CDI QUALITY INSTITUTE

Provider Led Entity

CDI Quality Institute PLE
Pulmonary Embolism AUC
2021 Update

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Appropriateness of advanced imaging procedures* in patients with the following suspected or known pulmonary embolism presentations:

*including CT pulmonary angiography (CTPA), CT, CT venography (CTV), MR angiography (MRA), MRI, MR venography (MRV), Ventilation/perfusion (V/Q) scan, and Perfusion (Q) scan

Abbreviation list:

AAFP	American Academy of Family Physicians
ACEP	American College of Emergency Physicians
ACP	American College of Physicians
ACR	American College of Radiology
AHA	American Heart Association
ASH	American Society of Hematology
AUC	Appropriate Use Criteria
BTS	British Thoracic Society
CT	Computed tomography
CTA	CT angiography
CTEPH	Chronic thromboembolic pulmonary hypertension
CTPA	Computed tomography pulmonary angiography
CTS	Canadian Thoracic Society
CTV	Computed tomography venography
DVT	Deep vein thrombosis
ERS	European Respiratory Society
ESC	European Society of Cardiology
ESVS	European Society for Vascular Surgery
IPAH	Idiopathic pulmonary arterial hypertension
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
MRV	Magnetic resonance venography
NICE	National Institute for Health and Care Excellence
PE	Pulmonary embolism / embolus
PERC	Pulmonary embolism rule-out criteria
PLE	Provider Led Entity
SEPAR	Spanish Society of Pneumology and Thoracic Surgery
SPECT	Single-photon emission computed tomography
THANZ	Thrombosis and Haemostasis Society of Australia and New Zealand
V/Q	Ventilation/perfusion
VTE	Venous thromboembolism

Appropriate Use Criteria: How to Use this Document

The CDI Quality Institute follows the recommendation framework defined by the Appraisal of Guidelines for Research & Evaluation (AGREE II), AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews) and a modified version of the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) to evaluate the strength of recommendations concerning advanced imaging. Considerations used to determine a recommendation are listed below.

Primary recommendation (green): A strong recommendation for initial imaging for this presentation; there is confidence that the desirable effects of imaging outweigh its undesirable effects.

Alternative recommendation (yellow): A conditional recommendation for imaging; the desirable effects of imaging likely outweigh its undesirable effects, although some uncertainty may exist. The individual patient's circumstances, preferences, and values should be considered on a case-by-case basis. This may include: contraindication to the primary recommendation, specific clinical circumstances that require use of the alternative recommendation, or the primary recommendation has results that are inconclusive or incongruent with the patient's clinical diagnosis. Case-by-case indications to consider have been noted in brackets when appropriate.

Recommendation against imaging (red): The undesirable effects of imaging outweigh any desirable effects. Additionally, the recommendation may be impractical or not feasible in the targeted population and/or practice setting(s).

Suspected Pulmonary Embolism AUC Summary:

- A validated clinical prediction rule should initially be used to estimate pretest probability or clinical suspicion of patients with a suspected PE or DVT.
  If clinical suspicion of PE is low, the Pulmonary Embolism Rule-Out Criteria (PERC) should be applied to help determine whether any further investigations for PE are needed:
  - In patients who meet all of the PERC, a diagnosis of PE can be excluded without need for D-dimer or advanced imaging.
  - In patients who do not meet all of the PERC, a high-sensitivity D-dimer can determine need for advanced imaging. An elevated (positive) D-dimer indicates that imaging should be obtained.

  If clinical suspicion of PE is intermediate, a high-sensitivity D-dimer can determine need for advanced imaging. An elevated (positive) D-dimer indicates that imaging should be obtained.
  If clinical suspicion of PE is high, imaging should be obtained.
- When advanced imaging is indicated, **CT pulmonary angiography (CTPA),** or optimized **CT chest with IV contrast**, is typically the procedure of choice.
- **Ventilation-Perfusion (V/Q) scanning** can also be utilized for imaging suspected PE, particularly when there is contraindication to CTPA or when CTPA is not available. However, there are concerns about applicability and availability in the outpatient setting. It is indicated as the initial imaging modality for suspected chronic thromboembolic pulmonary hypertension (CTEPH).
- Some guidelines note that **Pulmonary MR angiography** is not recommended for ruling out PE, and there are concerns about its applicability, expertise, and availability in an outpatient setting. It may be acceptable only when patient unable to receive CT contrast or when CTPA/CT is indeterminate.
- If deep vein thrombosis of the lower extremities is suspected and expertise is available, **ultrasound** should be utilized. When ultrasound expertise is not available, **CT venography** or **MR venography** can be useful.

Association of pulmonary embolism and COVID-19:

Patients with COVID-19 pneumonia are at increased risk of thromboembolic events (Barnes et al 2020, Poyiadji et al 2020). This risk extends to ambulatory patients and patients with non-critical illness, and therefore is within this guideline's scope (Gervaise et al 2020, Bompard et al 2020, Mestre-Gómez et al 2020). A retrospective study demonstrated that of 106 CTPA scans performed in patients with COVID-19, 32 (30%) had acute PE. This is higher than the incidence of PE typically encountered in critically ill patients without COVID-19 infection or in emergency department patients (Leonard-Lorant et al 2020).

COVID-19 patients present with elevated D-dimer levels at presentation (Yu et al 2020, Huang et al 2020, Bikdeli et al 2020). Guan et al (2020) reported that D-dimer levels were greater than 0.5mg/L [500ng/mL] in 43% of patients with non-severe illness and 60% of patients with severe illness. Elevation of the D-dimer in COVID-19 patients has been associated with poor outcome (e.g., Chen et al 2020), and indicates the development of a coagulopathy [or thromboembolism]. It can be seen in the presence of a systemic inflammatory response, sepsis or disseminated intravascular coagulation (DIC). Zhou et al (2020) identified a D-dimer level of >1µg/mL [>1000ng/mL] as a risk factor for a poor outcome in SARS-Cov-2 infection.

D-dimer is significantly elevated in COVID-19 patients with PE compared to COVID-19 patients without PE (Gervaise et al 2020, Leonard-Lorant et al 2020; Bompard et al 2020), however an optimal threshold for the presence of PE in COVID-19 patients has not been established. One retrospective study found that a D-dimer threshold of 2660 ug/L [2660ng/mL] enabled the detection of all COVID-19 patients with PE on chest CT (Leonard-Lorant et al 2020). Mestre-Gómez et al (2020) found that an elevated D-Dimer level was an independent predictor of PE with an optimal cut off level of 5000 µg/dL [50000ng/mL]. Prospective studies with larger sample sizes are required to obtain appropriate D-dimer cut-off values for COVID-19 patients when PE is suspected (Garcia-Olive et al 2020).

Although D-dimer is typically elevated in COVID-19 patients, 32–53% of COVID-19 patients still have a normal D-dimer, and the vast majority have D-dimer levels below 1000ng/mL (*ESC* 2020). Therefore, recommended diagnostic algorithms combining pre-test probability assessment and D-dimer can be used in cases of suspected acute PE (*ESC* 2020). In particular, those applying a pre-test probability dependent D-dimer threshold may yield a decent specificity (*ESC* 2020). A normal D-dimer level allows the safe exclusion of PE in COVID-19 patients with a low or intermediate clinical probability for PE. There is no recommendation to use D-dimer as a positive marker of thrombosis (Bompard et al 2020).

CT pulmonary angiography (CTPA) is indicated if there is a high likelihood for PE in patients with COVID-19. Some authors recommend that contrast-enhanced CT be performed to rule out PE if supplemental oxygen is needed in COVID-19 patients with limited disease extension (Revel et al 2020, Bompard et al 2020). The ESC recommends that CTPA should be performed when unenhanced CT findings cannot explain the severity of respiratory failure (*ESC* 2020).

Ventilation scanning should not be used to diagnose PE in patients with COVID-19, as it is an aerosolizing procedure. COVID-19 infection can spread through aerosolization of upper airway secretions in infected patients (Zuckier et al 2020; Kooraki et al 2020). In addition, ventilation systems are difficult to disinfect (*SNMMI* 2020). When imaging is indicated to evaluate for a PE in COVID-19 patients, alternatives to ventilation scanning should be considered such as CTPA, perfusion scanning if CTPA is contraindicated, or deep vein Doppler studies if leg symptoms are present (Zuckier et al 2020; Kooraki et al 2020).

Low pretest probability or low clinical suspicion for a pulmonary embolism based on a validated clinical prediction rule
AND
Patient meets all of the Pulmonary Embolism Rule-Out Criteria (PERC):

- **Green** –
- **Yellow** –
- **Red** – **CT pulmonary angiography (CTPA); CT; MR angiography; MRI; Ventilation-Perfusion (V/Q) scan; Perfusion (Q) scan; CT venography; MR venography**

Level of Evidence: High

Notes concerning applicability and/or patient preferences: none

Guideline and PLE expert panel consensus summary:
A validated clinical prediction rule (e.g., Wells or Geneva score) should initially be used to estimate the pretest probability of patients with suspected PE (Raja et al [*ACP*] 2015; Streiff et al 2016; Qaseem et al [*ACP/AAFP*] 2007; Konstantinides et al [*ESC*] 2019; Uresandi et al [*SEPAR*] 2013) or deep vein thrombosis (DVT) (Kakkos et al [ESVS] 2021: class I, level C evidence). If clinical suspicion of PE is low, the Pulmonary Embolism Rule-Out Criteria (PERC) should be applied to help determine whether any further investigations for PE are needed (*NICE* 2020; Raja et al [*ACP*] 2015; Lim et al [*ASH*] 2018). In patients who meet all of the PERC, a D-dimer test should not be obtained (Raja et al [*ACP*] 2015) and a diagnosis of PE can be excluded without further diagnostic testing (Wolf et al [*ACEP*] 2018, level B recommendation; Raja et al [*ACP*] 2015; (Tran et al [*THANZ*] 2019, strong recommendation/moderate level of evidence).

Clinical notes:

- The PERC are not a screening tool and were developed to guide physicians in the care of patients with a real clinical concern for PE who have a low pretest probability based on validated clinical prediction rules (Raja et al [*ACP*] 2015).
- The PERC has a sensitivity for PE of 97% and a specificity of 22% - the risk of missing a PE by using PERC was only 0.3% (Raja et al [*ACP*] 2015).
- Chest radiographs should be obtained in all patients with pulmonary symptoms to exclude other causes for the patient's symptoms and signs (*NICE* 2020; Kirsch et al [*ACR*] 2017).

Evidence update:
No articles were identified in the 2021 update that have impact on the guideline summary and recommendations listed above.

Normal (negative) plasma high sensitivity D-dimer test with either:

- **Low pretest probability or low clinical suspicion for PE based on a validated clinical prediction rule in patients who do not meet all the PERC; or**
- **Intermediate pretest probability or intermediate clinical suspicion for PE based on a validated clinical prediction rule.**

- **Green** –
- **Yellow** –
- **Red** – **CT pulmonary angiography (CTPA); CT; MR angiography; MRI; Ventilation-Perfusion (V/Q) scan; Perfusion (Q) scan; CT venography; MR venography**

Level of Evidence: High

Notes concerning applicability and/or patient preferences: none

Guideline and PLE expert panel consensus summary:
A validated clinical prediction rule (e.g., Wells or Geneva score) should initially be used to estimate the pretest probability of patients with suspected PE (Raja et al [*ACP*] 2015; Streiff et al 2016; Qaseem et al [*ACP/AAFP*] 2007; Konstantinides et al [*ESC*] 2019; Uresandi et al [*SEPAR*] 2013) or DVT (Kakkos et al [*ESVS*] 2021: class I, level C evidence). If clinical suspicion of PE is low, the Pulmonary Embolism Rule-Out Criteria (PERC) should be applied to help determine whether any further investigations for PE are needed (*NICE* 2020; Raja et al [*ACR*] 2015; Lim et al [*ASH*] 2018). In patients who do not meet all of the PERC with low pretest probability/clinical suspicion, or in patients with intermediate pretest probability, clinicians should obtain plasma high-sensitivity D-dimer testing (Raja et al [*ACP*] 2015; Konstantinides et al [*ESC*] 2019, class I recommendation; *NICE* 2020; Lim et al [*ASH*] 2018). A negative D-dimer or, in patients older than 50 years, a D-dimer level below the age-adjusted cutoff, rules out PE in those deemed to be low or intermediate risk for acute PE, and no additional testing or anticoagulation is required (Lim et al [*ASH*] 2018; Kirsch et al [*ACR*] 2017; Raja et al [*ACP*] 2015; Wolf et al [*ACEP*] 2018, level B recommendation; Tran et al., [*THANZ*] 2019, strong recommendation/high level of evidence. Clinicians should not use imaging studies as the initial test [in lieu of a D-dimer test] in patients with low or intermediate pretest probability of PE (Raja et al [*ACP*] 2015; Waxman et al [*SNMMI*] 2017).

Clinical notes:

- The PERC are not a screening tool and were developed to guide physicians in the care of patients with a real clinical concern for PE who have a low pretest probability based on validated clinical prediction rules (Raja et al [*ACP*] 2015).
    - There is insufficient evidence to support the use of the PERC in a non-low-risk population (Wolf et al [*ACEP*] 2018), and therefore the PERC should not be applied to patients at higher risk for PE (Raja et al [*ACP*] 2015).
- PERC has a sensitivity for PE of 97% and a specificity of 22%. The risk of missing a PE by using PERC is 0.3% (Raja et al [*ACP*] 2015).
- A negative D-dimer can, in combination with clinical probability, exclude the disease without further testing in ~30% of patients with suspected PE (Konstantinides et al [*ESC*] 2019).

- The following D-dimer recommendations pertain to the use of a highly sensitive (> 95%) D-dimer assay (e.g. ELISA, ELFA, immunoturbidimetric or other immunoassays) (Raja et al [*ACP*] 2015; Konstantinides et al [*ESC*] 2019; Riley et al 2016; Uresandi et al [*SEPAR*] 2013).
    - A generally accepted cutoff value for many D-dimer assays is 500ng/mL, however, reference ranges and cutoff values for D-dimer may vary by performing laboratory (Parry et al 2018; Riley et al 2016).
    - Point-of-care assays have a lower sensitivity and negative predictive value compared with laboratory-based D-dimer tests and should only be used in patients with a low pre-test probability (Konstantinides et al [*ESC*] 2019). When offering D-dimer testing for suspected DVT or PE, consider a point-of-care test if laboratory facilities are not immediately available. If using a point-of care D-dimer test, choose a fully quantitative test (*NICE* 2020).
    - When using a point-of-care or laboratory D-dimer test, consider an age-adjusted D-dimer test threshold for people aged over 50 (e.g., age x 10 ng/mL versus 500ng/mL when possible) (*NICE* 2020; Raja et al [*ACP*] 2015).
    - The use of age-adjusted thresholds is as safe as the standard cutoff and increases the diagnostic utility of the test (van Es et al 2016; Konstantinides et al [*ESC*] 2019; Woller et al 2014; Wilts et al 2017; Lim et al [*ASH*] 2018). Using a strategy of adjusting the D-dimer for age modestly increases the proportion of patients with a negative D-dimer result, which may reduce the need for advanced imaging in approximately 5% to 10% of patients, without a significant increase in missed cases of PE (Wolf et al [*ACEP*] 2018).
- D-dimer testing is 99.5-100% sensitive for excluding PE on CTPA in patients with intermediate clinical probability of PE (Kirsch et al [*ACR*] 2017).
    - Since D-dimer levels are elevated in any significant thrombotic process, their ability to predict the presence of pulmonary embolism and/or deep venous thrombosis is decreased in patients with recent surgery, significant trauma, cancer, or renal failure (e.g., Lindner et al 2014).
- Chest radiographs should be obtained in all patients with pulmonary symptoms to exclude other causes for the patient's symptoms and signs (*NICE* 2020; Kirsch et al [*ACR*] 2017).

<u>Evidence update (2014-present):</u>

High Level of Evidence:

Bates et al (2016), in a multicenter prospective cohort management study of 808 consecutive patients with suspected PE, evaluated whether PE can be safely excluded in patients with a negative D-dimer test without incorporating clinical probability assessment. Ninety-nine (12%) were diagnosed with VTE at presentation. Four hundred and twenty (52%) had a negative D-dimer level at presentation and were treated without anticoagulation; of these, one had VTE during follow-up. The negative predictive value of D-dimer testing for PE was 99.8% (95% CI, 98.7 – 99.9).

Crawford et al (2016), in a meta-analysis, concluded that a negative D-dimer test is valuable in ruling out PE in patients presenting to the emergency setting with a low pre-test probability. They noted high levels of false-positive results, especially among those > age 65, with estimates of specificity from 23% to 63%. No empirical evidence was available, however, to support an increase in the diagnostic threshold of interpretation of D-dimer results for those over the age of 65 years.

Moderate Level of Evidence:

Patel et al (2020), in a systematic review and meta-analysis of 61 studies, reviewed the accuracy of D-dimer assay, compression ultrasonography (CUS), CTPA, and V/Q scanning for the diagnosis of suspected

first and recurrent PE. Pooled estimates for D-dimer revealed sensitivity and specificity of 0.97 (95% CI, 0.96-0.98) and 0.41 (95% CI, 0.36-0.46) respectively. CTPA sensitivity and specificity were 0.94 (95% CI, 0.89-0.97) and 0.98 (95% CI, 0.97-0.99) and CUS sensitivity and specificity were 0.49 (95% CI, 0.31-0.66) and 0.96 (95% CI, 0.95-0.98). V/Q scans for which high probability scans were considered positive and low/nondiagnostic/normal scans were considered negative had a sensitivity and specificity of 0.58 (95% CI, 0.50-0.66) and 0.98 (95% CI, 0.96-0.99). The authors conclude that D-dimer had the highest sensitivity when compared with imaging, while CTPA and V/Q scans both had the highest specificity.

Kearon et al (2019), in a prospective study, tested the strategy of ruling out PE in 2,017 outpatients with a low pretest probability (PTP) and D-dimer level < 1,000 ng/mL, and in those with a moderate PTP and D-dimer level < 500ng/mL. A total of 7.4% of patients had PE on initial diagnostic testing. Of the 1,325 patients with low (n = 1,285) or moderate (n = 40) PTP and negative D-dimer, none had venous thromboembolism during follow-up (95% CI, 0.00 to 0.29%), including 315 patients with low PTP and D-dimer level of 500-999ng/mL (95% CI, 0.00 to 1.20%). The authors state that this diagnostic strategy (low PTP and D-dimer < 1,000ng/mL) resulted in use of chest imaging in 34.4% of patients, while a strategy of ruling out PE with low PTP and D-dimer < 500ng/mL would result in use of chest imaging in 51.9% (difference, -17.6 percentage points; 95% CI, -19.2 to -15.9). The authors conclude that use of this Pulmonary Embolism Graduated D-dimer (PEGeD) algorithm substantially reduced the number of chest-imaging studies performed in patients with suspected PE.

Low Level of Evidence:
Glober et al (2019), in a retrospective study, reviewed 8,486 emergency department visits for suspected PE, including 3,523 visits where both a D-dimer and imaging were ordered. D-dimer was positive ($\geq$ 240ng/mL) in 2,253 of these visits, yielding 198 PEs. A DAGMAR (D-dimer Assay-Guided Moderation of Adjusted Risk) Score was developed, with points predictive of PE designated positive values and points predictive of positive D-dimer designated negative values. A DAGMAR Score < 2 equated to overall PE risk < 1.2%, and specificity improved (38% to 59%) without compromising sensitivity (94% to 96%). Use of the DAGMAR Score, and consideration of factors that affect both D-dimer and PE, would have reduced CT scans from 2,253 to 1,556 and led to fewer false negative results.

McLenachan et al (2019) retrospectively compared the sensitivity and specificity of varying D-dimer cut-offs in the diagnosis of PE for 2,291 patients, of whom 2,125 were Wells “low risk”. A total of 46 (2.2%) patients had a PE. Sensitivity and specificity for each D-dimer threshold were: traditional threshold (95.6% and 65.6%), age-adjusted (93.5% and 71.7%), doubled traditional (69.6% and 85.5%) and YEARS criteria (80.4% and 84.0%). Utilizing an age-adjusted threshold, YEARS criteria, or doubled-traditional threshold would have resulted in 70, 217 and 245 fewer imaging investigations. The authors conclude that age-adjusted D-dimer provided good specificity, saved significant scans, and maintained high sensitivity when compared to YEARS and doubled-traditional threshold.

Sharif et al (2019) retrospectively compared the efficacy and safety of using age-adjusted D-dimer interpretation, clinical probability-adjusted D-dimer interpretation, and standard D-dimer approach to exclude PE in 1,075 emergency department patients deemed low or moderate probability. PE was excluded in 70.4% (95% CI 67.6–73.0%), 80.3% (95% CI 77.9–82.6%) and 68.9%; (95% CI 65.7–71.3%) with the age-adjusted, clinical probability-adjusted and standard D-dimer approach. The negative predictive values (NPVs) were 99.7% (95% CI 99.0–99.9%), 99.1% (95% CI 98.3–99.5%) and 100% (95% CI 99.4–100.0%) respectively. The authors conclude that the clinical probability-adjusted rule appears to exclude PE in a greater proportion of patients, with a very small reduction in NPV.

Lindner et al (2014) conducted a retrospective study to determine the diagnostic accuracy of D-dimer to rule out PE in 1,305 emergency department patients with renal insufficiency, in which D-dimer can be elevated. All patients had CTPA and D-dimer to work-up potential PE. Sensitivity of D-dimer for patients with an eGFR > 60 mL/min was 96% (95% CI: 0.93–0.99) and 100% (95% CI: 100-100%) for those with 30-60 mL/min eGFR, though specificity decreased significantly with impaired renal function. Because almost all patients with impaired renal function had elevated D-dimer irrespective of the presence of PE, the authors posit that future studies should be performed to determine renal function-adjusted D-dimer cutoffs for PE.

Elevated (positive) plasma high sensitivity D-dimer test with either:

- **Low pretest probability or low clinical suspicion for PE based on a validated clinical prediction rule in patients who do not meet all the PERC; or**
- **Intermediate pretest probability or intermediate clinical suspicion for PE based on a validated clinical prediction rule.**

- Green – **CT pulmonary angiography (CTPA)** or **CT chest with IV contrast**
- Yellow – **Ventilation-Perfusion lung scan (planar V/Q, V/Q SPECT, or VQ SPECT/CT)**
- Yellow – **Perfusion (Q) lung scan**
  [patient unable to undergo CT and unable to undergo V/Q scan]
- Yellow – **Pulmonary MR angiography**
  [patient unable to undergo CT; or when previous CT is indeterminate]
- Yellow – **CT venography or MR venography (lower extremities)**
  [suspect DVT and ultrasound not available]
- Red – **CT chest without IV contrast; CT chest without and with IV contrast; MRI chest**

Level of Evidence: High

Notes concerning applicability and/or patient preferences: Consulting and reporting requirements are not required for orders for applicable imaging services made by ordering professionals under the following circumstances (*42 C.F.R. § 414.94. 2015*):

- Emergency services when provided to individuals with emergency medical conditions.
- For an inpatient and for which payment is made under Medicare Part A.

V/Q SPECT and V/Q SPECT/CT were downgraded from green to yellow despite favorable accuracy in recent reports (Hess et al 2016; Kan et al 2015; Phillips et al 2015; Stubbs et al 2017) because of concern surrounding the applicability and availability of this evolving technology in the community outpatient setting (PLE expert panel consensus opinion).

Pulmonary MRA was downgraded from green to yellow despite favorable accuracy reported in the recent studies (Chen et al 2017; Squizzato et al 2017; and Pasin et al 2017) because of concerns about the applicability, expertise and availability of emergent pulmonary MRA in an outpatient setting. Pulmonary MRA was also downgraded because of concerns over the rate of nondiagnostic MRI studies which was reported to be 6.3-30.3% in three of the studies in the Squizzato et al 2017 review, and 18.89% in the Zhou et al 2015 study. The use of MRI is also limited by concerns over the need to exclude electrical implants, metallic implants and foreign bodies in patients undergoing emergent imaging. The expert panel thought that if pulmonary MRA is to be performed to exclude PE, it should only be done in MRI centers with high field strength MRI systems, experience, and appropriate clinical expertise in pulmonary imaging (PLE expert panel consensus opinion).

Guideline and PLE expert panel consensus summary:
A validated clinical prediction rule (e.g., Wells or Geneva score) should initially be used to estimate the pretest probability of patients with suspected PE (Raja et al *[ACP]* 2015; Streiff et al 2016; Qaseem et al [*ACP/AAFP*] 2007; Konstantinides et al [*ESC*] 2019; Uresandi et al [*SEPAR*] 2013) or DVT (Kakkos et al

[*ESVS*] 2021: class I, level C evidence). If clinical suspicion of PE is low, the Pulmonary Embolism Rule-Out Criteria (PERC) should be applied to help determine whether any further investigations for PE are needed (*NICE* 2020; Raja et al [*ACR*] 2015; Lim et al [*ASH*] 2018). In patients who do not meet all of the PERC with low pretest probability/clinical suspicion, or in patients with intermediate pretest probability, clinicians should obtain plasma high-sensitivity D-dimer testing (Raja et al [*ACP*] 2015; Konstantinides et al [*ESC*] 2019, class I recommendation; *NICE* 2020; Lim et al [*ASH*] 2018). If D-dimer is not readily available, alternative acceptable strategies include performing CTPA or VQ scan alone (Lim et al [*ASH*] 2018). In patients with an elevated D-dimer level, imaging should be obtained (Raja et al [*ACP*] 2015; *NICE* 2020; Lim et al [*ASH*] 2018), as a positive D-dimer result alone is not diagnostic of venous thromboembolism (VTE) (Tran et al [*THANZ*] 2019; Lim et al [*ASH*] 2018).

CT Pulmonary Angiography (CTPA) or CT Chest with IV contrast:
When available and without contraindication, CTPA [or optimized CT chest with IV contrast] is the procedure of choice to evaluate for PE in patients with positive D-dimer tests, or in patients with clinical suspicion for PE in whom D-dimer testing is not available (Raja et al [*ACP*] 2015; Kirsch et al [*ACR*] 2017; Konstantinides et al [*ESC*] 2019; *NICE* 2020; Lim et al [*ASH*] 2018; Tran et al [*THANZ*] 2019, GRADE: Strong; Evidence, High; Beache et al [*ACR*] 2020). A diagnosis of PE can be rejected (without further testing) if CTPA is normal in a patient with low or intermediate clinical probability, or if the patient is otherwise PE-unlikely (Konstantinides et al [*ESC*] 2019, class I recommendation; Lim et al [*ASH*] 2018; Tran et al[*THANZ*] 2019, strong recommendation/high level of evidence). Patients with a positive D-dimer should undergo CTPA (Lim et al [*ASH*] 2018. This strategy also applies to patients with suspected recurrent PE and an unlikely pretest probability (Lim et al [*ASH*] 2018).

V/Q Scanning:
For patients with low or intermediate pretest probability of PE who require additional testing after D-dimer, V/Q scanning can be used (Beache et al [*ACR*] 2020; Lim et al [*ASH*] 2018; Waxman et al [*SNMMI*] 2017), particularly in those with contraindication to CTPA (e.g., renal impairment or contrast allergy) or when CTPA is not available (Raja et al [*ACP*] 2015; *NICE* 2020; Tran et al [*THANZ*] 2019, GRADE: Strong; Evidence, High). V/Q scanning may be preferred over CTPA to avoid unnecessary radiation, particularly in pregnant patients or in young female patients in whom thoracic CT might raise the lifetime risk of breast cancer (Konstantinides et al [*ESC*] 2019). V/Q scanning may also be appropriate for lower extremity clots detected on ultrasound, but only when PE is likely and V/Q results are expected to change current therapy (Waxman et al [*SNMMI*] 2017; PLE expert panel consensus opinion). A normal VQ scan excludes PE in patients with a low or intermediate clinical likelihood of PE, and no additional testing is recommended (Tran et al [*THANZ*] 2019, strong recommendation/high level of evidence; Konstantinides et al [*ESC*] 2019, class I recommendation).

Perfusion (Q) scanning alone may be appropriate in patients who cannot cooperate for ventilation imaging or in patients with known or suspected COVID-19 (Waxman et al [*SNMMI*] 2017; Zuckier et al 2020; Kooraki et al 2020).

In patients with recent/prior documentation of PE (and suspected new PE), V/Q scan is appropriate if the prior imaging of PE was also completed with V/Q scan. If prior imaging was with CTPA, V/Q scan is rarely considered to be appropriate (Waxman et al [*SNMMI*] 2017).

The EANM recommends that either CTPA or V/Q SPECT be used as each of these modalities were shown to outperform planar V/Q (Phillips et al 2015). The authors of the ECS/ERS 2019 guideline state, however, that the evidence supporting the use of V/Q SPECT with or without CT is limited

(Konstantinides et al [*ESC*] 2019). They note that most of the studies are retrospective by design or include SPECT itself in the reference standard. They also found that few outcome studies were available and concluded that large prospective studies were needed to validate SPECT techniques (Konstantinides et al [*ESC*] 2019).

Pulmonary MR angiography:
Some guidelines note that MRA is not recommended for ruling out PE, as it has not been found to have the sensitivity or specificity required to detect segmental or subsegmental PEs and has a high proportion of inconclusive scans (Kirsch et al [*ACR*] 2017; Konstantinides et al [*ESC*] 2019, class III recommendation/level A evidence; Uresandi et al [*SEPAR*] 2013). Others note that MRA has potential use if pulmonary embolism is being considered (e.g., Beache et al [*ACR*] 2020). A recent systematic review/meta-analysis indicates that pulmonary MRA using newer techniques has a similar accuracy [to CT] for large vessel pulmonary embolism, and may have a higher sensitivity for subsegmental pulmonary embolism (Chen et al 2017). As such, pulmonary MRA may be acceptable in patients who are unable to undergo CT, or when CTPA/CT chest is unable to rule out PE in the main, lobar, or segmental arteries (PLE expert panel consensus opinion).

Ultrasound:
Ultrasound is the initial modality of choice for suspected deep vein thrombosis (DVT) (Hanley et al [*ACR*] 2018; Kakkos et al [*ESVS*] 2021: class I, level C evidence). Lower-limb ultrasound has largely replaced venography for diagnosing DVT, with a sensitivity of > 90% and a specificity of 95% for proximal symptomatic DVT (Konstantinides et al [*ESC*] 2019). When DVT is suspected, but a validated clinical prediction rule indicates it is unlikely, clinicians should first offer a D-dimer test, followed by a proximal or whole-leg ultrasound scan if the result is positive (NICE 2020; Kakkos et al [*ESVS*] 2021: class I, level C evidence). If D-dimer is not readily available, alternative acceptable strategies include performing ultrasound alone (Lim et al [*ASH*] 2018). In patients with low pretest probability and a negative ultrasound, no additional testing is recommended (Lim et al [*ASH*] 2018). For patients with suspected DVT and an intermediate or likely pretest probability, the *ASH* guideline panel suggests using whole leg ultrasound, or starting with proximal lower extremity ultrasound (Lim et al [*ASH*] 2018). For patients with suspected DVT with a likely pre-test probability and negative compression ultrasound scanning, repeat ultrasound assessment should be considered after 5-7 days (Kakkos et al [*ESVS*] 2021: class IIa, level C evidence). For patients with symptomatic calf deep vein thrombosis not receiving anticoagulation, clinical re-assessment and repeat whole leg ultrasound after one week is recommended (Kakkos et al [*ESVS*] 2021: class I, level B evidence).

CT Venography or MR venography:
Because CT uses ionizing radiation, compression ultrasound should be preferred over CT when indicated to exclude the presence of DVT (Kirsch et al [*ACR*] 2017). However, if ultrasound capability or expertise is not available, CT venography may be appropriate for suspected DVT (Hanley et al [*ACR*] 2018). For patients with suspected proximal deep vein thrombosis where ultrasound assessment is inconclusive or not feasible, computed tomography venography or magnetic resonance venography should be considered (Kakkos et al [*ESVS*] 2021: class IIa, level C evidence). CT venography is not recommended as an adjunct to CTPA (to increase the diagnostic yield) (Konstantinides et al [*ESC*] 2019, grade III recommendation/level B evidence; Uresandi et al [*SEPAR*] 2013). MR venography (MRV) is a noninvasive alternative to contrast catheter venography (Hanley et al [*ACR*] 2018).

Clinical notes:

- For patients with suspected PE in whom diagnostic imaging is required, baseline chest radiographs should be obtained in all patients with pulmonary symptoms to exclude other causes for the patient's symptoms and signs and potentially avoid further diagnostic imaging (*NICE* 2020; Kirsch et al [*ACR*] 2017; Lim et al [*ASH*] 2018).
- The PERC are not a screening tool and were developed to guide physicians in the care of patients with a real clinical concern for PE who have a low pretest probability based on validated clinical prediction rules (Raja et al [*ACP*] 2015).
- The Pulmonary Embolism Rule-Out Criteria (PERC) should be applied to all patients with a low pretest probability of PE, and the D-dimer test should be obtained in low-risk patients who do not meet one or more of the [PERC] criteria (Raja et al [*ACP*] 2015).
- PERC should not be applied to patients at intermediate or high risk for PE (Raja et al [*ACP*] 2015).
- When offering D-dimer testing for suspected DVT or PE, consider a point-of-care test if laboratory facilities are not immediately available. If using a point-of care D-dimer test, choose a fully quantitative test (*NICE* 2020).
- Point-of-care assays have a lower sensitivity and negative predictive value compared with laboratory-based D-dimer tests and should only be used in patients with a low pre-test probability (Konstantinides et al [*ESC*] 2019).
- When using a point-of-care or laboratory D-dimer test, consider an age-adjusted D-dimer test threshold for people aged over 50 (*NICE* 2020).
- A generally accepted cutoff value for many D-dimer assays is 500ng/mL, however, reference ranges and cutoff values for D-dimer may vary by performing laboratory (Riley et al 2016).
- As an alternative to the fixed D-dimer cut-off, a negative D-dimer test using an age-adjusted cut-off (age x 10ug/L [10ng/mL], in patients aged > 50 years) should be considered for excluding PE in patients with low or intermediate clinical probability, or those that are PE-unlikely (Konstantinides et al [*ESC*] 2019. The use of age-adjusted thresholds maintains the sensitivity for PE above 97% while increasing the specificity (van Es et al 2016).
- As an alternative to the fixed or age-adjusted D-dimer cut-off, D-dimer levels adapted to clinical probability should be considered to exclude PE (patients without clinical items and D-dimer levels < 1000ng/mL, or in patients with one or more clinical items and D-dimer levels < 500ng/mL (Konstantinides et al [*ESC*] 2019).
- These recommendations pertain to the use of a highly sensitive (>95%) D-dimer assay (e.g. ELISA, ELFA, immunoturbidimetric or other immunoassays) (Raja et al [*ACP*] 2015; Konstantinides et al [*ESC*] 2019; Riley et al 2016; Uresandi et al [*SEPAR*] 2013).
- CTPA has a sensitivity and specificity of 95-100% for PE in patients with low or intermediate pretest probability (Raja et al [*ACP*] 2015).
- The sensitivity of V/Q scanning for PE is 50-98% and the specificity 20-60% (Raja et al [*ACP*] 2015).
- Residual defects may complicate the interpretation of CTPA and V/Q in patients with recurrent PE (Choi et al 2016; den Exter et al 2015).
- If prior imaging is available, comparison of the previous and current imaging is warranted to determine whether the findings are new and represent recurrent PE (Lim et al [*ASH*] 2018).
- With an increasing clinical consensus that not all PEs should be treated, it is clear that PE imaging is best evaluated on the basis of outcomes rather than accuracy. In a prospective study comparing V/Q and CTPA, Anderson et al. (2007) showed that the outcomes (based on a 3-mo follow-up of negative cases) were similar (false-negative rate, ≤1%) despite the fact that more

PEs were detected with CTPA than with V/Q scans (17.7% for CTPA and 11.7% for V/Q) (Waxman et al [*SNMMI*] 2017).

- For patients diagnosed with DVT, the prevalence of clinically silent PE increases with age, and is higher in patients with proximal DVT, compared with those with calf DVT (Kakkos et al [ESVS] 2021). However, for patients with DVT, routine investigation for occult PE in the absence of symptoms or signs is not recommended (Kakkos et al [*ESVS*] 2021: class III, level C evidence).
- Lower extremity ultrasound may be beneficial in:
    - Patients with symptoms of acute PE and DVT (Raja et al [*ACP*] 2015; Konstantinides et al [*ESC*] 2019);
    - Patients being evaluated for acute PE with indeterminate or nondiagnostic CTPA or V/Q scans (PLE expert panel consensus opinion);
    - Patients in whom V/Q scanning cannot be done (Raja et al [*ACP*] 2015); or
- For patents presenting with signs or symptoms of both DVT and PE, carry out initial diagnostic investigations for either DVT or PE, basing the choice of diagnostic investigations of clinical judgment (*NICE* 2020).
- In general, a negative whole leg ultrasound is sufficient to exclude DVT (Tran et al [*THANZ*] 2019).
- Pulmonary angiography is not free of risk, and is rarely performed now as less-invasive CT angiography offers similar diagnostic accuracy (Konstantinides et al [*ESC*] 2019). Pulmonary angiography is invasive and should only be used in patients in whom the diagnosis is uncertain after V/Q scanning [and ultrasound of the lower extremity], or if CTPA is inadequate to rule out a PE in the main or lobar artery (Raja et al [*ACP*] 2015; PLE expert panel consensus opinion).

Technical notes:

- CTPA and chest CT with IV contrast should be optimized for pulmonary artery enhancement (Kirsch et al [*ACR*] 2017).
- Chest CT with IV contrast, if performed, should include sagittal and coronal high resolution reconstructions. CTPA and optimized Chest CT IV contrast exams differ only in the inclusion of 3D rendering with CTPA (Kirsch et al [*ACR*] 2017).

Evidence update (2014-present):

High Level of Evidence:

Hess et al (2016), in a systematic review and meta-analysis, reported the diagnostic performance of single-photon emission computed tomography (V/Q SPECT) with or without additional low-dose CT (SPECT/CT) and CT angiography (CTA). Eight articles met inclusion criteria. The authors concluded that V/Q SPECT, V/Q SPECT/CT, and CTA are all viable options, but consider V/Q SPECT/CT to be superior in most clinical settings with better overall diagnostic performance. Pooled sensitivities of V/Q SPECT/CT vs. CTA was (97.6 vs. 82.0%), specificities (95.9 vs. 94.9%), positive predictive values (93.0 vs. 93.8%), negative predictive values (98.6 vs. 84.7%), and accuracies (96.5 vs. 88.6%).

Fabiá Valls et al (2015) reported on a meta-analysis of four prospective studies evaluating a diagnostic algorithm using clinical prediction rules, D-dimer testing and CTPA in consecutive patients with clinically suspected PE and a history of VTE. Four studies concerning 1,286 patients were included with a pooled baseline PE prevalence of 36% (95% confidence interval [CI] 30–42). In only 217 patients (15%; 95% CI 11–20) PE could be excluded without CTPA. The three-month VTE incidence rate was 0.8% (95% CI 0.06–2.4) in patients managed without CTPA, 1.6% (95% CI 0.3–4.0) in patients in whom PE was excluded by CTPA and 1.4% (95% CI 0.6–2.7) overall. In the pooled studies, PE was safely excluded in patients with a

history of VTE based on a CPR followed by a D-dimer test and/or CTPA, although the efficiency of the algorithm is relatively low compared to patients without a history of VTE (high level of evidence). One of these studies explicitly excluded patients with ongoing anticoagulation therapy. Two studies excluded patients on vitamin K antagonists. It is assumed that the final study also excluded patients with long term anticoagulant therapy as anticoagulant therapy was withheld in patients with low probability and normal D-dimer levels.

Kan et al (2015), in a systematic review/meta-analysis, concluded that V/Q SPECT is an accurate method in acute PE patients with high sensitivity and high specificity in the diagnosis of PE. Nine studies met the inclusion criteria. The pooled sensitivity and specificity of V/Q SPECT in the diagnosis of acute PE patients, calculated on a per-patient-based analysis, was 96% (95% confidence interval 95-97%), and 97% (95% CI, 96-98%) respectively. The pooled negative LR, positive LR of V/Q SPECT in acute PE patients was 0.06 (range, 0.02-0.19) and 16.64 (range, 9.78-31.54). The area under the ROC curve of V/Q SPECT in the diagnosis of acute PE patients was 0.99.

Phillips et al (2015), in a systematic review and meta-analysis of 19 studies (n = 5923 patients), showed no performance difference between V/Q SPECT and CTPA; planar V/Q is inferior. CTPA is clearly the most cost effective technique. V/Q SPECT should be considered in situations where radiation dose is of concern or CTPA is inappropriate.

Moderate Level of Evidence:
Patel et al (2020), in a systematic review and meta-analysis of 61 studies, reviewed the accuracy of D-dimer assay, compression ultrasonography (CUS), CTPA, and V/Q scanning for the diagnosis of suspected first and recurrent PE. Pooled estimates for D-dimer revealed sensitivity and specificity of 0.97 (95% CI, 0.96-0.98) and 0.41 (95% CI, 0.36-0.46) respectively. CTPA sensitivity and specificity were 0.94 (95% CI, 0.89-0.97) and 0.98 (95% CI, 0.97-0.99) and CUS sensitivity and specificity were 0.49 (95% CI, 0.31-0.66) and 0.96 (95% CI, 0.95-0.98). V/Q scans for which high probability scans were considered positive and low/nondiagnostic/normal scans were considered negative had a sensitivity and specificity of 0.58 (95% CI, 0.50-0.66) and 0.98 (95% CI, 0.96-0.99). The authors conclude that D-dimer had the highest sensitivity when compared with imaging, while CTPA and V/Q scans both had the highest specificity.

Squizzato et al (2017) conducted a systematic review and meta-analysis of 13 studies (total n = 1170) to systematically assess the diagnostic accuracy of MRI for PE diagnosis. 11/13 studies used MR contrast. Only 3 (23.1%) studies reported rate of inconclusive MRI results, ranging from 6.3 to 30.3% (mean prevalence of 19%) of all performed MRI. All 3 studies required imaging down to subsegmental arteries to exclude PE. After exclusion of technical inadequate results, MRI bivariate weighted mean sensitivity was 80.9% (95% CI, 68.2-89.4%) with a bivariate weighted mean specificity of 96.4% (95% CI, 92.4-98.3%). The authors conclude that MRI has high specificity but limited sensitivity for the diagnosis of PE. Inconclusive results are a major limitation to the practical application of MRI.

Stubbs et al (2017), in a retrospective study of 1300 consecutive V/Q exams, found that indeterminate scans were decreased from 72/589 (12.2%) in the planar group ($P < 0.05$) to 42/542 (7.7%) in the SPECT group. The authors concluded that V/Q SPECT has greater diagnostic certainty of PE with a reduction in an indeterminate scan frequency compared with planar scintigraphy.

Li et al (2016), in a systematic review/meta-analysis, concluded that MRA can be used for the diagnosis of acute PE, however, due to limited sensitivity, cannot be used as a stand-alone test to exclude acute PE. Five studies were included in the meta-analysis. The pooled sensitivity 0.83 (0.78-0.88) and

specificity 0.99 (0.98-1.00) demonstrated that MRA diagnosis had limited sensitivity and high specificity in the detection of acute PE.

Low Level of Evidence:
Kornblum et al (2021) conducted a multisite retrospective study to evaluate the yield of CTPA for PE across a variety of care settings in a community-based healthcare system. A total of 7850 CTPA studies met criteria for inclusion and were reviewed. PE was found in 884 (11.3%) of studies performed. Outpatients had a lower yield of PE (3.8%, $p<0.001$) compared with inpatients (14.1%) and ED patients (10.7%, $p<0.001$). Patients with diagnosis of DVT or neoplasm had increased incidence of PE when compared to those without ($p<0.001$ for both). The authors conclude that overall yield of CTPA for PE in a community-based system is similar to that at academic centers.

Kaya et al (2019) prospectively examined diagnostic performance of contrast enhanced and unenhanced combined pulmonary and lower extremity MRI sequences (PA MRI and MRV) in diagnosing PE and DVT in 44 patients with suspected venous thromboembolism. Patients underwent CTPA for suspected PE, and also underwent PA MRI and MRV, and Doppler ultrasonography within 72 hours. Combined MRI included two sequences: unenhanced steady-state free precession (SSFP) and contrast-enhanced three-dimensional (3D) gradient echo (GRE). CTPA showed emboli in 33 patients (75%), while contrast-enhanced 3D-GRE MRI showed DVT in 34 (77%) subjects. Sensitivities for SSFP vs. 3D-GRE MRI in PE detection were 87.9% v. 100% on a per-patient basis, respectively, and 53.7% vs. 73% on a per-embolus basis, respectively. Of 34 patients with established DVT, 31 (91%) were detected by ultrasound and 29 (85%) detected by SSFP technique respectively. The authors conclude that both contrast-enhanced and unenhanced combined MRI are feasible one-stop-shopping techniques in patients with suspected thromboembolism.

Liu and Lacros (2019) prospectively evaluated whether hybrid SPECT/CT could significantly reduce potentially false-positive VQ SPECT studies or obviate the need for a ventilation study in suspected PE. Two specialists acquired SPECT/CT in 165 patients (mean age 64), and studies were compared to VQ SPECT and Q SPECT/CT. The authors noted two findings. First, that hybrid VQ SPECT/CT did not lead to a statistically significant decrease in the number of potentially false-positive VQ SPECT studies, and therefore its routine use is not justified. Secondly, CT did not obviate the need for a ventilation study.

Pressaco et al (2019) prospectively evaluated the feasibility and accuracy of a combined MRA-MRV protocol using contrast agents with blood pool properties (gadofosveset trisodium and gadobenate dimeglumine), compared with CTPA and Duplex ultrasound, in the evaluation of PE and DVT. A total of 40 emergency department patients with clinical suspicion for PE were included and received CTPA. Of these patients, 9 also underwent Duplex ultrasound for suspected DVT. MRA of the chest and MRV of the pelvis and thighs was then performed within 72 hours (95% of patients within 24 hours) using a single contrast injection. The results on a per-patient basis comparing MRA to CTPA for pulmonary embolus yielded 100% sensitivity and 97% specificity. In the subset of patients evaluated for DVT, MRV demonstrated sensitivity and specificity of 100%. The authors conclude that using contrast agents with blood pool properties to perform a relatively rapid combined MRA-MRV exam to image for PE and above knee DVT shows potential as an alternative imaging choice to CTPA.

Chen et al (2017) conducted a meta-analysis of 10 studies (590 total cases) to compare the effects of MRI and CT in the assessment of PE. The MRI technique and the use of MR contrast in each study was not stated in the meta-analysis. In addition, the article does not provide information on the number of inconclusive or nondiagnostic MRI exams in the studies. The pooled sensitivity of CT was 0.90 (95% CI,

0.85-0.93) and pooled specificity of CT was 0.88 (95% CI, 0.77-0.95). The pooled sensitivity of MRI was 0.92 (95% CI, 0.89-0.94) and pooled specificity of MRI was 0.91 (95% CI, 0.77-0.97). The SROC curve areas under the curve of CT and MRI were 0.94 (95% CI, 0.91-0.96) and 0.93 (95% CI, 0.91-0.95), respectively. The authors conclude that this meta-analysis demonstrates that MRI has better sensitivity and specificity in detecting subsegmental artery PE.

Pasin et al (2017) performed a prospective evaluation of the accuracy of a free breathing True-FISP MRI (without contrast) for PE in 93 patients, using CTPA as the gold standard. PE prevalence was 22%. During the 1-year follow-up period, eight patients died, and PE was responsible for death in 12.5% of cases. Of the patients who developed PE, only 5% died due to this condition. There were no differences between MR and CT embolism detection in these subjects. MR sequences had a sensitivity of 85%, specificity was 98.6% and accuracy was 95.6%. Agreement between readers was high (κ= 0.87). The authors concluded that compared with contrast-enhanced CT, unenhanced MR sequences demonstrate good accuracy and no differences in the mortality rates in 1 year were detected.

Zhou et al (2015) conducted a systematic review and meta-analysis of 15 studies for patient accuracy and 9 studies for vessel accuracy on MRI. The authors concluded that MRI exhibits a high diagnostic capability with proximal arteries, but lacks sensitivity for peripheral embolism. The patient-based analysis yielded an overall sensitivity of 0.75 (0.70-0.79) and 0.84 (0.80-0.87) for all patients and patients with technically adequate images, respectively. The overall specificity was 0.80 (0.77-0.83) and 0.97 (0.96-0.98). On average, MRI was technically inadequate in 18.89% of patients (range, 2.10%-27.70%).

Lindner et al (2014) conducted a retrospective study to determine the diagnostic accuracy of D-dimer to rule out PE in 1,305 emergency department patients with renal insufficiency, in which D-dimer can be elevated. All patients had CTPA and D-dimer to work-up potential PE. Sensitivity of D-dimer for patients with an eGFR > 60 mL/min was 96% (95% CI: 0.93–0.99) and 100% (95% CI: 100-100%) for those with 30-60 mL/min eGFR, though specificity decreased significantly with impaired renal function. Because almost all patients with impaired renal function had elevated D-dimer irrespective of the presence of PE, the authors posit that future studies should be performed to determine renal function-adjusted D-dimer cutoffs for PE.

High pretest probability and/or high clinical suspicion for a pulmonary embolism based on a validated clinical prediction rule:

- Green – **CT pulmonary angiography (CTPA)** or **CT chest with IV contrast**
- Yellow – **Ventilation-Perfusion lung scan (planar V/Q, V/Q SPECT, or V/Q SPECT/CT)**
- Yellow – **Perfusion (Q) lung scan**
  [patient unable to undergo CT and unable to undergo V/Q scan]
- Yellow – **Pulmonary MR angiography**
  [patient unable to undergo CT; or when previous CT is indeterminate]
- Yellow – **CT venography or MR venography (lower extremities)**
  [suspect DVT and ultrasound not available]
- Red – **CT chest without IV contrast; CT chest without and with IV contrast; MRI chest**

Level of Evidence: High

Notes concerning applicability and/or patient preferences: Consulting and reporting requirements are not required for orders for applicable imaging services made by ordering professionals under the following circumstances (*42 C.F.R. § 414.94. 2015*):

- Emergency services when provided to individuals with emergency medical conditions.
- For an inpatient and for which payment is made under Medicare Part A.

V/Q SPECT and V/Q SPECT/CT were downgraded from green to yellow despite favorable accuracy in recent reports (Hess et al 2016. 2015; Stubbs et al 2017) because of concern surrounding the applicability and availability of this evolving technology in the community outpatient setting (PLE expert panel consensus opinion).

Pulmonary MR angiography was downgraded from green to yellow despite favorable accuracy reported in the recent studies (Chen et al 2017; Squizzato et al 2017; and Pasin et al 2017) because of concerns about the applicability, expertise and availability of emergent pulmonary MRA in an outpatient setting. Pulmonary MRA was also downgraded because of concerns over the rate of nondiagnostic MRI studies which was reported to be 6.3-30.3% in three of the studies in the Squizzato et al 2017 review, and 18.89% in the Zhou et al 2015 study. The use of MRI is also limited by concerns over the need to exclude electrical implants, metallic implants and foreign bodies in patients undergoing emergent imaging. The expert panel thought that if pulmonary MRA is to be performed to exclude PE, it should only be done in MRI centers with high field strength MRI systems, experience, and appropriate clinical expertise in pulmonary imaging (PLE expert panel consensus opinion).

Guideline and PLE expert panel consensus summary:
A validated clinical prediction rule (e.g., Wells or Geneva score) should initially be used to estimate the pretest probability of patients with suspected PE (Raja et al [*ACP*] 2015; Streiff et al 2016; Qaseem et al [*ACP/AAFP*] 2007; Konstantinides et al [*ESC*] 2019; Uresandi et al [*SEPAR*] 2013) or DVT (Kakkos et al [*ESVS*] 2021: class I, level C evidence). In a population with high pretest probability, use of a positive D-dimer alone to diagnose PE is not recommended (Lim et al [*ASH*] 2018).

CT Pulmonary Angiography (CTPA) or CT Chest with IV contrast:
In patients with a high pretest probability or high clinical suspicion for PE, CTPA [or optimized CT chest with IV contrast] is the preferred method of diagnosis when available and the patient has no contraindications to contrast (Raja et al [*ACP*] 2015; Konstantinides et al [*ESC*] 2019; *NICE* 2020; Kirsch et

al [*ACR*] 2017; Tran et al [*THANZ*] 2019, GRADE: Strong; Evidence, High; Lim et al [*ASH*] 2018; Beache et al [*ACR*] 2020). The negative predictive value of CTPA is only 60% in patients with a high pretest probability for PE (Konstantinides et al [*ESC*] 2019). Therefore, providers should consider further testing in cases where there is a substantial discordance between the clinical judgment and the CTPA result (Konstantinides et al [*ESC*] 2019). Patients with suspected recurrent PE and a likely pretest probability should undergo CTPA (Lim et al [*ASH*] 2018).

V/Q Scanning:
Consider the use of a V/Q SPECT scan, or if not available, a V/Q planar scan, in patients with a clinical predication rule score indicating that PE is likely if CTPA is not available, in patients with an allergy to contrast media, in patients with severe renal impairment, or in patients with a high risk from irradiation (*NICE* 2020; Raja et al [*ACP*] 2015; Tran et al [*THANZ*] 2019, GRADE: Strong; Evidence, High; Lim et al [*ASH*] 2018; Waxman et al [*SNMMI*] 2017; Beache et al [*ACR*] 2020). The authors of the *ECS/ERS* 2019 guideline state, however, that the evidence supporting the use of V/Q SPECT with or without CT is limited (Konstantinides et al [*ESC*] 2019). They note that most of the studies are retrospective by design or include SPECT itself in the reference standard. They also found that few outcome studies were available and concluded that large prospective studies were needed to validate SPECT techniques (Konstantinides et al [*ESC*] 2019

In cases where clinical suspicion for PE remains high after CTPA (e.g., CTPA inconclusive or discordant with clinical probability), additional testing with V/Q scan may be considered (Lim et al [*ASH*] 2018). Proximal leg vein ultrasound can also be considered in these patients if DVT is suspected (*NICE* 2020). V/Q scanning may also be appropriate for lower extremity clots detected on ultrasound, but only when PE is likely and V/Q results are expected to change current therapy (Waxman et al [*SNMMI*] 2017; PLE expert panel consensus opinion). In patients with recent/prior documentation of PE (and suspected new PE), V/Q scan is appropriate if the prior imaging of PE was also completed with V/Q scan. If prior imaging was with CTPA, V/Q scan is rarely considered to be appropriate (Waxman et al [*SNMMI*] 2017).

Perfusion (Q) scan alone may be appropriate in patients who cannot cooperate for ventilation imaging and for patients with known or suspected COVID-19 (Waxman et al [*SNMMI*] 2017; Zuckier et al 2020; Kooraki et al 2020).

Pulmonary MR angiography:
Some guidelines note that MRA is not recommended for ruling out PE, as it has not been found to have the sensitivity or specificity required to detect segmental or subsegmental PEs and has a high proportion of inconclusive scans (Kirsch et al [*ACR*] 2017; Konstantinides et al [*ESC*] 2019, class III recommendation/level A evidence; Uresandi et al [*SEPAR*] 2013). Others note that MRA has potential use if pulmonary embolism is being considered (e.g., Beach et al [*ACR*] 2020). A recent systematic review/meta-analysis indicates that pulmonary MRA using newer techniques has a similar accuracy [to CT] for large vessel pulmonary embolism, and may have a higher sensitivity for subsegmental pulmonary embolism (Chen et al 2017). As such, pulmonary MRA may be acceptable in patients who are unable to undergo CT, or when CTPA/CT chest is unable to rule out PE in the main, lobar, or segmental arteries (PLE expert panel consensus opinion).

Ultrasound:
Ultrasound is the initial modality of choice for suspected deep vein thrombosis (DVT) (Hanley et al [*ACR*] 2018; Kakkos et al [*ESVS*] 2021: class I, level C evidence). Lower-limb ultrasound has largely replaced venography for diagnosing DVT, with a sensitivity of > 90% and a specificity of 95% for proximal

symptomatic DVT (Konstantinides et al [*ESC*] 2019). For those with a clinical prediction rule score indicating that DVT is likely, a proximal leg vein ultrasound scan should be offered, followed by a D-dimer test if the scan result is negative (NICE 2020). If PE is not identified by CTPA or V/Q scan, consider a proximal leg vein ultrasound if DVT is suspected (*NICE* 2020; Lim et al [*ASH*] 2018).

A strategy starting with proximal lower extremity or whole-leg ultrasound is suggested for assessing patients suspected of having DVT in a population with high pretest probability (Lim et al [*ASH*] 2018; Kakkos et al [*ESVS*] 2021: class I, level C evidence). This should be followed by serial ultrasound if the initial ultrasound is negative and no alternative diagnosis is identified (Lim et al [*ASH*] 2018). Patients with likely pretest probability for recurrent DVT should undergo proximal lower extremity ultrasound (Lim et al [*ASH*] 2018). For patients with suspected DVT with a likely pre-test probability and negative compression ultrasound scanning, repeat ultrasound assessment should be considered after 5-7 days (Kakkos et al [*ESVS*] 2021: class IIa, level C evidence). For patients with symptomatic calf deep vein thrombosis not receiving anticoagulation, clinical re-assessment and repeat whole leg ultrasound after one week is recommended (Kakkos et al [*ESVS*] 2021: class I, level B evidence).

CT Venography or MR venography:
Because CT uses ionizing radiation, compression ultrasound should be used instead of CT venography when indicated to exclude the presence of DVT (Kirsch et al [*ACR*] 2017). However, if ultrasound capability or expertise is not available, CT venography may be appropriate for suspected DVT (Hanley et al [*ACR*] 2018). For patients with suspected proximal deep vein thrombosis where ultrasound assessment is inconclusive or not feasible, computed tomography venography or magnetic resonance venography should be considered (Kakkos et al [*ESVS*] 2021: class IIa, level C evidence). CT venography is not recommended as an adjunct to CTPA (to increase the diagnostic yield) (Konstantinides et al [*ESC*] 2019, grade III recommendation/level B evidence; Uresandi et al [*SEPAR*] 2013). MR venography (MRV) is a noninvasive alternative to contrast catheter venography (Hanley et al [*ACR*] 2018).

<u>Clinical notes:</u>

- For patients with suspected PE in whom diagnostic imaging is required, a baseline chest radiograph may identify an alternate diagnosis and potentially avoid further diagnostic imaging (*NICE* 2020; Kirsch et al [*ACR*] 2017; Lim et al [*ASH*] 2018). PERC should not be applied to patients at intermediate or high risk for PE (Raja et al [*ACP*] 2015).
- D-dimer testing should not be obtained in patients with a high clinical suspicion or pretest probability for PE as the results will not eliminate the need for anticoagulation therapy (Raja et al [*ACP*] 2015; Uresandi et al [*SEPAR*] 2013). A normal value does not exclude PE in patients with a high pretest probability (Konstantinides et al [*ESC*] 2019).
- Residual defects may complicate the interpretation of CTPA and V/Q in patients with recurrent PE (Choi et al 2016; den Exter et al 2015). If prior imaging is available, comparison of the previous and current imaging is warranted to determine whether the findings are new and represent recurrent PE (Lim et al [*ASH*] 2018).
- CTPA has a sensitivity of 85-95% in patients with a high pretest probability of PE (Raja et al [*ACP*] 2015).
- The sensitivity of V/Q scanning for acute PE is 50-98% and the specificity 20-60% (Raja et al [*ACP*] 2015).
- With an increasing clinical consensus that not all PEs should be treated, it is clear that PE imaging is best evaluated on the basis of outcomes rather than accuracy. In a prospective study comparing V/Q and CTPA, Anderson et al (2007) showed that the outcomes (based on a 3-mo

follow-up of negative cases) were similar (false-negative rate, ≤1%) despite the fact that more PEs were detected with CTPA than with V/Q scans (17.7% for CTPA and 11.7% for V/Q) (Waxman et al [*SNMMI*] 2017).

- Additional testing should be considered in patients with a high clinical suspicion for PE and a negative CTPA (Uresandi et al [*SEPAR*] 2013; Moores et al 2016).
- For patients diagnosed with DVT, the prevalence of clinically silent PE increases with age, and is higher in patients with proximal DVT, compared with those with calf DVT (Kakkos et al [*ESVS*] 2021). However, for patients with DVT, routine investigation for occult PE in the absence of symptoms or signs is not recommended (Kakkos et al [*ESVS*] 2021: class III, level C evidence).
- Lower extremity ultrasound may be beneficial in:
    - Patients with symptoms of acute PE and DVT (Raja et al [*ACP*] 2015; Konstantinides et al [*ESC*] 2019);
    - Patients with a high pretest probability for PE with indeterminate or nondiagnostic CTPA or V/Q scans (PLE expert panel consensus opinion);
    - Patients in whom V/Q scanning cannot be done (Raja et al [ACP] 2015; or
    - Patients for whom CTPA is unable to rule out a PE in the main, lobar or segmental PA (PLE expert panel consensus opinion).
- For patients presenting with signs or symptoms of both DVT and PE, carry out initial diagnostic investigations for either DVT or PE, basing the choice of diagnostic investigations on clinical judgment (*NICE* 2020).
- An ultrasound at 3-6 months is useful as a baseline for comparison with future ultrasound for suspected recurrent DVT (Tran et al [*THANZ*] 2019).
- In general, a negative whole leg ultrasound is sufficient to exclude DVT (Tran et al [*THANZ*] 2019).
- Pulmonary angiography is not free of risk, and is rarely performed now as less-invasive CT angiography offers similar diagnostic accuracy (Konstantinides et al [*ESC*] 2019). Pulmonary angiography is invasive and should only be used in patients in whom the diagnosis is uncertain after V/Q scanning [and ultrasound or the lower extremity], or [if CTPA is inadequate to rule out a PE in the main or lobar artery] (Raja et al [*ACP*] 2015; PLE expert panel consensus opinion).
- The risk of recurrent VTE after discontinuation of treatment is related to the features of the index PE (or VTE) event (Konstantinides et al [*ESC*] 2019). Studies have found that the recurrence rate after discontinuation of treatment was < 3% per year after PE associated with known transient risk factors such as surgery. Patients with minor transient or reversible factors (such as pregnancy or a long-haul flight), non-malignant risk factors or no identifiable risk factor are at intermediate risk for recurrence (3-8%) and patients with active cancer or antiphospholipid antibody syndrome are at high risk for long term recurrence (>8%) (Konstantinides et al [ESC] 2019).

<u>Technical notes:</u>

- CTPA and chest CT with IV contrast should be optimized for pulmonary artery enhancement (Kirsch et al [*ACR*] 2017).
- Chest CT with IV contrast, if performed, should include sagittal and coronal high resolution reconstructions. CTPA and optimized Chest CT IV contrast exams differ only in the inclusion of 3D rendering with CTPA (Kirsch et al [*ACR*] 2017).

Evidence update (2014-present):

High Level of Evidence:

Hess et al (2016), in a systematic review and meta-analysis, reported the diagnostic performance of single-photon emission computed tomography (V/Q SPECT) with or without additional low-dose CT (SPECT/CT) and CT angiography (CTA). Eight articles met inclusion criteria. The authors concluded that V/Q SPECT, V/Q SPECT/CT, and CTA are all viable options, but consider V/Q SPECT/CT to be superior in most clinical settings with better overall diagnostic performance. Pooled sensitivities of V/Q SPECT/CT vs. CTA was (97.6 vs. 82.0%), specificities (95.9 vs. 94.9%), positive predictive values (93.0 vs. 93.8%), negative predictive values (98.6 vs. 84.7%), and accuracies (96.5 vs. 88.6%).

Fabiá Valls et al (2015) reported on a meta-analysis of four prospective studies evaluating a diagnostic algorithm using clinical prediction rules, D-dimer testing and CTPA in consecutive patients with clinically suspected PE and a history of VTE. Four studies concerning 1,286 patients were included with a pooled baseline PE prevalence of 36% (95% confidence interval [CI] 30–42). In only 217 patients (15%; 95% CI 11–20) PE could be excluded without CTPA. The three-month VTE incidence rate was 0.8% (95% CI 0.06–2.4) in patients managed without CTPA, 1.6% (95% CI 0.3–4.0) in patients in whom PE was excluded by CTPA and 1.4% (95% CI 0.6–2.7) overall. In the pooled studies, PE was safely excluded in patients with a history of VTE based on a CPR followed by a D-dimer test and/or CTPA, although the efficiency of the algorithm is relatively low compared to patients without a history of VTE (high level of evidence). One of these studies explicitly excluded patients with ongoing anticoagulation therapy. Two studies excluded patients on vitamin K antagonists. It is assumed that the final study also excluded patients with long term anticoagulant therapy as anticoagulant therapy was withheld in patients with low probability and normal D-dimer levels (high level of evidence).

Kan et al (2015), in a systematic review/meta-analysis, concluded that V/Q SPECT is an accurate method in acute PE patients with high sensitivity and high specificity in the diagnosis of PE. Nine studies met the inclusion criteria. The pooled sensitivity and specificity of V/Q SPECT in the diagnosis of acute PE patients, calculated on a per-patient-based analysis, was 96% (95% confidence interval 95-97%), and 97% (95% CI, 96-98%) respectively. The pooled negative LR, positive LR of V/Q SPECT in acute PE patients was 0.06 (range, 0.02-0.19) and 16.64 (range, 9.78-31.54). The area under the ROC curve of V/Q SPECT in the diagnosis of acute PE patients was 0.99.

Moderate Level of Evidence:

Patel et al (2020), in a systematic review and meta-analysis of 61 studies, reviewed the accuracy of D-dimer assay, compression ultrasonography (CUS), CTPA, and V/Q scanning for the diagnosis of suspected first and recurrent PE. Pooled estimates for D-dimer revealed sensitivity and specificity of 0.97 (95% CI, 0.96-0.98) and 0.41 (95% CI, 0.36-0.46) respectively. CTPA sensitivity and specificity were 0.94 (95% CI, 0.89-0.97) and 0.98 (95% CI, 0.97-0.99) and CUS sensitivity and specificity were 0.49 (95% CI, 0.31-0.66) and 0.96 (95% CI, 0.95-0.98). V/Q scans for which high probability scans were considered positive and low/nondiagnostic/normal scans were considered negative had a sensitivity and specificity of 0.58 (95% CI, 0.50-0.66) and 0.98 (95% CI, 0.96-0.99). The authors conclude that D-dimer had the highest sensitivity when compared with imaging, while CTPA and V/Q scans both had the highest specificity. Squizzato et al (2017) conducted a systematic review and meta-analysis of 13 studies (total n = 1170) to systematically assess the diagnostic accuracy of MRI for PE diagnosis. 11/13 studies used MR contrast. Only 3 (23.1%) studies reported rate of inconclusive MRI results, ranging from 6.3 to 30.3% (mean prevalence of 19%) of all performed MRI. All 3 studies required imaging down to subsegmental arteries to exclude PE. After exclusion of technical inadequate results, MRI bivariate weighted mean sensitivity was 80.9% (95% CI, 68.2-89.4%) with a bivariate weighted mean specificity of 96.4% (95% CI, 92.4-

98.3%). The authors conclude that MRI has high specificity but limited sensitivity for the diagnosis of PE. Inconclusive results are a major limitation to the practical application of MRI.

Stubbs et al (2017), in a retrospective study of 1300 consecutive V/Q exams, found that indeterminate scans were decreased from 72/589 (12.2%) in the planar group ($P < 0.05$) to 42/542 (7.7%) in the SPECT group. The authors concluded that V/Q SPECT has greater diagnostic certainty of PE with a reduction in an indeterminate scan frequency compared with planar scintigraphy.

Li et al (2016), in a systematic review/meta-analysis, concluded that MRA can be used for the diagnosis of acute PE, however, due to limited sensitivity, cannot be used as a stand-alone test to exclude acute PE. Five studies were included in the meta-analysis. The pooled sensitivity 0.83 (0.78-0.88) and specificity 0.99 (0.98-1.00) demonstrated that MRA diagnosis had limited sensitivity and high specificity in the detection of acute PE.

Moores et al (2016) conducted a prospective study of 498 patients with high probability of PE and a completed CTPA study. CTPA excluded PE in 134 patients; in these patients, the pooled incidence of VTE was 5.2% (seven of 134 patients; 95% confidence interval [CI] 1.5–9.0). None of the patients had a fatal PE during follow-up. The authors concluded that "a negative multi-detector CTPA result alone may not safely exclude PE in patients with a high clinical retest probability".

Low Level of Evidence:
Kornblum et al (2021) conducted a multisite retrospective study to evaluate the yield of CTPA for PE across a variety of care settings in a community-based healthcare system. A total of 7850 CTPA studies met criteria for inclusion and were reviewed. PE was found in 884 (11.3%) of studies performed. Outpatients had a lower yield of PE (3.8%, $p<0.001$) compared with inpatients (14.1%) and ED patients (10.7%, $p<0.001$). Patients with diagnosis of DVT or neoplasm had increased incidence of PE when compared to those without ($p<0.001$ for both). The authors conclude that overall yield of CTPA for PE in a community-based system is similar to that at academic centers.

Banerjee et al (2019) developed a machine learning model approach, based on EMR data, for predicting PE imaging outcomes of 3,214 patients (mean age 60) referred for CT imaging. The model was evaluated in both multi-institutional inpatient and outpatient settings, and compared with clinical scoring systems (Wells, PERC, and rGeneva). The best-performing model achieved an AUROC performance of predicting a positive PE study of 0.90 (95%CI, 0.87-0.91) on intra-institutional holdout data with an AUROC of 0.71 (95%CI, 0.69-0.72) on an external data set. The authors conclude that the machine learning model may consider multitudes of patient-specific risk factors and dependencies in retrospective structured EMR data to arrive at an imaging-specific PE likelihood recommendation and may accurately be generalized to new population distributions. The findings of this study suggest that this model may be used as an automated CDS tool to improve use of PE-CT imaging in referred patients.

Chen et al (2017) conducted a meta-analysis of 10 studies (590 total cases) to compare the effects of MRI and CT in the assessment of PE. The MRI technique and the use of MR contrast in each study was not stated in the meta-analysis. In addition, the article does not provide information on the number of inconclusive or nondiagnostic MRI exams in the studies. The pooled sensitivity of CT was 0.90 (95% CI, 0.85-0.93) and pooled specificity of CT was 0.88 (95% CI, 0.77-0.95). The pooled sensitivity of MRI was 0.92 (95% CI, 0.89-0.94) and pooled specificity of MRI was 0.91 (95% CI, 0.77-0.97). The SROC curve areas under the curve of CT and MRI were 0.94 (95% CI, 0.91-0.96) and 0.93 (95% CI, 0.91-0.95),

respectively. The authors conclude that this meta-analysis demonstrates that MRI has better sensitivity and specificity in detecting subsegmental artery PE.

Pasin et al (2017) performed a prospective evaluation of the accuracy of a free breathing True-FISP MRI (without contrast) for pulmonary embolism in 93 patients with CTPA as the gold standard. PE prevalence was 22%. During the 1-year follow-up period, eight patients died, and PE was responsible for death in 12.5% of cases. Of the patients who developed PE, only 5% died due to this condition. There were no differences between MR and CT embolism detection in these subjects. MR sequences had a sensitivity of 85%, specificity was 98.6% and accuracy was 95.6%. Agreement between readers was high (κ= 0.87). The authors concluded that compared with contrast-enhanced CT, unenhanced MR sequences demonstrate good accuracy and no differences in the mortality rates in 1 year were detected.

Phillips et al (2015), in a systematic review and meta-analysis of 19 studies (n = 5,923 patients), showed no performance difference between V/Q SPECT and CTPA; planar V/Q is inferior. CTPA is clearly the most cost effective technique. V/Q SPECT should be considered in situations where radiation dose is of concern or CTPA is inappropriate (high level of evidence for diagnostic accuracy).
Zhou et al. (2015) conducted a systematic review and meta-analysis of 15 studies for patient accuracy and 9 studies for vessel accuracy on MRI. The authors concluded that MRI exhibits a high diagnostic capability with proximal arteries, but lacks sensitivity for peripheral embolism. The patient-based analysis yielded an overall sensitivity of 0.75 (0.70-0.79) and 0.84 (0.80-0.87) for all patients and patients with technically adequate images, respectively. The overall specificity was 0.80 (0.77-0.83) and 0.97 (0.96-0.98). On average, MRI was technically inadequate in 18.89% of patients (range, 2.10%-27.70%).

Patients with history of thromboembolic disease and suspicion for chronic thromboembolic pulmonary hypertension (CTEPH):

- Green – **Ventilation-Perfusion lung scan (planar V/Q, V/Q SPECT, or V/Q SPECT/CT)**
- Yellow – **CT pulmonary angiography (CTPA)** or **CT chest with IV contrast**
- Yellow – **Perfusion (Q) lung scan**
  [patient unable to undergo V/Q scan]
- Red – **MRI chest; MR angiography chest; CT chest without IV contrast; CT chest without and with IV contrast; CT venography; MR venography**

Level of Evidence: Low

Notes concerning applicability and/or patient preferences: Consulting and reporting requirements are not required for orders for applicable imaging services made by ordering professionals under the following circumstances (*42 C.F.R. § 414.94. 2015*):

- Emergency services when provided to individuals with emergency medical conditions.
- For an inpatient and for which payment is made under Medicare Part A.

Lung perfusion MRI imaging has been reported to have a similar accuracy to V/Q scanning, however, access to this technology is currently limited (Helmersen et al [*CTS*] 2019). Lung perfusion MRI requires complex image acquisition and post processing needs, and expertise in this area is limited. This technology was downgraded as it is thought to have limited applicability in the community environment (PLE expert panel consensus opinion).

Guideline and PLE expert panel consensus summary:
Routine screening (or follow-up imaging) for the presence of CTEPH after an acute PE is not recommended in asymptomatic patients (Helmersen et al [*CTS*] 2019, GRADE 1C; Galiè et al [*ESC*] 2015; Tran et al [*THANZ*] 2019, Low; evidence moderate). However, specific subpopulations which warrant closer follow-up for post-acute PE include (Helmersen et al [*CTS*] 2019):

- Patients with acute PE who may already have CTEPH at initial presentation;
- Patients with acute PE who are at higher risk to develop CTEPH;
- Patients with acute PE who remain symptomatic despite 3 months of effective anticoagulation; and/or
- Other clinical indications for follow-up pulmonary vascular imaging.

V/Q Scanning:
V/Q scanning is recommended as the initial test in all patients with unexplained PH to assess for CTEPH (Sirajuddin et al [*ACR*] 2017; Jaff et al 2011; Galiè et al [*ESC*] 2015; Helmersen et al [*CTS*] 2019, GRADE 1C) and to differentiate CTEPH from other causes of PH (Sirajuddin et al [*ACR*] 2017).
Either planar or SPECT nuclear V/Q are acceptable modalities for initial testing to rule out CTEPH (Helmersen et al [*CTS*] 2019). Planar V/Q lung scan has 96-97% sensitivity and 90-95% specificity for the diagnosis. SPECT seems less sensitive than planar V/Q scanning if assessed at a level of individual segmental arteries, but it is unlikely to miss clinically relevant CTEPH in an individual patient (Konstantinides et al [*ESC*] 2019). A normal perfusion (Q) scan effectively rules out the possibility of CTEPH (Helmersen et al [*CTS*] 2019).

CT Pulmonary Angiography (CTPA) or **CT Chest with IV contrast:**
While CTPA is gaining ground as a diagnostic modality in CTEPH, however, a negative, indeterminate, or technically poor CTPA does not exclude CTEPH (Helmersen et al [*CTS*] 2019). If CTPA is used to differentiate CTEPH from IPAH, the exam should be performed in a center of excellence with 40- or 64-row MDCT technology and subspecialty radiologic expertise (PLE expert panel consensus opinion). High-resolution CT scan of the chest can be used as an alternative to CTPA, depending on institutional preference (Sirajuddin et al [*ACR*] 2017), and may assist in the differential diagnosis of CTEPH: showing emphysema, bronchial, or interstitial lung disease, as well as infarcts and vascular and thoracic wall malformations (Konstantinides et al [*ESC*] 2019). Patients with non-positive CTPA results and suspected CTEPH should be referred to an expert PH center for further diagnostic testing, such as conventional pulmonary angiography (Helmersen et al [*CTS*] 2019).

MR Imaging
Magnetic resonance imaging of the pulmonary vasculature is considered inferior to CT (Konstantinides et al [*ESC*] 2019), with CTPA having better sensitivity for detection of CTEPH (Sirajuddin et al [ACR} 2017). As such, the routine use of MR pulmonary angiography is not recommended to establish the diagnosis and/or to assess the anatomic extent and location of chronic thromboembolic material in patients with suspected CTEPH (Helmersen et al [*CTS*] 2019, GRADE 1C).

Clinical notes:

- Patients with unexplained dyspnea, exercise intolerance or clinical evidence of right-sided heart failure, with or without prior history of symptomatic VTE, should be evaluated for CTEPH (Jaff et al., [*AHA*] 2011/ Class I recommendation, level C evidence).
- When present, the clinical symptoms of CTEPH may resemble those of acute PE or of pulmonary artery hypertension (PAH). In the latter context edema and hemoptysis occur more often in CTEPH, while syncope is more common in PAH (Konstantinides et al [ESC] 2019).
- In patients with PH who are not anticoagulated, consider testing for acute PE according to clinical probability score. Acute PE can be an easily missed contributor to PH, particularly in patients with co-existing lung and heart diseases (Helmersen et al [*CTS*] 2019).
- V/Q scanning has a sensitivity of 90-100% and specificity of 90-100% for the differentiation of CTEPH and IPAH (Jaff et al [*AHA*] 2011; Sirajuddin et al [*ACR*] 2017; Galiè et al [*ESC*] 2015).
- A normal or low probability V/Q scan effectively excludes the diagnosis of CTEPH with a sensitivity of 90–100% and a specificity of 94–100% (Jaff et al [*AHA*] 2011; Sirajuddin et al [*ACR*] 2017; Tunariu et al 2007).
- A relatively normal CTPA can be observed in CTEPH despite substantial V/Q scan abnormalities (Jaff et al [*AHA*] 2011).
- Initial studies found that V/Q imaging was more sensitive for CTEPH compared to CTPA at 96-97.4% versus 51%. Subsequent studies with 40- or 64-row scanners have suggested that CTPA may be accurate for the detection of CTEPH in expert hands (Sirajuddin et al [*ACR*] 2017; Galiè et al [*ESC*] 2015). If CTPA is used to differentiate CTEPH from IPAH then 40- or 64- row MDCT technology is recommended at a center with local expertise (PLE expert panel consensus opinion).
- Findings of chronic thromboembolism on CTPA include intraluminal fibrous bands or webs, stenosis, partial occlusions, total occlusions (pouch defects), and eccentric organized thrombi that form an obtuse angle with the vessel wall (Helmersen et al [*CTS*] 2019; Konstantinides et al [*ESC*] 2019).

- A positive CTPA, confirming chronic thromboembolism, should prompt referral to an expert PH center for establishment of a formal diagnosis of CTEPH, and assessment of most appropriate treatment (Helmersen et al [*CTS*] 2019).
- Pulmonary angiographic and V/Q imaging data may be complementary when used for the planning of CTEPH treatments (Helmersen et al [*CTS*] 2019).

Technical notes:

- CTPA and chest CT with IV contrast should be optimized for pulmonary artery enhancement (Kirsch et al [*ACR*] 2017).
- Chest CT with IV contrast, if performed, should include sagittal and coronal high resolution reconstructions. CTPA and optimized Chest CT IV contrast exams differ only in the inclusion of 3D rendering with CTPA (Kirsch et al [*ACR*] 2017).
- CTPA images may be non-diagnostic or suboptimal due to technical issues. Specific recommended technical criteria include a short breath hold acquisition (3–5 sec) as well as thin collimation and thin-slice reconstruction (≤ 1mm) in axial, coronal and sagittal planes. 3-dimensional surface-shaded reconstructions may improve depiction of vessel cutoff. Maximum intensity projections and oblique reconstructions along the long axis of the left and right pulmonary arteries may also be helpful (Helmersen et al [*CTS*] 2019).

Evidence update (2015-present):

Moderate Level of Evidence:

Wang et al (2020) prospectively compared the performance of V/Q scanning, V/Q SPECT, and CTPA in CTEPH, using digital subtraction pulmonary angiography (PA) as the reference standard. A total of 150 participants (mean age 42 years) with suspected CTEPH were enrolled and underwent all four procedures within 1 week. Digital subtraction PA assessments confirmed CTEPH in 51 patients. All three imaging methods showed high sensitivity (V/Q SPECT, 98%; V/Q planar scintigraphy, 98%; CTPA, 94%) and specificity (V/Q SPECT, 89%; V/Q planar scintigraphy, 91%; CT PA, 96%) (all P > .05). However, both V/Q scanning techniques were more sensitive (V/Q SPECT: 85%, P < .001 vs CT PA: 67%; V/Q planar scintigraphy: 83%, P < .001 vs CT PA: 67%), and less specific (V/Q planar scintigraphy: 51%, P = .03 vs CT PA: 60%; V/Q SPECT: 42%, P < .01 vs CT PA: 60%) than was CTPA for segmental analysis. Areas under the curve for CTPA, V/Q planar scintigraphy, and V/Q SPECT were 0.95, 0.95, and 0.94, respectively (all P < .05), for individual analysis, and 0.64, 0.67, and 0.64, respectively, by segment (V/Q planar scintigraphy vs V/Q SPECT, P = .02; V/Q planar scintigraphy vs CT PA, P = .08; V/Q SPECT vs CT PA, P = .94). The authors conclude that V/Q scanning was more sensitive and less specific than CTPA for detecting vascular obstructions at the segmental pulmonary arterial level.

Dong et al (2015), in a systematic review and meta-analysis of 11 articles (n = 712), found CT as a favorable method to rule in CTEPH and to rule out pulmonary endarterectomy (PEA) patients for proximal branches. The patient-based analysis demonstrated a pooled sensitivity of 76% (95% confidence interval [CI]: 69% to 82%), and a pooled specificity of 96% (95% CI: 93%to 98%). This resulted in a pooled diagnostic odds ratio (DOR) of 191 (95% CI: 75 to 486).

Low Level of Evidence:

Masy et al (2018), in a retrospective study, compared concordance rates between dual-energy CT (DECT) perfusion and V/Q scanning in diagnosing CTEPH among 80 consecutive patients with pulmonary hypertension. Final diagnosis (36 with CTEPH, 44 with non-CTEPH) was established by multidisciplinary expert review (gold standard) according to recommended guidelines and standard CT angiographic information. Imaging criteria for diagnosing CTEPH relied on ≥ 1 segmental triangular perfusion defect

on DECT perfusion studies and V/Q mismatch on scintigraphy examinations. On DECT perfusion studies, there were 35 true positives, 6 false positives and 1 false negative (sensitivity 0.97, specificity 0.86, PPV 0.85, NPV 0.97). On V/Q scans, there were 35 true positives and 1 false negative (sensitivity 0.97, specificity 1, PPV 1, NPV 0.98). There was excellent agreement between CT perfusion and scintigraphy in diagnosing CTEPH (kappa value 0.80). Combined information from DECT perfusion and CT angiographic images enabled correct reclassification of the DECT perfusion studies. *The PLE expert panel noted that DECT perfusion scan is an emerging technology and has limited availability in the community outpatient setting*.

Evaluation for a new or recurrent pulmonary embolism in patients on therapy for thromboembolic disease (DVT or PE) and the results are expected to modify current therapy:

- Green – **CT pulmonary angiography (CTPA)** or **CT chest with IV contrast**
- Yellow – **Ventilation-Perfusion lung scan (planar V/Q** or **V/Q SPECT or V/Q SPECT/CT)**
- Yellow – **Perfusion (Q) lung scan**
  [patient unable to undergo CT and unable to undergo V/Q scan]
- Yellow – **Pulmonary MR angiography**
  [patient unable to undergo CT; or when previous CT is indeterminate]
- Yellow – **CT venography or MR venography (lower extremities)**
  [suspect DVT and ultrasound not available]
- Red – **CT chest without IV contrast; CT chest without and with IV contrast; MRI chest**

Level of Evidence: PLE expert panel consensus opinion

Notes concerning applicability and/or patient preferences: Consulting and reporting requirements are not required for orders for applicable imaging services made by ordering professionals under the following circumstances (*42 C.F.R. § 414.94. 2015*):

- Emergency services when provided to individuals with emergency medical conditions.
- For an inpatient and for which payment is made under Medicare Part A.

V/Q SPECT and V/Q SPECT/CT were downgraded from green to yellow despite favorable accuracy in recent reports (Hess et al 2016; Stubbs et al 2017) because of concern surrounding the applicability and availability of this evolving technology in the community outpatient setting (PLE expert panel consensus opinion).

Pulmonary MRA was downgraded from green to yellow despite favorable accuracy reported in the recent studies (Chen et al 2017; Squizzato et al 2017; and Pasin et al 2017) because of concerns about the applicability, expertise and availability of emergent pulmonary MRA in an outpatient setting. Pulmonary MRA was also downgraded because of concerns over the rate of nondiagnostic MRI studies which was reported to be 6.3-30.3% in three of the studies in the Squizzato et al 2017 review, and 18.89% in the Zhou et al 2015 study. The use of MRI is also limited by concerns over the need to exclude electrical implants, metallic implants and foreign bodies in patients undergoing emergent imaging. The expert panel thought that if pulmonary MRA is to be performed to exclude PE, it should only be done in MRI centers with high field strength MRI systems, experience, and appropriate clinical expertise in pulmonary imaging (PLE expert panel consensus opinion).

Guideline and PLE expert panel consensus summary:
Preventing frequent use of repeated CT requires thoughtful planning, and clinicians should educate patients about the risk of radiation from multiple CTs. When such patients develop symptoms, providers should review them in the context of their prior symptoms and discuss testing strategies with the patients and their primary care providers (Raja et al [*ACP*] 2015). In patients with recurrent VTE despite anticoagulation, it is important for providers to first assess adherence to therapy and identify clinical conditions associated with anticoagulation failure including cancer, antiphospholipid syndrome, heparin-induced thrombocytopenia and vascular compression syndromes (Streiff et al 2016).

CT Pulmonary Angiography (CTPA) or **CT Chest with IV contrast:**
CT angiography (CTA) is the clinical standard for excluding a pulmonary embolism (Beache et al [*ACR*] 2020), but should only be obtained if documentation of recurrent PE will change current therapy (PLE expert panel consensus opinion). Noncontrast chest CT can be used to assess for the presence of other noncardiac causes of chest pain (Beache et al [*ACR*] 2020).

V/Q Scanning:
Tc-99m ventilation-perfusion (V/Q) lung scan can also be useful to detect a pulmonary embolism (Beache et al [*ACR*] 2020), but should only be obtained if documentation of recurrent PE will change current therapy (PLE expert panel consensus opinion) or when otherwise clinically indicated (Waxman et al [*SNMMI*] 2017). V/Q scanning is to be used to evaluate for recurrent PE, the previous documentation of PE should also have been completed with V/Q, however, and not CTPA (Waxman et al [*SNMMI*] 2017).

Pulmonary MR angiography:
Some guidelines note that MRA is not recommended for ruling out PE, as it has not been found to have the sensitivity or specificity required to detect segmental or subsegmental PEs and has a high proportion of inconclusive scans (Kirsch et al [*ACR*] 2017; Konstantinides et al [*ESC*] 2019, class III recommendation/level A evidence; Uresandi et al [*SEPAR*] 2013). Others note that MRA has potential use if pulmonary embolism is being considered (e.g., Beache et al [*ACR*] 2020). A recent systematic review/meta-analysis indicates that pulmonary MRA using newer techniques has a similar accuracy for large vessel pulmonary embolism, and may have a higher sensitivity for subsegmental pulmonary embolism (Chen et al 2017). As such, pulmonary MRA may be acceptable in patients who are unable to undergo CT, or when CTPA (or CT) are unable to rule out PE (PLE expert panel consensus opinion).

Ultrasound:
Imaging of the lower extremity may be performed to exclude new or recurrent DVT (Kakkos et al [*ESVS*] 2021: class I, level C evidence). Because of the additional radiation, compression ultrasound should be used instead of CT venography when indicated to exclude the presence of DVT (Kirsch et al [*ACR*] 2017; Hanley et al [ACR] 2018).

CT Venography or MR venography:
For patients with suspected proximal deep vein thrombosis where ultrasound assessment is inconclusive or not feasible, computed tomography venography or magnetic resonance venography should be considered (Kakkos et al [*ESVS*] 2021: class IIa, level C evidence). Because CT uses ionizing radiation, compression ultrasound should be used instead of CT venography when indicated to exclude the presence of DVT (Kirsch et al [*ACR*] 2017). However, if ultrasound capability is not available, CT venography may be appropriate for suspected DVT (Hanley et al [*ACR*] 2018). CT venography is not recommended as a routine adjunct to CTPA (to increase the diagnostic yield) (Konstantinides et al [*ESC*] 2019, grade III recommendation/level B evidence; Uresandi et al [*SEPAR*] 2013). MR venography (MRV) is a noninvasive alternative to contrast catheter venography (Hanley et al [*ACR*] 2018).

<u>Clinical notes:</u>

- The standard diagnostic algorithms apply in patients with a history of treated PE, although they are less efficient, with CTPA avoided in only 15% of patients with this history (Fabiá Valls et al 2015).

- Residual defects may complicate the interpretation of CTPA and V/Q in patients with recurrent PE (Choi et al 2016; den Exter et al 2015).
- An ultrasound at 3-6 months is useful as a baseline for comparison with future ultrasound for suspected recurrent DVT (Tran et al [*THANZ*] 2019).
- In general, a negative whole leg ultrasound is sufficient to exclude DVT (Tran et al [*THANZ*] 2019).

Technical notes:

- CTPA and chest CT with IV contrast should be optimized for pulmonary artery enhancement (Kirsch et al [*ACR*] 2017).
- Chest CT with IV contrast, if performed, should include sagittal and coronal high resolution reconstructions. CTPA and optimized Chest CT IV contrast exams differ only in the inclusion of 3D rendering with CTPA (Kirsch et al [*ACR*] 2017).

Evidence update (2017-present):

Moderate Level of Evidence:

Patel et al (2020), in a systematic review and meta-analysis of 61 studies, reviewed the accuracy of D-dimer assay, compression ultrasonography (CUS), CTPA, and V/Q scanning for the diagnosis of suspected first and recurrent PE. Pooled estimates for D-dimer revealed sensitivity and specificity of 0.97 (95% CI, 0.96-0.98) and 0.41 (95% CI, 0.36-0.46) respectively. CTPA sensitivity and specificity were 0.94 (95% CI, 0.89-0.97) and 0.98 (95% CI, 0.97-0.99) and CUS sensitivity and specificity were 0.49 (95% CI, 0.31-0.66) and 0.96 (95% CI, 0.95-0.98). V/Q scans for which high probability scans were considered positive and low/nondiagnostic/normal scans were considered negative had a sensitivity and specificity of 0.58 (95% CI, 0.50-0.66) and 0.98 (95% CI, 0.96-0.99). The authors conclude that D-dimer had the highest sensitivity when compared with imaging, while CTPA and V/Q scans both had the highest specificity.

Squizzato et al (2017) conducted a systematic review and meta-analysis of 13 studies (total n = 1170) to systematically assess the diagnostic accuracy of MRI for PE diagnosis. 11/13 studies used MR contrast. Only 3 (23.1%) studies reported rate of inconclusive MRI results, ranging from 6.3 to 30.3% (mean prevalence of 19%) of all performed MRI. All 3 studies required imaging down to subsegmental arteries to exclude PE. After exclusion of technical inadequate results, MRI bivariate weighted mean sensitivity was 80.9% (95% CI, 68.2-89.4%) with a bivariate weighted mean specificity of 96.4% (95% CI, 92.4-98.3%). The authors conclude that MRI has high specificity but limited sensitivity for the diagnosis of PE. Inconclusive results are a major limitation to the practical application of MRI.

Low Level of Evidence:

Chen et al (2017) conducted a meta-analysis of 10 studies (590 total cases) to compare the effects of MRI and CT in the assessment of PE. The MRI technique and the use of MR contrast in each study was not stated in the meta-analysis. In addition, the article does not provide information on the number of inconclusive or nondiagnostic MRI exams in the studies. The pooled sensitivity of CT was 0.90 (95% CI, 0.85-0.93) and pooled specificity of CT was 0.88 (95% CI, 0.77-0.95). The pooled sensitivity of MRI was 0.92 (95% CI, 0.89-0.94) and pooled specificity of MRI was 0.91 (95% CI, 0.77-0.97). The SROC curve areas under the curve of CT and MRI were 0.94 (95% CI, 0.91-0.96) and 0.93 (95% CI, 0.91-0.95), respectively. The authors conclude that this meta-analysis demonstrates that MRI has better sensitivity and specificity in detecting subsegmental artery PE.

Surveillance of established thromboembolic disease prior to completion of anticoagulation therapy

- **Green** –
- **Yellow** –
- **Red** – **CT pulmonary angiography (CTPA); CT; MR angiography; MRI; Ventilation-Perfusion (V/Q) scan; Perfusion (Q) scan; CT venography; MR venography**

Level of Evidence: PLE expert panel consensus opinion

Notes concerning applicability and/or patient preferences: none

Guideline and PLE expert panel consensus summary:
In patients with a history of PE, use of thoracic imaging tests is not recommended to evaluate the persistence of residual thrombosis or reperfusion of the initial defects (Uresandi et al [*SEPAR*] 2013). The patency of the pulmonary arterial bed is restored in the majority of PE survivors within the first few months following the acute episode; therefore, no routine follow-up CTPA imaging is needed in such patients treated for PE (Konstantinides et al [*ESC*] 2019).

Clinical notes:

- The presence of residual defects on CTPA at 6 months is not predictive of recurrent VTE (den Exter et al 2015).

Evidence update (2015-present):
Moderate Level of Evidence:
den Exter et al (2015) conducted a prospective multi-center cohort study of 157 patients with acute PE diagnosed by CT pulmonary angiography (CTPA) who underwent follow-up CTPA-imaging after six months of anticoagulant treatment. After six months of treatment, complete PE resolution had occurred in 84.1% of the patients (95% confidence interval (CI): 77.4–89.4%). During follow-up, 16 (10.2%) patients experienced recurrent VTE. The presence of residual thromboembolic obstruction was not associated with recurrent VTE (adjusted hazard ratio: 0.92; 95% CI: 0.2–4.1). The authors conclude "These findings, combined with the absence of a correlation between residual thrombotic obstruction and recurrent VTE, do not support the routine use of follow-up CTPA-imaging in patients treated for acute PE".

Low Level of Evidence:
Begic et al (2015) conducted a prospective observational study of 269 patients with suspected PE and no history of PE who underwent V/Q SPECT at index with follow-up at three and six months. They found that of the 100 patients with PE, 71% (48/67) had a normal V/Q scan at three months. Of the 35 patients with a normal V/Q scan (without risk factors) who stopped anticoagulation at three months, none developed a recurrent PE. The authors conclude that normalization of perfusion at three months was a reliable indicator that therapy could be withdrawn.

Guideline exclusions:

- Cases meeting the definition of a suspected or confirmed emergency medical condition
- Use of echocardiography in the diagnosis of CTEPH
- Positron emission tomography (PET) imaging
- Detection of PE in patients during pregnancy
- Pediatric patients

AUC Revision History:

Revision Date	New Clinical Scenario	Approval Body
07/25/2017	Initial Document Development	CDI Quality Institute's Multidisciplinary Committee
07/31/2018	N/A	CDI Quality Institute's Multidisciplinary Committee
09/10/2019	N/A	CDI Quality Institute's Multidisciplinary Committee
10/20/2020	N/A	CDI Quality Institute's Multidisciplinary Committee
11/09/2021	N/A	CDI Quality Institute's Multidisciplinary Committee

Information on our evidence development process, including our conflicts of interest policy is available on our website at **https://www.mycdi.com/ple**

Provider Led Entity

Appropriateness of Advanced Imaging in Patients with Pulmonary Embolism Bibliography

11/09/2021

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