CDI QUALITY INSTITUTE

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CDI Quality Institute PLE
Cough / Dyspnea AUC
2021 Update

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Appropriateness of advanced imaging procedures* in patients with cough and/or dyspnea:

*Including MRI, CT, MR angiography, CT angiography, Nuclear medicine scanning and FDG-PET scanning

Abbreviation list:

ACCP	American College of Chest Physicians
ACOEM	American College of Occupational and Environmental Medicine
ACR	American College of Radiology
ARI	Acute respiratory illness
ATS	American Thoracic Society
BTS	British Thoracic Society
CAP	Community acquired pneumonia
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CT	Computed tomography
CTPA	CT pulmonary angiography
CTA	CT angiography
CTS	Canadian Thoracic Society
ECMM	European Confederation of Medical Mycology
EORTC	European Organization for Research & Treatment of Cancer
ESCMID	European Society of Clinical Microbiology & Infectious Diseases
ERS	European Respiratory Society
FDG-PET	Fludeoxyglucose-positron emission tomography
GERD	Gastroesophageal reflux disease
GGO	Ground-glass opacity
GRS	German Respiratory Society
HRCT	High-resolution computed tomography
ICS	Indian Chest Society
IDSA	Infectious Diseases Society of America
ILD	Interstitial lung disease
IPA	Invasive pulmonary aspergillosis
IPF	Idiopathic pulmonary fibrosis
LDCT	Low dose computed tomography
MRI	Magnetic resonance imaging
MSGERC	Mycoses Study Group Education & Research Consortium
NCCP	National College of Chest Physicians
NICE	National Institute for Health and Care Excellence
PFT	Pulmonary function testing
RSNA	Radiological Society of North America
RT-PCR	Reverse transcription polymerase chain reaction
TB	Tuberculosis
TSA	Thoracic Society of Australia
ULD	Ultra-low dose
US	Ultrasound
WHO	World Health Organization

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).

Cough/dyspnea AUC summary:

- Cough due to viral infection of the upper and/or lower respiratory tract is a very common reason for a medical consultation. In the adult patient, acute cough lasts up to 3 weeks.
- A history and physical examination are typically sufficient for the diagnosis of acute/subacute cough. Indications for further investigation typically require red flags (e.g., hemoptysis, suspected pneumonia or tuberculosis, immunocompromised state, high grade fever) or chronic cough that persists after ruling out the most common causes. Chronic cough is defined by recent guidelines as one lasting 8 weeks or more.
- After ruling out the most common causes, such as upper airway cough syndrome, GERD, eosinophilic bronchitis, or asthma, a chest CT is usually appropriate for patients with persistent chronic cough and/or dyspnea.
  - Lung disease may generally be classified as restrictive (e.g., interstitial lung disease) or obstructive (e.g., COPD, bronchiectasis) in its pattern.
  - In most instances, a CT of the chest without IV contrast is the most appropriate initial imaging modality.
  - CT of the chest with IV contrast is primarily helpful in scenarios where alternative diagnoses such as pulmonary embolism, malignancy, or abscess are being considered.
- MRI of the chest is not indicated as an initial imaging modality for patients with cough and/or dyspnea, but may be useful to detect or characterize suspected diseases of the pleura, such as pleurisy, pleural effusion, or pneumothorax.
- CT angiography chest or CT pulmonary angiography (CTPA) may be useful to further evaluate hemoptysis cases, and to exclude vascular causes of cough, such as a suspected pulmonary embolism (see separate AUC document for guidance).
- Chest CT may be helpful in some instances of cough with suspicion of COVID-19, such as when testing is delayed or unavailable, or when symptoms are moderate-to-severe. However, advanced imaging should not be used in all scenarios.

Cough and/or dyspnea with suspicion of lung cancer:

While cough is a symptom of lung cancer, this AUC does not specifically address patients with suspected or confirmed lung cancer, whether primary or metastatic. Instead, an AUC specific to lung cancer should be used to address the advanced imaging for patients meeting this clinical scenario.

Cough and/or dyspnea presenting with a high clinical suspicion for pneumonia and negative/indeterminate chest radiographs:

- Green – **CT chest without IV contrast**
- Yellow – **CT chest with IV contrast**
- Yellow – **MRI chest**
  [detect or characterize suspected pleural involvement]
- Yellow – **CT angiography chest** or **CT pulmonary angiography (CTPA)**
  [evaluate hemoptysis or suspected vascular involvement]
- Red – **Scintigraphy; PET**; **MR angiography**; **CT chest without and with IV contrast**; **SPECT**

Level of Evidence: CT: 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.

Guideline and PLE expert panel consensus opinion summary:

CT chest

For outpatient adults with acute cough and abnormal vital signs secondary to suspected pneumonia, it is suggested that chest radiographs be initially ordered to improve diagnostic accuracy (Hill et al 2019: grade 2C recommendation). CT of the thorax should not be performed routinely in patients with community acquired pneumonia (Gupta et al [*ICS/NCCP*] 2012). Its use may be warranted, however, in certain patients (e.g., patients who cannot reliably follow-up, with advanced age, or with significant comorbidities) when initial chest radiograph is negative or equivocal (Jokerst et al [*ACR*] 2018) and a definitive diagnosis is needed (PLE expert panel consensus opinion). In up to 27% of cases, pneumonia might be demonstrated on CT following a negative or non-diagnostic chest radiograph (Gupta et al [*ICS/NCCP*] 2012). In patients with acute respiratory illness with a positive physical examination, abnormal vital signs, or other risk factors and negative or equivocal initial chest radiographs, a CT chest without IV contrast is considered to be usually appropriate (Jokerst et al [*ACR*] 2018).

CT chest with IV contrast is not routinely indicated in patients with high clinical suspicion of pneumonia (Jokerst et al [*ACR*] 2018). Its use is limited to scenarios where alternative diagnoses (e.g., pulmonary embolus or malignancy) or complications of pneumonia such as abscess or empyema are being considered (PLE expert panel consensus opinion).

MRI chest

While data suggest a potential role for MRI in detecting bacterial pneumonia, the sensitivity of CT appears to be slightly superior (Jokerst et al [*ACR*] 2018). Therefore, whenever a definitive diagnosis of bacterial pneumonia is needed, CT should be the recommended imaging procedure of choice (PLE expert panel consensus opinion). MRI has been shown to be able to detect pleural effusions, pleural adhesions and pleural loculations, and therefore, its use may be appropriate in certain circumstances (Jokerst et al [ACR] 2018).

CT angiography

CTA chest is not routinely indicated in the evaluation of patients with suspected pneumonia. CT chest with IV contrast, CTA or CTPA may be indicated in pneumonia patients with suspected PE or in pneumonia patients with hemoptysis (PLE expert panel consensus opinion). The *ACR* states that CT chest with IV contrast or CTA is usually appropriate for the evaluation of patients with nonmassive non–life-threatening hemoptysis (Olsen et al [ACR] 2020).

<u>Clinical notes:</u>

- The diagnosis of community acquired pneumonia is a clinical diagnosis (PLE expert panel consensus opinion).
- Acute cough is a classic symptom of pneumonia; typical pneumococcal pneumonia may be accompanied by hemoptysis (Kardos et al [GRS] 2020).
- In most instances, the diagnosis of community acquired pneumonia (CAP) is made with certainty based on clinical features and chest radiograph findings (Gupta et al [*ICS/NCCP*] 2012):
    - In the absence of chest radiography, CAP is defined as (a) symptoms of an acute lower respiratory tract illness for less than 1 week; and (b) at least one systemic feature (fever, chills, and/or severe malaise); and (c) new focal chest signs on examination (bronchial breath sounds and/or crackles); with (d) no other explanation for the illness.
    - When chest radiography is available, CAP is defined as: symptoms and signs as above with new radiographic opacity for which there is no other explanation (not due to pulmonary edema or infarction).
- The need for imaging in the acute respiratory illness (ARI) patient may depend on a number of factors, which can include severity of illness; presence of fever, leukocytosis, or hypoxemia; clinical history; physical examination findings; patient age; and the presence of other risk factors (Jokerst et al [*ACR*] 2018).
- The primary role of imaging in patients with acute respiratory illness (ARI) is to aid in the diagnosis or exclusion of bacterial pneumonia (Jokerst et al [*ACR*] 2018) and to assess patients who do not respond to initial therapy (see next scenario).
- There is a growing body of literature suggesting that bedside lung ultrasound can be a useful tool in the diagnosis and management of bacterial pneumonia (particularly its complications), but it may be difficult to identify bacterial pneumonia that is not adjacent to the pleura (Jokerst et al [*ACR*] 2018). The accuracy of ultrasound is very operator-dependent (Kuzniewski et al [ACR] 2021; PLE expert panel consensus opinion).

<u>Evidence update (2016-present):</u>

High Level of Evidence:

None

Moderate Level of Evidence:

Prendki et al (2018) prospectively assessed whether low-dose CT (LDCT) modified the probability of pneumonia diagnosis in 200 elderly (mean age 84) patients. All patients had chest radiograph and LDCT within 72 hours of inclusion; the treating clinician assessed probability of pneumonia before and after the LDCT scan using a Likert scale. An adjudication committee retrospectively rated the probability of pneumonia (reference for diagnosis). Main outcome was the difference in the clinician's pneumonia probability estimates before and after LDCT and the proportion of modified diagnoses which matched the reference diagnosis (the net reclassification improvement (NRI)). After LDCT, the estimated probability of pneumonia changed in 90 patients (45%), of which 60 (30%) were downgraded and 30

(15%) were upgraded. The NRI was 8% (NRI event (−6%) + NRI non-event (14%)). The authors conclude that LDCT mostly helped to exclude a diagnosis of pneumonia and hence to reduce unnecessary antimicrobial therapy.

Low Level of Evidence:
Loubet et al (2020), in a post hoc analysis of a multicenter study, proposed an algorithm to facilitate diagnosis of community-acquired pneumonia (CAP) and guide CT scan in 319 patients. All had previously undergone chest CT scan and detection of respiratory pathogens through nasopharyngeal polymerase chain reactions (PCRs). An adjudication committee assigned the final CAP probability (reference standard). Variables associated with confirmed CAP (cough, chest pain, fever, positive PCR, C-RP ≥ 50m/L: one point each, and chest radiograph parenchymal infiltrate: two points) were used to create weighted CAP diagnostic scores. The authors proposed a CT scan would be needed only in those with a diagnostic score between 3 and 5 (55% of the sample). Scores < 3 had a low probability of CAP (17%), and scores > 5 had a high probability of CAP (88%). The algorithm showed sensitivity 73% (95% CI 66-80), specificity 89% (95% CI 83-94), PPV 88% (95% CI 81-93), NPV 76% (95% CI 69-82) and area under the curve (AUC) 0.81 (95% CI 0.77-0.85). The algorithm displayed similar performance in a validation cohort (sensitivity 88% (95% CI 81-92), specificity 72% (95% CI 60-81), PPV 86% (95% CI 79-91), NPV 75% (95% CI 63-84) and AUC 0.80 (95% CI 0.73-0.87).

Seo et al (2019) retrospectively investigated the clinical and radiological features of patients with community-acquired pneumonia (CAP) identified on CT but not on chest radiography (CR). Of 1,925 CAP patients, 94 (4.9%) were included in the negative CR group. Negative CR findings were attributed to lesion location and CT pattern with low attenuation, such as ground-glass opacity (GGO). The negative CR group was also characterized by a higher frequency of aspiration pneumonia, lower incidences of complicated parapneumonic effusion or empyema and pleural drainage, and lower blood levels of inflammatory markers than the control group. On CT, the negative CR group exhibited higher rates of GGO- and bronchiolitis-predominant patterns and a lower rate of consolidation pattern. The authors conclude that chest CT scan should be considered in suspected CAP patients with a negative CR.

Cough and/or dyspnea *with pneumonia* that is not responding to treatment and/or with suspected complications:

- Green – **CT chest without IV contrast** or **CT chest with IV contrast**
- Yellow – **MRI chest**
  [detect or characterize suspected pleural involvement]
- Yellow – **CT angiography chest** or **CT pulmonary angiography (CTPA)**
  [evaluate hemoptysis or suspected vascular involvement]
- Red – **Scintigraphy**; **PET; SPECT; MR angiography**; **CT without and with IV contrast**

Level of Evidence: CT: low; MRI: very 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.

Guideline and PLE expert panel consensus opinion summary:

CT chest

CT of the chest should be performed in patients with non-resolving pneumonia and/or for the assessment of complications of community acquired pneumonia, such as lung abscess or empyema (Gupta et al [*ICS/NCCP*] 2012, 2A recommendation). Either CT chest with IV contrast or CT chest without IV contrast are usually appropriate for pneumonia patients with suspected complications (Jokerst et al [ACR] 2018). The use of intravenous contrast can increase the conspicuity of empyemas and other pleural complications (Jokerst et al [*ACR*] 2018). In severe cases of bacterial pneumonia, CT can demonstrate the overall extent of disease, which may provide important prognostic information and can also demonstrate necrotizing bacterial pneumonia and abscess formation long before the findings become visible on a chest radiograph (Jokerst et al [*ACR*] 2018). The superior contrast resolution of CT also allows it to detect obstructing masses, delineate lesions such as sequestrations, and characterize patterns of parenchymal disease, such that a particular etiology (e.g., bacterial pneumonia) can sometimes be suggested (Jokerst et al [*ACR*] 2018).

MRI chest

There is limited evidence evaluating the use of MRI in this specific clinical scenario, however it has been shown to be able to detect pleural effusions, pleural adhesions and pleural loculations (Jokerst et al [*ACR*] 2018). Therefore, MRI chest without and with IV contrast, or MRI chest without IV contrast may be appropriate in certain circumstances (Jokerst et al [ACR] 2018), such as when CT findings are indeterminate and ultrasound expertise is not available (PLE expert panel consensus opinion).

CT angiography

CTA chest is not routinely indicated in the evaluation of patients with suspected pneumonia. CT chest with IV contrast, CTA or CTPA may be indicated in pneumonia patients with suspected PE or in pneumonia patients with hemoptysis (PLE expert panel consensus opinion). The ACR states that CT chest with IV contrast or CTA is usually appropriate for the evaluation of patients with nonmassive non–life-threatening hemoptysis (Olsen et al [ACR] 2020).

Clinical/Imaging notes:

- Chest radiographs are a useful initial imaging modality for complicated bacterial pneumonia, but they are inferior to other modalities for evaluating the pleura, for guiding interventions, or for assessing an opacity that has been refractory to therapy (Jokerst et al [*ACR*] 2018).
- Although the chest radiograph is of little value in predicting the causative organisms of pulmonary infections, it remains useful in determining the extent of pulmonary disease and in screening for complicating features of pneumonia, such as empyema or abscess (Lee et al [ACR] 2019).
- Ultrasound is a useful adjunct for the evaluation of parapneumonic effusions in immunocompetent patients with pneumonia, as it is superior to chest radiographs for demonstrating pleural thickening and adhesions. It is superior to noncontrast CT for detecting septations in complex effusions, and can be used to guide biopsies, thoracentesis and thoracostomy placement (Jokerst et al [*ACR*] 2018). The accuracy of ultrasound is very operator-dependent (Kuzniewski et al [ACR] 2021; PLE expert panel consensus opinion).

Evidence update (2016-present):

High Level of Evidence:
None

Moderate Level of Evidence:
None

Low Level of Evidence:
None

Cough and/or dyspnea in an immunocompromised patient:

- Green – **CT chest without IV contrast**
- Yellow – **CT chest with IV contrast**
- Yellow – **MRI chest**
  [detect or characterize suspected pleural involvement]
- Yellow – **CT angiography chest** or **CT pulmonary angiography (CTPA)**
  [evaluate hemoptysis or suspected vascular involvement]
- Red – **PET**; **SPECT**; **MR angiography**; **CT without and with IV contrast, scintigraphy**

Level of Evidence: CT: moderate; CTPA: low; MRI: 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.

Guideline and PLE expert panel consensus opinion summary:

CT chest

Chest CT without IV contrast is usually appropriate as the next imaging study [following radiographs] for immunocompromised patients with acute respiratory illness (Lee et al [ACR] 2019). Further investigation with CT is warranted when chest radiographs show multiple, diffuse, or confluent opacities, and in patients who do not respond to initial therapy (Lee et al [ACR] 2019). CT may also be of value in those with a normal or near-normal radiograph by revealing abnormal lymph nodes or subtle parenchymal disease (Ravenel et al [*ACR*] 2017).

A chest CT scan is recommended whenever there is clinical suspicion for invasive pulmonary aspergillosis (IPA), regardless of chest radiograph results (Patterson et al [IDSA] 2016: strong recommendation/high-quality evidence). This includes patients at risk for IPA with fever or clinical symptoms of lower respiratory tract infection who remain febrile despite board-spectrum antibacterial treatment (Ullmann et al [*ESCMID-ECMM-ERS*] 2018). The routine use of contrast during a chest CT scan for a suspicion of IPA is not recommended (Patterson et al [IDSA] 2016: strong recommendation, moderate-quality evidence). However, contrast is generally indicated when a nodule or mass is close to a large vessel (Patterson et al [*IDSA*] 2016: strong recommendation, moderate-quality evidence).

For immunocompromised hosts with suspected tuberculosis and/or mycobacterial disease, particularly those with a low CD4 count, computed tomography (CT) should be considered, along with appropriate sputum microbiological evaluation (Ravenel et al [*ACR*] 2017; PLE expert panel consensus opinion).

CT angiography

CTA chest with IV contrast is usually appropriate for the initial imaging of patients with nonmassive or recurrent hemoptysis (Olsen et al [ACR] 2020). Pulmonary CT angiography may be useful in the early diagnosis of IPA by depicting directly vessel occlusion at the level of a suspicious fungal lesions, and is required in cases with hemoptysis (Ullmann et al [*ESCMID-ECMM-ERS*] 2018; Patterson et al [IDSA] 2016).

MRI chest
MRI should not be the initial imaging study performed in the evaluation of acute respiratory infection in immunocompromised patients (Lee et al [ACR] 2019). However, while CT is preferable to MRI, the latter can be considered as an alternative imaging modality when chest radiographs show multiple, diffuse, or confluent opacities (Lee et al [ACR] 2019). Additionally, MRI has been shown to be at least as sensitive as CT for detecting pleural effusions in immunocompromised patients (Jokerst et al [*ACR*] 2018), and in selected patients with IPA where CT is not wanted or not feasible (Ullmann et al [*ESCMID-ECMM-ERS*] 2018).

Scintigraphy
Scintigraphy has limited use in immunocompromised patients, as those with a positive CT would most likely get bronchoscopy or CT-guided biopsy, regardless of whether scintigraphy was performed or not (PLE expert panel consensus opinion).

<u>Clinical/Imaging notes:</u>

- Infections comprise nearly 75% of all pulmonary complications in immunosuppressed patients (Lee et al [ACR] 2019).
- Noninfectious causes of acute respiratory illness in immunocompromised patients include pulmonary edema, drug-induced lung disease, malignancy, radiation-induced lung disease, pulmonary hemorrhage, diffuse alveolar damage, organizing pneumonia, and pulmonary thromboembolic disease (Lee et al [ACR] 2019).
- In patients with a history of HIV infection, solid organ and bone marrow transplant, or history of immunosuppressive therapy for lymphoma or vasculitis, investigation for bronchiectasis may be appropriate with symptoms of chronic productive cough or recurrent chest infections (Hill et al [*BTS*] 2019).
- In immunocompromised patients, the initial diagnostic algorithm for patients with acute, subacute, and chronic cough is the same as that for immunocompetent persons, taking into account an expanded list of differential diagnoses relative to the type and severity of immune defect and geographic factors (Irwin et al [*ACCP*] 2006; Rosen [*ACCP*] 2006a).
- Chest radiography is the initial imaging modality of choice for the diagnostic assessment of immunocompromised patients presenting with acute respiratory infection, however, radiographs have low sensitivity and can be normal in up to 10% of patients with proven disease (Alexander et al [EORTC/MSGERC] 2021; Lee et al [ACR] 2019).
- Chest CT is more sensitive than chest radiography for detecting subtle pulmonary abnormalities and provides better characterization of pulmonary parenchymal abnormalities (Lee et al [ACR] 2019; Alexander et al [EORTC/MSGERC] 2021).
- Volumetric thin-section (high-resolution) CT with a slice thickness of approximately 1 mm is the method of choice for lung imaging for invasive fungal disease, interstitial lung disease and bronchiectasis (Alexander et al [EORTC/MSGERC] 2021).

<u>Evidence update (2013-present):</u>
High Level of Evidence:
None

Moderate Level of Evidence:
None

Low Level of Evidence:

Ekinci et al (2017) prospectively investigated the utility of MRI in diagnosis and surveillance of immunocompromised patients with pneumonia. 40 patients with positive findings for suspected pulmonary infection on thoracic CT were included. All patients were examined by MRI within 48 hours of CT exam. All images were obtained with balanced fast field echo, T1-weighted turbo spin-echo (TSE), and T2-weighted TSE. Lung abnormalities were evaluated using CT and MRI. Infection was determined in 36 patients (90%), while causative organism was unknown in four (10%). In all patients, CT findings were consistent with infection, although three patients showed no abnormal findings on MRI. CT was superior to MRI in detecting tree-in-bud nodules, centrilobular nodules, and halo sign ($P < 0.001$, for all). A significant difference was observed between MRI sequences and CT in terms of number of detected nodules ($P < 0.001$). Authors conclude that although CT is superior to MRI in diagnosis of pneumonia in immunocompromised patients, MRI is an important imaging modality that can be used, particularly in the follow-up of these patients, thus avoiding ionizing radiation exposure.

Henzler et al (2017) retrospectively evaluated the diagnostic accuracy of CTPA in a cohort of 455 immunocompromised patients with proven/probable invasive pulmonary aspergillosis (IPA). CTPA studies of 78 consecutive patients (mean age 60) were analyzed, and 45 immunocompromised patients without IPA served as a control group. Diagnostic performance of CTPA-detected vessel occlusion sign (VOS) and radiological signs not requiring contrast-media were analyzed. Of 12 evaluable radiological signs, five were found to be significantly associated with IPA. The VOS showed the highest diagnostic performance, with sensitivity of 0.94, specificity of 0.71 and diagnostic odds-ratio of 36.8. Regression analysis revealed the two strongest independent radiological predictors for IPA to be VOS and the halo sign. The authors conclude that VOS as observed on CTPA examinations is superior to classic CT signs observed in non-contrast enhanced studies to diagnose invasive pulmonary aspergillosis in immunocompromised patients.

Chronic cough in patients with suspected active tuberculosis and non-diagnostic/indeterminate chest radiographs:

- Green – **CT chest without IV contrast**
- Yellow – **CT chest with IV contrast**
- Yellow – **MRI chest**
  [detect or characterize suspected pleural involvement]
- Yellow – **CT angiography chest** or **CT pulmonary angiography (CTPA)**
  [evaluate hemoptysis or suspected vascular involvement]
- Red – **MR angiography**; **PET**; **SPECT**; **CT without and with IV contrast**; **scintigraphy**

Level of Evidence: CT: moderate

Notes concerning applicability and/or patient preferences: None

Guideline and PLE expert panel consensus opinion summary:

CT chest

While chest radiography provides the first indication of suspicion of tuberculosis (TB), it has a relatively poor specificity due to overlap of findings with nontuberculous pulmonary infection (Ravenel et al [*ACR*] 2017). The major advantage of CT imaging it to increase the likelihood of the diagnosis of pulmonary TB, and therefore CT may not always be needed when the disease is already suspected (Ravenel et al [ACR] 2017). In cases in which a chest radiograph does not show "classic" findings of TB, CT may be helpful to better show distinct findings such as cavitation or endobronchial spread with tree-in-bud nodules (Ravenel et al [*ACR*] 2017). CT chest without contrast is the primary imaging choice whenever radiographs are equivocal (Ravenel et al [ACR] 2017), while the use of CT with IV contrast can be useful in patients with signs of vascular involvement or to characterize abnormalities on noncontrast CT (PLE expert panel consensus opinion). CT with IV contrast is also the primary modality to determine hemoptysis etiology (Olsen et al [ACR] 2020). In patients with suspected TB who are also immunocompromised, particularly those with a low CD4 count, CT should be considered (Ravenel et al [*ACR*] 2017). The workup of TB must include microbial data, either by sputum or bronchoalveolar lavage (PLE expert panel consensus opinion).

CT angiography

CTA chest with IV contrast is usually appropriate for the initial imaging of patients with nonmassive or recurrent hemoptysis (Olsen et al [ACR] 2020). CTA has proven to be beneficial in detecting bronchial and nonbronchial arteries in preprocedural planning for patients with hemoptysis (Olsen et al [ACR] 2020).

MRI chest

Although MRI is technically feasible, it has not been specifically evaluated as a primary imaging modality for patients with suspected or proven TB (Ravenel et al [ACR] 2017). Signs of pleural TB include unilateral pleural effusion; sometimes the effusion is too small to be detected clinically and so there are no localizing clinical signs at all. In these cases, effusion is detected radiologically, including by MRI (*NICE* 2016; PLE expert panel consensus opinion).

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Nuclear medicine
Evidence for the use of nuclear imaging to diagnose active TB is limited to either small single-site studies or several small studies, and the impact on clinical practice and patient care at this time is minimal (Ravenel et al [*ACR*] 2017).

Clinical/Imaging notes:

- While not a common cause of chronic cough, it is important to consider TB as a possible cause, as the cough promotes the spread of TB bacteria (Kardos et al [GRS] 2020).
- The initial suspicion of active TB should be made based on clinical symptoms and demographics (Ravenel et al [*ACR*] 2017).
- In patients with chronic cough who live in areas with a high prevalence of TB, or in those who have significant risk factors for TB, this diagnosis should be considered, but not to the exclusion of more common etiologies. Sputum smears and cultures for acid-fast bacilli and a chest radiograph should be obtained whenever possible (Irwin et al [*ACCP*] 2006; Rosen [*ACCP*] 2006b; PLE expert panel consensus opinion).
- Using radiographs in combination with clinical evaluation results in a high sensitivity for the diagnosis of TB but a relatively low specificity for both latent and active TB (Ravenel et al [*ACR*] 2017).

Evidence update (2016-present):
High Level of Evidence:
None

Moderate Level of Evidence:
None

Low Level of Evidence:
None.

Chronic cough and/or dyspnea with a restrictive ventilatory pattern and/or suspicion of interstitial lung disease or pleural disease
AND
Common etiologies of cough - upper airway cough syndrome, GERD, non-asthmatic eosinophilic bronchitis - have been ruled out:

- Green – **CT chest without IV contrast**
- Yellow – **CT chest with IV contrast**
- Yellow – **MRI chest**
- [detect or characterize suspected pleural involvement]
- Yellow – **FDG-PET**
  [evaluate patients with asbestos exposure]
- Red – **Scintigraphy**; **PET/CT**; **SPECT**; **MR angiography**; **CT angiography**; **CT without and with IV contrast**

Level of Evidence: CT: moderate; FDG-PET: low; MRI (for pleural/chest wall disease): low

Notes concerning applicability and/or patient preferences:

Guideline and PLE expert panel consensus opinion summary:
Initial evaluation
The most common causes of chronic cough include smoking–related lung disease, upper airway cough syndrome, asthma, gastroesophageal reflux disease (GERD), and nonasthmatic eosinophilic bronchitis (Kuzniewski et al [ACR] 2021). In the case of chronic cough, diagnosis should be initiated immediately, usually with chest radiographs and a pulmonary function test, and completed according to standard clinical algorithms (Morice et al [ERS] 2020: good practice statement; Kuzniewski et al [ACR] 2021; PLE expert panel consensus opinion). When diagnosis and management of chronic cough using standard algorithms with minimal investigation has failed to result in diagnosis, or when empiric sequential treatment for the most common etiologies fails to resolve symptoms, further investigative modalities are typically recommended (Kuzniewski et al [ACR] 2021).

CT chest
It is suggested that clinicians not routinely perform a chest CT scan in patients with chronic cough who have a normal chest radiograph and physical examination (Morice et al [ERS] 2020: conditional recommendation, very low evidence). However, if cough persists after consideration of the most common causes, a noncontrast high resolution CT (HRCT) scan should be performed and, if necessary, a bronchoscopic evaluation (Irwin et al [*ACCP*] 2006; Prakash [*ACCP*] 2006, low level of evidence/grade of recommendation: B). Chest CT is considered the reference standard for the noninvasive diagnosis of interstitial lung disease (Kuzniewski et al [ACR] 2021; Raghu et al [*ATS*] 2018; Johannson et al [*CTS*] 2017*).

Idiopathic pulmonary fibrosis/interstitial lung disease
When there is suspicion of idiopathic pulmonary fibrosis/interstitial lung disease, patients should be assessed with a detailed history, lung function testing, chest radiographs, and a CT of the thorax, including high-resolution images (NICE 2013; McComb et al [ACR] 2018). Chest radiography serves as the

primary function of excluding alternative diagnoses, with HRCT findings offering the best characterization of lung disease (Cox et al [ACR] 2020). However, multiple studies demonstrate the increased sensitivity and specificity of CT over radiographs for evaluation of diffuse lung disease (Hobbs et al [ACR] 2021). In subjects with diseases that predispose them to ILD (e.g., connective tissue disease) it is reasonable to consider CT rather than radiography as the primary screening modality (McComb et al [*ACR*] 2018). CT findings and patterns of diffuse lung disease are often sufficient to permit either a limited differential or confident single diagnosis and play a role in multiple clinical diagnosis algorithms (Hobbs et al [ACR] 2021). There is no relevant literature to support the use of IV contrast for initial imaging of diffuse lung disease; however, it may be of use in evaluating alternative diagnoses with overlapping clinical features or conditions also involving the pleura, mediastinum, and luminary vessels (Hobbs et al [ACR] 2021; Kuzniewski et al [ACR] 2021).

Occupational exposure
When there is suspicion of idiopathic pulmonary fibrosis/interstitial lung disease with occupational exposure, patients should be assessed with a detailed history, lung function testing, chest radiographs, and a CT of the thorax, including high-resolution images (PLE expert panel consensus opinion). High resolution CT scans are strongly recommended for the diagnosis of coal workers' pneumoconiosis, asbestosis, or chronic beryllium disease (Hegmann et al [ACOEM] 2019: level A evidence, high level of confidence). High-resolution CT scans are also moderately recommended for the diagnosis of silicosis (Hegmann et al [ACOEM] 2019: level B evidence, high level of confidence) and is recommended for the early diagnosis of patients with suspected arc welders pneumoconiosis (AWP) of early-stage disease before progression to fibrosis (Takahashi et al 2018). If there are atypical features or subtle abnormalities on routine radiography, and/or competing causes for the findings, then a CT scan may be especially helpful in confirming or excluding a diagnosis of occupational ILD (Hegmann et al [ACOEM] 2019). CT with IV contrast can be helpful in identifying nonpulmonary manifestations of occupational exposure (Cox et al [ACR] 2020; McComb et al [ACR] 2018).

Pleural disease
For patients with chronic dyspnea and suspected disease of the pleura, radiographs, CT chest with IV contrast, or CT chest without IV contrast are considered usually appropriate (McComb et al [ACR] 2018). CT is superior to radiographs in detecting and characterizing pleural disease, differentiating it from parenchymal and chest wall disease, and determining the extent of involvement (McComb et al [*ACR*] 2018).

CT angiography
CTA chest is not routinely indicated in the evaluation of patients with suspected pneumonia. CT chest with IV contrast, CTA or CTPA may be indicated in pneumonia patients with suspected PE or in pneumonia patients with hemoptysis (PLE expert panel consensus opinion). The ACR states that CT chest with IV contrast or CTA is usually appropriate for the evaluation of patients with nonmassive non–life-threatening hemoptysis (Olsen et al [ACR] 2020).

FDG-PET
There is no relevant literature to support the use of FDG-PET or FDG-PET/CT in the initial evaluation of chronic cough, including those with suspected diffuse lung disease or occupation-associated ILD (Kuzniewski et al [ACR] 2021; Cox et al [ACR] 2020; Hegmann et al [ACOEM] 2019). However, increased FDG activity correlates with disease severity and prognosis (Hobbs et al [ACR] 2021), and thus FDG-PET/CT may have a secondary role in ILD evaluation (McComb et al [ACR] 2018; Hobbs et al [ACR] 2021; Kuzniewski et al [ACR] 2021). The limited literature suggests an increased sensitivity of PET/CT to various

inflammatory processes before morphological changes are demonstrated on CT, indicating a possible role in the evaluation of mesothelioma and pleural metastatic disease, and assisting in follow-up and monitoring of treatment response (Kuzniewski et al [ACR] 2021; McComb et al [ACR] 2018). PET/CT can provide benefit in diagnosing pleural and lung malignancies in asbestos exposure (Cox et al [ACR] 2020).

MRI chest

There is no relevant literature to support the use of chest MRI in the initial evaluation of chronic cough, and its use should be reserved for the evaluation of indeterminate findings on other imaging modalities (Kuzniewski et al [ACR] 2021; Hegmann et al [ACOEM] 2019). MRI offers improved soft-tissue-contrast, with advanced sequences able to identify soft-tissue characteristics to the cellular level (Kuzniewski et al [ACR] 2021). Some MRI sequences in the setting of diffuse lung disease may provide additional information on tissue characterization, gas transfer efficiency, and lung elasticity (Hobbs et al [ACR] 2021). Small studies have shown good concordance with CT, but in general, MRI does not yet display the same level of parenchymal detail that is available with CT (McComb et al [*ACR*] 2018). There is limited research supporting the use of MRI in diffuse lung disease or occupational lung disease, and none to support its use as the initial imaging modality (Cox et al [ACR] 2020; Hobbs et al [ACR] 2021; McComb et al [ACR] 2018). There is no relevant literature evaluating IV contrast versus noncontrast MRI in the setting of chronic cough, and decisions should be made on a case-by-case basis (Kuzniewski et al [ACR] 2021).

For chronic dyspnea patients with pleural/chest wall disease, MRI chest without and with IV contrast or MRI chest without IV contrast may provide improved characterization and assessment of the extent of pleural and chest wall abnormalities compared to CT (McComb et al [*ACR*] 2018).

*This guideline did not pass the AGREE II rigor of development scaled domain score cutoff. It was included, however, because of its direct relevance to this clinical scenario.

<u>Clinical/Imaging notes:</u>

- In patients with chronic cough, uncommon causes should be considered when cough persists after evaluation for common causes and when the diagnostic evaluation suggests an uncommon cause (Irwin et al [*ACCP*] 2006; Prakash [*ACCP*] 2006).
- A normal chest radiograph in the setting of suspected ILD does not exclude the possibility of clinically important ILD (McComb et al [*ACR*] 2018).
- Chest radiographs are moderately recommended for diagnosis of silicosis, asbestosis, or coal workers' pneumoconiosis, and recommended with insufficient evidence for diagnosing other occupational ILD (Hegmann et al [ACOEM] 2019).
- Chest radiographs can often diagnose pleural effusion. However, they may be limited in their ability to determine the exact location of an abnormality (McComb et al [*ACR*] 2018).
- A high-resolution CT (HRCT) protocol that uses thin-section imaging (multislice CT thorax scan with 1 mm reconstructions) of the lung parenchyma is essential for imaging of diffuse lung diseases. Adjunct sequences including expiratory images and prone images are frequently of benefit in evaluating these conditions (Hobbs et al [ACR] (2021; Kardos et al [GRS] 2020).

<u>Evidence update:</u>

High Level of Evidence:

None

Moderate Level of Evidence:

Takahashi et al (2018) assessed CT appearance of arc-welders' pneumoconiosis (AWP; n = 66) and compared findings with those of silicosis (n = 33). The lung parenchymal profusion scores on chest radiograph were compared with semi-quantitative CT score, and relationships were compared between AWP and silicosis. The study showed that incidence of ill-defined centrilobular nodule/ ground-glass opacity or centrilobular branching opacity was significantly higher in AWP than in silicosis (p=0.0031), while incidence of large opacity and mediastinal lymphadenopathy with or without calcification was significantly higher in silicosis (p < 0.0001). In addition, chest radiography had a tendency to underestimate lung parenchymal profusion abnormality of AWP, compared with that of silicosis. The authors conclude that CT should be considered for the assessment of patients with suspected AWP of early-stage disease before progression to fibrosis.

Manners et al (2017) examined the relationship between ultra-low dose computed tomography (ULDCT)-detected interstitial lung disease (ILD) and measures of pulmonary function in an asbestos-exposed population. Subjects were included if they had undergone a ULDCT chest exam and had concurrent gas transfer measurements. From a possible 906 participants, 143 were included (median age 73). Two thoracic radiologists independently categorized ULDCT scans for ILD appearances as absent (score 0), probable (1) or definite (2) without knowledge of asbestos exposure or lung function. Of 143 ULDCTs, 80 (55.9%) were reported as no ILD, 25 (17.5%) as probable ILD and 38 (26.6%) as definite ILD. Inter-observer agreement was good (k=0.613, p<0.001). There was a statistically significant correlation between ILD score and both percent predicted FEV1 and FVC (r = -0.17, p=0.04 and r = -0.20, p = 0.02), but not with cumulative asbestos exposure (r = 0.04, p = 0.69) or FEV1/FVC ratio (r = -0.01, p=0.88). There was a strong correlation between ILD score and diffusing capacity to carbon monoxide (DLCO) (r = -0.34, p<0.0001). Authors conclude that in asbestos-exposed populations, ULDCT may be adequate to detect radiological changes consistent with asbestosis.

Low Level of Evidence:
Marcia-Suarez et al (2017) assessed whether low voltage chest CT can be used to successfully diagnose disease in patients with asbestos exposure. Fifty-six patients (mean age 68) who were candidates to receive a standard-dose chest CT due to occupational exposure to asbestos were included. Immediately after initial CT, they underwent a second acquisition using low-dose chest CT parameters, based on a low potential (80 kV) and limited tube current. Findings of the CT protocols were compared based on typical diseases associated with asbestos exposure. Good correlation between routine and low-dose CT was demonstrated for most parameters with mean radiation dose reduction of up to 83% of the effective dose. The authors conclude that low-dose chest CT is useful for patients with an asbestos exposure background.

Salisbury et al (2016) investigated clinical and HRCT characteristics as predictors of idiopathic pulmonary fibrosis (IPF) in fibrotic interstitial lung disease (ILD) patients without radiologic honeycombing. Prospectively collected clinical and CT data from 200 patients enrolled in the Lung Tissue Research Consortium (LTRC) was used. Results showed that increasingly extensive reticular densities (OR 2.93, CI 95% 1.55-5.56, p= 0.001) predicted IPF, while increasing ground glass densities predicted a diagnosis other than IPF (OR 0.55, CI 95% 0.34-0.89, p= 0.02). In those aged $\geq$ 60 and with reticular densities occupying at least 1/3 of lung volume, probability of IPF exceeded 80%, with specificity for IPF diagnosis of 96%. The authors concluded that in ILD patients with HRCT fibrosis but no honeycombing, IPF can be confidently diagnosed without surgical lung biopsy in selected patients, especially in those $\geq$ 60 years and with at least 1/3 of total lung having reticular densities.

Schaal et al (2016) evaluated diagnostic performance of Ultra-Low-Dose Chest CT (ULD CT) for detection of any asbestos-related lesions and specific asbestos-related abnormalities. The study prospectively included 55 male patients (mean age 55.7) with occupational asbestos exposure $\geq$ 15 years. Patients underwent a standard unenhanced chest CT and an ULD CT to screen for asbestos-related pleuropulmonary diseases. Two chest radiologists independently and blindly read the examinations, following a detailed protocol. The study showed that radiation dose for the ULD-CT was 16x lower than standard CT. For detection of global abnormalities related to asbestos, the ULD had a specificity and a PPV of 100%, a NPV of 97.8% and a sensitivity of 90.9%. The authors concluded that ULD CT could be proposed as a first line screening test, with full dose CT acquisition completed only in doubtful or positive cases.

Chronic cough and/or dyspnea with suspicion of an obstructive lung disease (e.g., severe asthma, COPD, or bronchiectasis)

AND

Common etiologies of cough - upper airway cough syndrome, GERD, non-asthmatic eosinophilic bronchitis - have been ruled out:

- Green – **CT chest without IV contrast**
- Yellow – **CT chest with IV contrast**
- Yellow – **MRI chest**
  [detect or characterize suspected pleural involvement]
- Yellow – **CT angiography chest** or **CT pulmonary angiography (CTPA)**
  [evaluate hemoptysis or suspected vascular involvement]
- Red – **Scintigraphy; PET**; **SPECT**; **MR angiography**; **CT without and with IV contrast**

Level of Evidence: CT: moderate; MRI (for central airways disease): low

Notes concerning applicability and/or patient preferences:

Guideline and PLE expert panel consensus opinion summary:

Initial evaluation

The most common causes of chronic cough include smoking–related lung disease, upper airway cough syndrome, asthma, gastroesophageal reflux disease (GERD), and nonasthmatic eosinophilic bronchitis (Kuzniewski et al [ACR] 2021). In the case of chronic cough, diagnosis should be initiated immediately (usually with chest radiographs and a pulmonary function test) and completed according to standard clinical algorithms (Morice et al [ERS] 2020: good practice statement; Kuzniewski et al [ACR] 2021; PLE expert panel consensus opinion). When diagnosis and management of chronic cough using standard algorithms with minimal investigation has failed to result in diagnosis, or when empiric sequential treatment for the most common etiologies fails to resolve symptoms, further investigative modalities are typically recommended (Kuzniewski et al [ACR] 2021).

CT chest

It is suggested that clinicians not routinely perform a chest CT scan in patients with chronic cough who have a normal chest radiograph and physical examination (Morice et al [ERS] 2020: conditional recommendation, very low evidence). If cough persists after consideration of the most common causes, a chest CT is generally recommended (Kuzniewski et al [ACR} 2021; Irwin et al [*ACCP*] 2006; Prakash [*ACCP*] 2006, low level of evidence/grade of recommendation: B). For most routine applications, IV contrast is not needed, although it may be added when vascular abnormalities [e.g. pulmonary embolus] are in the differential diagnosis (McComb et al [*ACR*] 2018).

COPD/Bronchiectasis

The evidence shows that in patients with suspected COPD, investigations like high resolution CT (HRCT) scans are accurate tests for situations of diagnostic difficulty or whenever clinically indicated (*NICE* 2018; Gupta et al [*ICS/NCCP*] 2013: 2A recommendation). For COPD patients, CT has greater sensitivity and specificity than chest radiographs in determining the type, extent, and distribution of emphysema and bronchial wall abnormalities (McComb et al [*ACR*] 2018). A chest HRCT should also be considered in adults with COPD who have had $\geq$ 3 exacerbations per year, very severe disease (FEV_1 < 30% predicted or requiring domiciliary oxygen) or whose sputum contains organisms atypical for COPD (i.e., Aspergillus species, *Pseudomonas aeruginosa* or non-tuberculous mycobacteria) to evaluate for bronchiectasis and other lung pathologies (Chang et al [*TSA*] 2015: GRADE-low, low level of evidence; *NICE* 2018).

A noncontrast CT is considered the reference standard for the noninvasive diagnosis of bronchiectasis (Kuzniewski et al [ACR] 2021). In patients with suspected bronchiectasis without a characteristic chest radiograph finding, an HRCT scan should be ordered, as it is the diagnostic procedure of choice to confirm the diagnosis (Irwin et al [*ACCP*] 2006; Rosen [*ACCP*] 2006c: low level of evidence, grade B recommendation; Hill et al [*BTS*] 2019: level C recommendation; Chang et al [*TSA*] 2015: GRADE-strong, moderate level of evidence).

Severe asthma
In severe asthma without specific indications for chest HRCT based on history, symptoms and/or results of prior investigations, it is suggested that a chest HRCT only be done when the presentation is atypical (Chung et al [*ERS/ATS*] 2014: conditional recommendation, very low quality evidence). A chest CT without contrast can also be useful in severe asthma if alternative diagnoses are being considered, such as bronchiectasis, asthma/COPD overlap syndrome, allergic bronchopulmonary aspergillosis, acute hypersensitivity pneumonitis, or pneumothorax (Jokerst et al [ACR] 2018; PLE expert panel consensus opinion). CT chest with contrast can be appropriate when there is suspected vascular involvement or pleural disease (PLE expert panel consensus opinion).

Other obstructive lung disease
In chronic dyspnea patients with suspected central airways disease, chest radiographs or CT chest without IV contrast are usually appropriate (McComb et al [*ACR*] 2018). Examples of airway conditions that may result in chronic dyspnea and can be accurately diagnosed by CT include [tracheobronchial] stenosis, tumors, and end-expiratory airway collapse / tracheobronchomalacia, with strong correlations when compared with bronchoscopy (McComb et al [*ACR*] 2018). Contrast-enhanced CT studies offer improved visualization of cardiopulmonary vasculature, mediastinal structures, and soft-tissue abnormalities (Kuzniewski et al [ACR] 2021).

CT angiography
CTA chest is not routinely indicated in the evaluation of patients with suspected pneumonia. CT chest with IV contrast, CTA or CTPA may be indicated in pneumonia patients with suspected PE or in pneumonia patients with hemoptysis (PLE expert panel consensus opinion). The ACR states that CT chest with IV contrast or CTA is usually appropriate for the evaluation of patients with nonmassive non–life-threatening hemoptysis (Olsen et al [ACR] 2020).

MRI chest
There is no relevant literature to support the use of thoracic MRI in the initial evaluation of chronic cough, and its use should be reserved for the evaluation of indeterminate findings on other imaging modalities (Kuzniewski et al [ACR] 2021). MRI offers improved soft-tissue-contrast, with advanced sequences able to identify soft-tissue characteristics to the cellular level (Kuzniewski et al [ACR] 2021). There is no relevant literature evaluating IV contrast versus noncontrast MRI in the setting of chronic cough, and decisions should be made on a case-by-case basis (Kuzniewski et al [ACR] 2021).

Scintigraphy
While clearance of inhaled radiolabeled tracers from the lung is impaired in bronchiectasis, this is non-

specific and seen in other airway diseases, so cannot be considered diagnostic of bronchiectasis (Hill et al [*BTS*] 2019).

Clinical/imaging notes:

- In patients with chronic cough, uncommon causes should be considered when cough persists after evaluation for common causes, and when the diagnostic evaluation suggests an uncommon cause (Irwin et al [*ACCP*] 2006; Prakash [*ACCP*] 2006).
- Severe asthma is defined as asthma that requires treatment with high dose inhaled corticosteroids plus a second controller and/or systemic corticosteroids to prevent it from becoming "uncontrolled" or that remains "uncontrolled" despite this therapy (Chung et al [*ERS/ATS*] 2014).
- An atypical presentation of severe asthma includes such factors as excessive mucus production, rapid decline in lung function, and reduced carbon monoxide transfer factor coefficient (Chung et al [*ERS/ATS*] 2014).
- Asthma is found in higher prevalence in patients with bronchiectasis than in the general population, and bronchiectasis appears more commonly in asthma, particularly in difficult to treat disease (Hill et al [*BTS*] 2019). As many as 40% of newly referred patients with difficult to control asthma and a chronic cough have bronchiectasis (Chung [*ERS/ATS*] 2014).
- Between 29-50% of people with COPD and as many as 40% of newly referred patients with difficult to control asthma and a chronic cough have bronchiectasis (Chang et al [*TSA*] 2015).
- Probable risk factors for COPD include poorly treated asthma. Patients with active asthma have been found to have 10-fold increased risk of chronic bronchitis and 17-fold increased risk of emphysema as compared to those without asthma (Gupta et al [*ICS/NCCP*] 2013).
- Investigation for bronchiectasis should be considered in the following (Hill et al [*BTS*] 2019):
    - Cough that persists > 8 weeks, especially with sputum production or history of an appropriate trigger;
    - Persistent production of mucopurulent or purulent sputum, particularly with relevant associated risk factors;
    - Frequent COPD exacerbations (two or more annually) and a previous positive sputum culture for *P. aeruginosa* while stable;
    - Inflammatory bowel disease, rheumatoid arthritis, or other connective tissue disease if they have a chronic productive cough or recurrent chest infections;
    - Chronic rhinosinusitis with symptoms of chronic productive cough or recurrent chest infections.
- Roles of CT scan of the thorax in people with COPD (*NICE* 2018):
    - To investigate symptoms that seem disproportionate to the spirometric impairment,
    - To investigate signs that may suggest another lung diagnosis (such as fibrosis, malignancy, or bronchiectasis),
    - To investigate abnormalities seen on chest radiographs,
    - To assess suitability for lung volume reduction procedures, and
    - To evaluate for malignancy.

Evidence update (2017-present):

High Level of Evidence:

None

Moderate Level of Evidence:

Bajc et al (2017) aimed to diagnose and grade COPD severity and identify pulmonary comorbidities associated with COPD with V/P SPECT. Ninety-four patients (age $\geq$ 40) with a stable clinical diagnosis of COPD, based on 2011 Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria were enrolled and examined with V/P SPECT and spirometry. Ventilation and perfusion defects were analyzed blindly. Total preserved lung function and penetration grade were assessed by V/P SPECT and compared to GOLD stages and spirometry. Signs of small airway obstruction in the ventilation SPECT images were found in 92 patients, and emphysema was identified in 81 patients. The penetration grade of Technegas in V SPECT and total preserved lung function correlated significantly to GOLD stages (r=0.63 and -0.60, respectively, P,0.0001). The authors conclude that V/P SPECT, using Technegas as the functional ventilation imaging agent, is a new tool to diagnose COPD and grade its severity.

Low Level of Evidence:
Chen et al (2017) analyzed quantitative measurements of lung and bronchial parameters provided by low-dose computed tomography (CT) to differentiate COPD and asthma from an imaging perspective. A total of 69 COPD patients (mean age 46.6, range 29-78), 52 asthma patients (mean age 46.6, range 18-65), and 20 healthy subjects (mean age 42.8, range 23-67) were recruited. All subjects underwent CT, and PFTs 1 week after CT exam. There were differences among groups, with differences more significant among inspiratory emphysema index, expiratory lung volume, expiratory mean lung density (MLD), and expiratory EI –950 (%) and EI –850 (%). The COPD group had a significantly higher EI –950 (%) than the asthma group (p = 0.008). There were significant differences among the three groups in lumen area, wall area, total area, and Pi10WA. The asthma group had significantly higher WA%/WV% than both the COPD (p = 0.002) and the control group (p = 0.012). The authors conclude that, to aid the diagnosis, CT can provide quantitative measurements to differentiate between COPD and asthma patients.

Tamada et al (2017) investigated prevalence rate of patients with both fixed airflow limitation (FL) and COPD components in elderly asthma. The multicenter study enrolled 242 outpatients with stable asthma who were > 50 years old. All underwent a multi detector chest CT scan and pulmonary function test. Two spirometric definitions for FL were used: (a) FEV1/FVC <70% (= FL_{70}) and (b) FEV1/FVC < 5th percentile (lower limits of normal, LLN) (= FLLLN). The study used DLco %predicted < 80% and the appearance of low attenuation areas (LAA) in HRCT as candidate markers of COPD components with lung diffusion impairment and emphysematous findings, respectively. The results showed that prevalence of patients with FEV1/FVC < 70% was 31.0% of those in their 5Os, 40.2% of those in their 60s and 61.9% of those $\geq$ 70. The prevalence of patients with lung diffusion impairment (i.e. percent predicted values of diffusing capacity of the lung for carbon monoxide (DLco %predicted) < 80%) or emphysematous findings in HRCT (i.e. the appearance of LAA) was 18.3% of those in their 50s, 13.8% of those in their 60s and 35.7% of those $\geq$ 70. The authors conclude that nearly half of patients with FL_{70} in elderly asthma showed coexisting COPD components and the remaining half of FL were considered to have asthmatic airway remodeling.

den Harder et al (2017) examined whether mild stage COPD can be detected on chest radiography without substantial overdiagnosis. Among 783 patients scheduled for cardiothoracic surgery, 155 mild COPD case patients (mean age 66.5; 24% never-smokers) and 155 controls (mean age 62.4; 45.8% never-smokers) were included. Patients underwent both preoperative spirometry and chest radiograph. Diagnostic accuracy of chest radiography for diagnosing mild COPD was investigated using objective measurements and overall appearance specific for COPD. Inter-observer variability was investigated and variables with a kappa > 0.40 as well as baseline characteristics were used to make a diagnostic model aimed at achieving a high positive predictive value (PPV). The PPV of overall appearance specific for COPD alone was low (37–55%). Factors in the diagnostic model were age, type of surgery, gender, distance of the right diaphragm apex to first rib, retrosternal space, sternodiaphragmatic angle, maximum height right diaphragm (lateral view) and subjective impression of COPD (using both views). The model resulted in a PPV of 100%, negative predictive value (NPsV) of 82%, sensitivity of 10% and specificity of 100% with an area under the curve of 0.811. The authors conclude that detection of mild COPD without substantial overdiagnosis was not feasible on chest radiographs in this cohort.

Cough and/or dyspnea in patients with suspected or confirmed COVID-19, and any of the following:

- **Viral testing is not available or results are delayed;**
- **Clinical worsening; and/or**
- **Risk factors for disease progression**

- Green – **CT chest without IV contrast**
- Yellow – **CT chest with IV contrast , CT angiography chest** or **CT pulmonary angiography (CTPA)** [evaluate for pulmonary embolism]
- Red – **Scintigraphy; PET**; **MRI; MR angiography**; **CT chest without and with IV contrast**; **SPECT**

Level of Evidence: low/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.

The differential diagnoses and potential complications for each specific case should be considered when choosing an imaging modality (WHO 2020). If feasible, the patient should be provided with information regarding the imaging modality to be used and the likelihood of requiring subsequent imaging procedures (WHO 2020).

Guideline and consensus opinion summary:
Chest imaging is not suggested for the initial diagnostic workup of COVID-19 in symptomatic patients when RT-PCR testing is available with timely results (WHO 2020: conditional recommendation, low certainty evidence; ACR 2020). In general, imaging is not indicated for patients with mild features of COVID-19 unless they are at risk for disease progression (Rubin et al 2020*). Although beyond the scope of this clinical scenario, imaging is also not routinely indicated as a screening test for COVID-19 in asymptomatic individuals (Rubin et al 2020*), nor is it suggested for COVID-19 diagnostic purposes (WHO 2020: conditional recommendation, expert opinion). A relatively low negative predictive value (42%) suggests that CT may not be valuable as a screening test for these patients, at least in earlier stages of the disease (Simpson et al 2020; ACR 2020), particularly given the high sensitivity and rapid-turnaround of viral RT-PCR testing (PLE expert panel consensus opinion).

Indications for chest imaging
For symptomatic patients with suspected COVID-19, chest imaging is suggested for the diagnostic workup of COVID-19 when: (1) RT-PCR testing is not available; (2) RT-PCR testing is available, but results are delayed; or (3) initial RT-PCR testing is negative, but there remains a high clinical suspicion of COVID-19 (WHO 2020: conditional recommendation, low certainty evidence). Imaging is also indicated for patients with moderate to severe features of COVID-19 regardless of COVID-19 test results, or patients with evidence of worsening respiratory status (Rubin et al 2020*). Compared to chest CT, chest radiography appears to have lower sensitivity and might have higher specificity (WHO 2020). In a resource-constrained environment where access to CT is limited, chest radiography may be preferred

for patients with COVID-19 unless worsening respiratory features warrant the use of CT (Rubin et al 2020*). Chest CT has a relatively high sensitivity but a relatively low specificity and can be useful in patients with some pre-existing pulmonary diseases. However, the absence of radiological signs of pneumonia cannot completely exclude a viral infection (WHO 2020; ACR 2020).

*This guideline did not pass the AGREE II rigor of development scaled domain score cutoff. It was included, however, because of its direct relevance to this clinical scenario.

<u>Clinical/imaging notes:</u>

- RT-PCR should be performed to confirm diagnosis of COVID-19 (WHO 2020; ACR 2020). COVID-19 testing is indicated in patients incidentally found to have findings suggestive of COVID-19 on a CT scan (Rubin et al 2020).
- Imaging should be used as one element of the diagnostic workup that includes clinical and laboratory data (WHO 2020). Patients who are most likely to benefit from imaging include are those who (WHO 2020; PLE expert panel consensus opinion):
  - Are at high risk of disease progression
  - Have associated comorbidities or other chronic diseases and/or are aged over 60 years
  - Live with individuals at high risk of morbidity and mortality associated with COVID-19
  - Are unvaccinated or incompletely vaccinated for COVID-19.
- When performing chest radiography and/or chest CT, minimize radiation dose while maintaining diagnostic image quality (e.g., low-dose CT protocols) and use digital imaging rather than film-screen equipment (Akl et al 2021).
- Proposed reporting language for CT findings related to COVID-19 (Simpson et al 2020):
  - <u>Typical appearance:</u>
    - Peripheral, bilateral, ground glass opacities (GGO) with or without consolidation or visible intralobular lines (“crazy paving”)
    - Multifocal GGO of rounded morphology with or without consolidation or visible intralobular lines (“crazy paving”)
    - Reverse halo sign or other findings of organizing pneumonia (seen later in the disease)
  - <u>Indeterminate appearance:</u>
    - Absence of typical features AND presence of:
      - Multifocal, diffuse, perihilar, or unilateral GGO with or without consolidation lacking a specific distribution and are nonrounded or nonperipheral
      - Few very small GGO with a nonrounded and nonperipheral distribution
  - <u>Atypical appearance:</u>
    - Absence of typical or indeterminate features AND presence of:
      - Isolated lobar or segmental consolidation without GGO
      - Discrete small nodules (centrilobular, “tree-in-bud”)
      - Lung cavitation
      - Smooth interlobular septal thickening with pleural effusion
- Most viral pneumonias, cryptogenic organizing pneumonia, and drug-induced lung injury can also present similarly. Thus, it becomes imperative to endorse a detailed history and physical examination before settling on the diagnosis of COVID-19 purely based on chest imaging (Ghosh et al 2021).

- Lung ultrasound has very low-certainty evidence supporting its diagnostic accuracy, but might be helpful with the appropriate expertise as a supplemental or alternative modality (WHO 2020).

Evidence update (2019-present):

**Note: all reviewed individual studies below, including those included in relatively well-designed systematic reviews and/or meta-analyses, were graded as low or very low evidence.*

Islam et al (2021), in a *Cochrane Library* systematic review, evaluated the diagnostic accuracy of thoracic imaging (CT, radiographs, and ultrasound) for suspected COVID-19. A total of 51 studies were included (total n = 19,775; 10,155 had a final diagnosis of COVID-19), with all using RT-PCR as reference standard for diagnosis. Risk of bias was high or unclear in 32 (63%) studies with respect to participant selection, 40 (78%) studies with respect to reference standard, 30 (59%) studies with respect to index test, and 24 (47%) studies with respect to participant flow. For chest CT (41 studies, 16,133 participants), sensitivity ranged from 56.3%-100%, and specificity ranged from 25.4%-97.4%. The pooled sensitivity of chest CT was 87.9% (95% CI 84.6 to 90.6) and pooled specificity was 80.0% (95% CI 74.9 to 84.3). For chest radiography (9 studies, 3,694 participants) the sensitivity ranged from 51.9% to 94.4% and specificity ranged from 40.4% to 88.9%. The pooled sensitivity of chest radiographs was 80.6% (95% CI 69.1 to 88.6) and pooled specificity was 71.5% (95% CI 59.8 to 80.8). For lung ultrasound (5 studies, 446 participants) the sensitivity ranged from 68.2% to 96.8% and specificity ranged from 21.3% to 78.9%. The pooled sensitivity of ultrasound was 86.4% (95% CI 72.7 to 93.9) and the pooled specificity was 54.6% (95% CI 35.3 to 72.6). The authors conclude that findings indicate that chest CT is sensitive and moderately specific for the diagnosis of COVID-19. Chest radiographs are moderately sensitive and moderately specific for the diagnosis of COVID-19. Ultrasound is sensitive but not specific for the diagnosis of COVID-19. Thus, chest CT and ultrasound may have more utility for excluding COVID-19 than for differentiating SARS-CoV-2 infection from other causes of respiratory illness.

Garg et al (2021), in a systematic review and meta-analysis, evaluated pooled prevalence, sensitivity, and specificity of chest CT and radiographic findings for COVID-19 pneumonia. A total of 56 studies (total n = 6,007) were included. Mean interval between symptom onset and CT acquisition was 1-8 days. On CT, pooled prevalence of ground glass opacities (GGO), GGO plus consolidation, and consolidation only was 66.9% (95% CI 60.8–72.4%), 44.9% (38.7–51.3%), and 32.1 (23.6–41.9%) respectively. Pooled sensitivity and specificity of GGO on CT was 73% (71%–80%) and 61% (41%–78%), respectively. For GGO plus consolidation and consolidation only, the pooled sensitivities/ specificities were 58% (48%–68%)/ 58% (41%–73%) and 49% (20%–78%)/ 56% (30%–78%), respectively. The pooled prevalence of GGO and consolidation on chest radiograph was 38.7% (22.2%–58.3%) and 46.9% (29.7%–64.9%), respectively. The authors conclude that GGO on CT has the highest diagnostic performance for COVID-19. However, the moderate to low sensitivity and specificity suggest that CT should not be used as the primary tool for diagnosis.

Revel et al (2021) conducted a multicenter retrospective cohort study to evaluate the sensitivity and specificity of CT for COVID-19 patients, using RT-PCR as the reference standard. A total of 10,735 patients (mean age = 65) from 20 university hospitals were included. Subjects presenting to the ED underwent both thoracic CT and RT-PCR. CT images were read blinded to clinical information and outcome. A total of 6,448 (60%) had a positive RT-PCR result. The sensitive and specificity of CT were 80.2% (95%CI: 79.3, 81.2) and 79.7% (95%CI: 78.5, 80.9), respectively, with strong agreement between junior and senior radiologists (Gwet's AC1 coefficient: 0.79). Of all variables analyzed, the extent of pneumonia on CT (OR 3.25, 95% CI: 2.71, 3.89) was the best predictor of severe outcome at one month.

Khatami et al (2020) conducted a systematic review and meta-analysis to determine the diagnostic value of an initial chest CT scan in patients with COVID-19 in comparison with RT-PCR. Among 1,022 articles, 60 studies were eligible (total n = 5,744 patients). The overall sensitivity, specificity, positive predictive value, and negative predictive value of chest CT scan compared to RT-PCR were 87% (95% CI 85–90%), 46% (95% CI 29–63%), 69% (95% CI 56–72%), and 89% (95% CI 82–96%), respectively. The authors conclude that, due to lower diagnostic sensitivity of chest-CT scan in comparison to RT-PCR, performing RT-PCR is mandatory for any individuals with suspicious symptoms.

Ojha et al (2020) conducted a systematic review to evaluate the key imaging manifestations of COVID-19 on chest CT. A total of 45 studies (total n = 4,410) were included. Ground glass opacities (GGO), in isolation (50.2%) or coexisting with consolidations (44.2%), were the most common lesions. Distribution of GGOs was most commonly bilateral, peripheral/subpleural, and posterior with predilection for lower lobes. Common ancillary findings included pulmonary vascular enlargement (64%), intralobular septal thickening (60%), adjacent pleural thickening (41.7%), air bronchograms (41.2%), subpleural lines, crazy paving, bronchus distortion, bronchiectasis, and interlobular septal thickening. CT in the early follow-up period generally showed an increase in size, number, and density of GGOs, with progression into mixed areas of GGOs plus consolidations and crazy paving, peaking at 10–11 days, before gradually resolving or persisting as patchy fibrosis. The authors conclude that CT imaging can help in early diagnosis, stratification, and initial follow-up of patients with COVID-19.

Salehi et al (2020) conducted a systematic review to identify CT features of COVID-19. A total of 30 studies (total n = 919) were included. Features of COVID-19 on initial CT include bilateral multilobar ground-glass opacification (GGO) with a peripheral or posterior distribution, mainly in the lower lobes and less frequently within the right middle lobe. Atypical initial imaging presentation of consolidative opacities superimposed on GGO may be found in a smaller number of cases, mainly in the elderly population. Septal thickening, bronchiectasis, pleural thickening, and subpleural involvement are some of the less common findings, mainly in the later stages of the disease. Pleural effusion, pericardial effusion, lymphadenopathy, cavitation, CT halo sign, and pneumothorax are uncommon but may be seen with disease progression. Greatest severity of CT findings is visible around day 10 after symptom onset. Imaging patterns corresponding to clinical improvement usually occur after week 2 of the disease and include gradual resolution of consolidative opacities and decrease in the number of lesions and involved lobes.

Freund et al (2020) retrospectively assessed whether COVID-19 is associated with pulmonary embolism (PE) in emergency department (ED) patients undergoing a CT pulmonary angiogram (CTPA). A total of 3,358 patients from 26 EDs in six countries were included; patients had a CTPA performed for suspected PE during a 2-month period. Among them, 974 (30%) were diagnosed with COVID-19 (mean age 61), either on CT or RT-PCR testing. A PE was diagnosed on CTPA in 500 patients (15%); the risk of PE was similar between COVID-19 patients and others (15% in both groups). Using a multivariable binary logistic regression model, COVID-19 was not associated with higher risk of PE (adjusted odds radio (0.98, 95% CI = 0.76-1.26). The authors note that their results suggest that conventional diagnostic strategies for PE in ED patients with suspected COVID-19 are safe.

Gaia et al (2020) assessed the potential role of chest CT in early detection of COVID-19 and explore its role in emergency department (ED) patients. A total of 314 patients with clinically suspected COVID-19 were evaluated with arterial blood gas, RT-PCR, and chest CT. Results from RT-PCT testing was used as the reference standard. Images were independently evaluated by two radiologists who were blinded to

RT-PCR results. According to RT-PCR results, 152 patients were COVID-19 negative (48%) and 162 were COVID-19 positive (52%). There was substantial agreement between RT-PCR and CT findings ($p<0.000001$), and near perfect agreement between readers. Mixed ground-glass opacity and consolidation pattern with peripheral and bilateral distribution, multifocal or diffuse abnormalities localized in both upper lung and lower lung, in association with interlobular septal thickening, bronchial wall thickening and air bronchogram, had higher frequency in COVID-positive patients. The authors conclude that chest CT has a useful role in early detection and management of COVID-19 pneumonia.

Gross et al (2020) respectively analyzed the diagnostic performance of chest CT for COVID-19 using structured reporting in a routine clinical setting. A total of 96 consecutive patients with clinical suspicion of COVID-19 and moderate-to-severe symptoms were included. CTs were performed and reported before RT-PCR result (which served as the reference standard) was available. A structured reporting system was performed and agreed upon by three radiologists, concluding in a recently described five-grade score ("CO-RADS") that indicated level of suspicion for pulmonary involvement of COVID-19 from 1 = very low to 5 = very high. RT-PCR was positive in 20 (21%) cases. CT features significantly more common in RT-PCR-positive patients were ground-glass opacities as dominant feature, crazy paving, hazy margins of opacities, and multifocal bilateral distribution ($p < 0.05$). Using a cut-off point between CO-RADS 3 and 4, sensitivity was 90%, specificity 91%, positive predictive value 72%, negative predictive value 97%, and accuracy 91%. ROC analysis showed an AUC of 0.938. The authors conclude that the use of structured reporting of chest CT with a five-grade scale was feasible and helpful.

Som et al (2020) retrospectively assessed the performance of the Radiological Society of North America (RSNA) guidelines and quantified interobserver variability in application of the guidelines in 89 consecutive patients undergoing chest CT for suspected COVID-19 pneumonia. One positive or two negative RT-PCR tests for COVID-19 were considered the reference standard for diagnosis. Each chest CT scan was evaluated using RSNA guidelines by nine readers (six fellowship-trained thoracic radiologists and three radiology resident trainees). Clinical information was obtained from the electronic medical record. Results found strong concordance of findings between radiology training levels, with agreement ranging from 60% to 86% among attending physicians and trainees (k, 0.43 to 0.86). Sensitivity and specificity of typical CT findings for COVID-19 per the RSNA guidelines were on average 86% (range, 72%–94%) and 80.2% (range, 75%–93%), respectively. Combined typical and indeterminate findings had a sensitivity of 97.5% (range, 94%–100%) and specificity of 54.7% (range, 37%–62%). A total of 163 disagreements were seen out of 801 observations (79.6% total agreement).

Guideline exclusions:

- Cases meeting the definition of a suspected or confirmed emergency medical condition
- Known neoplasm or metastatic disease
- Known pulmonary vascular disease
- Known cardiovascular disease
- Restrictive lung disease secondary to diaphragmatic weakness, scoliosis, or neuromuscular disease
- Cystic fibrosis, primary ciliary dyskinesia, and other congenital abnormalities
- Rare lung or mediastinal disorders (pulmonary alveolar proteinosis, pulmonary histiocytosis, pulmonary eosinophilia, idiopathic pulmonary hemosiderosis)
- Environmental hypoxia
- Anemia
- Hemoglobinopathy
- Behavioral factors (e.g., anxiety)
- Chest trauma
- Pregnant patients
- Pediatric patients and conditions frequently seen in pediatrics (e.g., bronchiolitis)
- AI and other post-processing algorithms

AUC Revision History:

Revision Date	**New Clinical Scenario**	**Approval Body**
05/07/2019	Initial Document Development	CDI Quality Institute’s Multidisciplinary Committee
09/14/2021	COVID-19	CDI Quality Institute’s Multidisciplinary Committee

Provider Led Entity

Cough/Dyspnea AUC

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09/14/2021

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