect to sensitivity of high probability V/Q scans and specificity of low probability V/Q</p>

radiograph
Not specified

scans. Accuracy of the two criteria based on ROC curve analysis

Secondary: NA

Follow-up: NA

4107 CC = complex composite; CT = computed Tomography; CTPA = computed tomography pulmonary angiography; DSA = digital
4108 subtraction angiography; MRI = magnetic Resonance Imaging; PE = pulmonary embolism; PIOPED = Prospective Investigation of
4109 Pulmonary Embolism Diagnosis; PISAPED = Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis; SC = simple
4110 composite; SPECT = single photon emission tomography; VQ = ventilation-perfusion; VTE = venous thromboembolism; NA = not
4111 available;

4112

4113 **Table 10-K: Studies in non-pregnant patients with VQ-SPECT as index test**

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
Ibanez-Bravo 2016¹⁷² Spain; November 2011 to October 2014 Single; Emergency Department	N = 53 Non-Pregnant NA NA	V/Q SPECT lung scintigraphy (VQ-SPECT) Interpreted according to the European Association of Nuclear Medicine and Molecular Imaging (EANMMI) guidelines - positive if there was V/Q mismatch in at least one segment or two subsegments,	CTPA (CT) Positive studies were defined as showing definite PE (occlusive or no occlusive). Negative studies showed normal enhancement of pulmonary vasculature. Indeterminate CTPAs were attributed to	Primary: Diagnosis of PE by CTPA or V/Q SPECT Secondary: NA Follow-up: 6 months

		as negative if the perfusion was normal or there was a maximum of one sub-segmental mismatch, and as non-diagnostic if the V/Q abnormalities did not allow a positive or negative diagnosis.	patient or technical factors.	
Quirce 2014 ¹⁶⁵	N = 102	V/Q SPECT (VQ-SPECT)	CTPA (CT)	Primary: NA
Spain; November 2011 to February 2013 Single; Secondary or tertiary inpatient care	Non-Pregnant 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). NA	V/Q analyzed by modified PIOPED criteria; V/Q SPECT by EANMMI guideline	NA	Secondary: NA Follow-up: NA
Skarlovnik 2014 ¹⁴⁶	N = 147	V/Q SPECT (VQ-SPECT)	Composite diagnosis absed on clinical decision and 12 months follow-up where all investigations including CTPA were taken into account (CC)	Primary: NA
Slovenia; 2010 Multi-National or Regional; Secondary or tertiary inpatient care	Non-Pregnant NA Technically inadequate scans,	Criteria from EANM guidelines. Perfusion abnormalities compatible with PE reported in %. Using 0.5 segment mismatch criteria and revised PIOPED II. PE present: ?2 segments of V/Q mismatch or ?3 V/Q mismatch defects >50% of segment.	0.5 segment mismatch criteria; ?2 segments of V/Q mismatch ?3 V/Q mismatch defects >50% of segment	Secondary: NA Follow-up: 12 month

<p>Kyrtatos 2013 ²⁰⁴ UK; May to August 2012 Single; NA</p>	<p>N = 81 Non-Pregnant Underwent V/Q SPECT for suspected PE Did not undergo both ventilation and perfusion scans; did not undergo both SPECT and planar study</p>	<p>V/Q SPECT - reprojected two dimensional planar-like images from the three-dimensional SPECT data set (VQ-SPECT) PE present/absent/scan inconclusive; PE was considered present if there was at least one segmental mismatched perfusion defect or at least two subsegmental mismatched perfusion defects. The images were considered indeterminate in the presence of any one of the following: only one subsegmental mismatch, one or more nonsegmental mismatches, perfusion image of inadequate quality, or ventilation image of inadequate quality (when perfusion was abnormal). Any other scenario was considered negative for PE.</p>	<p>traditional Planar V/Q (VQ) PE was considered present if there was at least one segmental mismatched perfusion defect or at least two subsegmental mismatched perfusion defects. The images were considered indeterminate in the presence of any one of the following: only one subsegmental mismatch, one or more nonsegmental mismatches, perfusion image of inadequate quality, or ventilation image of inadequate quality (when perfusion was abnormal). Any other scenario was considered negative for PE.</p>	<p>Primary: number of defects Secondary: NA Follow-up: NA</p>
<p>Mahdavi 2013 ¹¹⁰ US; January 2007 to December 2008 Single; Secondary/Tertiary</p>	<p>N = 100 Non-Pregnant Admitted and underwent both V/Q and CTA within a 3 day period</p>	<p>V/Q SPECT (VQ-SPECT) NA</p>	<p>CTPA (CT) NA</p>	<p>Primary: degree of agreement between the two tests Secondary: NA</p>

Care	NA			Follow-up: None
Le Duc-Pennec 2012¹⁶⁶ France; April 2004 to September 2006 Single; Secondary/Tertiary Care	N = 321 Non-Pregnant Over 18 years old, high clinical probability of PE, or non-high clinical probability but abnormal plasma enzyme-linked immunosorbent assay D-dimer concentration (>500 ug/mL) Pregnancy, breastfeeding, life expectancy 48 h at the time of screening, and a previously confirmed PE	V/Q SPECT (VQ-SPECT) Revised PIOPED criteria proposed by Gottschalk et al 18 for planar / scan interpretation were used for SPECT scan interpretation	Planar V/Q scan (VQ) NA	Primary: Prevalence of PE in each SPECT V/Q scan probability group Secondary: NA Follow-up: 3 month
Le Roux 2012⁴⁸³ France; April 2004 to September 2006 Single; Secondary/Tertiary Care	N = 246 Non-Pregnant ≥18 years, symptoms suggestive of PE, high clinical probability of PE or nonhigh clinical probability but abnormal plasma ELISA D-dimer concentration	V/Q SPECT (VQ-SPECT) Revised PIOPED criteria proposed by Gottschalk et al 18 for planar / scan interpretation were used for SPECT scan interpretation	Lower limb vein compression ultrasonography followed by Planar V/Q scan (Sequential) PE was considered to be present in patients with proximal deep venous thrombosis. no DVT on CUS underwent V/Q planar lung	Primary: Prevalence of PE in each SPECT V/Q scan probability group Secondary: NA Follow-up: 3

	(>500ug/ml)		scan. PE was ruled out in patients with (a) a normal V/Q scan result; (b) a low or intermediate clinical probability of PE and a low probability V/Q scan result; and in those with © a low clinical probability and an intermediate probability V/Q scan result.	months
	NA			
Gutte 2010 ¹⁵⁸	N = 36	V/Q SPECT (VQ-SPECT)	Planar Lung Scintigraphy (VQ)	Primary: sens, spec
Denmark; June 2006 to February 2008	Non-Pregnant	Diagnosed if one or more perfusion defects (> 0.5 segment) with normal ventilation (mismatch) were present	NA	Secondary: NA
Single; Secondary/Tertiary Care	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			Follow-up: 6 months
	Contraindication to CT including allergy to contrast agents, impaired renal function (P-creatinine level >0.120 mmol/L), women			

<p>Gutte 2009 ¹¹¹</p> <p>Denmark; June 2006 to February 2008</p> <p>Multi-National or Regional; Secondary/Tertiary Care</p>	<p>N = 81</p> <p>Non-Pregnant</p> <p>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</p> <p>Contraindication to CT including allergy to contrast agents, impaired renal function (P-creatinine level >0.120 mmol/L), women</p>	<p>V/Q SPECT (VQ-SPECT)</p> <p>Diagnosed if one or more mismatched perfusion defects with normal ventilation were present</p>	<p>Composite: Side-by-side consensus based on MDCT, V/Q SPECT and all available information (ECG, echo, LUS, D-dimer, clinical data and follow-up of 6 months) (CC)</p> <p>NA</p>	<p>Primary: Diagnostic accuracy (sens/spec)</p> <p>Secondary: NA</p> <p>Follow-up: 6 months</p>
<p>Miles 2009 ¹⁶⁷</p> <p>Australia; March 18 2004 to May 26 2006</p> <p>Multi-National or Regional; Secondary or tertiary inpatient care</p>	<p>N = 79</p> <p>Non-Pregnant</p> <p>NA</p> <p>Patients</p>	<p>V/Q SPECT (VQ-SPECT)</p> <p>A SPECT scan was considered to be positive for PE if at least one mismatched defect of > 0.5 of a lung segment was present.</p>	<p>Final diagnosis made by respiratory physicians who were provided with the planar scintigraphy and CTPA reports and with extensive clinical information, including d-dimer levels, modified Wells score, and patient status at the 3-month follow-up (CC)</p>	<p>Primary: NA</p> <p>Secondary: NA</p> <p>Follow-up: 3 months</p>

			NA	
Bajc 2008 ¹⁶⁸	N = 1785	SPECT V/Q (VQ-SPECT)	Follow up of 6 months (FU)	Primary: Sensitivity, specificity
Sweden; January 2004 to December 2005	Non-Pregnant NA	Considered: Clinical information, chest x-ray, recognition of patterns typical for PE based upon segmental charts, recognition of patterns of other diseases than PE	NA	Secondary: NA
Single; Secondary/Tertiary Care	NA			Follow-up: 6 months
Weinmann 2008 ¹⁷¹	N = 142	V/Q SPECT (VQ-SPECT)	Multidetector-Row CT (CT)	Primary: NA
France; NA	Non-Pregnant	lung scans were classified as normal, very low, low, intermediate, or high probability for PE according to the updated criteria of the PIOPED II study. Lung scans of low and intermediate probability were considered non-diagnostic.	the diagnosis of PE was confirmed if: (1) multidetector-row CT showed a picture of 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	Secondary: NA
NA; NA	Clinical suspicion of acute PE (CT already undergone, pregnancy, age	V/Q SPECT lung scan: the images of patients with a non-contributive planar scintigraphy were separately visually interpreted by two independent experienced readers unaware of the results of CT scan and lower-limb US. In case of discordant reading, a simultaneous interpretation was performed by the two readers in order to	(2) US showed a thrombus or/and non compressibility of the vein.	Follow-up: 6 month

reach a consensus. V/Q SPECT lung scan: the images of patients with a non-contributive planar scintigraphy were separately visually interpreted by two independent experienced readers unaware of the results of CT scan and lower-limb US. In case of discordant reading, a simultaneous interpretation was performed by the two readers in order to reach a consensus. ;

Very high probability (at least one segmental or sub-segmental (>15% of a segment) perfusion defect with a normal corresponding ventilation (mismatch defect)

<p>Harris 2007 ¹⁶⁹ Australia; NA Single; Secondary/Tertiary Care</p>	<p>N = 50 Non-Pregnant Suspected PE Past medical history of PE, renal disfunction, significant contrast hypersensitivity, unable to comply with study protocol, if imaging was</p>	<p>V/Q SPECT (VQ-SPECT) Reports were issued according to standard modified PIOPED criteria (ref 28)</p>	<p>Composite: Consensus panel of 3 physicians with access to all clinical details, including VQ, CTPA, and CTV (CC) NA</p>	<p>Primary: AUROC Secondary: NA Follow-up: 3 month</p>
--	--	---	--	--

	unable to be completed within 24 hours of presentation, patients			
Leblanc 2007 ²⁰⁵	N = 584	V/Q SPECT (VQ-SPECT)	3 month follow-up (FU)	Primary: NA
Canada; October 2004 to July 2005	Non-Pregnant	In patients with a normal chest X-ray, absence of any mismatched defect was interpreted as negative (no evidence of PTE), while the presence of any clear-cut perfusion vascular-type defect, regardless of size, with normal ventilation (mismatched) was interpreted as positive (compatible with PTE). In patients with an abnormal chest X-ray, indeterminate scans were defined only for cases having matching vascular-type defects of the same size (triple match). Otherwise, if the perfusion defect did not have a vascular configuration as defined above, they were classified as negative (no evidence of PTE).	NA	Secondary: NA
Single;	NA			Follow-up: 3 months
Secondary/Tertiary Care	NA			
Reinartz 2006 ¹⁷⁰	N = 53	V/Q SPECT (VQ-SPECT)	MDCT (CT)	Primary:
Germany; July 2003	Non-Pregnant	All cases with mismatch defects of at least half-segment size	NA	Sensitivity, specificity, and

<p>to July 2005</p> <p>Single; NA</p>	<p>Had V/Q lung scintigraphy using the SPECT technique and multidetector-row spiral CT (MDCT) within an interval of 48 h</p> <p>NA</p>	<p>were assessed as PEs</p>		<p>accuracy of the conventional visual assessment</p> <p>Secondary: NA</p> <p>Follow-up: 6 months</p>
<p>Bajc 2004 ¹⁷³</p> <p>Sweden; NA</p> <p>Single; Secondary or tertiary center</p>	<p>N = 53</p> <p>Non-Pregnant</p> <p>Included whenever the dual head gamma camera was available</p> <p>NA</p>	<p>V/Q SPECT (VQ-SPECT)</p> <p>A segmental reduction or a subsegmental total deficiency was attributed 1 point; a segmental total deficiency was attributed 2 points.; No embolism - absence of unmatched perfusion defects; Embolism = >1 segmental or subsegmental defect of mismatch (at least 2 points); Other pathology: matched defects with typical patterns for other lung diseases; Nondiagnostic</p>	<p>V/Q Planar (VQ)</p> <p>A segmental reduction or a subsegmental total deficiency was attributed 1 point; a segmental total deficiency was attributed 2 points. For</p>	<p>Primary: NA</p> <p>Secondary: NA</p> <p>Follow-up: 6 months</p>
<p>Reinartz 2004 ¹⁰⁵</p> <p>Germany; January 2001 to April 2003</p> <p>Single; NA</p>	<p>N = 83</p> <p>Non-Pregnant</p> <p>Had V/Q lung scintigraphy in SPECT technique as well as</p>	<p>V/Q lung scintigraphy (VQ)</p> <p>PIOPED criteria</p>	<p>Multislice CT (CT)</p> <p>PE was diagnosed if one or more embolic clots were detected in the pulmonary arteries</p>	<p>Primary: NA</p> <p>Secondary: NA</p> <p>Follow-up: at least 5 months (max 10</p>

	multislice spiral CT within an interval of 3 d			months)
	NA			
Collart 2002 ¹⁶⁰	N = 70	VQ SPECT and VQ Planar (VQ and VQ-SPECT)	Positive CT, high probability VQ + abnormal D-dimer + positive LUS, high probability VQ + abnormal D-dimer + positive CT (CC)	Primary: NA Secondary: NA Follow-up: 2 months
Belgium; November 1997 to September 1998	Non-Pregnant Clinical suspicion of PE on the basis of history, clinical examination, chest X-ray, electrocardiogram and blood gas values were included prospectively	Planar perfusion scans used PISA-PED criteria; V/Q used PIOPED; V/Q SPECT - perfusion defects indicated by this technique were considered as evidence of PE when they presented a wedge shaped morphology with the sharp angle oriented towards the corresponding segmental artery with sharp borders and three plane visualization, whatever the degree of photopenia; One or more wedge shaped defect with sharp borders, three- plane visualization whatever the photopenia	PE was considered to be present in the following situations. . All positive chest spiral CT in a central pulmonary region (lobar arteries included), whatever the results of the other investigations. . All high probability V/Q scans associated with Ddimers 4500 ngml ⁻¹ and positive leg ultrasonography. . All high probability V/Q scans associated with Ddimers 4500 ngml ⁻¹ and positive chest spiral CT, whatever the localization (central or peripheral).	
Single; Secondary or tertiary center	NA			

4114 CC = complex composite; CT = computed Tomography; CTPA = computed tomography pulmonary angiography; DVT = deep vein
4115 thrombosis; PE = pulmonary embolism; PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis; SPECT = single
4116 photon emission tomography; VQ = ventilation-perfusion; NA = not available;

4117

4118 **Table 10-L: Studies in non-pregnant patients with VQ-SPECT-CT as index test**

4119

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
Bhatia 2016 ¹⁷⁴ Australia; May 2012 to November 2013 Single; Secondary/Tertiary Care	N = 102 Non-Pregnant Undergone SPECT-CT/VQ scanning, CTPA during the same admission with NA	SPECT-CT V/Q (VQ-SPECT-CT) NA	CTPA (CT) By Radiologist - no other detail	Primary: Sensitivity, specificity Secondary: NA Follow-up: NA
Le Roux 2015 ¹⁵⁶ France; April 2011 to March 2013 Single; Secondary/Tertiary Care	N = 393 Non-Pregnant >=18 years, symptoms suggestive of PE, high clinical probability of PE or nonhigh clinical probability but abnormal plasma ELISA D-dimer concentration (>500ug/ml).	V/Q SPECT-CT (VQ-SPECT-CT) V/Q SPECT was interpreted by the nuclear medicine physician in charge using a diagnostic cutoff of one segmental or two subsegmental mismatched defects	Composite: Final diagnostic conclusion was established by the physician in charge of patient care on the basis of clinical symptoms, laboratory tests, V/Q SPECT and other imaging procedures performed. (CC) NA	Primary: NA Secondary: NA Follow-up: 3 months

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
	NA			
Le Roux 2013 ⁵¹ France; April 2004 to September 2007 Single; Secondary/Tertiary Care	N = 249 Non-Pregnant 18 years or older, symptoms suggestive of PE, high clinical probability of PE or non high clinical probability but abnormal plasma ELISA D-dimer concentration (>500ug/ml) were considered for inclusion. Pregnancy, breastfeeding, life expectancy 48 h at the time of screening, and a previously confirmed PE.	V/Q SPECT-CT (VQ-SPECT-CT) Revised PIOPED criteria proposed by Gottschalk et al 18 for planar / scan interpretation were used for SPECT scan interpretation	Standardized diagnostic strategy (LUS, VQ, CT) (Sequential) NA	Primary: NA Secondary: NA Follow-up: 3 months
Ling 2012 ¹⁷⁵ Australia; 2009 Single; Secondary/Tertiary	N = 106 Non-Pregnant NA NA	V/Q SPECT (VQ-SPECT) PE present: >50% perfusion mismatch in an anatomical segment or 2 regions of	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	Primary: Sensitivity, specificity Secondary: NA

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
Care		perfusion mismatch regardless of size	was not PE and there was no occurrence of venous thromboembolism (VTE) at 6 months (CC) NA	Follow-up: 6 months
Gutte 2009 ¹¹¹ Denmark; June 2006 to February 2008 Multi-National or Regional; Secondary/Tertiary Care	N = 81 Non-Pregnant 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 Contraindication to CT including allergy to contrast agents, impaired renal function (P-creatinine level >0.120 mmol/L), women	V/Q SPECT (VQ-SPECT) Diagnosed if one or more mismatched perfusion defects with normal ventilation were present	Composite: Side-by-side consensus based on MDCT, V/Q SPECT and all available information (ECG, echo, LUS, D-dimer, clinical data and follow-up of 6 months) (CC) NA	Primary: Diagnostic accuracy (sens/spec) Secondary: NA Follow-up: 6 months

4120 CC = complex composite; CT = computed Tomography; CTPA = computed tomography pulmonary angiography; PE = pulmonary
 4121 embolism; PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis; SPECT = single photon emission tomography;
 4122 VQ = ventilation-perfusion; VTE = venous thromboembolism; NA = not available;

4123

4124

4125 **Table 10-M: Studies in non-pregnant patients using diagnostic pathways**

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
Galipienzo 2012¹⁷⁷ Spain; May 2007 to December 2008 Single; Emergency department, setting unclear	N = 241 Non-Pregnant 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, were eligible for the study. Age 24 hours, logistic reasons (eg, unavailability of CT, patient too ill to undergo CT scanning), or hemodynamic instability.	Pathway (Wells clinical decision rule, D-dimer testing, and CT) (PW) A CT was positive for PE if contrast material outlined a central intraluminal defect or if a vessel was totally occluded in at least two different projections.	3 month follow-up (FU) 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

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
				<p>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.</p> <p>Follow-up: 3 months</p>
<p>Righini 2008 ¹⁸⁵ Switzerland; France; Brussels; January 2005 to August 2006 Multi-International; General and teaching hospitals</p>	<p>N = 1819 included, 6 withdrew and one died prior to testing, leaving 1812 who entered testing (intention-to-diagnose). 1693 completed testing per protocol (Primary analysis group)</p> <p>Non-Pregnant</p> <p>>18 years with clinical suspicion of PE (acute onset of new or</p>	<p>Pathway (Clinical probability assessment - D-dimer, LUS, and CT): Calculated clinical probability of PE (revised Geneva score)</p> <p>Randomized D-dimer test for patients with low or intermediate probability If D-dimer concentration = no PE, no further testing If D-dimer concentration > 500 ng/mL or if high clinical</p>	<p>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</p>	<p>Primary: 3-month thromboembolic risk in patients left untreated because PE was excluded</p> <p>Secondary: Adverse events. Clinical outcomes of treatment.</p> <p>Follow-up: 3 months</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
	<p>worsening SOB or chest pain without another obvious cause).</p> <p>Contraindication to CT (allergy/at risk of allergic reaction to contrast) or impaired renal function, pregnancy, age</p>	<p>probability → venous compression U/S If proximal DVT on U/S → anticoagulate, no further testing If no proximal DVT → MSCT If MSCT showed PE → anticoagulate If MSCT negative and low/intermediate probability → r/o PE, no further testing If MSCT negative + high clinical probability → V/Q scan or pulmonary angiography If MSCT non-conclusive or isolated subsegmental PE, any clinical probability → V/Q scan or pulmonary angiography If V/Q scan high probability → anticoagulate If V/Q scan normal → no PE, no further testing If V/Q scan intermediate → pulmonary angiography (PW)</p> <p>D-Dimer: ≤ 500 nm.ML no PE; >500 ng/mL possible</p>	<p>PE, no further testing If D-dimer concentration > 500 ng/mL or if high clinical probability → MSCT If MSCT showed PE → anticoagulate</p> <p>If MSCT negative + high clinical probability → V/Q scan or pulmonary angiography If MSCT non-conclusive or isolated subsegmental PE, any clinical probability → V/Q scan or pulmonary angiography If V/Q scan high probability → anticoagulate If V/Q scan normal → no PE, no further testing If V/Q scan intermediate → pulmonary</p>	

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
		PE proceed to US; U/S positive: Incomplete compressibility of proximal deep vein MSCT: Positive if contrast material outlined intraluminal defect or vessel totally occluded by low attenuation	angiography (APW) See interpretation of index test	
Bosson 2007 ¹⁷⁶ France; February 1999 to November 1999 Single; Emergency department, Internal medicine, surgery, cardiology, respiratory departments Teaching hospital	N = 1134 Non-Pregnant Clinically suspected of acute non-severe PE in a 2000-bed teaching hospital. Severe life threatening PE or interval of >72 hours between clinical suspicion for PE and entry to the algorithm.	Pathway: Wells, DD, US, VQ, CT (PW) PE diagnosis was established according to previous published criteria, see reference 6	3 month follow-up (FU) NA	Primary: Incidence of DVT or PE Secondary: NA Follow-up: 3 months
Jouveshomme 2007 ¹⁸⁰	N = 400 Pregnant	MDCT; if normal/inconclusive then CUS; if both negative	No comparator (FU) NA	Primary: Failure Rate Secondary: Incidental

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
France; December 2002 and February 2005 Single; Secondary care hospital	Inpatients referred for diagnostic imaging with clinically suspected PE Not hospitalised for >24 hours; patients without 3 month follow-up data	confirmation by V/Q or DSA based on physician discretion (PW) Read on high-quality workstations (CT); Lack of compressibility (CUS); PIOPED criteria (V/Q)		findings (alternative diagnoses) Follow-up: 3 months
Hogg 2006¹⁷⁹ UK; February 2002 to May 2003 Single; Secondary/Tertiary Care	N = 425 Non-Pregnant Pleuritic chest pain Trauma, pregnancy, pneumothorax, myocardial infarction, cardiac ischemia, pericarditis, hypoxia with Pao ₂ 140 kg	Pathway including Wells, D-dimer, VQ, CT, PA (PW) PIOPED criteria	Follow up of three months (FU) NA	Primary: Safety Secondary: NA Follow-up: 3 months
Vigo 2006¹⁸⁴ Italy; April 2001 to November 2005 Multi-National or Regional; Outpatients and	N = 702 Non-Pregnant Clinical suspicion of the first episode of PE Previous venous thromboembolism (VTE)	CT / D-dimer / VQ (PW) With CT, a PE was considered present if contrast material outlined an intraluminal filling defect or if a vessel was totally occluded by low-	Follow up of 6 months (FU) NA	Primary: VTE events Secondary: NPV, safety of withholding anticoagulation from patients with negative CT and negative D-dimer (estimated rate of

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
inpatients referred to six Italian centers	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	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.		alternative diagnoses on spiral CT in patients free from PE) Follow-up: 6 months
Ghanima 2005¹⁷⁸ Norway; February 1, 2002, and December 31, 2003 Single; Emergency Department of stfold	N = 329 Non-Pregnant Clinical suspicion of PE de?ned as acute onset of dyspnea, chest pain, palpitation, or syncope,	Pathway of D-dimer, Multi-slice spiral CT, and bilateral compression US, Q scint, or PA (PW) CT: PE was diagnosed if a ?lling defect or complete occlusion was seen in	Follow up of 3 months (FU) 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

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
<p>Hospital Trust in Fredrikstad, Norway</p>	<p>>= 18 years of age.</p> <p>Clinical probability not assessed in patients normal D-dimer, CT not performed, anticoagulation, iodinated contrast medium, pregnancy, expected survival</p>	<p>proximal, segmental or subsegmental arteries. PE was considered absent when the pulmonary vasculature, including subsegmental branches, was visualized and was free of filling defects. The diagnosis was considered inconclusive when poor opacification or major motion artefact was observed or due to the ambiguity of findings as irregular arterial walls or the presence of an adjacent pulmonary abnormality.</p> <p>Ultrasonography Bilateral compression ultrasonography of the lower extremities consisting of B-mode examination of the common femoral and popliteal veins was recommended to be</p>	<p>PE and had not received anticoagulation for >48 h during the follow-up period</p> <p>Secondary: The efficacy of the diagnostic strategy was assessed in terms of the proportion of patients in whom a definite diagnosis was made according to the diagnostic algorithm.</p> <p>Deaths were adjudicated by an independent committee on the basis of autopsy reports, death certificates and hospital charts as definitely caused by PE, definitely unrelated to PE, or possibly related to PE if the cause of death could not be clearly established.</p> <p>Follow-up: 3-months</p>	

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
		<p>performed on patients with inconclusive CT scan; lack of vein compressibility was considered as the main criterion for the diagnosis of DVT</p> <p>D-dimer test was performed as the initial diagnostic test in all patients. high clinical probability and a normal D-dimer as well as those with elevated D-dimer proceeded to MSCT. In case of an inconclusive MSCT, bilateral compression ultrasonography of the lower extremities to rule out DVT was recommended followed by perfusion scintigraphy and/or pulmonary angiography if no DVT was revealed.</p>		
Perrier 2005 ¹⁸³	N = 756	Strategy of d-dimer	Follow up of three	Primary: proportion of

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
<p>Switzerland; France; August 1, 2002, to November 30, 2003</p> <p>Multi-International; Emergency departments of three teaching hospitals</p>	<p>Pregnant</p> <p>Suspicion of PE, defined as acute onset of new or worsening shortness of breath or chest pain without another obvious cause.</p> <p>Contraindication to CT (i.e., known allergy to contrast agents or risk of allergic reaction); impaired renal function, defined as a creatinine clearance below 30 ml per minute, as calculated by the CockcroftGault formula; pregnancy); ongoing anticoagulant therapy for a reason other than venous thromboembolism; a decision not to participate in the study (41); inability to give informed consent (15); a life expectancy of 24 hours before</p>	<p>measurement and multidetector-row CT, without the use of lower-limb ultrasonography (PW)</p> <p>CT: A clot was considered present if contrast material outlined an intraluminal defect or if a vessel was totally occluded by low-attenuation material.</p> <p>In patients without a high clinical probability (i.e., either a low or intermediate probability), we measured plasma d-dimer levels by enzyme-linked immunosorbent assay (ELISA) and ruled out PE in patients with a level below the cutoff value of 500 g per liter. a d-dimer level of 500 g per liter or above underwent proximal venous-compression ultrasonography of the lower limbs and</p>	<p>months (FU)</p> <p>NA</p>	<p>patients with proximal deep venous thrombosis and negative findings on CT</p> <p>Secondary: estimate of the three-month risk of thromboembolism if lower-limb ultrasonography had not been performed</p> <p>Follow-up: 3-months</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
	<p>admission (3); inability to undergo CT because of hemodynamic instability (3); transfer to another facility (1); absence of peripheral venous access (1); and other reasons (9).</p> <p>Another 73 (7.2%) were excluded because of violations in study protocol.</p>	<p>multidetector-row CT. CT that was positive for PE or ultrasonography that showed a deep venous thrombosis warranted anticoagulant treatment, whereas such therapy was withheld in patients in whom both tests were negative.</p> <p>In patients with a high clinical probability of PE, we did not obtain a d-dimer measurement. These patients thus proceeded directly to CT and lower-limb ultrasonography. Patients in whom either test was positive were treated, but those with a high clinical probability and negative findings on both CT and ultrasonography proceeded to pulmonary angiography, and their cases were managed</p>		

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
accordingly.				
Miniati 2003 ¹⁸¹ Italy; April 2000 to September 2001 Single; Hospital	N = 425 patients referred, 390 entered study Pregnant Referred for selected PE Contraindication to pulmonary angiography, >3 days anticoagulant therapy	Pathway: Assessment of pretest probability V/Q scan suggestive of PE + moderately high/high pretest probability: PE present V/Q scan normal/near normal: PE absent V/Q scan abnormal not suggestive of PE + low pretest probability V/Q scan abnormal suggestive of PE + low or intermediate pretest probability → pulmonary angiography Pulmonary angiography positive: PE present Pulmonary angiography negative: PE absent (PW) V/Q: normal, near normal, abnormal suggestive of PE (single or multiple wedge-shaped perfusion defects), abnormal not suggestive of PE (single or multiple perfusion defects other	Clinical follow-up (FU) NA	Primary: Proportion of patients diagnosed by pathway Secondary: Failure rate Follow-up: 1 year

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
		<p>than wedge-shaped)</p> <p>Pulmonary angiography: identification of embolus obstructing a vessel or outline of embolus within a vessel</p>		
<p>Miron 1999¹⁸²</p> <p>Switzerland; June 1995 to June 1997</p> <p>Single; Hospital - Surgical or Medical Wards</p>	<p>N = 114 included</p> <p>Non-Pregnant</p> <p>>=16 years, admitted for medical or surgical procedure, with PE suspected during their stay</p>	<p>Pathway: V/Q scan high probability: PE present, no further testing V/Q scan normal/near normal: PE absent, no further testing V/Q scan non-diagnostic –</p> <p>> Clinical probability</p> <p>Clinical probability high: PE present Clinical probability low: PE absent Clinical probability intermediate –></p> <p>D-dimer D-dimer D-dimer</p> <p>>= 500 ug/L –> Ultrasound</p> <p>U/S shows DVT: PE present, no further testing U/S negative –> pulmonary angiography Pulmonary angiography positive: PE present Pulmonary angiography negative: PE</p>	<p>FU (FU)</p> <p>NA</p>	<p>Primary: Proportion of patients who could be diagnosed by a non-invasive workup (excluding pulmonary angiography)</p> <p>Secondary: NA</p> <p>Follow-up: 3 months</p>

Study information, country and time of conduct, setting	Number of patients, inclusion and exclusion criteria	Index test (as coded), details	Reference test (as coded), details	Primary outcomes, secondary outcomes, follow-up
		absent (PW) Individual tests: V/Q scans by PIOPED, normal, near-normal/very low, low, intermediate, high probability U/S positive: common femoral or popliteal vein noncompressible		

4126 CT = computed Tomography; DSA = digital subtraction angiography; DVT = deep vein thrombosis; PE = pulmonary embolism;
 4127 PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis; VQ = ventilation-perfusion; VTE = venous
 4128 thromboembolism; NA = not available.

DRAFT

4130 **Appendix 16: Quality Assessment of Included Primary Studies for**
 4131 **Clinical Review (Questions 2 and 3)**

4132
 4133 Quality appraisal detailed displays contain all DTA studies, including those that were not
 4134 included in the meta-analyses due to being a post-hoc analysis, or reporting use of the index
 4135 test as part of the reference.

4136 Key to abbreviations for individual questions:

4137 **QUADAS II: Questions and key**
 4138

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

4139 **ROBINS-I: Questions and key**
 4140

	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?

4141
4142
4143

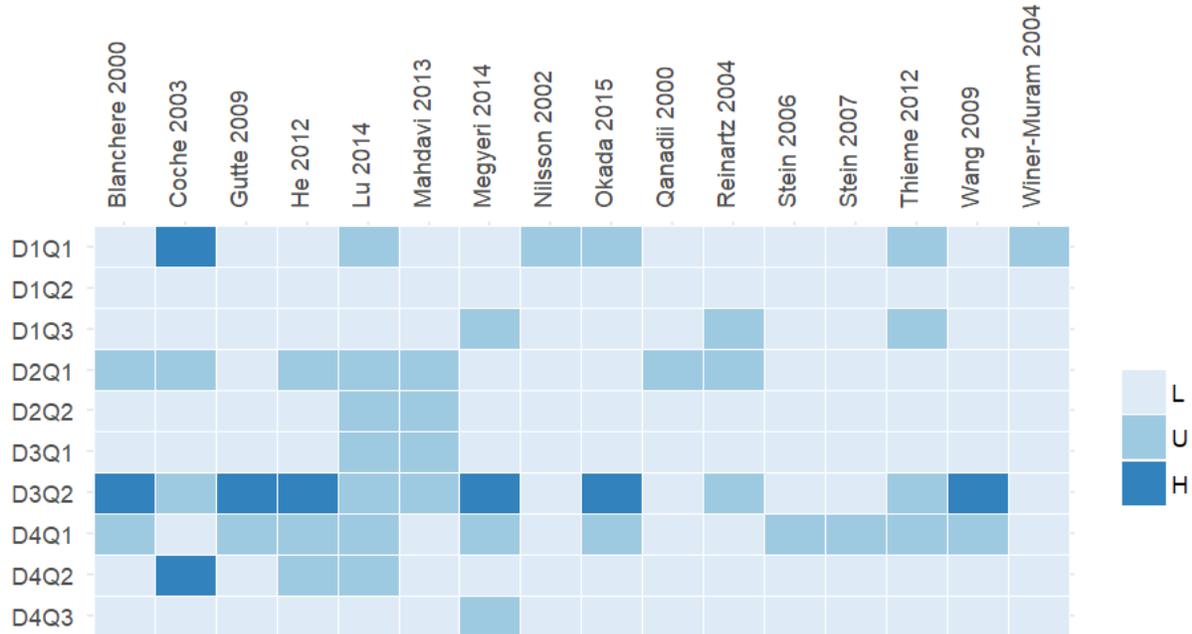
Moga checklist: Questions and key

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?

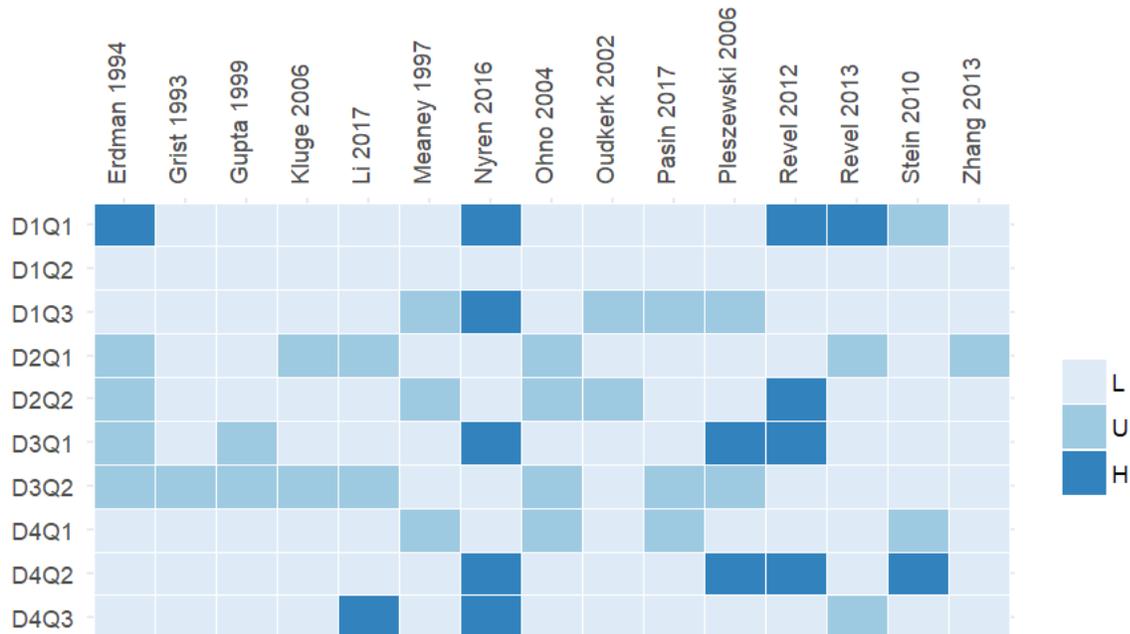
4144
4145
4146

Table 16-A: QUADAS II risk of bias and applicability assessment for DTA studies of CT



4147
4148
4149

Table 16-B: QUADAS II risk of bias and applicability assessment for DTA studies of MRI



4150
4151
4152

4153 **Table 16-C: QUADAS II risk of bias an applicability assessment for DTA studies of US**



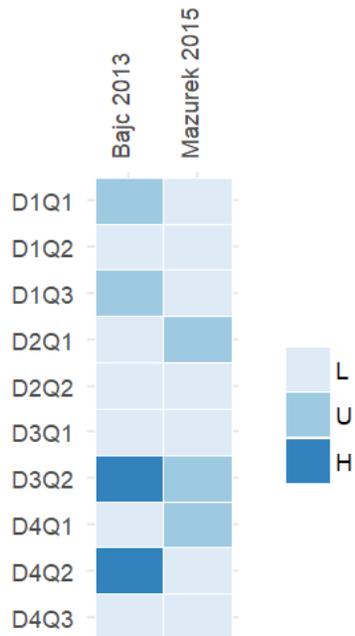
4154
4155
4156
4157

Table 16-D: QUADAS II risk of bias and applicability assessment for DTA studies of perfusion (Q)

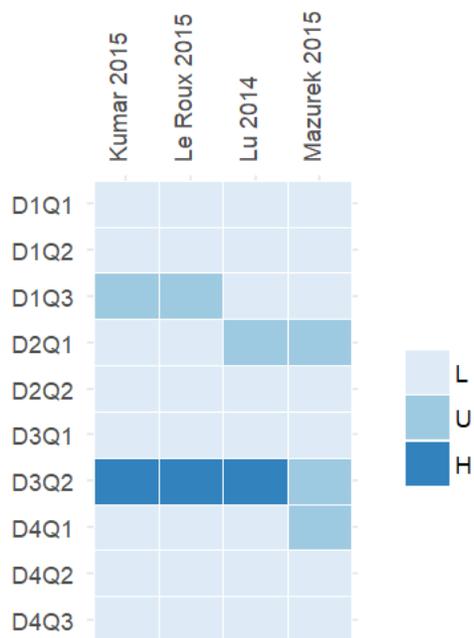


4158
4159

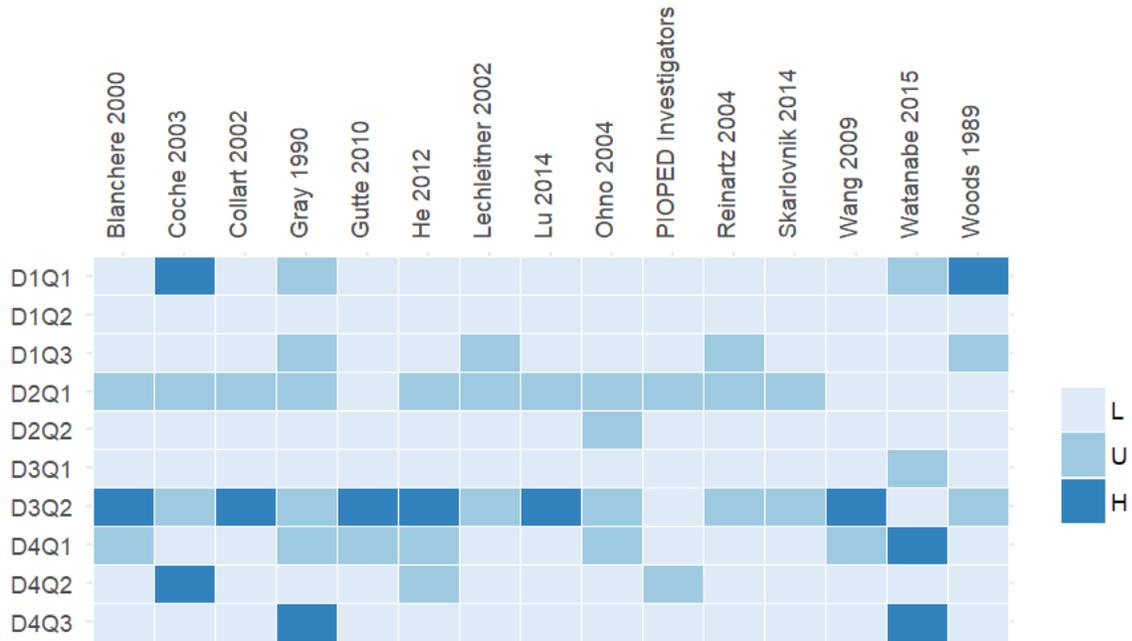
4160 **Table 16-E: QUADAS II risk of bias and applicability assessment for DTA studies of Q-**
 4161 **SPECT**



4162 **Table 16-F: QUADAS II risk of bias and applicability assessment for DTA studies of Q-**
 4163 **SPECT-CT**
 4164
 4165
 4166



4169 **Table 16-G: QUADAS II risk of bias and applicability assessment for DTA studies of VQ**



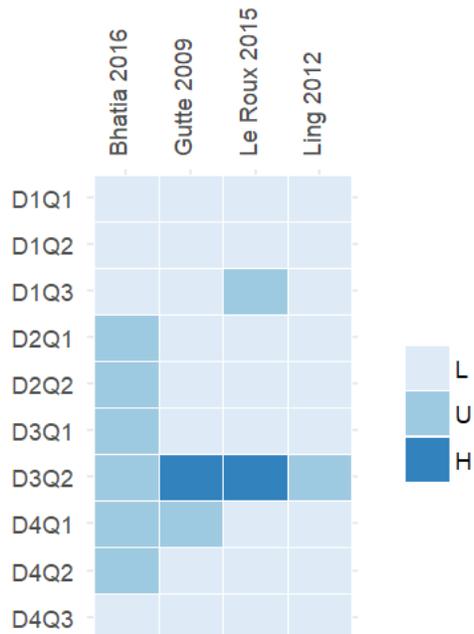
4170
4171
4172
4173

Table 16-H: QUADAS II risk of bias and applicability assessment for DTA studies of VQ-SPECT



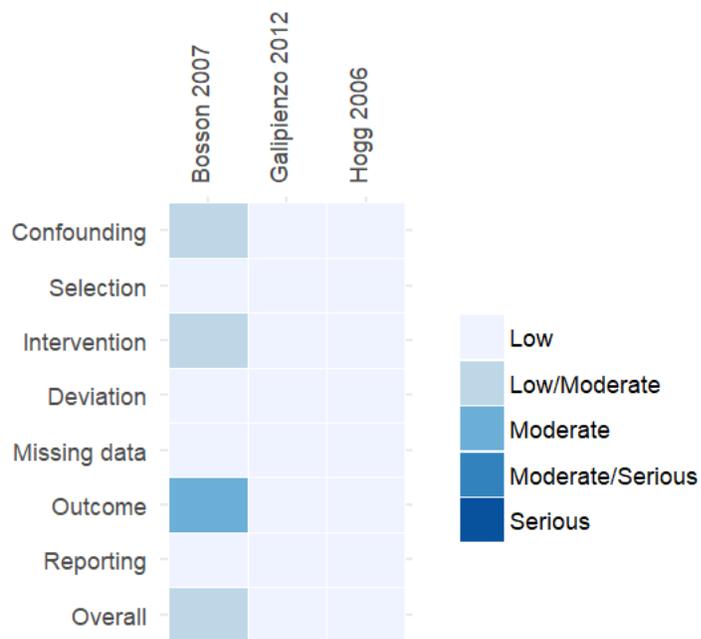
4174
4175

4176 **Table 16-J: QUADAS II risk of bias and applicability assessment for DTA studies of VQ-**
 4177 **SPECT-CT**



4178
4179

4180 **Figure 16-K: ROBINS-I quality assessment of PW utility and safety studies**



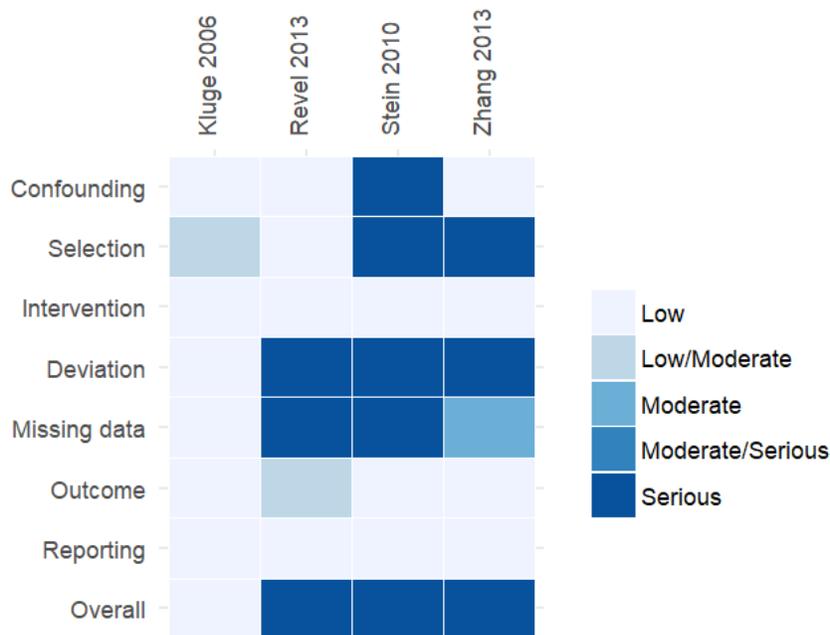
4181
4182

4183 **Figure 16-L: ROBINS-I quality assessment of CT utility and safety studies**



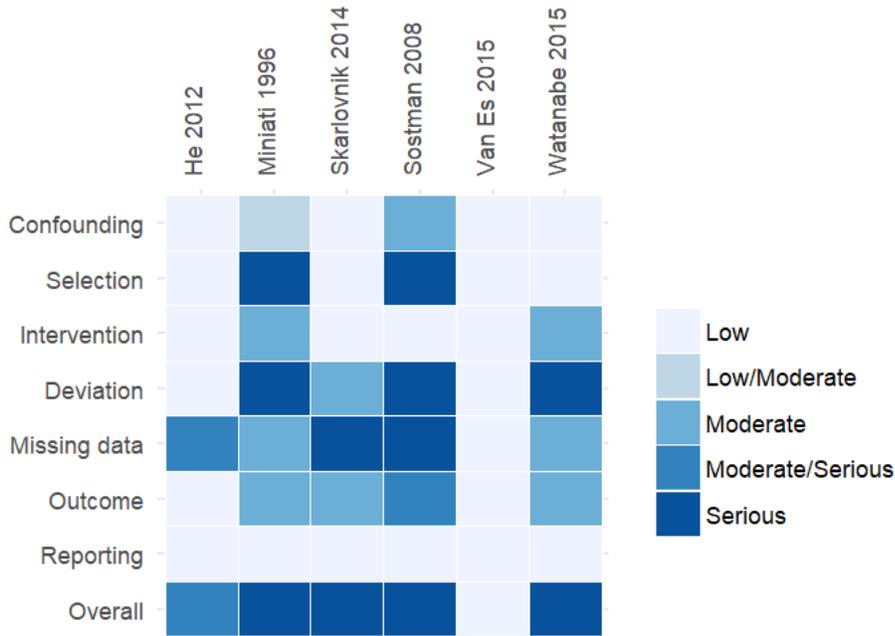
4184
4185
4186

Figure 16-M: ROBINS-I quality assessment of MRI utility and safety studies

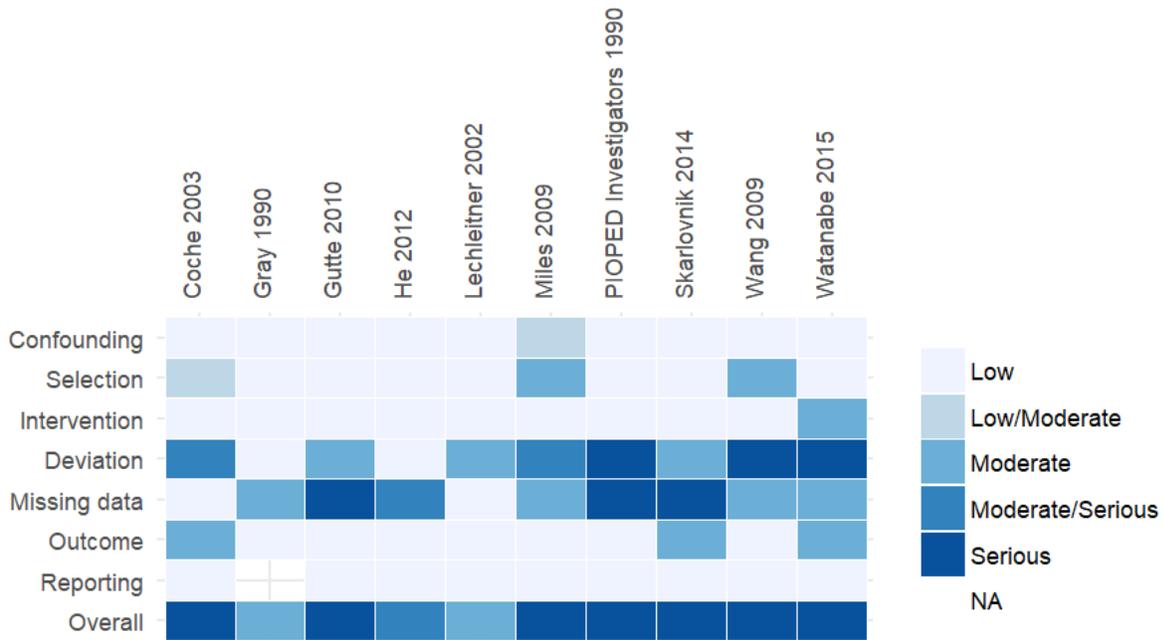


4187

4188 **Figure 16-N: ROBINS-I quality assessment of Q utility and safety studies**

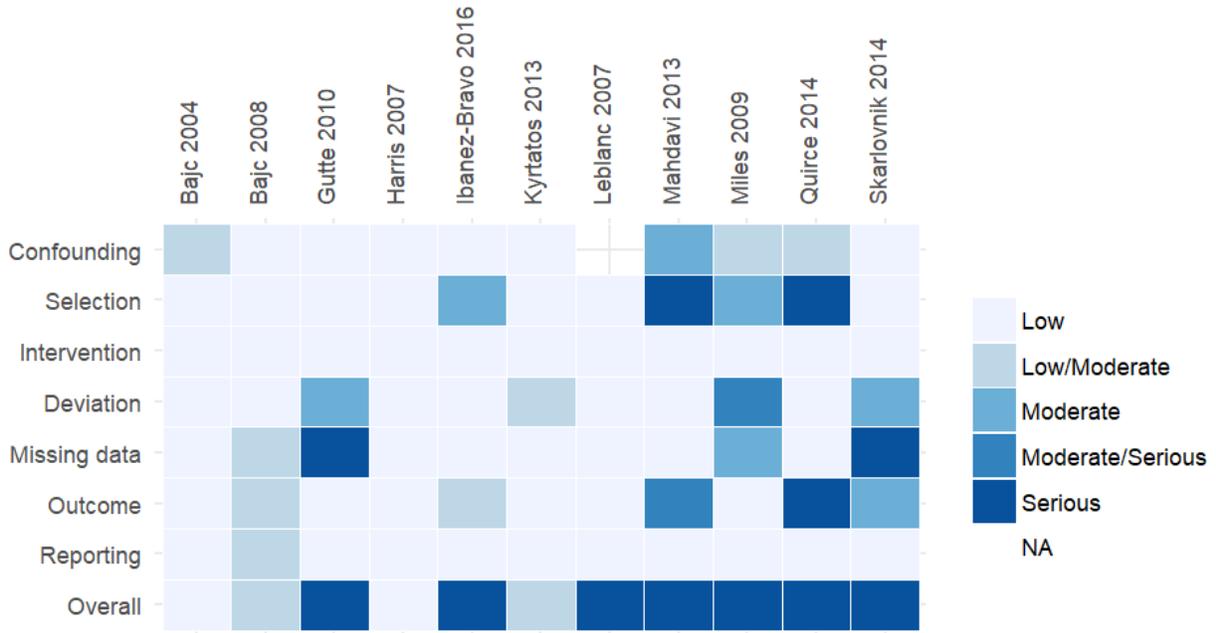


4189
4190 **Figure 16-O: ROBINS-I quality assessment of VQ utility and safety studies**



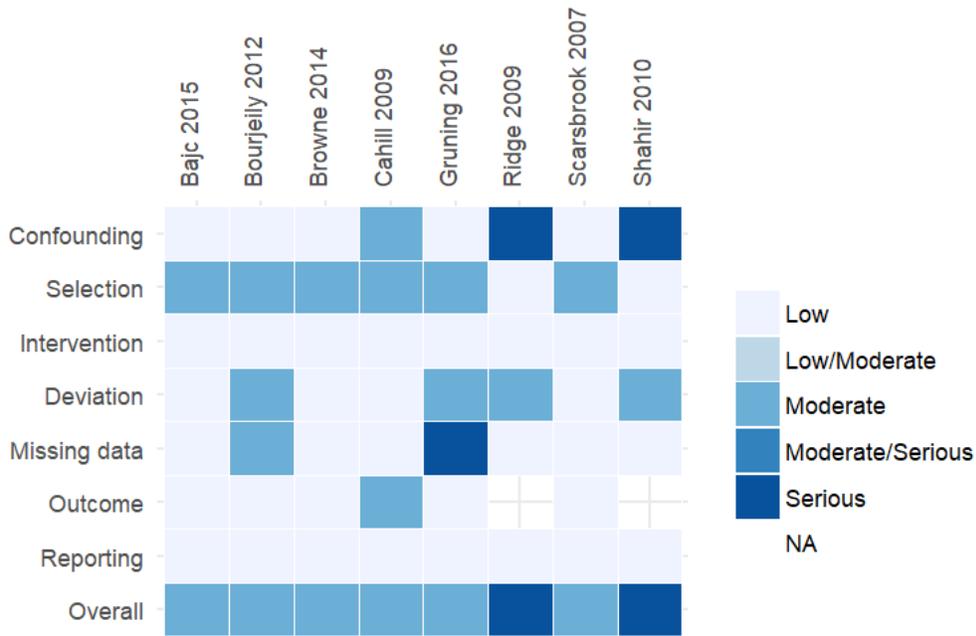
4191

4192 **Figure 16-P: ROBINS-I quality assessment of VQ-SPECT utility and safety studies**



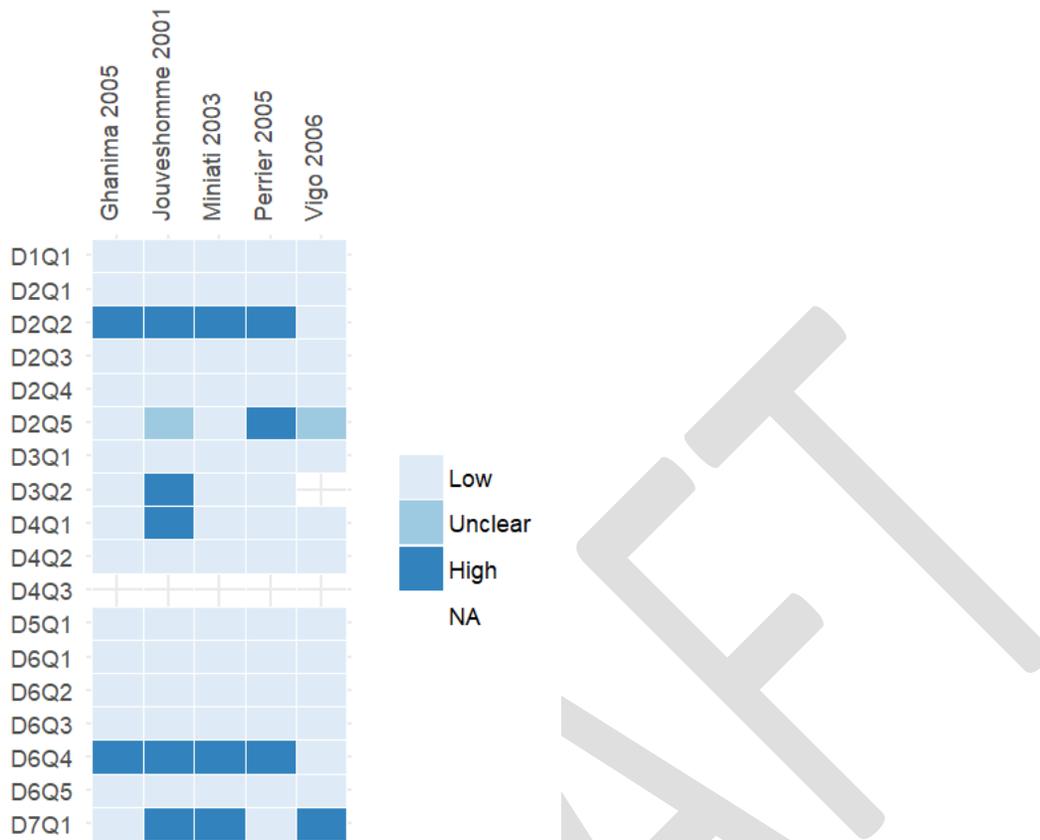
4193
4194
4195

Figure 16-Q: ROBINS-I quality assessment of utility and safety studies in pregnancy



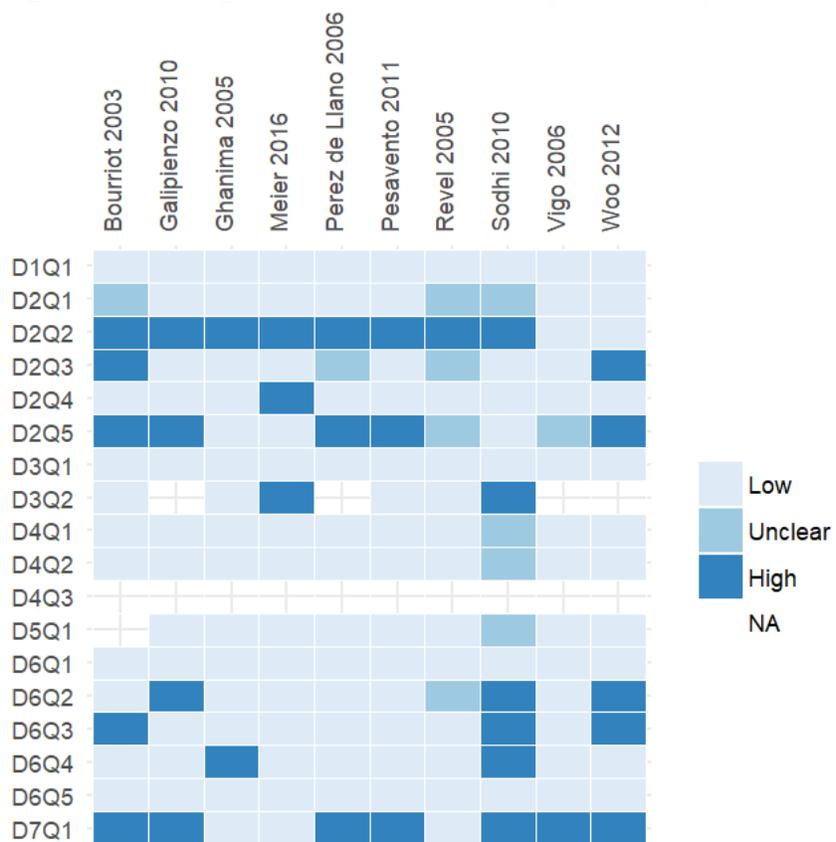
4196
4197

4198 **Figure 16-R: Moga checklist for pathway utility and safety studies**



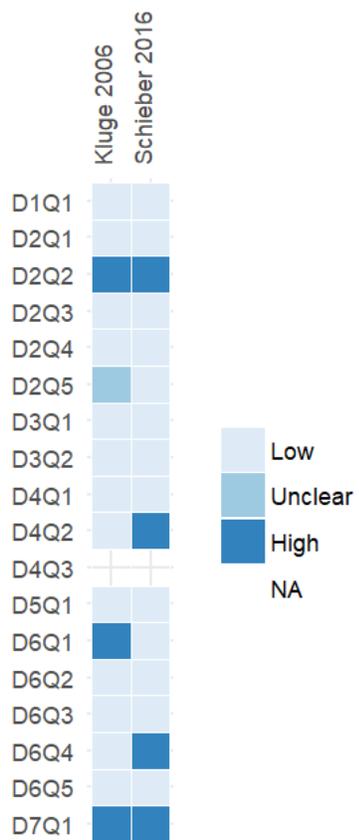
4199
4200

4201 **Figure 16-S: Moga checklist for CT utility and safety studies**



4202
4203
4204

4205 **Figure 16-T: Moga checklist for MRI utility and safety studies**



4206
4207

DRAFT

4208 **Appendix 17: Individual Study Diagnostic Test Accuracy Data (Questions 2 and 3)**

4209

4210 Notes to tables in Appendix 18: TP, FP, FN, TN are true positive, false positive, false negative, and true negative, respectively. SN is
 4211 sensitivity, SP specificity, PPV positive predictive value, and NPV negative predictive value. 95% CI represents the 95% confidence
 4212 interval.

4213

4214 Italicized entries in TP, FP, FN, TN columns have are derived data from other information provided in the study. Sensitivity,
 4215 specificity, PPV, NPV and their confidence intervals are calculated from the 2x2 table, using the exact binomial formula for the
 4216 confidence intervals.

4217

4218 **Table 17-A: Diagnostic test accuracy data for CT as index test in non-pregnant patients**

4219

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 ¹¹⁰	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 ¹¹²	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 ¹¹²	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 ¹⁰²	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 ¹⁰²	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 ¹¹³	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 ¹¹³	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)

Study Information	Index	Reference	Post hoc/ subset	TP	FP	FN	TN	SN (95% CI)	SP (95% CI)	PPV (95% CI)	NPV (95% CI)
Megyeri 2014 ¹¹³	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 ¹¹⁴	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 ¹¹⁴	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 ¹¹⁴	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 ¹¹⁴	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 ¹⁰³	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 ¹⁰³	CT	VQ-SPECT- CT	No/No	6	1	1	7	0.857 (0.421- 0.996)	0.875 (0.473- 0.997)	0.857 (0.421- 0.996)	0.875 (0.473- 0.997)
Gutte 2009 ¹¹¹	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 ¹¹¹	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 ¹⁰⁴	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 ¹¹⁶	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 ¹¹⁶	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)

Study Information	Index	Reference	Post hoc/ subset	TP	FP	FN	TN	SN (95% CI)	SP (95% CI)	PPV (95% CI)	NPV (95% CI)
Stein 2007 ¹¹⁶	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 ⁶⁴	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 ⁶⁴	CT	SC	No/Yes (High)	22	6	1	9	0.957 (0.781-0.999)	0.6 (0.323-0.837)	0.786 (0.59-0.917)	0.9 (0.555-0.997)
Stein 2006 ⁶⁴	CT	SC	No/Yes (Intermediate)	93	15	8	121	0.921 (0.85-0.965)	0.89 (0.825-0.937)	0.861 (0.781-0.92)	0.938 (0.881-0.973)
Stein 2006 ⁶⁴	CT	SC	No/Yes (Low)	22	6	16	158	0.579 (0.408-0.737)	0.963 (0.922-0.986)	0.786 (0.59-0.917)	0.908 (0.855-0.947)
Reinartz 2004 ¹⁰⁵	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 ¹⁰⁶	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 ¹⁰⁹	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 ¹⁰⁷	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 ¹¹⁵	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 ¹⁰⁸	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.

4220
4221
4222

4223 **Table 17-B: Diagnostic test accuracy data for CTCTV as index test in non-pregnant patients**
 4224

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 ¹¹⁶	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 ¹¹⁶	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 ¹¹⁶	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 ⁶⁴	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 ⁶⁴	CTCTV	SC	No/Yes (High)		27	2	1	9	0.964 (0.817-0.999)	0.818 (0.482-0.977)	0.931 (0.772-0.992)	0.9 (0.555-0.997)
Stein 2006 ⁶⁴	CTCTV	SC	No/Yes (Intermediate)		100	10	11	114	0.901 (0.83-0.949)	0.919 (0.857-0.961)	0.909 (0.839-0.956)	0.912 (0.848-0.955)
Stein 2006 ⁶⁴	CTCTV	SC	No/Yes (Low)		24	5	18	146	0.571 (0.41-0.723)	0.967 (0.924-0.989)	0.828 (0.642-0.942)	0.89 (0.832-0.934)

4225 SC = Simple composite.

4226 **Table 17-C: Diagnostic test accuracy data for MRI as index test in non-pregnant patients**
 4227
 4228

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 ¹¹⁹	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 ¹²⁰	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 ¹²¹	MRI	CT	No/No	No/2D angio	27	0	2	4	0.931 (0.772-	1 (0.398-1)	1 (0.872-1)	0.667 (0.223-

Study Information	Index	Reference	Post hoc/subset	Details	TP	FP	FN	TN	Sn (95% CI)	SP (95% CI)	PPV (95% CI)	NPV (95% CI)
									0.992)			0.957)
Nyren 2016 ¹²¹	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 ¹²²	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 ¹²²	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 ¹²³	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)
Revel 2013 ¹²³	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 ¹²³	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 ¹²³	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 ¹²³	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 ¹²³	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 ¹²³	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 ¹²³	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 ¹²³	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 ¹²³	MRI	CT	Yes/No	No/2D angio	67	1	37	65	0.644 (0.544-	0.985 (0.918-1)	0.985 (0.921-1)	0.637 (0.536-

Study Information	Index	Reference	Post hoc/subset	Details	TP	FP	FN	TN	Sn (95% CI)	SP (95% CI)	PPV (95% CI)	NPV (95% CI)
									0.736)			0.73)
Revel 2012 ¹²⁴	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 ¹²⁴	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 ¹²⁴	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 ¹²⁴	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 ¹³⁰	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 ¹³⁰	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 ¹³³	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 ¹²⁵	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)
Kluge 2006 ¹²⁵	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 ¹²⁵	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 ¹²⁵	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 ¹³¹	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 ¹³¹	MRI	CC	No/No	Yes/3D MRA	11	2	1	34	0.917	0.944	0.846	0.971

Study Information	Index	Reference	Post hoc/subset	Details	TP	FP	FN	TN	Sn (95% CI)	SP (95% CI)	PPV (95% CI)	NPV (95% CI)
									(0.615-0.998)	(0.813-0.993)	(0.546-0.981)	(0.851-0.999)
Ohno 2004 ¹³¹	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 ¹²⁷	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 ¹²⁸	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 ¹²⁹	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 ¹³²	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 ¹³²	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 ¹²⁶	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)

4229 CC = Complex composite; CT = Computed Tomography; MRI = Magnetic Resonance Imaging; SC = Simple composite.

4230

4231 **Table 17-D: Diagnostic test accuracy data for MRI-MRV as index test in non-pregnant patients**

4232

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 2010 ¹³⁰	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 ¹³⁰	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)

4233 CC = Complex composite.

4234

4235 **Table 18-E: Diagnostic test accuracy data for MRI-VQ as index test in non-pregnant patients**

4236

Study Information	Index	Reference	Post hoc/subset	Details	TP	FP	FN	TN	Sn (95% CI)	SP (95% CI)	PPV (95% CI)	NPV (95% CI)
Ohno 2004 ¹³¹	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)

4237 CC = Complex composite.

4238

4239 **Table 17-F: Diagnostic test accuracy data for US as index test in non-pregnant patients**

4240

Study Information	Index	Reference	Post hoc/subset	Details	TP	FP	FN	TN	Sn (95% CI)	SP (95% CI)	PPV (95% CI)	NPV (95% CI)
Abootalebi 2016 ¹³⁴	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 ¹³⁵	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 ¹³⁵	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 ¹³⁵	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 ¹³⁶	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 ¹³⁷	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 ¹³⁸	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)
Mohn 2003 ¹³⁹	US	CC	No/No		22	10	9	33	0.71 (0.52-	0.767 (0.614-	0.688 (0.5-	0.786 (0.632-

									0.858)	0.882)	0.839)	0.897)
Lechleitner 2002 ¹⁴⁰	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 ¹⁴¹	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 ¹⁴¹	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 ¹⁴³	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 ¹⁴³	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 ¹⁴²	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)

4241 CC = Complex composite; CT = Computed Tomography; MRI = Magnetic Resonance Imaging; SC = Simple composite; VQ =
4242 Ventilation-Perfusion;
4243
4244
4245

Table 17-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 ¹⁵¹	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 ¹⁵²	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 ¹⁴⁸	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 ¹⁴⁶	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 ¹¹⁴	Q	CC	No/No	PISAPED	276	45	42	181	0.868 (0.826-0.903)	0.801 (0.743-0.851)	0.86 (0.817-0.896)	0.812 (0.754-0.861)
He 2012 ¹¹⁴	Q	CC	No/Yes (Low)	PISAPED	16	22	72	108	0.182 (0.108-0.278)	0.831 (0.755-0.891)	0.421 (0.263-0.592)	0.6 (0.524-0.672)
He 2012 ¹¹⁴	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)
He 2012 ¹¹⁴	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)
Wang 2009 ¹⁰⁴	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 ¹⁴⁹	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 ¹⁴⁹	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 ¹⁴⁹	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 ¹⁴⁹	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 ¹⁵⁰	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 ¹⁴⁷	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)

Miniati 1996 ¹⁵³	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 ¹⁵³	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)

4246 CC = Complex composite; CT = Computed Tomography; PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis;
4247 PISAPED = Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis; SC = Simple composite;
4248
4249
4250

Table 17-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 ¹⁵¹	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 ¹⁵⁵	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)

4251 CC = Complex composite
4252
4253
4254

Table 17-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 ¹⁵⁷	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 ¹⁵⁶	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 ¹⁵¹	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 ¹⁴⁸	Q-SPECT-	CC	No/No		20	5	2	79	0.909 (0.708-	0.94 (0.867-	0.8 (0.593-	0.975 (0.914-

4255
4256
4257
4258
4259
4260

	CT									0.989)	0.98)	0.932)	0.997)
--	----	--	--	--	--	--	--	--	--	--------	-------	--------	--------

CC = Complex composite; CT = Computed Tomography; PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis;
VQ = Ventilation-Perfusion;

Table 17-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 ¹⁴⁵	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 ¹⁴⁸	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 ¹⁴⁶	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 ¹⁴⁶	VQ	CC	No/No	PIOPED II Revised	3	1	1	77	0.75 (0.194-0.994)	0.987 (0.931-1)	0.75 (0.194-0.994)	0.987 (0.931-1)
He 2012 ¹¹⁴	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 ¹¹⁴	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 ¹¹⁴	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 ¹¹⁴	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 ¹⁵⁸	VQ	CC	No/No		7	7	4	18	0.636 (0.308-	0.72 (0.506-	0.5 (0.23-	0.818 (0.597-

									0.891)	0.879)	0.77)	0.948)
Wang 2009 ¹⁰⁴	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 ¹⁶³	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 ¹³¹	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 ¹⁰⁵	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 ¹⁰⁹	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)
Collart 2002 ¹⁶⁰	VQ	CC	No/No	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)
Lechleitner 2002 ¹⁴⁰	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 ¹¹⁵	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)
Stein 1992 ¹⁶⁴	VQ	PA	Yes/No		14	1	15	37	0.483 (0.294- 0.675)	0.974 (0.862- 0.999)	0.933 (0.681- 0.998)	0.712 (0.569- 0.829)
Stein 1992 ¹⁶⁴	VQ	PA	Yes/No	PIOPED	15	1	14	37	0.517 (0.325- 0.706)	0.974 (0.862- 0.999)	0.938 (0.698- 0.998)	0.725 (0.583- 0.841)
Gray 1990 ¹⁶¹	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	VQ	PA	No/No	PIOPED	102	14	44	249	0.699 (0.617-	0.947 (0.912-	0.879 (0.806-	0.85 (0.804-

1990 ¹⁵⁹									0.772)	0.971)	0.932)	0.889)
Woods 1989 ¹⁶²	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 ¹⁶²	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)

4261 CC = Complex composite; CT = Computed Tomography; MRI = Magnetic Resonance Imaging; PIOPED = Prospective Investigation
4262 of Pulmonary Embolism Diagnosis; PISAPED = Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis; SC =
4263 Simple composite; VQ = Ventilation-Perfusion;
4264
4265
4266

Table 17-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 ¹⁷²	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 ¹⁷²	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 ¹⁷²	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 ¹⁶⁵	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 ¹⁴⁶	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 ¹⁶⁶	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	VQ-SPECT	VQ	No/No	Revised PIOPED	27	2	6	170	0.818 (0.645-	0.988 (0.959-	0.931 (0.772-	0.966 (0.927-

166									0.93)	0.999)	0.992)	0.987)
Le Roux 2012 ⁴⁸³	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 ¹⁵⁸	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 ¹⁵⁸	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 ¹¹¹	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 ¹¹¹	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 ¹¹¹	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 ¹¹¹	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 ¹⁶⁷	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 ¹⁶⁸	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 ¹⁷¹	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)
Harris 2007 ¹⁶⁹	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 ¹⁶⁹	VQ-SPECT	CC	No/No	Modified PIOPED	8	0	4	35	0.667 (0.349-	1 (0.9-1)	1 (0.631-	0.897 (0.758-

									0.901)		1)	0.971)
Reinartz 2006 ¹⁷⁰	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 ¹⁷³	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 ¹⁷³	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 ¹⁰⁵	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)
Collart 2002 ¹⁶⁰	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; CT = Computed Tomography; PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis; SC = Simple composite; VQ = Ventilation-Perfusion;

Table 17-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 ¹⁷⁴	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 ¹⁵⁶	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)
Le Roux 2013 ⁵¹	VQ-SPECT-CT	Sequential	Yes/No	2 segmental or subsegmental mismatches	43	10	6	190	0.878 (0.752-0.954)	0.95 (0.91-0.976)	0.811 (0.68-0.906)	0.969 (0.935-0.989)
Le Roux 2013 ⁵¹	VQ-SPECT-CT	Sequential	Yes/No	1 segmental mismatch	42	14	7	186	0.857 (0.728-0.941)	0.93 (0.885-0.961)	0.75 (0.616-0.856)	0.964 (0.927-0.985)

Le Roux 2013 ⁵¹	VQ-SPECT-CT	Sequential	Yes/No	1 segmental or 2 subsegmental mismatches	45	18	4	182	0.918 (0.804-0.977)	0.91 (0.861-0.946)	0.714 (0.587-0.821)	0.978 (0.946-0.994)
Le Roux 2013 ⁵¹	VQ-SPECT-CT	Sequential	Yes/No	2 segmental mismatches	31	6	18	194	0.633 (0.483-0.766)	0.97 (0.936-0.989)	0.838 (0.68-0.938)	0.915 (0.869-0.949)
Le Roux 2013 ⁵¹	VQ-SPECT-CT	Sequential	Yes/No	3 segmental or subsegmental mismatches	33	2	16	198	0.673 (0.525-0.801)	0.99 (0.964-0.999)	0.943 (0.808-0.993)	0.925 (0.881-0.957)
Le Roux 2013 ⁵¹	VQ-SPECT-CT	Sequential	Yes/No	greater than 1 segmental mismatch	40	8	9	192	0.816 (0.68-0.912)	0.96 (0.923-0.983)	0.833 (0.698-0.925)	0.955 (0.917-0.979)
Le Roux 2013 ⁵¹	VQ-SPECT-CT	Sequential	Yes/No	1 segmental or subsegmental mismatch	45	32	4	168	0.918 (0.804-0.977)	0.84 (0.782-0.888)	0.584 (0.466-0.696)	0.977 (0.942-0.994)
Ling 2012 ¹⁷⁵	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 ¹¹¹	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;

4272
4273
4274

DRAFT

4276 **Appendix 18: Individual Study Utility and Safety Data (Questions 2**
 4277 **and 3)**

- 4278 - Failure rates, nondiagnostic studies, and rates of incidental findings appear in Tables XX through
 4279 XX.
 4280 - Details of incidental findings appear in Table XX.
 4281 - Safety data appears in Table XX.

4282

4283 **Table 18-A: Failure rates, nondiagnostic studies, and incidental findings for CT as an**
 4284 **index test**

Study Information	Index	Reference	Failure, index	Failure, reference	Nondiagnostic, index	Nondiagnostic, reference	Incidental findings, index	Incidental findings, reference
Meier 2016 ¹⁹²	CT (CT low-CM)	CT	0/34 (0)	0/36 (0)	17/82 (0.207)	8/83 (0.096)		
Watanabe 2015 ¹⁴⁵	CT (CTPA)	FU			2/129 (0.016)			
Moore 2015 ¹⁹³	CT (CT)	CC	2/129 (0.016)	0/43 (0)			26/134	
Megyeri 2014 ¹¹³	CT (CTPA (BW < 100kg))	CC	0/189 (0)	0/186 (0)				
He 2012 ¹¹⁴	CT (CT)	CC			16/544 (0.029)			
Woo 2012 ¹⁹⁹	CT (CT)	None			21/1424 (0.015)			
Pesavento 2011 ¹⁹⁶	CT (CT)	FU	0/367 (0)		9/545 (0.017)		108/545	
Sodhi 2010 ¹⁹⁸	CT (CT)	CC	1/21 (0.048)	0/20 (0)			15/50	
Hantous-Zannad 2010 ¹⁹⁰	CT (CTPA)	FU	1/29 (0.034)					
Galipienzo 2010 ¹⁸⁶	CT (MCTPA)	FU	1/242 (0.004)					
Gimber 2009 ¹⁸⁹	CT (CTPA)	FU			21/353 (0.059)			
Wang 2009 ¹⁰⁴	CT (CTPA)	CC			2/82 (0.024)			
Anderson 2007 ⁵³	CT (CTPA)	VQ	2/500 (0.004)	6/100 (0.06)				
Stein	CT	SC			51/824	87/824		

2006 ⁶⁴	(MDCT Angiography)				(0.062)	(0.106)		
Huisman 2006 ¹⁹¹	CT (CT)	FU	18/1385 (0.013)		40/1999 (0.02)			
Vigo 2006 ¹⁸⁴	CT (CT)	FU	6/536 (0.011)			15/702 (0.021)	144/536	
Perez de Llano 2006 ¹⁹⁵	CT (Helical CT)	FU	1/87 (0.011)					
Hogg 2006 ¹⁷⁹	CT (CTPA)	FU	2/381 (0.005)					
Ghanima 2005 ¹⁷⁸	CT (MSCT (Spiral))	FU	2/211 (0.009)		15/329 (0.046)			
Revel 2005 ¹⁹⁷	CT (CT Angiography)	FU	2/109 (0.018)		20/220 (0.091)			
Coche 2003 ¹⁰⁹	CT (MDCT)	SC	0/65 (0)	0/58 (0)	1/94 (0.011)	7/94 (0.074)	19/66	
Donato 2003 ¹⁸⁸	CT (CT)	FU	4/239 (0.017)					
Bourriot 2003 ¹⁸⁷	CT (SCT)	FU	3/117 (0.026)			26/196 (0.133)		
Ost 2001 ¹⁹⁴	CT (Spiral CT)	PA	1/68 (0.015)		10/103 (0.097)			
Qanadli 2000 ¹⁰⁸	CT (Dual section Helical CT)	PA			17/314 (0.054)	11/316 (0.035)	1/158	
Blachere 2000 ¹¹⁵	CT (CT angiography)	CC	3/107 (0.028)		5/179 (0.028)			

4285 BW = body weight; CC = complex composite; CM = contrast medium; CT = computed tomography;
4286 CTPA = computed tomography pulmonary angiography; MDCT = multidetector computed tomography;
4287 SC = simple composite; VQ = ventilation-perfusion.

4288

4289
4290

Table 18-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 ¹²²	MRI (MRPA)	CT			0/27 (0)	0/27 (0)		
Schiebler 2013 ⁵⁰	MRI (MRA)	FU	5/148 (0.034)		5/190 (0.026)			
Revel 2013 ¹²³	MRI (MRA Unenhanced free-breathing)	CT			128/274 (0.467)			
Revel 2013 ¹²³	MRI (MRA Unenhanced breath-hold)	CT			106/274 (0.387)			
Revel 2013 ¹²³	MRI (MRA Native Perfusion Reader)	CT			111/274 (0.405)			
Revel 2013 ¹²³	MRI (MRA Perfusion with mask subtraction)	CT			120/274 (0.438)			
Revel 2013 ¹²³	MRI (MRA Contrast-enhanced angiography)	CT			130/274 (0.474)			
Revel 2012 ¹²⁴	MRI (MRI)	CT			80/274 (0.292)			
Stein 2010 ¹³⁰	MRI (MRA)	CC			92/371 (0.248)			
Kluge 2006 ²⁰³	MRI (MRI)	MRI			0/218 (0)		97/218	
Kluge 2006 ²⁰³	MRI (MRI)	MRI			1/218 (0.005)		97/218	
Kluge 2006 ²⁰³	MRI (MRI)	MRI			26/218 (0.119)		97/218	
Kluge 2006 ¹²⁵	MRI (MRI)	CT			0/62 (0)			
Kluge 2006 ¹²⁵	MRI (MRI)	CT			0/62 (0)			
Kluge	MRI (MRI)	CT			0/62 (0)		8/62	9/62

2006 ¹²⁵							(0.145)	(0.145)
---------------------	--	--	--	--	--	--	---------	---------

4291 CC = complex composite; CT = computed tomography; MRI = magnetic resonance imaging.

4292

4293 **Table 18-C: Failure rates, nondiagnostic studies, and incidental findings for US as an**
 4294 **index test**

Study Information	Index	Reference	Failure, index	Failure, reference	Nondiagnostic, index	Nondiagnostic, reference	Incidental findings, index	Incidental findings, reference
Mohn 2003 ¹³⁹	US (Transthoracic Sonography)	CC		0/43 (0)				
Lechleitner 2002 ¹⁴⁰	US (Chest ultrasound)	MRI			3/55 (0.055)	0/55 (0)		

4295 CC = complex composite; MRI = magnetic resonance imaging.

4296

4297 **Table 18-D: Failure rates, nondiagnostic studies, and incidental findings for Q as an**
 4298 **index test**

Study Information	Index	Reference	Failure, index	Failure, reference	Nondiagnostic, index	Nondiagnostic, reference	Incidental findings, index	Incidental findings, reference
Watanabe 2015 ¹⁴⁵	Q (Q-only PISAPE D)	FU			0/129 (0)			
van Es 2015 ¹⁵²	Q (V/Q with CXR)	CT		0/6 (0)	2/76 (0.026)	0/76 (0)		
Skarlovnik 2014 ¹⁴⁶	Q (No)	CC			21/98 (0.214)			
He 2012 ¹¹⁴	Q (Q-only PISA-PED)	CC			0/544 (0)			
Sostman 2008 ¹⁴⁹	Q (Q + CXR Modified PIOPED II Reader)	DSA or CT			183/889 (0.206)			

	1)							
Sostman 2008 ¹⁴⁹	Q (Q + CXR PISAPED Reader 1)	DSA or CT			0/889 (0)			
Miniati 1996 ¹⁵³	Q (Q)	PA				21/413 (0.051)		

4299 CC = complex composite; CT = computed tomography; CXR = chest X-ray; DSA = digital subtraction
4300 angiography; PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis; PISAPED =
4301 Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis.

4302

4303 **Table 18-E: Failure rates, nondiagnostic studies, and incidental findings for Q-SPECT as**
4304 **an index test**

Study Information	Index	Reference	Failure, index	Failure, reference	Nondiagnostic, index	Nondiagnostic, reference	Incidental findings, index	Incidental findings, reference
Bajc 2013 ¹⁵⁵	Q-SPECT (Q-SPECT)	CT	0/88 (0)	0/93 (0)	0/152 (0)			

4305 CT = computed tomography; SPECT = single photon emission tomography.

4306

4307 **Table 18-F: Failure rates, nondiagnostic studies, and incidental findings for VQ as an**
4308 **index test**

Study Information	Index	Reference	Failure, index	Failure, reference	Nondiagnostic, index	Nondiagnostic, reference	Incidental findings, index	Incidental findings, reference
Watanabe 2015 ¹⁴⁵	VQ (V/Q mod PISAPED)	FU			74/129 (0.574)			
Skarlovnik 2014 ¹⁴⁶	VQ (No)	CC			16/98 (0.163)			
He 2012 ¹¹⁴	VQ (VQ PIOPED II)	CC			67/544 (0.123)			
Gutte 2010 ¹⁵⁸	VQ	CC			0/36 (0)	5/41 (0.122)		
Miles	VQ	CT			25/99			

2009 ¹⁶⁷					(0.253)			
Wang 2009 ¹⁰⁴	VQ (VQ Perfusion and CR)	CC			2/28 (0.071)			
Sostman 2008 ¹⁶³	VQ (V/Q High probabilit y or very low/norm al)	DSA or CT			241/910 (0.265)			
Coche 2003 ¹⁰⁹	VQ	CT			7/94 (0.074)	1/94 (0.011)	(0.242)	16/66 (0.242)
Lechleitn er 2002 ¹⁴⁰	VQ (V/Q scintigrap hic scans)	MRI			18/55 (0.327)	0/55 (0)		
PIOPED Investigat ors 1990 ¹⁵⁹	VQ (V/Q)	PA	0/21 (0)		364/931 (0.391)			
Gray 1990 ¹⁶¹	VQ	PA	0/28 (0)	0/51 (0)	30/78 (0.385)	0/78 (0)		

4309 CC = complex composite; CT = computed tomography; DSA = digital subtraction angiography; MRI =
4310 magnetic resonance imaging; PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis;
4311 PISAPED = Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis; VQ = ventilation-
4312 perfusion.

4313 **Table 18-G: Details of alternative diagnoses and incidental findings, all modalities**

Study	Number (%) of patients	Details
CT		
Moores 2015 ¹⁹³	26/134 (19.4)	Pneumonia 13, emphysema 6, cancer 3, heart failure 3, pneumothorax 1.
Pesavento 2011 ¹⁹⁶	108/545 (19.8)	Pneumonia 50, pleural effusion 27, malignancy 11, other 20.
Sodhi 2010 ¹⁹⁸	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 ¹⁸⁴	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 ¹⁰⁹	Non-PE: 19/66 (28.8)	Pneumonia 7, heart failure 5, small airways diseases 4, pleural diseases 2, and pulmonary fibrosis 1.
Qanadli 2000 ¹⁰⁸	1/158 (0.6)	Intramural hematoma of ascending aorta 1.
MRI		
Kluge 2006 ²⁰³	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 ¹²⁵	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 ¹⁴⁰	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.

4314 CAD = coronary artery disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary
4315 disease

4316 **Table 18-H: Safety, all modalities**

	Index test	Reference test	Safety Outcome	Incidence and details
Pesavento 2011 ¹⁹⁶	CT	None	Severe acute renal failure	CT: 1 (0.27%)
Stein 2006 ⁶⁴	CT	CC	Allergic reaction	CT: 4 (>1%) Mild.
Yazici 2016 ²⁰¹	CT	None	Contrast nephropathy	24 (13%)

	Index test	Reference test	Safety Outcome	Incidence and details
			(laboratory definition)	
Coche 2003 ¹⁰⁹	CT	CT, VQ	Contrast nephropathy (creatinine increase)	1/69
Mitchell 2006 ²⁰⁰	CT	None	Contrast nephropathy (creatinine increase)	All: 44/1224 (4%) or paired: 44/354 (12%)
			Severe acute renal failure	0/1224
Revel 2012 ¹²⁴	MRI	CT	Extravasation of contrast	MRI: 1 (patient could not complete protocol)
Stein 2010 ¹³⁰	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 ²⁰³	MRI-MRV	None	Adverse events	No complications related to MRI or contrast media
Pleszewski 2006 ¹³³	MRI	Sequential	Adverse events	Reported "All 48 MR angiographic examinations were completed successfully without adverse effects"
Righini 2008 ¹⁸⁵	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 ¹⁶¹	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.

4317

4318 DD = D-dimer; PW = pathway; APW = alternative pathway.

Appendix 19: Study Characteristics of Studies in Pregnant Patients

Study	Study Design	Subject Characteristics	Intervention	Comparator	Study N	Mean age (years), range or SD
Gruning, 2016 ²¹³	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)	V/Q SPECT or Q SPECT	CT	168 (control group of 89 non-pregnant women)	28 (range 17 to 43; SD = 6)
Bajc, 2015 ²¹¹	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 V/Q SPECT	CT	127	30 (range 18 to 48)
Browne, 2014 ²¹²	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 ²¹⁵	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	Retrospective	Pregnant patients	CT	Q	199 (100	31

2010 ²⁰⁷	cohort study	with suspicion of PE; Stage of gestation: 54 (27%) first trimester; 61 (31%) second trimester; 84 (42%) third trimester		scintigraphy	CT, 99 Q, 6 received both)	years (range 18 to 39)
Cahill 2009 ²⁰⁸	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	V/Q	304	29.2 (5.1) for CT; 30.8 (6.3) for V/Q
Ridge 2009 ²⁰⁹	Retrospective cohort study	Pregnant women with suspected PE; Stage of gestation NR	CT	V/Q	50 (25 CTA; 25 VQ)	32.6 (5.6) for CT; 31.8 (5.4) for V/Q
Scarsbrook 2007 ²¹⁴	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 ²¹⁰	Prospective cohort study	Pregnant women with suspected PE (>12 weeks to <28 weeks gestation)	V/Q	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; V/Q = ventilation perfusion scintigraphy

4320
4321
4322
4323
4324

4325 **Appendix 20: Results of individual studies reporting stratified results**
 4326 **and multiple imaging conditions**

4327 **20-A Individual studies reporting stratified results**

Study	Reference	Strata	N	Sensitivity (95% CI)	Specificity (95% CI)
CT					
Stein 2007 ¹¹⁶	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 ¹¹⁶	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 ¹¹⁴	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 ⁶⁴	CC (VQ, DSA, US)	Low risk (Wells)	202	0.579 (0.408 to 0.733)	0.967 (0.922 to 0.986)
		Moderate risk (Wells)	237	0.921 (0.850 to 0.965)	0.890 (0.825 to 0.937)
		High risk (Wells)	38	0.957 (0.781 to 0.999)	0.600 (0.323 to 0.837)
Megyeri 2014 ¹¹³	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 ⁶⁴	CC (DSA, VQ, US)	Low risk (Wells)	193	0.571 (0.410 to 0.723)	0.818 (0.482 to 0.977)
		Moderate risk (Wells)	235	0.901 (0.830 to 0.949)	0.919 (0.857 to 0.961)
		High risk (Wells)	39	0.964 (0.817 to 0.999)	0.967 (0.924 to 0.989)
MRI					
Revel 2012 ¹²⁴	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 ¹¹⁴	CC (CT, VQ, PA)	Low risk (Wells)	218	0.182 (0.108 to 0.278)	0.831 (0.755 to 0.891)
		Moderate risk (Wells)	236	0.848 (0.785 to 0.899)	0.789 (0.676 to 0.877)
		High risk (Wells)	90	0.928 (0.839 to 0.976)	0.810 (0.581 to 0.946)

Study	Reference	Strata	N	Sensitivity (95% CI)	Specificity (95% CI)
Sostman 2008 ¹⁴⁹	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)
VQ					
He 2012 ¹¹⁴	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 ¹⁷²	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)

4328 ^a Total number of patients in risk category. Number of nondiagnostic exams was not reported for
4329 individual strata.

4330 ^b Study reported results from two readers, which differed. Pooled results could not be calculated from
4331 available data.

4332
4333

20-B Individual studies reporting multiple MRI imaging conditions

Study	Comparator	Contrast / conditions	Sensitivity	Specificity
Revel 2013 ¹²³	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 ¹²⁵	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)

4334 ^a Study reported results from two readers, which differed. Pooled results could not be calculated from
4335 available data.

4336
4337
4338
4339

4340 **Appendix 21: Statistical Appendix (Questions 2 and 3)**

4341 This appendix contains:

- 4342 • further details of data management
- 4343 • how data were coded for analysis
- 4344 • code for statistical models
- 4345 • results for diagnostic test accuracy meta-analysis models
- 4346 • details for explorations of heterogeneity

4347 **Question 2: Diagnostic Test Accuracy**

4348 Data management

4349 *Back-calculation of 2x2 tables*

4350 The 2x2 diagnostic test accuracy table consisting of true positive, true negative, false positive
4351 and false negative was extracted if available. If the 2x2 table was not available, then it was
4352 derived from available data for sensitivity and specificity (or positive predictive value and
4353 negative predictive value), number of cases as measured by the reference standard, and total
4354 number of patients contributing to the diagnostic test results. See Section 2.2.4 of the Centre for
4355 Reviews and Dissemination handbook, Systematic Reviews
4356 (<https://www.york.ac.uk/crd/SysRev/ISSI/WebHelp/SysRev3.htm>)

4357 If a study reported the comparison of multiple index tests with a common comparator and
4358 provided information on concordant or discordant results between the two index tests, as well as
4359 accounting for missing data, then in some cases it was possible also to extract the 2x2 table for
4360 a direct comparison. The best example of this is Watanabe 2015¹⁴⁵, which supplied a
4361 supplementary table listing discordant and missing results for all three modalities investigated,
4362 as well as 2x2 tables reporting comparisons with a common composite consisting of all
4363 information (and therefore excluded from the planned pool).

4364 *Data coding*

4365 Following data extraction, index tests and reference standards and covariates of interest were
4366 coded to reduce the number of categories. Covariates included:

- 4367 • Study setting (Primary, Secondary or Tertiary healthcare setting)
- 4368 • Patient origins (Inpatients, Outpatients, ER patients)
- 4369 • Study funding

4370 Modalities were pooled according to their index test category (Table 21A), and comparators
4371 were pooled according to their reference test category (Table 21B).

4372

4373 **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
	Unknown T

Index test category	Index test description
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	V/Q
	V/Q 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

4374
4375

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
Other	Other
Alternative pathways	CPR and D-dimer and CTPA

Reference test category	Reference test description
Alternative pathways	Sequenced reference tree

- 4376
- 4377 Setting
- 4378
- 4379 Following the definitions in
- 4380 https://www.ehealthontario.on.ca/images/uploads/pages/documents/Health_Care_eBook_Final.pdf
- 4381 the type of centre was coded to indicate the level of healthcare
- 4382 • Primary = First level of entry to healthcare system, physician's offices, nurse
 - 4383 practitioner's offices, community health centres, nursing stations
 - 4384 • Secondary = Specialist and others, community hospital, acute care services
 - 4385 • Tertiary = Specialized care typically for inpatients, academic teaching facility or large
 - 4386 community care facility
 - 4387 • Secondary / Tertiary = Secondary or Tertiary centre
 - 4388 • Secondary / ER = Secondary centre ER
 - 4389 • Tertiary / ER = Tertiary centre ER
 - 4390 • Secondary / Tertiary / ER = Secondary or Tertiary centre ER
- 4391
- 4392 Study centre
- 4393 • Single = Single centre study
 - 4394 • Multi-national or regional = Multiple centres within a single country or region
 - 4395 • Multi-International = Multiple studies in more than one country
- 4396
- 4397 Patient origins
- 4398 • Inpatients
 - 4399 • Outpatients
 - 4400 • ER = Patients presenting to an ER
 - 4401 • Inpatients / Outpatients = Study included both inpatients and outpatients
 - 4402 • Inpatients / Outpatients / ER = Study included inpatients, outpatients, and ER patients
- 4403 Funding
- 4404 • None
 - 4405 • Government or Academic/Institutional Grant
 - 4406 • Industry
 - 4407 • Private
 - 4408 • Multiple Sources
 - 4409 • Not reported
- 4410 PE risk, according to structured assessment
- 4411 • High
 - 4412 • Moderate
 - 4413 • Low
 - 4414 • Mixed (included a mixture of at least two of high, moderate, and low)

4415 • Not reported

4416 In addition, studies were coded as:

- 4417 • Post-hoc analyses of studies already included
- 4418 • Studies in which the index test was part of the reference
- 4419 • Pregnant/Non-pregnant
- 4420 • Interpretation criteria for Q and VQ

4421 *Exclusions from pooling*

4422 The following studies and comparisons were excluded from pooling:

- 4423 • Studies that reported re-analysis of patient groups who were already included as part of
4424 another study, e.g., re-analyses of data to examine the effect of covariates or different
4425 interpretation criteria. These studies were incorporated where indicated in narrative
4426 reviews of the effect of covariates or interpretation criteria.
- 4427 • Comparisons where the index modality was explicitly included in the reference standard.
4428 Where it is unclear whether this is the case, the study was retained. In some instances, it
4429 was possible to extract or derive an isolated comparison of the index modality with one
4430 of the imaging modalities used in the reference, in which case affected comparisons
4431 were excluded and the study was retained.

4432 *Handling of multiple sets of results from a single study*

4433 Where a study reported multiple sets of results, these were handled as follows:

- 4434 • If results for more than one reader were reported, the four cells of the 2x2 tables were
4435 averaged across readers with rounding to the nearest integers, to create a summary 2xw
4436 table.
- 4437 • If more than one contrast was reported, e.g., CT versus VQ and CT versus CC, then the
4438 2x2 table that gave the highest accuracy (true positives plus true negatives, divided by
4439 the total number of patients) was included in the overall pool. The individual contrasts
4440 contributed to sub-pools, if there were enough studies.
- 4441 • Where results from multiple scan conditions (MRI sequences) or multiple interpretation
4442 criteria (Q, VQ SPECT) that gave the highest accuracy (i.e., true positives plus true
4443 negatives / total patients) were included in the overall pool.
- 4444 • Sensitivity analyses explored the effect of including results that gave the lowest
4445 accuracy, highest and lowest sensitivity, and highest and lowest specificity.

4446 *Handling of nondiagnostic tests*

4447 One or more studies reported data for nondiagnostic examinations for CT, MRI, Q, Q-SPECT,
4448 VQ, VQ-SPECT, and PW. Studies could be non-diagnostic on account of technical inadequacy,
4449 or non-diagnostic because, while technically adequate, their results were indeterminate. In
4450 clinical practice, studies that are non-diagnostic due to technical inadequacy are likely to be
4451 repeated, while patients with an indeterminate exam results usually undergo a different
4452 examination. For the nuclear medicine modalities in particular (Q, Q-SPECT, Q-SPECT-CT, VQ,
4453 VQ-SPECT, VQ-SPECT-CT), a substantial number of exams are technically adequate but non-
4454 diagnostic, assessed as intermediate probability, intermediate or low probability, or intermediate

4455 / low / very low probability, depending on the interpretation scale and the definitions used in the
4456 study.

4457 Studies approached the reporting and analysis of nondiagnostic exams in different ways

- 4458 • excluding patients with nondiagnostic exams from the diagnostic 2x2 table
 - 4459 • reporting only the total number of non-diagnostic tests (sometimes separating out non-
4460 diagnostic due to technical inadequacy from technically adequate but indeterminate)
 - 4461 • reporting the number of non-diagnostic cases and non-diagnostic non-cases
 - 4462 • a Bayesian adjustment of the sensitivity and specificity calculated from the results of
4463 exams were nondiagnostic.
- 4464

4465 An attempt was made to estimate the effect of non-diagnostic exams on the meta-analysis
4466 results by applying the conservative ITD assumption: non-diagnostic cases would be assumed
4467 to be FN, and non-diagnostic cases would be assumed to be FP. Because of the variability in
4468 approaches, and the number of studies that did not report usable data for the 3x2 diagnostic
4469 table, the resulting datasets were small and numerically heterogeneous, and a meta-analysis is
4470 not feasible at this time. The effect of non-diagnostic studies were summarized narratively.

4471 The protocol definition of test failure was VTE in the first 30 days in a patient who had tested
4472 negative (negative DI) and was not receiving anticoagulation. Failure rate was reported in
4473 pathway studies and studies with index tests CT, MRI, Q-SPECT, VQ, VQ-SPECT, although the
4474 majority of studies reported failure rate over 3 or 6 months.

4475 Diagnostic test meta-analysis: Sample WinBUGS programs

4476 *HSROC model assuming imperfect reference standard with conditional independence.*

4477 Example for CT meta-analysis, 11 studies. Reference standards are identified by their class, as
4478 described under data management.

```
4479 model {  
4480  
4481     for(i in 1:11) {  
4482  
4483         theta[i] ~ dnorm(THETA,prec[1])  
4484         alpha[i] ~ dnorm(LAMBDA,prec[2])  
4485  
4486         p[1,i] <- phi(-(theta[i] - 0.5*alpha[i])/exp(beta/2))  
4487         p[2,i] <- phi(-(theta[i] + 0.5*alpha[i])*exp(beta/2))  
4488  
4489         prob[i,1] <- pi[i]*( p[1,i] * s2[ref[i]] ) + (1-pi[i])*( p[2,i] * (1-  
4490 c2[ref[i]] ) )  
4491         prob[i,2] <- pi[i]*( p[1,i] * (1-s2[ref[i]] ) + (1-pi[i])*( p[2,i] *  
4492 c2[ref[i]] ) )  
4493         prob[i,3] <- pi[i]*( (1-p[1,i]) * s2[ref[i]] ) + (1-pi[i])*( (1-p[2,i]) *  
4494 (1-c2[ref[i]] ) )  
4495         prob[i,4] <- pi[i]*( (1-p[1,i]) * (1-s2[ref[i]] ) + (1-pi[i])*( (1-  
4496 p[2,i]) * c2[ref[i]] ) )  
4497  
4498         results[i,1:4] ~ dmulti(prob[i,1:4],n[i])  
4499         n[i]<-sum(results[i,1:4])  
4500  
4501         pi[i] ~ dbeta(1,1)  
4502  
4503         se[i] <- p[1,i]  
4504         sp[i] <- 1-p[2,i]  
4505
```

```

4506     }
4507
4508
4509     for(j in 1:2) {
4510
4511         prec[j] <- pow(sigma[j],-2)
4512         sigma[j] ~ dunif(0,2)
4513     }
4514
4515     THETA ~ dunif(-1.5,1.5)
4516     beta ~ dunif(-0.75,0.75)
4517
4518     S_a ~ dnorm(0,1) # S_overall=phi(S_a)
4519     C_a ~ dnorm(0,1) # C_overall=phi(C_a)
4520
4521     LAMBDA <- S_a*exp(beta/2) + C_a*exp(-beta/2)
4522
4523     S_overall<-phi(-(THETA-LAMBDA/2)/exp(beta/2))
4524     C_overall<-phi((THETA+LAMBDA/2)*exp(beta/2))
4525
4526     theta_new ~ dnorm(THETA,prec[1])
4527     alpha_new ~ dnorm(LAMBDA,prec[2])
4528
4529     S_new<-phi(-(theta_new-alpha_new*0.5)/exp(beta*0.5))
4530     C_new<-phi((theta_new+alpha_new*0.5)*exp(beta*0.5))
4531
4532
4533     for(h in 1:5) {
4534
4535         s2[h] ~ dunif(0.5,1) ;
4536         c2[h] ~ dunif(0.5,1) ;
4537     }
4538
4539 }
4540
4541
4542 HSROC model assuming a perfect reference standard
4543
4544 model {
4545
4546     for(i in 1:11) {
4547
4548         theta[i] ~ dnorm(THETA,prec[1])
4549         alpha[i] ~ dnorm(LAMBDA,prec[2])
4550
4551         p[1,i] <- phi(-(theta[i] - 0.5*alpha[i])/exp(beta/2))
4552         p[2,i] <- phi(-(theta[i] + 0.5*alpha[i])*exp(beta/2))
4553
4554         prob[i,1] <- pi[i]*( p[1,i] * s2 ) + (1-pi[i])*(p[2,i] * (1-c2) )
4555         prob[i,2] <- pi[i]*( p[1,i] * (1-s2) ) + (1-pi[i])*( p[2,i] * c2 )
4556         prob[i,3] <- pi[i]*( (1-p[1,i]) * s2 ) + (1-pi[i])*( (1-p[2,i]) * (1-c2) )
4557     )
4558     prob[i,4] <- pi[i]*( (1-p[1,i]) * (1-s2) ) + (1-pi[i])*( (1-p[2,i]) * c2 )
4559 )
4560
4561     results[i,1:4] ~ dmulti(prob[i,1:4],n[i])
4562     n[i]<-sum(results[i,1:4])
4563
4564     pi[i] ~ dbeta(1,1)
4565
4566     se[i] <- p[1,i]

```

```

4567         sp[i] <- 1-p[2,i]
4568     }
4569
4570
4571     for(j in 1:2) {
4572
4573         prec[j] <- pow(sigma[j],-2)
4574         sigma[j] ~ dunif(0,2)
4575     }
4576
4577     THETA ~ dunif(-1.5,1.5)
4578     beta ~ dunif(-0.75,0.75)
4579
4580     S_a ~ dnorm(0,1) # S_overall=phi(S_a)
4581     C_a ~ dnorm(0,1) # C_overall=phi(C_a)
4582
4583     LAMBDA <- S_a*exp(beta/2) + C_a*exp(-beta/2)
4584
4585     S_overall<-phi(-(THETA-LAMBDA/2)/exp(beta/2))
4586     C_overall<-phi((THETA+LAMBDA/2)*exp(beta/2))
4587
4588     theta_new ~ dnorm(THETA,prec[1])
4589     alpha_new ~ dnorm(LAMBDA,prec[2])
4590
4591     S_new<-phi(-(theta_new-alpha_new*0.5)/exp(beta*0.5))
4592     C_new<-phi((theta_new+alpha_new*0.5)*exp(beta*0.5))
4593
4594     s2 <- 1
4595     c2 <- 1
4596
4597 }
4598
4599

```

4600 Diagnostic test accuracy meta-analyses: results

4601 This section reports the results for the diagnostic test meta-analyses. Three models were run:

- 4602 • Bivariate (Reitsma) = standard bivariate meta-analysis assuming perfect reference
- 4603 standard. All published systematic reviews retrieved so far used this model, therefore
- 4604 these were run for comparison with published work.
- 4605 • HSROC perfect = hierarchical summary receiver operating characteristics (HSROC)
- 4606 model assuming perfect reference standard. This model was run for comparison with the
- 4607 adjusted model.
- 4608 • HSROC imperfect = HSROC model assuming imperfect reference standard with
- 4609 conditional independence.

4610 The HSROC model assuming an imperfect reference standard with conditional independence
4611 was included in the main body of the report. The others are included for the purposes of
4612 comparison.

4614 **Table 21C: Pooled results for sensitivity and specificity of CT, MRI, US, VQ, and VQ-
4615 SPECT by three meta-analysis models.**

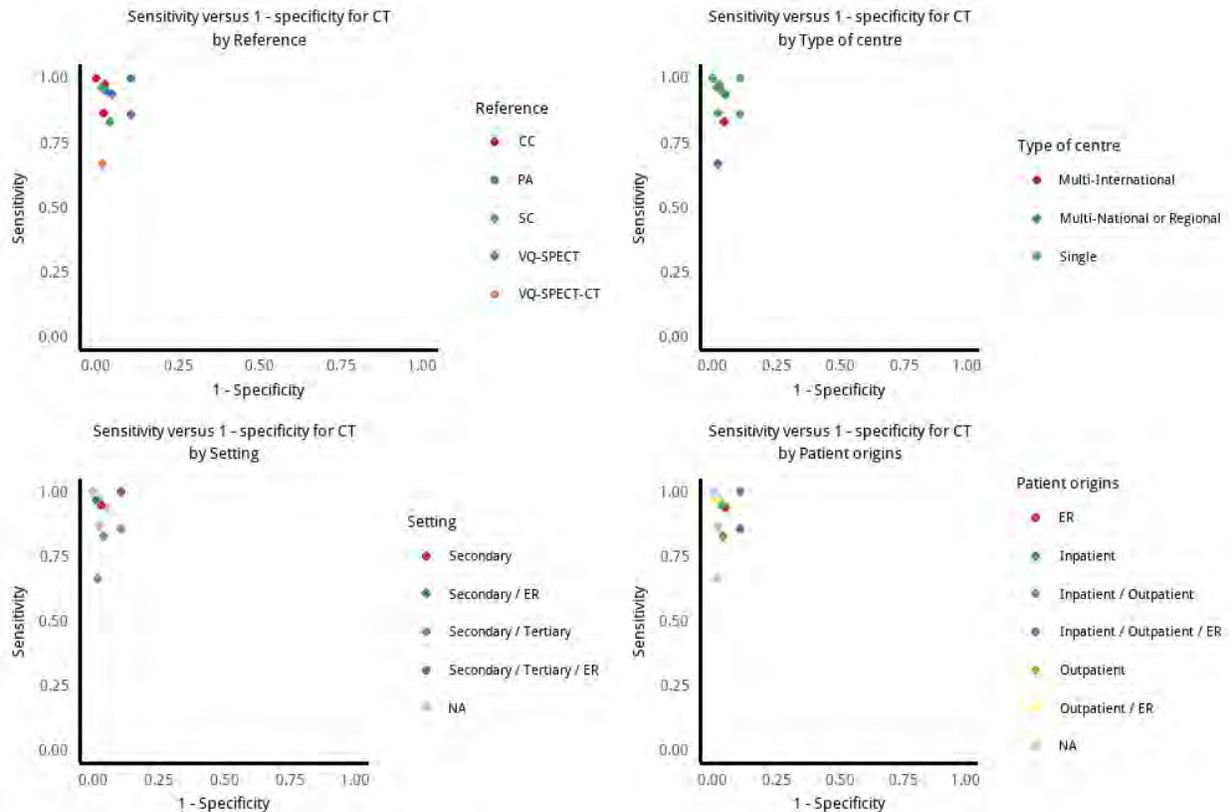
	Analysis	Sensitivity (95% CI/CrI)	Specificity (95% CI/CrI)
CT n = 11	Bivariate (Reitsma)	0.894 (0.828-0.937)	0.944 (0.922-0.960)
	HSROC prefect	0.913 (0.840-0.970)	0.959 (0.925-0.983)

	HSROC imperfect	0.972 (0.916-1.00)	0.987 (0.960-1.00)
MRI n = 14	Bivariate (Reitsma)	0.863 (0.820-0.898)	0.949 (0.909-0.972)
	HSROC prefect	0.902 (0.843-0.958)	0.964 (0.927-0.986)
	HSROC imperfect	0.949 (0.888-0.995)	0.984 (0.950-1.00)
US n = 10	Bivariate (Reitsma)	0.848 (0.791-0.892)	0.790 (0.697-0.860)
	HSROC prefect	0.857 (0.777-0.919)	0.793 (0.683-0.880)
	HSROC imperfect	0.950 (0.865-0.999)	0.888 (0.752-0.986)
VQ n = 10	Bivariate (Reitsma)	0.778 (0.704-0.837)	0.904 (0.853-0.939)
	HSROC prefect	0.789 (0.686-0.870)	0.920 (0.855-0.963)
	HSROC imperfect	0.868 (0.740-0.968)	0.974 (0.915-1.00)
VQ-SPECT n = 12	Bivariate (Reitsma)	0.856 (0.777-0.910)	0.888 (0.780-0.940)
	HSROC prefect	0.906 (0.804-0.974)	0.893 (0.785-0.961)
	HSROC imperfect	0.970 (0.892-1.00)	0.947 (0.849-0.997)

4616
4617

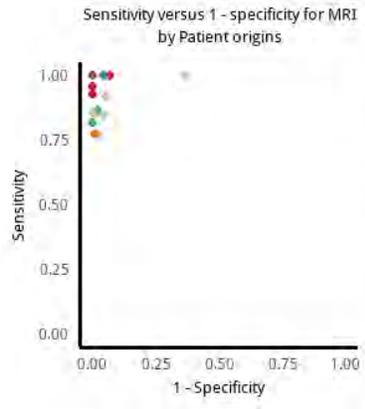
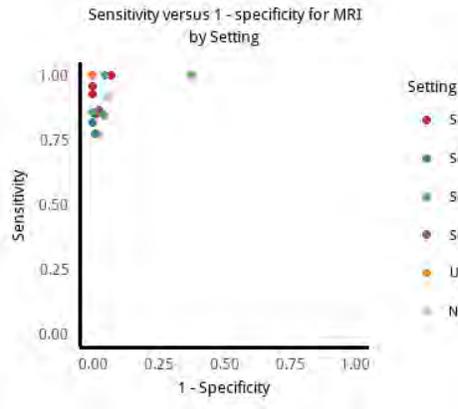
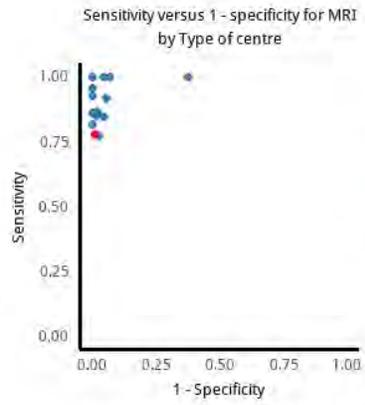
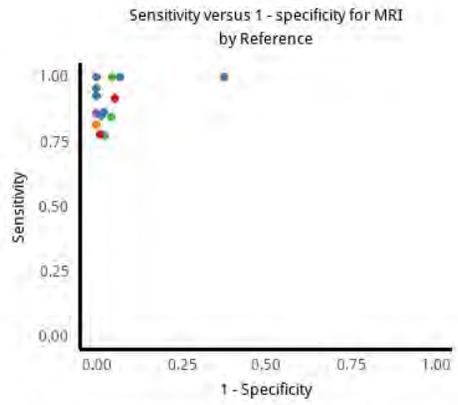
4618 *Diagnostic test meta-analysis: Exploration of heterogeneity*

4619 **Figure 21A Sensitivity versus 1-specificity for covariates for CT**



4620
4621
4622
4623
4624

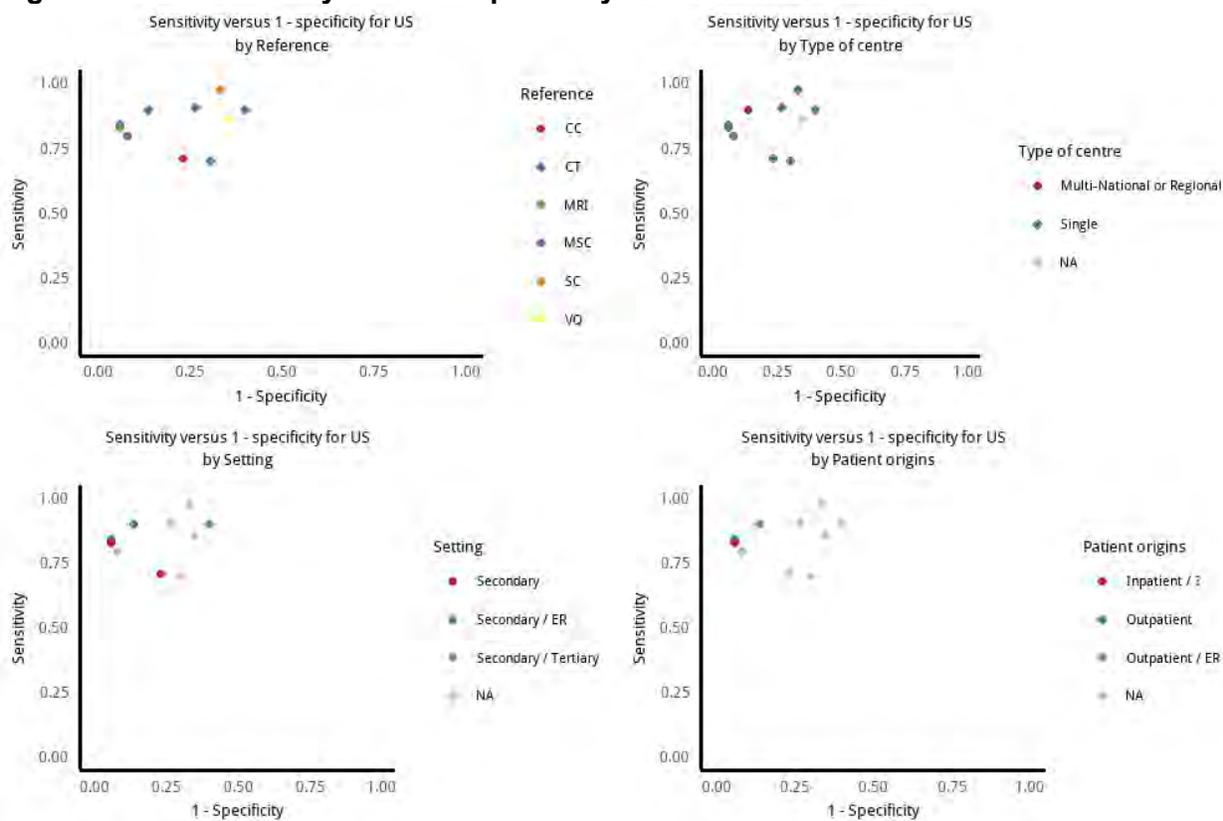
Figure 21B Sensitivity versus 1-specificity for covariates for MRI



4625
4626

DRAFT

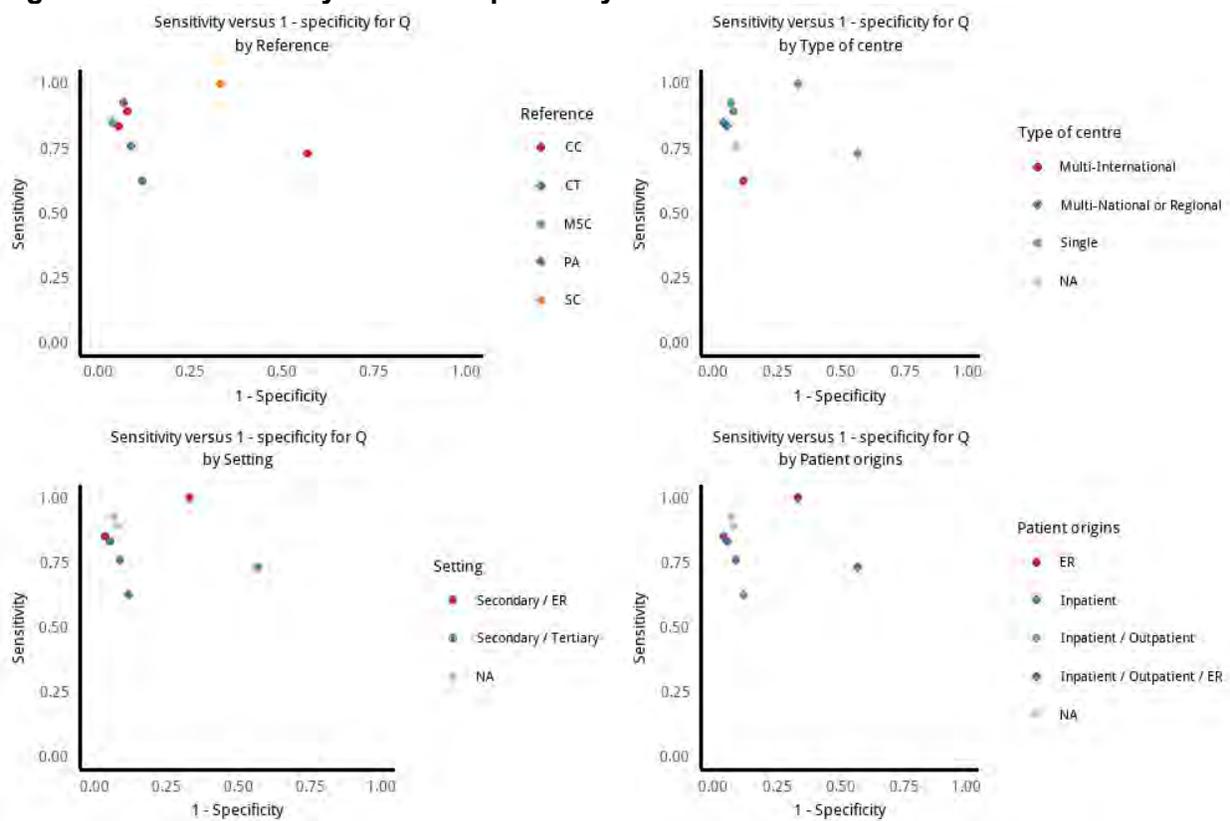
4627 **Figure 21C Sensitivity versus 1-specificity for covariates for US**



4628
4629
4630

DRAFT

4631 **Figure 21D Sensitivity versus 1-specificity for covariates for Q**

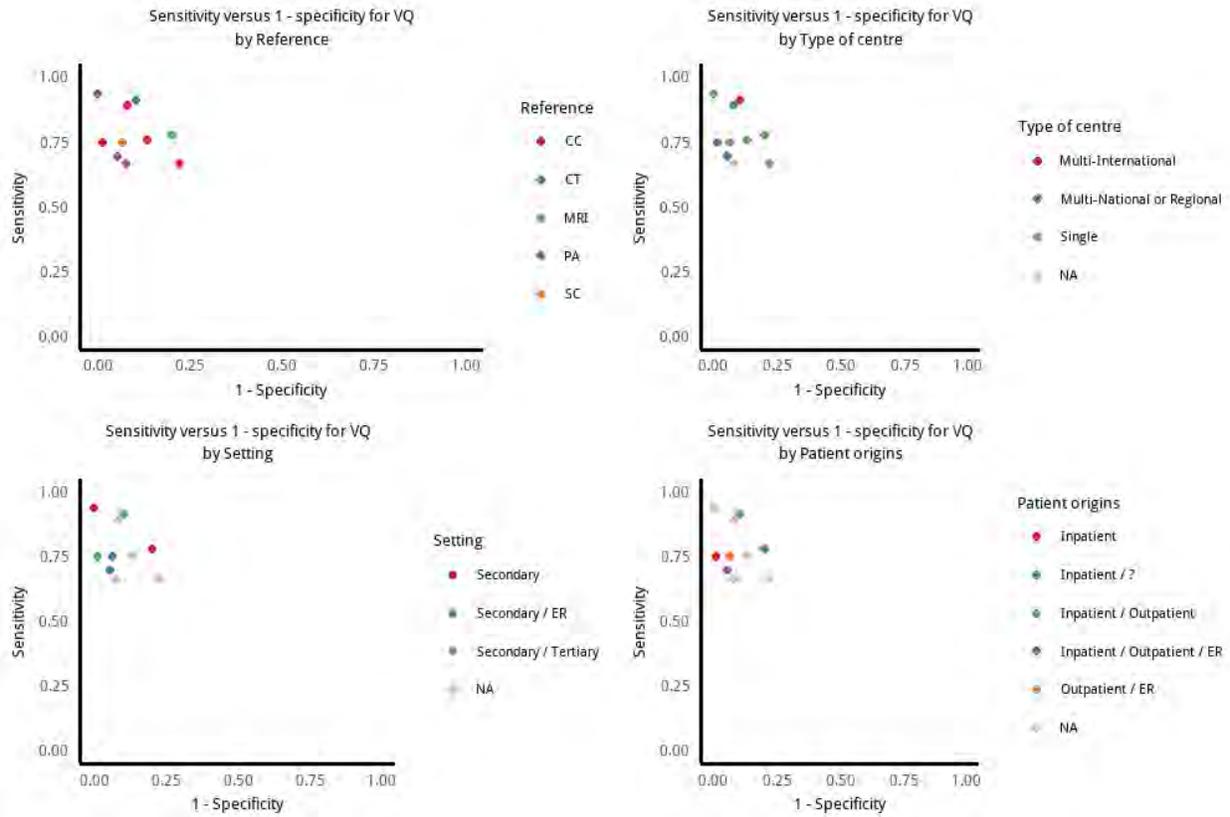


4632
4633

DRAFT

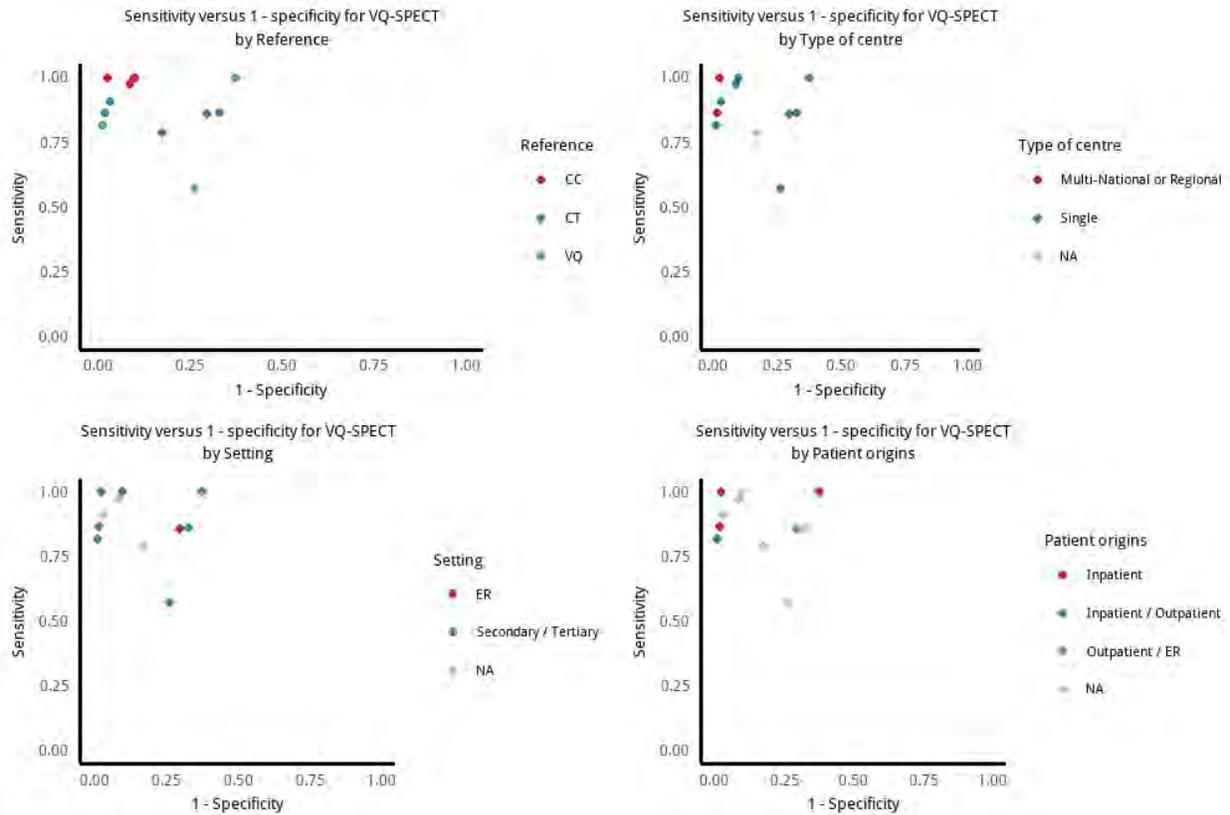
4634

Figure 21E Sensitivity versus 1-specificity for covariates for VQ



4635
4636

Figure 21F Sensitivity versus 1-specificity for covariates for VQ-SPECT



4637

4638 **Question 3: Utilities and safety**

4639 Data management

4640 *Data coding*

4641 Utilities and safety data were coded using the same categories as described for the diagnostic
4642 test meta-analysis.

4643 *Exclusions from pooling*

4644 There were no exclusions from pooling based on comparators (e.g., composites, follow-up
4645 alone).

4646 *Handling of missing data*

4647 No imputation was attempted. Available data were included in summaries.

4648 Meta-analysis of utilities data

4649
4650 No covariates were identified from the available data.

4651
4652 **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 = 14)	Proportion nondiagnostic		0.036 (0.024-0.050)	86.5	89.2 [13] <0.0001
MRI (n = 6)	Proportion nondiagnostic		0.153 (0.033-0.338)	98.4	212.1 [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	0.009 (0.006-0.014)	29.6	25.4 [17] 0.086

4653
4654
4655
4656

DRAFT

4657
4658

Appendix 22: Risk Stratification: Parameters for the Economic Evaluation

Primary studies from SRs	CDR/ Author, Year of Source SR					
	3-Level Wells - assuming moderate goes to D-dimer/ Sanders, 2015 ⁹⁹					
	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 ⁹⁹					
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 ⁹⁹					
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 ³⁵¹					
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
	GESTALT- under 15/ Sanders, 2015 ⁹⁹					
Runyon, 2005	0.69	0.72	99	45	662	1671
Kabrhel, 2009	0.69	0.70	378	167	2197	5190
Kline, 2008	0.71	0.69	392	163	2321	5262
	GESTALT-under 20/ Sanders, 2015 ⁹⁹					
Carrier et al, 2006	0.86	0.38	67	11	219	135
Sanson, 2000	0.91	0.16	115	11	240	47

	LEG US/ Da Costa Rodrigues, 2016 ³²					
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

DRAFT

4659

4660 **Appendix 23: 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 ⁴⁸⁴	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 ²²³	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 ²²⁴	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 ²³⁰	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, 2021 ²²¹	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 ²²²	Canada, TPP	Patients who participated in PIOPED study	Sequence of diagnostic imaging modalities following non-confirmatory VQ findings	3 strategies: VQ+CT VQ+single leg US+CT VQ+serial leg US+CT	Trial-based economic evaluation	• Undefined, noted as long-term	• VQ+serial leg US+CT*
Larcos, 2000 ⁴⁸⁵	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 ²²⁷	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 ²²⁹	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 ²³¹	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 ²²⁸	Switzerland, TPP	Patients suspected of PE presenting in emergency department, based on two prospective studies	Diagnostic pathway	4 strategies: i. Geneva+d-dimer+leg US+CT ii. Geneva+d-dimer+CT iii. Geneva+leg US+CT iv. CT	Model; decision tree	• 3 months	• < 80 years: Geneva+d-dimer+CT • ≥ 80 years:CT [‡]
Van Erkel, 1996 ²²⁶	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 ²²⁵	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 ⁴⁸⁶	US, Societal	59 year old, female suspected of new-onset PE	Ancillary test + diagnostic imaging NOTE: decision to obtain CT already made through risk stratification (not captured in the model)	2 strategies: i. Leg US+CT ii. CT	Model, hybrid model (decision tree [short-term diagnostic] and Markov model [long-term])	• Lifetime	• Leg US+CT

4661
4662
4663
4664
4665
4666

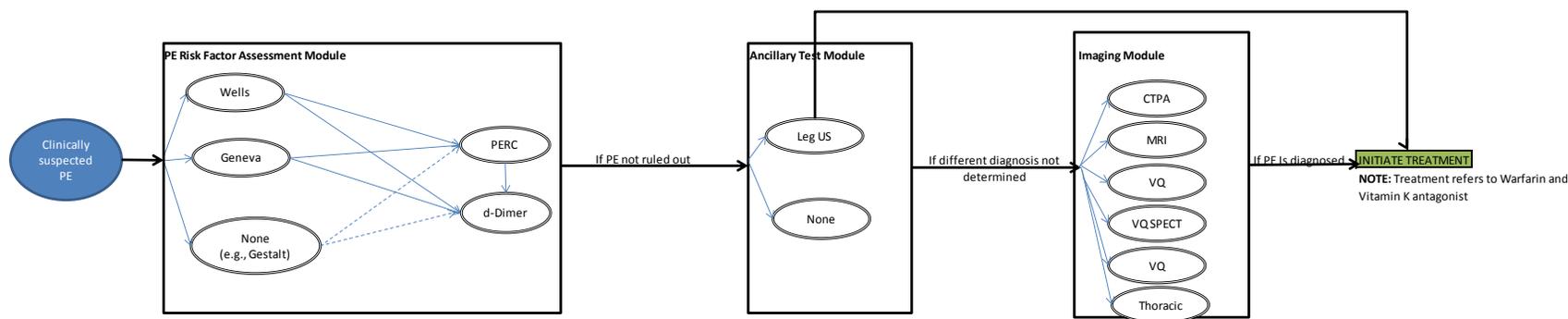
CT = computed tomography pulmonary angiogram; CUS = compression ultrasound; NR = not reported; PA = pulmonary angiography; PE = pulmonary embolism; RCT = randomized controlled trial; TPP = third-party payer; UK = United Kingdom; US = United States of America; VQ = ventilation-perfusion scan

*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.

4667 **Appendix 24: Diagnostic Pathway**



4668
4669
4670

Risk Factor Assessment Module (Risk stratification + Rule Out Test)

RISK STRATIFICATION			
STRATEGY	DFN OF OUTCOME	POSS. OUTCOME (IN TERMS OF CLINICAL MANAGEMENT) [^]	SITUATION IN MODEL (condition test result)
Wells (3-tier model) Outcome: Low, Moderate, High	<u>Low:</u> <2 points <u>Moderate:</u> 2-6 points <u>High:</u> >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	<u>PE Unlikely:</u> 0-4 points <u>PE Likely:</u> >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	<u>Low:</u> 0-3 <u>Intermediate:</u> 4-10 <u>High:</u> >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 low risk	CONTINUE (within)	Patients w/ PE Below threshold Patients w/out PE Below threshold

	can vary. Clinical review identified: <15%, <20% and undefined	CONTINUE (within or NEXT)†	Patients w/ PE Above threshold Patients w/out PE Above threshold
RULE OUT TEST			
PERC Outcome: negative, positive	<u>Negative:</u> No to all items <u>Positive:</u> 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	<u>Negative:</u> d-dimer>500 mcg/L <u>Positive:</u> 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

^ 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

4671

Ancillary Test Module

STRATEGY	DFN OF OUTCOME	POSS. OUTCOME (IN TERMS OF CLINICAL MANAGEMENT) [^]	SITUATION IN MODEL
US Outcome: Positive, Negative	<u>Positive:</u> Either no compression of vein or absence of blood flow (=DVT) <u>Negative:</u> 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

[^] 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) [^]	SITUATION IN MODEL
CT Outcome: Positive, Negative	<u>Positive:</u> Thombus in segmental or larger pulmonary artery <u>Negative:</u> 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	<u>Positive:</u> Partially occlusive intra-luminal filling defect or complete arterial occlusion with termination of the contrast material <u>Negative:</u> 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	<u>High:</u> ≥2 mismatched segmental defects <u>Intermediate†</u> <u>Low:</u> • Nonsegmental perfusion abnormalities; w/ no other perfusion defect in either lung • Perfusion defect smaller than corresponding radiographic lesion • ≥2 matched V/Q 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	PROCEED WITH TXT	Patients w/ PE High Patients w/out PE High
		STOP	Patients w/ PE Low Patients w/out PE Low
VQ SPECT Outcome: negative, positive	<u>Positive:</u> 1 segmental or 2 subsegmental mismatches <u>Negative:</u> 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: <i>negative, positive</i>	<u>Positive:</u> ≥1 wedge-shaped peripheral defect (≥50% of pulmonary segmnet w/out CT image abnormality seen in three orthogonal plane <u>Negative:</u> 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	<u>Positive:</u> One or more typical pleural-based/subpleural hypochoic lesions with or without pleural effusion <u>Negative:</u> Nonspecific subpleural lesions more than 5 mm in size, pure-free pleural effusion,	PROCEED WITH TXT	Patients w/ PE Positive Patients w/out PE Positive
		STOP	Patients w/ PE Negative

normal sonographic findings

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.

DRAFT

4672
4673

Appendix 25: List of 120 Diagnostic Algorithms Considered in the Economic Model

Strategy No	Risk Stratification	Rule Out Test	Ancillary Tests	Diagnostic Imaging
1	Gestalt (<15)	None	None	CT
2	Gestalt (<15)	None	None	MRI
3	Gestalt (<15)	None	None	VQ Planar Scintigraphy
4	Gestalt (<15)	None	None	VQ SPECT
5	Gestalt (<15)	None	Leg US	CT
6	Gestalt (<15)	None	Leg US	MRI
7	Gestalt (<15)	None	Leg US	VQ Planar Scintigraphy
8	Gestalt (<15)	None	Leg US	VQ SPECT
9	Gestalt (<15)	PERC>d-dimer	None	CT
10	Gestalt (<15)	PERC>d-dimer	None	MRI
11	Gestalt (<15)	PERC>d-dimer	None	VQ Planar Scintigraphy
12	Gestalt (<15)	PERC>d-dimer	None	VQ SPECT
13	Gestalt (<15)	PERC>d-dimer	Leg US	CT
14	Gestalt (<15)	PERC>d-dimer	Leg US	MRI
15	Gestalt (<15)	PERC>d-dimer	Leg US	VQ Planar Scintigraphy
16	Gestalt (<15)	PERC>d-dimer	Leg US	VQ SPECT
17	Gestalt (<15)	d-dimer	None	CT
18	Gestalt (<15)	d-dimer	None	MRI
19	Gestalt (<15)	d-dimer	None	VQ Planar Scintigraphy
20	Gestalt (<15)	d-dimer	None	VQ SPECT
21	Gestalt (<15)	d-dimer	Leg US	CT
22	Gestalt (<15)	d-dimer	Leg US	MRI
23	Gestalt (<15)	d-dimer	Leg US	VQ Planar Scintigraphy
24	Gestalt (<15)	d-dimer	Leg US	VQ SPECT
25	Gestalt (<20)	None	None	CT
26	Gestalt (<20)	None	None	MRI
27	Gestalt (<20)	None	None	VQ Planar Scintigraphy
28	Gestalt (<20)	None	None	VQ SPECT
29	Gestalt (<20)	None	Leg US	CT
30	Gestalt (<20)	None	Leg US	MRI
31	Gestalt (<20)	None	Leg US	VQ Planar Scintigraphy
32	Gestalt (<20)	None	Leg US	VQ SPECT
33	Gestalt (<20)	PERC>d-dimer	None	CT
34	Gestalt (<20)	PERC>d-dimer	None	MRI
35	Gestalt (<20)	PERC>d-dimer	None	VQ Planar Scintigraphy
36	Gestalt (<20)	PERC>d-dimer	None	VQ SPECT
37	Gestalt (<20)	PERC>d-dimer	Leg US	CT
38	Gestalt (<20)	PERC>d-dimer	Leg US	MRI

39	Gestalt (<20)	PERC>d-dimer	Leg US	VQ Planar Scintigraphy
40	Gestalt (<20)	PERC>d-dimer	Leg US	VQ SPECT
41	Gestalt (<20)	d-dimer	None	CT
42	Gestalt (<20)	d-dimer	None	MRI
43	Gestalt (<20)	d-dimer	None	VQ Planar Scintigraphy
44	Gestalt (<20)	d-dimer	None	VQ SPECT
45	Gestalt (<20)	d-dimer	Leg US	CT
46	Gestalt (<20)	d-dimer	Leg US	MRI
47	Gestalt (<20)	d-dimer	Leg US	VQ Planar Scintigraphy
48	Gestalt (<20)	d-dimer	Leg US	VQ SPECT
49	Gestalt (none)	None	None	CT
50	Gestalt (none)	None	None	MRI
51	Gestalt (none)	None	None	VQ Planar Scintigraphy
52	Gestalt (none)	None	None	VQ SPECT
53	Gestalt (none)	None	Leg US	CT
54	Gestalt (none)	None	Leg US	MRI
55	Gestalt (none)	None	Leg US	VQ Planar Scintigraphy
56	Gestalt (none)	None	Leg US	VQ SPECT
57	Gestalt (none)	PERC>d-dimer	None	CT
58	Gestalt (none)	PERC>d-dimer	None	MRI
59	Gestalt (none)	PERC>d-dimer	None	VQ Planar Scintigraphy
60	Gestalt (none)	PERC>d-dimer	None	VQ SPECT
61	Gestalt (none)	PERC>d-dimer	Leg US	CT
62	Gestalt (none)	PERC>d-dimer	Leg US	MRI
63	Gestalt (none)	PERC>d-dimer	Leg US	VQ Planar Scintigraphy
64	Gestalt (none)	PERC>d-dimer	Leg US	VQ SPECT
65	Gestalt (none)	d-dimer	None	CT
66	Gestalt (none)	d-dimer	None	MRI
67	Gestalt (none)	d-dimer	None	VQ Planar Scintigraphy
68	Gestalt (none)	d-dimer	None	VQ SPECT
69	Gestalt (none)	d-dimer	Leg US	CT
70	Gestalt (none)	d-dimer	Leg US	MRI
71	Gestalt (none)	d-dimer	Leg US	VQ Planar Scintigraphy
72	Gestalt (none)	d-dimer	Leg US	VQ SPECT
73	Wells (3 criteria)	PERC>d-dimer	None	CT
74	Wells (3 criteria)	PERC>d-dimer	None	MRI
75	Wells (3 criteria)	PERC>d-dimer	None	VQ Planar Scintigraphy
76	Wells (3 criteria)	PERC>d-dimer	None	VQ SPECT
77	Wells (3 criteria)	PERC>d-dimer	Leg US	CT
78	Wells (3 criteria)	PERC>d-dimer	Leg US	MRI
79	Wells (3 criteria)	PERC>d-dimer	Leg US	VQ Planar Scintigraphy
80	Wells (3 criteria)	PERC>d-dimer	Leg US	VQ SPECT
81	Wells (3 criteria)	d-dimer	None	CT

82	Wells (3 criteria)	d-dimer	None	MRI
83	Wells (3 criteria)	d-dimer	None	VQ Planar Scintigraphy
84	Wells (3 criteria)	d-dimer	None	VQ SPECT
85	Wells (3 criteria)	d-dimer	Leg US	CT
86	Wells (3 criteria)	d-dimer	Leg US	MRI
87	Wells (3 criteria)	d-dimer	Leg US	VQ Planar Scintigraphy
88	Wells (3 criteria)	d-dimer	Leg US	VQ SPECT
89	Wells (2-level)	PERC>d-dimer	None	CT
90	Wells (2-level)	PERC>d-dimer	None	MRI
91	Wells (2-level)	PERC>d-dimer	None	VQ Planar Scintigraphy
92	Wells (2-level)	PERC>d-dimer	None	VQ SPECT
93	Wells (2-level)	PERC>d-dimer	Leg US	CT
94	Wells (2-level)	PERC>d-dimer	Leg US	MRI
95	Wells (2-level)	PERC>d-dimer	Leg US	VQ Planar Scintigraphy
96	Wells (2-level)	PERC>d-dimer	Leg US	VQ SPECT
97	Wells (2-level)	d-dimer	None	CT
98	Wells (2-level)	d-dimer	None	MRI
99	Wells (2-level)	d-dimer	None	VQ Planar Scintigraphy
100	Wells (2-level)	d-dimer	None	VQ SPECT
101	Wells (2-level)	d-dimer	Leg US	CT
102	Wells (2-level)	d-dimer	Leg US	MRI
103	Wells (2-level)	d-dimer	Leg US	VQ Planar Scintigraphy
104	Wells (2-level)	d-dimer	Leg US	VQ SPECT
105	Revised Geneva	PERC>d-dimer	None	CT
106	Revised Geneva	PERC>d-dimer	None	MRI
107	Revised Geneva	PERC>d-dimer	None	VQ Planar Scintigraphy
108	Revised Geneva	PERC>d-dimer	None	VQ SPECT
109	Revised Geneva	PERC>d-dimer	Leg US	CT
110	Revised Geneva	PERC>d-dimer	Leg US	MRI
111	Revised Geneva	PERC>d-dimer	Leg US	VQ Planar Scintigraphy
112	Revised Geneva	PERC>d-dimer	Leg US	VQ SPECT
113	Revised Geneva	d-dimer	None	CT
114	Revised Geneva	d-dimer	None	MRI
115	Revised Geneva	d-dimer	None	VQ Planar Scintigraphy
116	Revised Geneva	d-dimer	None	VQ SPECT
117	Revised Geneva	d-dimer	Leg US	CT
118	Revised Geneva	d-dimer	Leg US	MRI
119	Revised Geneva	d-dimer	Leg US	VQ Planar Scintigraphy
120	Revised Geneva	d-dimer	Leg US	VQ SPECT

4674
4675

Lifetime Economic Results of 120 Diagnostic Algorithms

Strategy	Risk Stratification	Rule Out Test	Ancillary Tests	Diagnostic Imaging	Expected		Incremental		
					Costs	Utilities	Cost	Utilities	ICER

105	Revised Geneva	PERC>d-dimer	None	CT	3,966	17.4437	-ref-		
73	Wells (3 criteria)	PERC>d-dimer	None	CT	3,975	17.4461	9	0.0024	3,808
106	Revised Geneva	PERC>d-dimer	None	MRI	4,092	17.4091	117	-0.0370	Dominant
89	Wells (2-level)	PERC>d-dimer	None	CT	4,109	17.4632	134	0.0171	7,839
113	Revised Geneva	d-dimer	None	CT	4,115	17.4620	6	-0.0012	Dominant
74	Wells (3 criteria)	PERC>d-dimer	None	MRI	4,120	17.4088	11	-0.0544	Dominant
81	Wells (3 criteria)	d-dimer	None	CT	4,122	17.4632	12	0.0000	Extended dominance (904,828)
107	Revised Geneva	PERC>d-dimer	None	VQ Planar Scintigraphy	4,159	17.4019	49	-0.0613	Dominant
9	Gestalt (<15)	PERC>d-dimer	None	CT	4,161	17.4675	51	0.0043	11,852
75	Wells (3 criteria)	PERC>d-dimer	None	VQ Planar Scintigraphy	4,194	17.4010	33	-0.0666	Dominant
97	Wells (2-level)	d-dimer	None	CT	4,225	17.4716	64	0.0041	15,707
90	Wells (2-level)	PERC>d-dimer	None	MRI	4,255	17.4276	31	-0.0440	Dominant
17	Gestalt (<15)	d-dimer	None	CT	4,264	17.4737	40	0.0021	18,769
114	Revised Geneva	d-dimer	None	MRI	4,278	17.4244	13	-0.0494	Dominant
82	Wells (3 criteria)	d-dimer	None	MRI	4,294	17.4245	29	-0.0493	Dominant
108	Revised Geneva	PERC>d-dimer	None	VQ SPECT	4,316	17.4171	51	-0.0567	Dominant
76	Wells (3 criteria)	PERC>d-dimer	None	VQ SPECT	4,316	17.4198	52	-0.0539	Dominant
57	Gestalt (none)	PERC>d-dimer	None	CT	4,327	17.4747	62	0.0010	Extended dominance (61,073)
115	Revised Geneva	d-dimer	None	VQ Planar Scintigraphy	4,332	17.4205	68	-0.0533	Dominant
10	Gestalt (<15)	PERC>d-dimer	None	MRI	4,332	17.4295	68	-0.0443	Dominant
83	Wells (3 criteria)	d-dimer	None	VQ Planar Scintigraphy	4,349	17.4207	85	-0.0531	Dominant
91	Wells (2-level)	PERC>d-dimer	None	VQ Planar Scintigraphy	4,349	17.4191	85	-0.0546	Dominant
98	Wells (2-level)	d-dimer	None	MRI	4,369	17.4374	105	-0.0363	Dominant
65	Gestalt (none)	d-dimer	None	CT	4,393	17.4772	129	0.0035	Extended dominance (37,258)
11	Gestalt (<15)	PERC>d-dimer	None	VQ Planar Scintigraphy	4,406	17.4241	142	-0.0496	Dominant
109	Revised Geneva	PERC>d-dimer	Leg US	CT	4,430	17.4622	166	-0.0116	Dominant
77	Wells (3 criteria)	PERC>d-dimer	Leg US	CT	4,445	17.4646	181	-0.0091	Dominant
18	Gestalt (<15)	d-dimer	None	MRI	4,457	17.4346	193	-0.0391	Dominant
33	Gestalt (<20)	PERC>d-dimer	None	CT	4,459	17.4750	195	0.0012	Extended dominance

									(157,490)
58	Gestalt (none)	PERC>d-dimer	None	MRI	4,483	17.4405	219	-0.0332	Dominant
92	Wells (2-level)	PERC>d-dimer	None	VQ SPECT	4,496	17.4365	231	-0.0372	Dominant
41	Gestalt (<20)	d-dimer	None	CT	4,497	17.4772	233	0.0035	Extended dominance (66,566)
99	Wells (2-level)	d-dimer	None	VQ Planar Scintigraphy	4,509	17.4255	245	-0.0482	Dominant
116	Revised Geneva	d-dimer	None	VQ SPECT	4,522	17.4347	257	-0.0390	Dominant
78	Wells (3 criteria)	PERC>d-dimer	Leg US	MRI	4,538	17.4471	274	-0.0266	Dominant
84	Wells (3 criteria)	d-dimer	None	VQ SPECT	4,539	17.4356	275	-0.0381	Dominant
110	Revised Geneva	PERC>d-dimer	Leg US	MRI	4,541	17.4432	277	-0.0305	Dominant
19	Gestalt (<15)	d-dimer	None	VQ Planar Scintigraphy	4,557	17.4278	293	-0.0459	Dominant
66	Gestalt (none)	d-dimer	None	MRI	4,575	17.4411	310	-0.0326	Dominant
59	Gestalt (none)	PERC>d-dimer	None	VQ Planar Scintigraphy	4,581	17.4340	317	-0.0397	Dominant
12	Gestalt (<15)	PERC>d-dimer	None	VQ SPECT	4,582	17.4402	317	-0.0335	Dominant
111	Revised Geneva	PERC>d-dimer	Leg US	VQ Planar Scintigraphy	4,612	17.4394	348	-0.0343	Dominant
1	Gestalt (<15)	None	None	CT	4,633	17.4792	369	0.0055	Extended dominance (66,874)
25	Gestalt (<20)	None	None	CT					
49	Gestalt (none)	None	None	CT					
79	Wells (3 criteria)	PERC>d-dimer	Leg US	VQ Planar Scintigraphy	4,643	17.4408	379	-0.0329	Dominant
34	Gestalt (<20)	PERC>d-dimer	None	MRI	4,650	17.4390	386	-0.0347	Dominant
93	Wells (2-level)	PERC>d-dimer	Leg US	CT	4,661	17.4822	397	0.0085	Extended dominance (46,811)
117	Revised Geneva	d-dimer	Leg US	CT	4,665	17.4810	401	0.0073	Extended dominance (55,061)
85	Wells (3 criteria)	d-dimer	Leg US	CT	4,676	17.4822	412	0.0085	Extended dominance (48,526)
100	Wells (2-level)	d-dimer	None	VQ SPECT	4,676	17.4439	412	-0.0298	Dominant
42	Gestalt (<20)	d-dimer	None	MRI	4,678	17.4425	414	-0.0313	Dominant
112	Revised Geneva	PERC>d-dimer	Leg US	VQ SPECT	4,720	17.4481	456	-0.0256	Dominant
67	Gestalt (none)	d-dimer	None	VQ Planar Scintigraphy	4,723	17.4312	459	-0.0425	Dominant
20	Gestalt (<15)	d-dimer	None	VQ SPECT	4,730	17.4460	466	-0.0277	Dominant
80	Wells (3 criteria)	PERC>d-dimer	Leg US	VQ SPECT	4,733	17.4507	468	-0.0231	Dominant
13	Gestalt (<15)	PERC>d-dimer	Leg US	CT	4,744	17.4866	480	0.0129	Extended dominance (37,157)

94	Wells (2-level)	PERC>d-dimer	Leg US	MRI	4,772	17.4641	508	-0.0096	Dominant
118	Revised Geneva	d-dimer	Leg US	MRI	4,786	17.4622	522	-0.0115	Dominant
86	Wells (3 criteria)	d-dimer	Leg US	MRI	4,798	17.4633	534	-0.0104	Dominant
2	Gestalt (<15)	None	None	MRI	4,799	17.4470	535	-0.0267	Dominant
60	Gestalt (none)	PERC>d-dimer	None	VQ SPECT	4,823	17.4469	559	-0.0268	Dominant
50	Gestalt (none)	None	None	MRI	4,823	17.4451	559	-0.0287	Dominant
35	Gestalt (<20)	PERC>d-dimer	None	VQ Planar Scintigraphy	4,833	17.4272	568	-0.0465	Dominant
101	Wells (2-level)	d-dimer	Leg US	CT	4,844	17.4908	579	0.0171	Extended dominance (33,937)
43	Gestalt (<20)	d-dimer	None	VQ Planar Scintigraphy	4,868	17.4304	603	-0.0433	Dominant
14	Gestalt (<15)	PERC>d-dimer	Leg US	MRI	4,871	17.4677	606	-0.0060	Dominant
119	Revised Geneva	d-dimer	Leg US	VQ Planar Scintigraphy	4,891	17.4571	627	-0.0166	Dominant
95	Wells (2-level)	PERC>d-dimer	Leg US	VQ Planar Scintigraphy	4,892	17.4580	627	-0.0157	Dominant
87	Wells (3 criteria)	d-dimer	Leg US	VQ Planar Scintigraphy	4,898	17.4587	634	-0.0151	Dominant
68	Gestalt (none)	d-dimer	None	VQ SPECT	4,902	17.4496	638	-0.0242	Dominant
21	Gestalt (<15)	d-dimer	Leg US	CT	4,908	17.4929	644	0.0192	33,499
26	Gestalt (<20)	None	None	MRI	4,912	17.4379	3	-0.0550	Dominant
102	Wells (2-level)	d-dimer	Leg US	MRI	4,965	17.4726	56	-0.0203	Dominant
27	Gestalt (<20)	None	None	VQ Planar Scintigraphy	4,965	17.4379	57	-0.0551	Dominant
15	Gestalt (<15)	PERC>d-dimer	Leg US	VQ Planar Scintigraphy	4,985	17.4625	77	-0.0305	Dominant
36	Gestalt (<20)	PERC>d-dimer	None	VQ SPECT	5,012	17.4471	104	-0.0459	Dominant
61	Gestalt (none)	PERC>d-dimer	Leg US	CT	5,013	17.4940	105	0.0010	Extended dominance (102,813)
3	Gestalt (<15)	None	None	VQ Planar Scintigraphy	5,016	17.4343	108	-0.0586	Dominant
120	Revised Geneva	d-dimer	Leg US	VQ SPECT	5,022	17.4663	114	-0.0266	Dominant
96	Wells (2-level)	PERC>d-dimer	Leg US	VQ SPECT	5,024	17.4674	115	-0.0256	Dominant
88	Wells (3 criteria)	d-dimer	Leg US	VQ SPECT	5,030	17.4676	122	-0.0254	Dominant
44	Gestalt (<20)	d-dimer	None	VQ SPECT	5,060	17.4493	151	-0.0436	Dominant
51	Gestalt (none)	None	None	VQ Planar Scintigraphy	5,060	17.4312	152	-0.0617	Dominant
22	Gestalt (<15)	d-dimer	Leg US	MRI	5,063	17.4729	155	-0.0201	Dominant
103	Wells (2-level)	d-dimer	Leg US	VQ Planar Scintigraphy	5,076	17.4678	168	-0.0251	Dominant
69	Gestalt (none)	d-dimer	Leg US	CT	5,120	17.4965	211	0.0035	60,193
62	Gestalt	PERC>d-	Leg US	MRI	5,124	17.4771	4	-0.0193	Dominant

	(none)	dimer							
16	Gestalt (<15)	PERC>d-dimer	Leg US	VQ SPECT	5,125	17.4718	6	-0.0247	Dominant
23	Gestalt (<15)	d-dimer	Leg US	VQ Planar Scintigraphy	5,166	17.4691	46	-0.0273	Dominant
37	Gestalt (<20)	PERC>d-dimer	Leg US	CT	5,229	17.4941	109	-0.0023	Dominant
104	Wells (2-level)	d-dimer	Leg US	VQ SPECT	5,237	17.4760	118	-0.0205	Dominant
52	Gestalt (none)	None	None	VQ SPECT	5,256	17.4512	137	-0.0453	Dominant
4	Gestalt (<15)	None	None	VQ SPECT	5,262	17.4511	142	-0.0454	Dominant
63	Gestalt (none)	PERC>d-dimer	Leg US	VQ Planar Scintigraphy	5,265	17.4713	145	-0.0252	Dominant
70	Gestalt (none)	d-dimer	Leg US	MRI	5,267	17.4778	148	-0.0187	Dominant
28	Gestalt (<20)	None	None	VQ SPECT	5,271	17.4509	152	-0.0456	Dominant
45	Gestalt (<20)	d-dimer	Leg US	CT	5,289	17.4964	170	0.0000	Dominant
24	Gestalt (<15)	d-dimer	Leg US	VQ SPECT	5,333	17.4779	213	-0.0186	Dominant
38	Gestalt (<20)	PERC>d-dimer	Leg US	MRI	5,421	17.4736	302	-0.0228	Dominant
46	Gestalt (<20)	d-dimer	Leg US	MRI	5,439	17.4783	319	-0.0181	Dominant
71	Gestalt (none)	d-dimer	Leg US	VQ Planar Scintigraphy	5,454	17.4704	334	-0.0261	Dominant
64	Gestalt (none)	PERC>d-dimer	Leg US	VQ SPECT	5,485	17.4786	366	-0.0179	Dominant
29	Gestalt (<20)	None	Leg US	CT	5,512	17.4985	393	0.0020	196,225
53	Gestalt (none)	None	Leg US	CT	5,512	17.4985			
5	Gestalt (<15)	None	Leg US	CT	5,512	17.4985			
39	Gestalt (<20)	PERC>d-dimer	Leg US	VQ Planar Scintigraphy	5,581	17.4683	69	-0.0302	Dominant
72	Gestalt (none)	d-dimer	Leg US	VQ SPECT	5,587	17.4814	6	0.0132	Dominant
47	Gestalt (<20)	d-dimer	Leg US	VQ Planar Scintigraphy	5,626	17.4716	39	-0.0098	Dominant
54	Gestalt (none)	None	Leg US	MRI	5,698	17.4793	72	0.0077	Dominant
30	Gestalt (<20)	None	Leg US	MRI	5,720	17.4783	22	-0.0010	Dominant
40	Gestalt (<20)	PERC>d-dimer	Leg US	VQ SPECT	5,730	17.4791	10	0.0007	Dominant
6	Gestalt (<15)	None	Leg US	MRI	5,755	17.4767	25	-0.0023	Dominant
48	Gestalt (<20)	d-dimer	Leg US	VQ SPECT	5,805	17.4813	50	0.0046	Dominant
31	Gestalt (<20)	None	Leg US	VQ Planar Scintigraphy	5,875	17.4740	69	-0.0073	Dominant
55	Gestalt (none)	None	Leg US	VQ Planar Scintigraphy	5,918	17.4722	44	-0.0017	Dominant
7	Gestalt (<15)	None	Leg US	VQ Planar Scintigraphy	5,929	17.4718	10	-0.0004	Dominant
8	Gestalt (<15)	None	Leg US	VQ SPECT	6,074	17.4834	145	0.0115	Dominant
32	Gestalt (<20)	None	Leg US	VQ SPECT	6,088	17.4832	14	-0.0002	Dominant
56	Gestalt (none)	None	Leg US	VQ SPECT	6,094	17.4831	6	-0.0001	Dominant

Appendix 26: Additional Sensitivity Analysis Results

Strategy				ICUR (cost/QALYs)
Risk stratification		Ancillary Tests	Dx Imaging	
Discount rate (5%)				
Revised Geneva	PERC>d-dimer	None	CT	-ref-
Wells: 3 tier	PERC>d-dimer	None	CT	5,792
Wells: 2 tier	PERC>d-dimer	None	CT	11,936
Gestalt: <15	PERC>d-dimer	None	CT	18,068
Wells: 2 tier	d-dimer	None	CT	23,992
Gestalt: <15	d-dimer	None	CT	28,670
Gestalt: <15	d-dimer	Leg US	CT	51,481
Gestalt (pooled)	d-dimer	Leg US	CT	93,025
Gestalt	None	Leg US	CT	313,789
Undiscounted (0%)				
Revised Geneva	PERC>d-dimer	None	CT	-ref-
Wells: 3 tier	PERC>d-dimer	None	CT	3,097
Wells: 2 tier	PERC>d-dimer	None	CT	6,345
Gestalt: <15	PERC>d-dimer	None	CT	9,574
Wells: 2 tier	d-dimer	None	CT	12,666
Gestalt: <15	d-dimer	None	CT	15,136
Gestalt: <15	d-dimer	Leg US	CT	26,863
Gestalt (pooled)	d-dimer	Leg US	CT	48,218
Gestalt	None	Leg US	CT	155,119
VQ, VQ SPECT, MRI (lower proportion of non-diagnostic finding) ¹				
Revised Geneva	PERC>d-dimer	None	CT	-ref-
Wells: 3 tier	PERC>d-dimer	None	CT	3,808
Wells: 2 tier	PERC>d-dimer	None	CT	7,839
Gestalt: <15	PERC>d-dimer	None	CT	11,852
Wells: 2 tier	d-dimer	None	CT	15,707
Gestalt: <15	d-dimer	None	CT	18,769
Gestalt: <15	d-dimer	Leg US	CT	33,499
Gestalt (pooled)	d-dimer	Leg US	CT	60,193
Gestalt	None	Leg US	CT	196,225
Different diagnostic test accuracy data for Gestalt <20% (sensitivity=0.86; specificity=0.38)				
Revised Geneva	PERC>d-dimer	None	CT	-ref-
Wells: 3 tier	PERC>d-dimer	None	CT	3,843
Wells: 2 tier	PERC>d-dimer	None	CT	8,007
Gestalt: <15	PERC>d-dimer	None	CT	12,154
Wells: 2 tier	d-dimer	None	CT	16,131
Gestalt: <15	d-dimer	None	CT	19,309
Gestalt: <15	d-dimer	Leg US	CT	34,420
Gestalt (pooled)	d-dimer	Leg US	CT	62,150
Gestalt	None	Leg US	CT	204,016
Management of non-Dx CT findings: none receive treatment				
Revised Geneva	PERC>d-dimer	None	CT	-ref-
Wells: 3 tier	PERC>d-dimer	None	CT	3,835
Wells: 2 tier	PERC>d-dimer	None	CT	7,995
Gestalt: <15	PERC>d-dimer	None	CT	12,138
Wells: 2 tier	d-dimer	None	CT	16,177
Gestalt: <15	d-dimer	None	CT	19,271
Gestalt: <15	PERC>d-dimer	Leg US	CT	19,776
Wells: 2 tier	d-dimer	Leg US	CT	24,565
Gestalt: <15	d-dimer	Leg US	CT	30,786
Gestalt (pooled)	d-dimer	Leg US	CT	61,869
Gestalt	None	Leg US	CT	202,718
Management of non-Dx CT findings: Provide Leg US to confirm diagnosis (applicable to strategies that do not include Leg US)				
Revised Geneva	PERC>d-dimer	None	CT	-ref-

Wells: 3 tier	PERC>d-dimer	None	CT	3,757
Wells: 2 tier	PERC>d-dimer	None	CT	7,906
Gestalt: <15	PERC>d-dimer	None	CT	12,016
Wells: 2 tier	d-dimer	None	CT	15,913
Gestalt: <15	d-dimer	None	CT	19,093
Gestalt: <15	d-dimer	Leg US	CT	33,562
Gestalt (pooled)	d-dimer	Leg US	CT	61,869
Gestalt	None	Leg US	CT	203,869
Anticoagulation treatment (i.e., apixaban)				
Revised Geneva	PERC>d-dimer	None	CT	-ref-
Wells: 3 tier	PERC>d-dimer	None	CT	2,229
Wells: 2 tier	PERC>d-dimer	None	CT	5,389
Gestalt: <15	PERC>d-dimer	None	CT	9,402
Wells: 2 tier	d-dimer	None	CT	12,839
Gestalt: <15	d-dimer	None	CT	15,531
Gestalt: <15	d-dimer	Leg US	CT	28,125
Gestalt (pooled)	d-dimer	Leg US	CT	51,874
Gestalt	None	Leg US	CT	164,872
Utilities from original Markov model ²³⁶				
Revised Geneva	PERC>d-dimer	None	CT	-ref-
Wells: 3 tier	PERC>d-dimer	None	CT	3,206
Wells: 2 tier	PERC>d-dimer	None	CT	6,619
Gestalt: <15	PERC>d-dimer	None	CT	10,035
Wells: 2 tier	d-dimer	None	CT	13,321
Gestalt: <15	d-dimer	None	CT	15,972
Gestalt: <15	d-dimer	Leg US	CT	28,409
Gestalt (pooled)	d-dimer	Leg US	CT	52,268
Gestalt	None	Leg US	CT	184,525

4678
4679
4680

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

4681 **Appendix 27: CADTH Survey Questions**

A. Demographics and Clinical Setting

4682
4683
4684
4685
4686
4687
4688
4689
4690
4691
4692
4693
4694
4695
4696
4697
4698

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

4699
4700
4701
4702

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.).

[Empty text box for response to Question 2]

4703

B. Diagnostic Strategy

4704
4705
4706
4707
4708

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).

[Empty text box for response to Question 3]

4709
4710
4711
4712
4713

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

[Empty text box for response to Question 4]

4714
4715
4716
4717
4718
4719
4720

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

4721

4722 6. Do you currently use any of the following risk stratification tools when diagnosing PE? Please
4723 select all that apply.

4724 Pulmonary Embolism Rule-Out Criteria

4725 Wells' Criteria for Pulmonary Embolism

4726 Geneva Score

4727 None of the above

4728 Other (please describe):

4729 7. Do you have ready access (i.e., equipment is available in your centre) to the following rule-out or
4730 ancillary tests when diagnosing PE? Please select all that apply.

4731 Arterial blood gas

4732 Capnography

4733 Chest X-ray

4734 D-dimer testing

4735 Echocardiography

4736 Electrocardiography

4737 Leg compression ultrasound

4738 None of the above

4739 Other (please describe):

4741 8. Do you have ready access (i.e., equipment is available in your centre) to the following imaging
4742 modalities when diagnosing PE? Please select all that apply.

4743 Ventilation/Perfusion scintigraphy

4744 Ventilation/Perfusion SPECT (single-photon emission computed tomography)

4745 Ventilation/Perfusion SPECT-CT

4746 CT (computerized tomography)

4747 Thoracic ultrasound

4748 MRI (magnetic resonance imaging)

4749 PET (positron emission tomography) modalities

4750 None of the above

4751 Other (please describe):

4753 9. If you had different or more resources available would that change your strategy for diagnosing
4754 PE? What additional resources would you use and how would your approach to diagnosing PE
4755 change?
4756

4757 10. What are the main challenges you face in diagnosing PE? For example, please describe any
4758 issues around clinical capacity and expertise to perform testing, available machinery being used for
4759 other purposes, time constraints, or any other challenges you might face.
4760

4761

4762 11. Do you currently transport patients out of your centre to diagnose suspected PE?

4763 Yes (please proceed to question 12)

4764 No (please proceed to question 13)

4765
4766 12. Could you please tell us more about transporting patients out of your centre so that a PE diagnosis
4767 can be made? For example, how far do you send them, how are costs covered, what patient
4768 characteristics might warrant travel, and any other related issues.

4769

C. Permission to Contact and CADTH Environmental Scan Use

4770

4771 13. Would you be willing to be consulted further on this topic, either through an informal phone call or
4772 by email?

4773 Yes

4774 No

4775

4776

DRAFT

4777 **Appendix 28: 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 ²⁸³	London, Ontario	<i>"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)."</i> (pg. 394)	Survey, retrospective chart review	PE	2 academic, tertiary care ED
Aranson, 2007 ²⁸⁴	Ottawa, Ontario	<i>"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."</i> (pg. 195)	Retrospective chart review	VTE	Academic, tertiary care hospital (ED and inpatient)
Ballantine, 2012 ²⁸⁵	Exeter, Ontario	<i>"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)."</i> (pg. 18)	Retrospective chart review	PE	Rural ED
Chen, 2015 ²⁸⁶	Toronto, Ontario	<i>"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."</i> (pg. 222)	Retrospective chart review, review of physician characteristics	PE	Academic, tertiary care ED
Ingber, 2014 ²⁸⁷	Ontario	<i>"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."</i> (pg. 54)	Retrospective chart review	VTE	Academic, tertiary care ED
Le Roux, 2015 ²⁸⁸	Canada (un-specified)	<i>"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 V/Q SPECT. The aim of this study was, therefore, to assess these practices in nuclear medicine centers."</i> (pg. 1213)	Survey	PE	48 nuclear medicine departments
Smith, 2008 ³⁴	Hamilton,	<i>"Our objectives were to measure the documentation rate of</i>	Retrospective chart	VTE	Academic,

	Ontario	<i>PTP for ED patients on whom a SimpliRED D-dimer was performed for suspected venous thromboembolism (VTE) and to determine if the clinical management decisions by the clinicians were in keeping with current recommendations.” (pg. 520)</i>	review		tertiary care centre
Southern, 2014 ²⁸⁹	pan-Canadian	<i>“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)</i>	Surveys, interviews, GIS mapping	VTE	658 acute care hospitals across 10 provinces and 3 territories
Spencer Netto, 2012 ²⁹⁰	Toronto, Ontario	<i>“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)</i>	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; V/Q = ventilation/perfusion; VTE = venous thromboembolism

4778
4779

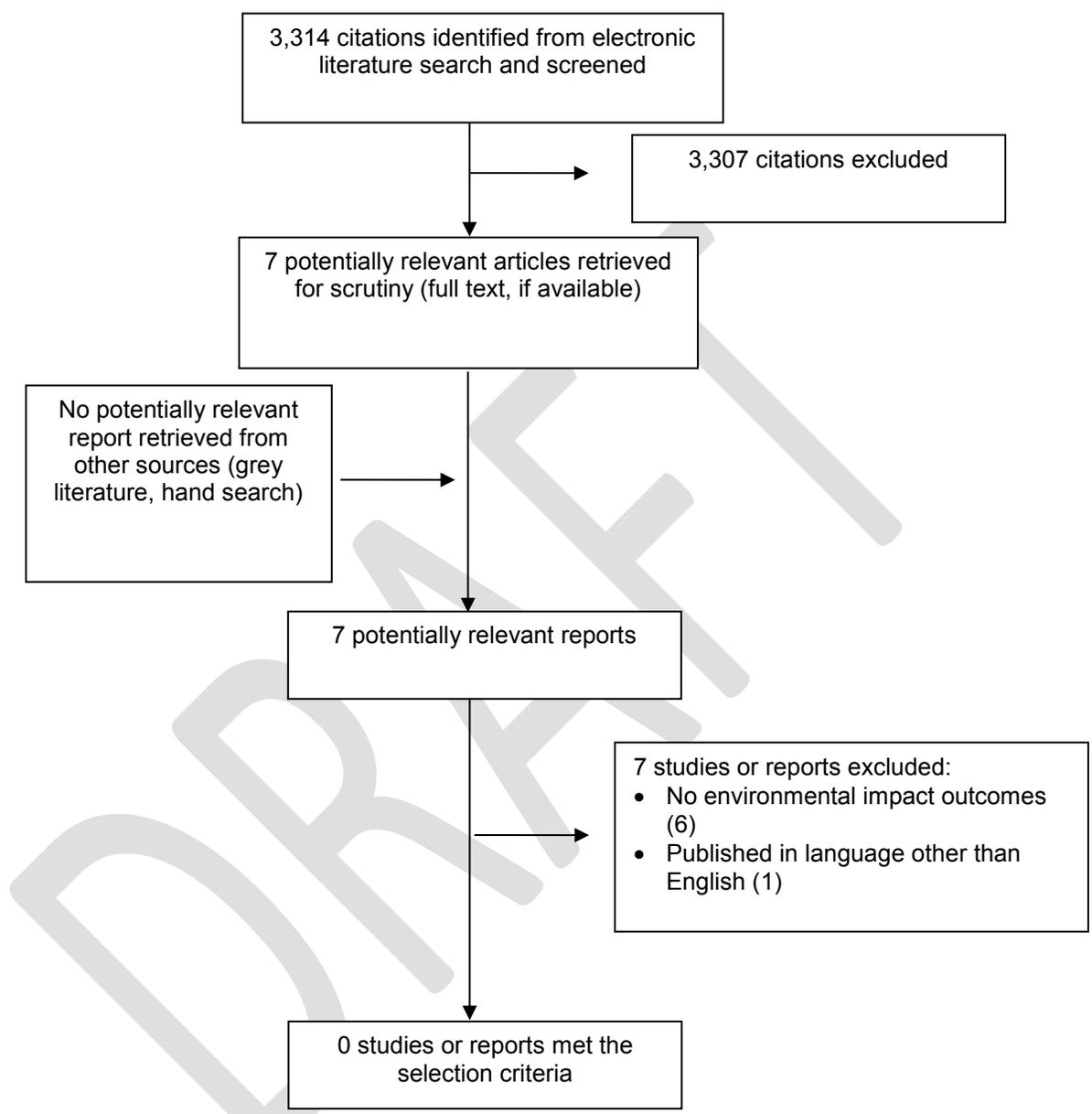
4780 **Appendix 29: Survey Respondents – Self Identified Description**

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

4781
4782
4783
4784

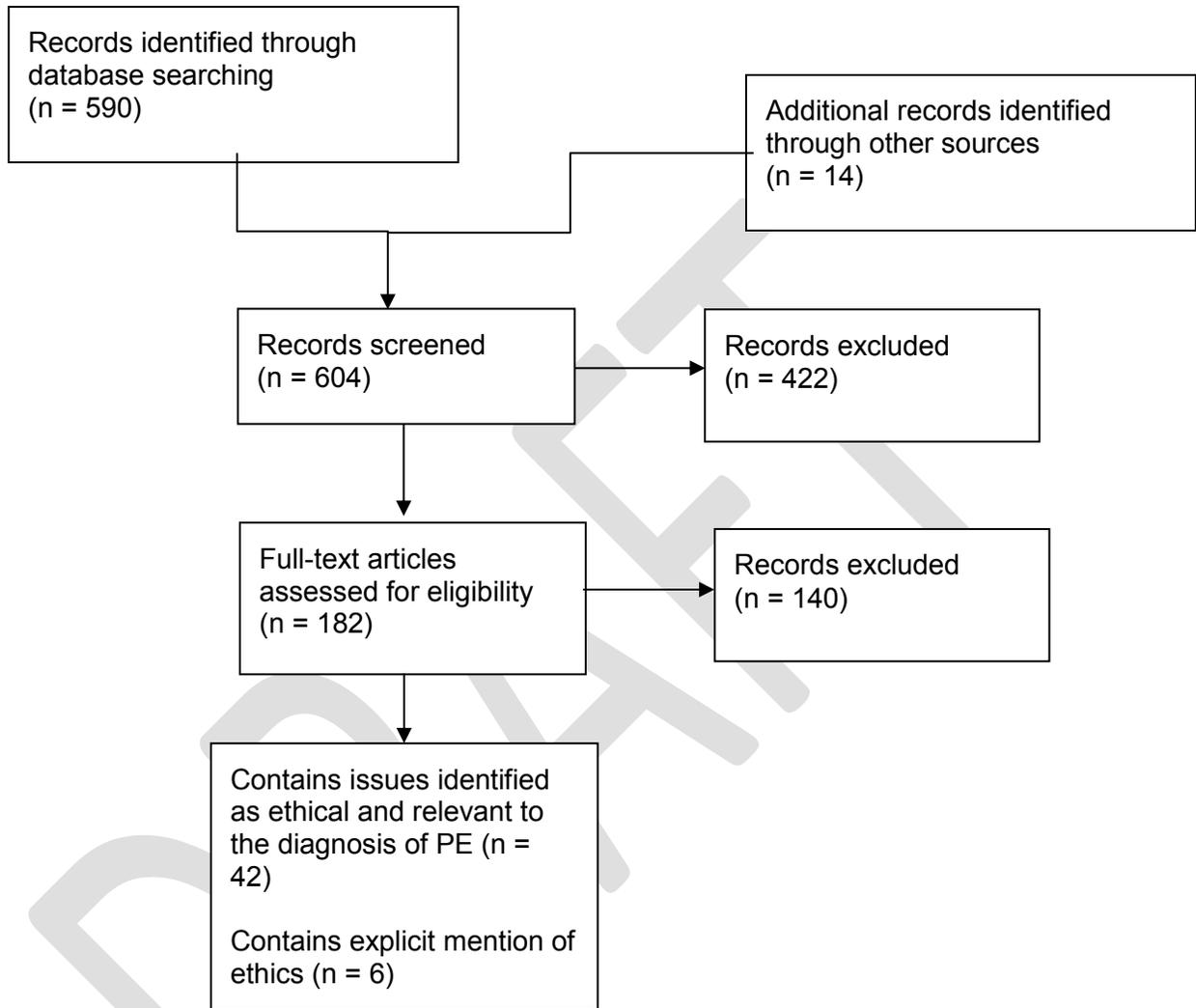
4785 **Appendix 30: Selection of Studies on Environmental Impact**

4786
4787
4788
4789
4790



4791 **Appendix 31: Selection of Studies on Ethics Analysis**

4792
4793
4794
4795
4796
4797
4798
4799
4800
4801
4802
4803
4804
4805
4806
4807
4808
4809
4810
4811
4812
4813
4814
4815
4816
4817
4818
4819
4820
4821
4822
4823
4824
4825
4826
4827



DRAFT