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Cough / Dyspnea AUC

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

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*Including MRI with and/or w/o IV contrast, CT with and/or w/o IV contrast, MRA, CTA, Nuclear medicine scanning and FDG-PET scanning

Abbreviation list:

ACCP	American College of Chest Physicians
ACOEM	American College of Occupational and Environmental Medicine
ACOS	Asthma-COPD overlap syndrome
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
CT	Computed tomography
CTPA	CT pulmonary angiography
CTA	CT angiography
CTS	Canadian Thoracic Society
DTPA	Diethylenetriamine penta acetate
ERS	European Respiratory Society
FDG-PET	Fludeoxyglucose-positron emission tomography
Ga-67	Gallium-67
GERD	Gastroesophageal reflux disease
HRCT	High-resolution computed tomography
IA	Invasive aspergillosis
ICS	Indian Chest Society
IDSA	Infectious Diseases Society of America
ILD	Interstitial lung disease
IPA	Invasive pulmonary aspergillosis
IPF	Idiopathic pulmonary fibrosis
LUS	Lung ultrasound
MRI	Magnetic resonance imaging
NAEB	Nonasthmatic eosinophilic bronchitis
NCCP	National College of Chest Physicians
NICE	National Institute for Health and Care Excellence
NTM	Non-tuberculous mycobacteria
PFT	Pulmonary function testing
PJP	*Pneumocystis jirovecii* pneumonia
PNA	Bacterial pneumonia
SSc	Systemic sclerosis
TB	Tuberculosis
Tc-99m	Technetium-99m
TSA	Thoracic Society of Australia
UACS	Upper airway cough syndrome
UIP	Usual interstitial pneumonia
ULD	Ultra-low dose
US	Ultrasound

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

- **Green** – CT chest without IV contrast
- **Yellow** – CT chest with IV contrast or CTPA or CTA
- **Red** – Scintigraphy, FDG- PET, PET/CT, MRI, MRA, CT chest without and with IV contrast, SPECT, SPECT/CT

Level of Evidence: CT: low

Notes concerning applicability and/or patient preferences:

Guideline and PLE expert panel consensus opinion summary:
CT of the thorax should not be performed routinely in patients with community acquired pneumonia (Gupta et al [*ICS/NCCP*] 2012).

In patients with a high pretest probability of bacterial pneumonia presenting with an acute asthma exacerbation, those who cannot reliably follow-up or for whom any delay in diagnosis of bacterial pneumonia could be life-threatening may warrant a CT if the chest radiograph is negative or equivocal (Jokerst et al [*ACR*] 2018).

For the clinical scenario of *acute respiratory illness in immunocompetent patients with positive physical examination, abnormal vital signs, organic brain disease, or other risk factors and negative or equivocal initial chest radiograph, next imaging study,* the *American College of Radiology* recommends CT chest without IV contrast (usually appropriate) (Jokerst et al [*ACR*] 2018). *The expert panel recommends CT in patients with suspected pneumonia (with negative or indeterminate chest radiographs) whenever a definitive diagnosis is needed* (PLE expert panel consensus opinion).

CT chest with IV contrast or ultrasound chest also *may be appropriate* (Jokerst et al [*ACR*] 2018). *Contrast is not routinely indicated in patients with high clinical suspicion of pneumonia undergoing CT. However, it may be indicated if alternative diagnoses are being considered* (e.g., pulmonary embolus) (PLE expert panel consensus opinion).

Data suggest a potential role for MRI in detecting bacterial pneumonia in situations where initial chest radiograph findings are negative or equivocal; however, the sensitivity of CT appears to be slightly superior to MRI (Jokerst et al [*ACR*] 2018). *The expert panel thought that MRI is not indicated for the initial diagnosis of bacterial pneumonia. The panel recommends CT as the imaging procedure of choice for suspected bacterial pneumonia whenever a definitive diagnosis is needed* (PLE expert panel consensus opinion).

Clinical notes:

- The diagnosis of community acquired pneumonia is a clinical diagnosis (PLE expert panel consensus opinion).
- 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 radiograph, 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 radiograph 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). In up to 27% of cases, pneumonia might be demonstrated on CT with a negative or non-diagnostic chest radiograph. However, studies investigating interventions and treatment decisions based on HRCT findings compared to chest radiography are lacking (Gupta et al [*ICS/NCCP*] 2012).
- Chest CT may be warranted in certain patients (e.g., those who cannot reliably follow-up, those with advanced age, those with significant comorbidities) when initial chest radiograph is negative or equivocal (Jokerst et al [*ACR*] 2018).
- 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 may have difficulty identifying bacterial pneumonia that is not adjacent to the pleura (Jokerst et al [*ACR*] 2018). *The expert panel noted that accuracy of ultrasound is very operator-dependent* (PLE expert panel consensus opinion).

<u>Evidence update (2016-present):</u>
There were no new studies significantly affecting the evidence and recommendations included in the guidelines cited above.

Cough and/or dyspnea in patients with pneumonia that is not responding to treatment and/or with suspected complications (e.g., abscess, empyema):

- **Green** – CT chest without IV contrast or CT chest with IV contrast*
- **Orange** - MRI chest, except when CT findings are indeterminate
- **Red** – Scintigraphy, FDG-PET, PET/CT, SPECT, SPECT/CT, MRA, CTA, CT without and with IV contrast

*Ultrasound can complement or supplement CT in the detection of and management of parapneumonic effusions (Jokerst et al [*ACR*] 2018; PLE expert panel consensus opinion).

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

Notes concerning applicability and/or patient preferences:

Guideline and PLE expert panel consensus opinion summary:
CT of the chest should be performed in [patients] with non-resolving pneumonia and for the assessment of complications of community acquired pneumonia [such as lung abscess, empyema, or underlying malignancy] (Gupta et al [*ICS/NCCP*] 2012, 2A recommendation).

For the clinical scenario of *acute respiratory illnesses in immunocompetent patients with pneumonia complicated by suspected parapneumonic effusion or abscess on initial chest radiograph, next imaging study,* the *American College of Radiology* recommends CT chest with IV contrast or CT chest without IV contrast (usually appropriate). MRI chest without and with IV contrast, MRI chest without IV contrast, or ultrasound chest also *may be appropriate* in this scenario. (Jokerst et al [*ACR*] 2018). *The expert panel thought that MRI would not be indicated in this patient population unless CT findings were indeterminate and ultrasound expertise was not available* (PLE expert panel consensus opinion).

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 (Heitkamp et al [*ACR*] 2015).
- 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 (PNA) and abscess formation long before the findings become visible on a chest radiograph (Jokerst et al [*ACR*] 2018).
- The superior contrast resolution of CT 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).
- The use of intravenous contrast can increase the conspicuity of empyemas and other pleural complications (Jokerst et al [*ACR*] 2018).
- 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 and utility of ultrasound is very operator dependent* (Expert panel consensus opinion).

- 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).

Evidence update (2016-present):

There were no new studies significantly affecting the evidence and recommendations included in the guidelines cited above.

Cough and/or dyspnea in an immunocompromised patient:

- **Green** – CT chest without IV contrast
- **Yellow** – CT chest with IV contrast
- **Yellow** – CTPA or CTA for suspected invasive aspergillosis
- **Orange** – Scintigraphy
- **Orange** – MRI chest, except to evaluate suspected or known pleural/chest wall disease
- **Red** – FDG-PET, PET/CT, SPECT/CT, MRA, CT without and with IV contrast

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

Notes concerning applicability and/or patient preferences:

Guideline and PLE expert panel consensus opinion summary:
For immunocompromised patients with *cough, dyspnea, chest pain, fever,* the *American College of Radiology* recommends x-ray chest (9) (Heitkamp et al [*ACR*] 2015).

For immunocompromised patients with *negative, equivocal, or nonspecific chest radiograph,* the *American College of Radiology* recommends CT chest without IV contrast (9). If hemoptysis is present, consider CT chest with IV contrast (3) (Heitkamp et al [*ACR*] 2015).

For immunocompromised patients with *positive chest radiograph, multiple, diffuse, or confluent opacities,* the *American College of Radiology* recommends CT chest without IV contrast… (5). If hemoptysis is present, consider CT chest with IV contrast (3) (Heitkamp et al [*ACR*] 2015).

For immunocompromised patients with *positive chest radiograph, noninfectious disease suspected,* the *American College of Radiology* recommends CT chest without IV contrast (8) or CT chest with IV contrast (if hemoptysis is present) (5)… (Heitkamp et al [*ACR*] 2015).

Nuclear scintigraphy (Ga-67 or Tc-99m DTPA) has a very specific but rarely used role in the evaluation of immunocompromised patients with acute respiratory infection. Ga-67 can be used to help diagnose *Mycobacterium avium intracellulare*, *Mycobacterium tuberculosis*, and lymphoma based on increased radiotracer activity in hilar and mediastinal lymph nodes. However, this finding is nonspecific, and distinguishing between a malignant and infectious or inflammatory etiology may require a tissue diagnosis. Additionally, Ga-67 can be used to evaluate for the presence of *Pneumocystis jirovecii* pneumonia (PJP) within the lungs in cases where conventional imaging has turned up normal or equivocal findings (Heitkamp et al [*ACR*] 2015). *The expert panel thought that scintigraphy would have limited use as patients 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).

Invasive pulmonary aspergillosis:
Patterson et al [IDSA] recommend performing a chest computed tomographic (CT) scan whenever there is a clinical suspicion for invasive pulmonary aspergillosis (IPA) regardless of chest radiograph results (strong recommendation/high-quality evidence). Routine use of contrast during a chest CT scan for a suspicion of IPA is not recommended (strong recommendation/moderate-quality evidence). Contrast is recommended when a nodule or mass is close to a large vessel (strong recommendation/moderate-quality evidence) (Patterson et al [*IDSA*] 2016).

Patterson et al [IDSA] suggest a follow-up chest CT scan to assess the response of IPA to treatment after a minimum of 2 weeks of treatment; earlier assessment is indicated if the patient clinically deteriorates (IDSA 2016, weak recommendation/low-quality evidence). When a nodule is close to a large vessel, more frequent monitoring may be required (Patterson et al [*IDSA*] 2016, weak recommendation/low-quality evidence).

In patients at risk for invasive aspergillosis [IPA] with fever of unknown origin or clinical symptoms of lower respiratory tract infection who remain febrile despite broad-spectrum antibacterial treatment, thin-section chest CT at optimized dose is the imaging modality of choice (Ullmann et al [*ESCMID-ECMM-ERS*] 2018).

Pulmonary CT angiography may be of interest in the early diagnosis of IPA by depicting directly vessel occlusion at the level of a suspicious fungal lesions … and is required in case of hemoptysis (Ullmann et al [*ESCMID-ECMM-ERS*] 2018).

In selected patients [with IPA] where CT is not wanted or not feasible, MRI of the lungs may represent an alternative to thin-section multislice CT, positron emission tomography-CT being of modest interest in the diagnostics of IA (Ullmann et al [*ESCMID-ECMM-ERS*] 2018).

For immunocompromised hosts [with suspected TB and 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).

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

- In patients with immune deficiency, 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 that considers the type and severity of immune defect and geographic factors (Irwin et al [*ACCP*] 2006; Rosen [*ACCP*] 2006a).
- Chest radiography is indicated early in the evaluation of the immunocompromised patient with acute respiratory infection. If the radiograph demonstrates a single, focal airspace abnormality and the patient presents with symptoms of an acute bacterial pneumonia, further imaging with CT may not be needed unless the patient's clinical picture worsens or fails to improve with therapy (Heitkamp et al [*ACR*] 2015).
- CT may be of value in the severely immunocompromised patient with a normal or near-normal radiograph by revealing abnormal lymph nodes or subtle parenchymal disease (Ravenel et al [*ACR*] 2017).
- MRI has been shown to be at least as sensitive as CT for detecting pleural effusions in immunocompromised patients (Jokerst et al [*ACR*] 2018).
- In patients with a history of HIV-1 infection, solid organ and bone marrow transplant, and history of immunosuppressive therapy for lymphoma and vasculitis, investigation for bronchiectasis may be appropriate with symptoms of chronic productive cough or recurrent chest infections (Hill et al [*BTS*] 2019).

<u>Evidence update (2013-present):</u>

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 the causative organism remained unknown in four patients (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 (low level of evidence).

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 (51 males, mean age 60) with proven/probable IPA 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 the 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 (low level of evidence).

Chronic cough in patients with suspected active tuberculosis and a non-diagnostic or indeterminate chest radiograph*:

- **Green** – CT chest without IV contrast
- **Yellow** – CT chest with IV contrast or CTA or CTPA when there is suspected vascular involvement or to further characterize findings identified on non-contrast chest CT
- **Orange** - Scintigraphy
- **Red** – MRI, MRA, FDG-PET, PET/CT, SPECT, SPECT/CT, CT without and with IV contrast

*Chest radiography is indicated for the initial evaluation of patients with suspected active TB (Ravenel et al [ACR] 2017).

Level of Evidence: CT: moderate

Notes concerning applicability and/or patient preferences:

Guideline and PLE expert panel consensus opinion summary:
The major advantage of CT is increasing the [likelihood] of the diagnosis of [pulmonary] TB; therefore, CT is often not necessary in the acute setting, particularly when the disease is already suspected and appropriate precautions and testing are already underway. CT may be able to better show distinct findings such as cavitation or endobronchial spread with tree-in-bud nodules and may be helpful in cases in which the chest radiograph does not show "classic" findings of TB (Ravenel et al [*ACR*] 2017).

CT with IV contrast is appropriate in patients with hemoptysis, in patients with signs of vascular involvement, or to characterize abnormalities on noncontrast CT (PLE expert panel consensus opinion).

For immunocompromised hosts [with suspected TB], particularly those with a low CD4 count, computed tomography (CT) should be considered (Ravenel et al [*ACR*] 2017).

For patients with *suspected active tuberculosis,* the *American College of Radiology* recommends x-ray chest (9), CT chest without IV contrast (7), or CT chest with IV contrast (6). CT chest without contrast is recommended if x-ray is equivocal (Ravenel et al [*ACR*] 2017).

MRI has not been specifically evaluated as a primary imaging modality for patients with suspected or proven TB (Ketai et al [ACR] 2014).

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:

- 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, 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).

- [Patients with suspected active TB] should undergo chest radiography as the initial test. Chest radiographs have been shown to have a high sensitivity for detecting manifestations of active TB. However, chest radiography has a relatively poor specificity owing to the overlap of findings with nontuberculous pulmonary infection (Ravenel et al [*ACR*] 2017).
- 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).
- Signs [of pleural tuberculosis] 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 by chest radiographs, CT, ultrasound, or MRI (*NICE* 2016; PLE expert panel consensus opinion).

Evidence update (2016-present):
There were no new studies significantly affecting the evidence and recommendations included in the guidelines cited above.

Chronic cough and/or dyspnea that persists after ruling out or empirically treating the most common causes (e.g., upper airway cough syndrome, GERD, non-asthmatic eosinophilic bronchitis, asthma), with a restrictive ventilatory pattern and/or a suspicion for an interstitial lung disease or pleural/chest wall disease:

- **Green** – CT chest without IV contrast
- **Yellow** – CT chest with IV contrast
- **Orange** – FDG-PET, except to evaluate suspected or known mesothelioma
- **Orange** – MRI chest, except to evaluate suspected or known pleural/chest wall disease
- **Red** – Scintigraphy, PET/CT, SPECT, SPECT/CT, MRA, CTA, CT without and with IV contrast

Level of Evidence: CT: moderate-to-high; 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:
Chest radiography, O2 saturation, and spirometry are indicated in the evaluation of chronic cough (Morice et al [*BTS*] 2006; PLE expert panel consensus opinion).

If cough persists after consideration of the most common causes, perform a chest CT scan and, if necessary, a bronchoscopic evaluation (Irwin et al [*ACCP*] 2006; Prakash [*ACCP*] 2006, low level of evidence/grade of recommendation: B).

High resolution computed tomography may be of use in patients with chronic cough in whom other more targeted investigations are normal (Morice et al [*BTS*] 2006).

Interstitial lung disease:
Assess everyone with suspected idiopathic pulmonary fibrosis [interstitial lung disease] by (*NICE* 2013):

- Taking a detailed history, carrying out a clinical examination and performing blood tests to help exclude alternative diagnoses, including lung diseases associated with environmental and occupational exposure, with connective tissue diseases and with drugs
- Performing lung function testing (spirometry and gas transfer)
- Reviewing results of chest x-ray and
- Performing CT of the thorax (including high-resolution images).

For the clinical scenario of *chronic dyspnea, suspected interstitial lung disease, initial imaging,* the *American College of Radiology* recommends radiography chest or CT chest without IV contrast (usually appropriate). CT chest with IV contrast also *may be appropriate.* 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).

All patients being evaluated for fibrotic ILD should undergo high-resolution computed tomography (HRCT) imaging of the chest, unless contraindicated (Johannson et al [*CTS*] 2017*).

MRI does not currently have an established clinical role in the evaluation of ILD, although small studies have shown good concordance with CT. In general, MRI does not yet display the same level of parenchymal detail that is available with CT (McComb et al [*ACR*] 2018).

FDG-PET/CT may have a secondary role in ILD evaluation. It can be used…to reveal inflammatory activity before morphological changes are demonstrated on CT, and assist in follow-up and monitoring of treatment response (McComb et al [*ACR*] 2018).

Interstitial lung disease with occupational/environmental exposure:
Assess everyone with suspected interstitial lung disease and occupational exposure by (PLE Expert panel consensus opinion):

- Taking a detailed history, carrying out a clinical examination and performing blood tests to help exclude alternative diagnoses, including lung diseases associated with environmental and occupational exposure, with connective tissue diseases and with drugs
- Performing lung function testing (spirometry and gas transfer)
- Reviewing results of chest x-ray and
- Performing CT of the thorax (including high-resolution images).

For patients with *silica exposure, suspected silicosis,* the *American College of Radiology* recommends x-ray chest (9) and CT chest without IV contrast (9). Both of these tests should be performed (Bacchus et al [*ACR*] 2016).

For patients with *coal dust exposure,* the *American College of Radiology* recommends x-ray chest (9) and CT chest without IV contrast (9). Both of these tests should be performed (Bacchus et al [*ACR*] 2016).

For patients with *asbestos exposure, suspected interstitial lung disease,* the *American College of Radiology* recommends CT chest without IV contrast (9) and x-ray chest (8). Both of these tests should be performed (Bacchus et al [*ACR*] 2016).

For patients with *asbestos exposure, suspected mesothelioma,* the *American College of Radiology* recommends CT chest with IV contrast (9), x-ray chest (8), CT chest without IV contrast (7), FDG-PET/CT chest (6), and MRI chest without and with IV contrast (5). X-ray chest and CT chest should both be performed. FDG-PET may have utility in terms of defining mediastinal and distal metastatic disease, otherwise the role of FDG-PET is limited (Bacchus et al [*ACR*] 2016).

CT chest without contrast suffices for routine analysis of patients with occupational lung disease in most scenarios. In some situations, utilizing contrast-enhanced CT chest may be of utility if there is a clinical question of pulmonary embolism and in assessing for adenopathy/masses. Rarely is there a need for performing CT chest without and with contrast (Bacchus et al [*ACR*] 2016).

High-resolution computed tomography (HRCT) scans are strongly recommended (evidence level A) for diagnosis of asbestosis, coal workers' pneumoconiosis, or chronic beryllium disease. An HRCT scan is moderately recommended (evidence level B) for diagnosis of silicosis (Litow et al [*ACOEM*] 2015**).

Although useful in diagnosis of occupational ILD, an HRCT scan is not an essential part of the evaluation if chest radiographs document an occupational ILD that is consistent with the workers' exposure (Litow et al [*ACOEM*] 2015**).

FDG-PET may have utility in patients with suspected mesothelioma in terms of defining mediastinal and distal metastatic disease and perhaps localizing a potential biopsy site. Otherwise, the role of FDG-PET is limited (Bacchus et al [*ACR*] 2016).

In general, MRI is not regarded as appropriate in the evaluation of occupational lung diseases. MRI, though known to be limited in detecting abnormalities in the predominantly air-filled lungs, may have a role in evaluation of some parenchymal and pleural abnormalities (Bacchus et al [*ACR*] 2016).

Pleural/chest wall disease:
For the clinical scenario of *chronic dyspnea, suspected disease of the pleura or chest wall, initial imaging,* the *American College of Radiology* recommends radiography chest, CT chest with IV contrast, or CT chest without IV contrast (usually appropriate). MRI chest without and with IV contrast, MRI chest without IV contrast, or ultrasound chest also *may be appropriate* (McComb et al [*ACR*] 2018).

*The *CTS* guideline by Johannson et al (2017) 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.

**The *ACOEM* guideline by Litow et al (2015) did not pass the AGREE II cutoff or 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 and normal chest radiograph findings who are non-smokers and are not receiving therapy with an ACE inhibitor or an angiotensin II receptor blocker (ARB), the diagnostic approach should focus on the detection and treatment of UACS, asthma, NAEB, or GERD, alone or in combination. This approach is most likely to result in a high rate of success in achieving cough resolution (Irwin et al [*ACCP*] 2006; Pratter [*ACCP*] 2006).
- 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, pulmonary as well as extrapulmonary (Irwin et al [*ACCP*] 2006; Prakash [*ACCP*] 2006).

Interstitial lung disease:

- A normal chest radiograph in the setting of suspected ILD does not exclude the possibility of clinically important ILD (McComb et al [*ACR*] 2018).
- The diagnosis and classification of interstitial lung disease requires that the patient undergo high resolution computed tomography (HRCT) (Raghu et al. [*ATS*] 2018.

Interstitial lung disease with occupational or environmental exposure:

- Chest radiographs are moderately recommended (evidence level B) for use in diagnosing asbestosis, silicosis, or coal workers' pneumoconiosis. They are recommended, but with insufficient evidence, for other occupational ILDs (Litow et al [*ACOEM*] 2015).
- Workup of occupational lung diseases usually begins with routine chest radiography. However, the greater resolution of CT chest over chest radiograph allows for more sensitive and accurate detection and characterization of lung and pleural abnormalities (Bacchus et al [*ACR*] 2016).
- If there are atypical features, subtle abnormalities on routine radiography, and/or competing causes for the findings, then an HRCT scan may be especially helpful in confirming or excluding a diagnosis of occupational ILD (Litow et al [*ACOEM*] 2015).

Pleural/chest wall disease:

- 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).
- 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).
- MRI may provide improved characterization and assessment of the extent of pleural and chest wall abnormalities compared to CT (McComb et al [*ACR*] 2018).
- FDG-PET/CT remains a secondary test that may be used in the staging of mesothelioma and pleural metastatic disease (McComb et al [*ACR*] 2018).

Evidence update:

Interstitial Lung Disease (2016 – Present):

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 increasingly extensive reticular densities (OR 2.93, CI 95% 1.55-5.56, p= 0.001) predicted IPF, while increasing ground glass densities predicted 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 exceeds 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 (low level of evidence).

Occupational Lung Disease (2015 – Present):

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 (GGO) 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 than in AWP ($p < 0.0001$). In addition, chest radiograph had a tendency to underestimate lung parenchymal profusion abnormality of AWP, compared with that of silicosis. The authors concluded that CT should be considered for the assessment of patients with suspected AWP of early-stage disease before progression to fibrosis (moderate level of evidence).

Manners et al (2017) aimed to determine 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 (92% male, 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 (moderate 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 former employees (mean age 68) of the shipbuilding industry 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 (low level of evidence).

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 (low level of evidence).

Chronic cough and/or dyspnea that persists after ruling out or empirically treating the most common causes (e.g., upper airway cough syndrome, GERD, non-asthmatic eosinophilic bronchitis, asthma) with severe asthma and/or suspicion for COPD, bronchiectasis, or central airways disease/obstruction:

- **Green** – CT chest without IV contrast
- **Yellow** – CT chest with IV contrast or CTA or CTPA when there is suspected vascular involvement or to further characterize findings identified on non-contrast chest CT
- **Orange** – MRI chest, except when there is suspected or confirmed central airways disease/obstruction
- **Red** – Scintigraphy, FDG-PET, PET/CT, SPECT, SPECT/CT, MRA, CT without and with IV contrast

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

Notes concerning applicability and/or patient preferences:

Guideline and PLE expert panel consensus opinion summary:
Chest radiography, O2 saturation, and spirometry are indicated in the evaluation of chronic cough (Morice et al [*BTS*] 2006; PLE expert panel consensus opinion).

If cough persists after consideration of the most common causes, perform a chest CT scan and, if necessary, a bronchoscopic evaluation (Irwin et al [*ACCP*] 2006; Prakash [*ACCP*] 2006, low level of evidence/grade of recommendation: B).

High resolution computed tomography [with inspiratory and expiratory views] may be of use in patients with chronic cough in whom other more targeted investigations are normal (Morice et al [*BTS*] 2006).

For most routine applications, IV contrast is not needed, although it may be added when vascular abnormalities [e.g. PE] are in the differential diagnosis (McComb et al [*ACR*] 2018).

COPD:
For the clinical scenario of *chronic dyspnea, suspected chronic obstructive pulmonary disease (COPD), initial imaging,* the *American College of Radiology* recommends radiography chest (usually appropriate). CT chest without IV contrast or CT chest with IV contrast also *may be appropriate*, as 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).

[In patients with symptoms suggestive of COPD] special investigations like HRCT scan, lung volumes, diffusing capacity of the lungs for carbon monoxide (DLCO), and exercise testing should be done in situations of diagnostic difficulty or whenever clinically indicated (Gupta et al [*ICS/NCCP*] 2013, 2A).

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 a chest x-ray,

- To assess suitability for lung volume reduction procedures, and
- To evaluate for malignancy.

Before offering prophylactic antibiotics [for COPD], ensure that the person has had a CT scan of the thorax to rule out bronchiectasis and other lung pathologies (*NICE* 2018).

Consider a chest HRCT in adults with COPD and either $\geq$ 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] (Chang et al [*TSA*] 2015, GRADE-low/low level of evidence).

Severe asthma:
In…severe asthma without specific indications for chest HRCT based on history, symptoms and/or results of prior investigations Chung et al [ERS/ATS] suggest that a chest HRCT only be done when the presentation is atypical (Chung et al [*ERS/ATS*] 2014, conditional recommendation/very low quality evidence). *The expert panel thought that chest CT without contrast can be useful in severe asthma if alternative diagnoses are being considered, such as bronchiectasis, asthma/COPD overlap syndrome (ACOS), allergic bronchopulmonary aspergillosis (APBA), acute hypersensitivity pneumonitis, or pneumothorax.* (PLE expert panel consensus opinion).

For the clinical scenario of *acute asthma exacerbation in immunocompetent patients, complicated (suspected pneumonia or pneumothorax), initial imaging,* the *American College of Radiology* recommends radiography chest (usually appropriate). CT chest with IV contrast, CT chest without IV contrast or ultrasound chest also *may be appropriate* (Jokerst et al [*ACR*] 2018). *The expert panel thought that CT chest with contrast can be appropriate when there is suspected vascular involvement or pleural disease* (PLE expert panel consensus opinion).

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

Perform baseline imaging during clinically stable disease as this is optimal for diagnostic and serial comparison purposes (Hill et al [*BTS*] 2019, D level recommendation).

Central airways disease/obstruction:
For the clinical scenario of *chronic dyspnea, suspected central airways disease, initial imaging,* the *American College of Radiology* recommends radiography chest or CT chest without IV contrast (*usually appropriate*). CT chest with IV contrast, MRI chest without and with IV contrast, or MRI chest without IV contrast *may be appropriate* (McComb et al [*ACR*] 2018).

Clinical/imaging notes:

- In patients with chronic cough and normal chest radiograph findings who are non-smokers and are not receiving therapy with an ACE inhibitor or angiotensin II receptor blocker (ARB), the diagnostic approach should focus on the detection and treatment of UACS, asthma, NAEB, or GERD, alone or in combination. This approach is most likely to result in a high rate of success in

achieving cough resolution (Irwin et al [*ACCP*] 2006; Pratter [*ACCP*] 2006, low level of evidence/grade of recommendation: B).

- 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, pulmonary as well as extrapulmonary (Irwin et al [*ACCP*] 2006; Prakash [*ACCP*] 2006).

COPD:

- The evidence shows that CT scans and chest radiographs are accurate tests for identifying people who would test positive for COPD using spirometry, including people without symptoms (*NICE* 2018).

Severe asthma:

- 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 common 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).
- 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).

Bronchiectasis:

- 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).
- Although chronic productive cough is the cardinal feature of bronchiectasis, this symptom occurs far more commonly in patients with chronic bronchitis, asthma, UACS, and GERD (Rosen [*ACCP*] 2006c).
- 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.
- 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).

Central airway disease/obstruction:

- Chest radiographs have the potential to identify conditions of the trachea. Compared to CT, radiographs have an accuracy of 89% (McComb et al [*ACR*] 2018).
- Examples of airway conditions that may result in chronic dyspnea and can be accurately diagnosed by CT include stenosis, tumors, and end-expiratory airway collapse / tracheobronchomalacia, with strong correlations when compared with bronchoscopy (McComb et al [*ACR*] 2018).

Evidence update (2017-present):

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 with a clinical diagnosis of COPD, based on 2011 Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria with postbronchodilator ratio of FEV1 over FVC < 0.70, were enrolled. Patients had current or former smoking history or verified biomass exposure, were aged ≥ 40 years, and had stable disease and no exacerbation or respiratory infection within 6 weeks prior to study entry. Patients were examined with V/P SPECT and spirometry. Ventilation and perfusion defects were analyzed blindly. Total preserved lung function and penetration grade of Technegas in V SPECT 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. 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 to grade its severity (moderate 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. 69 COPD patients (68 males, mean age 46.6, range 29-78), 52 asthma patients (25 males, mean age 46.6, range 18-65), and 20 healthy subjects (10 males, mean age 42.8, range 23-67) were recruited. All subjects underwent CT, and PFTs 1 week after CT examination. 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 (low level of evidence).

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 asthma outpatients, who were > 50 years old and in a stable period at time of enrollment. 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 ≥ 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 (low level of evidence).

den Harder et al (2017) determined 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 (126 males; mean age 66.5; 24% never-smokers) and 155 controls (91 males; 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 (NPV) 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 (low level of evidence).

Chronic cough and/or dyspnea with suspicion of lung cancer (lung cancer screening):

The PLE expert panel thought that a separate discussion of the use of advanced imaging to detect cancer in patients with chronic cough and/or dyspnea was not warranted as cancer is in the differential diagnosis of symptomatic patients with both restrictive and obstructive physiologies. The risk of cancer is increased in patients with a smoking history and/or occupational exposure, however will be detected with the application of CT in the imaging algorithms detailed above. Screening for cancer in high risk asymptomatic patients is addressed in the *NCCN* guideline (Wood et al 2018) recommendations: *Lung Cancer Screening* (PLE expert panel consensus opinion).

Guideline exclusions:

- Known neoplasm or metastatic disease
- Bronchiolitis
- Primary spontaneous pneumothorax
- Hemothorax
- Pulmonary vascular disease
- Cardiovascular causes of cough/dyspnea
- Acute respiratory distress syndrome
- 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
- Renal disease
- Behavioral factors (anxiety, panic)
- Trauma
- Pregnant patients
- Pediatric patients
- Semiquantitative analysis and postprocessing algorithms.