American College of Radiology
ACR Appropriateness Criteria®
Chronic Cough

Variant 1: **Chronic cough lasting more than 8 weeks. No known risk factors for lung cancer. Initial imaging.**

Procedure	Appropriateness Category	Relative Radiation Level
Radiography chest	Usually Appropriate	☢
CT chest with IV contrast	May Be Appropriate	☢☢☢
CT chest without IV contrast	May Be Appropriate	☢☢☢
MRI chest without and with IV contrast	Usually Not Appropriate	O
MRI chest without IV Contrast	Usually Not Appropriate	O
CT chest without and with IV contrast	Usually Not Appropriate	☢☢☢
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	☢☢☢☢

Variant 2: **Chronic cough lasting more than 8 weeks. Increased risk for lung cancer. Initial imaging.**

Procedure	Appropriateness Category	Relative Radiation Level
Radiography chest	Usually Appropriate	☢
CT chest with IV contrast	May Be Appropriate	☢☢☢
CT chest without IV contrast	May Be Appropriate	☢☢☢
MRI chest without and with IV contrast	Usually Not Appropriate	O
MRI chest without IV Contrast	Usually Not Appropriate	O
CT chest without and with IV contrast	Usually Not Appropriate	☢☢☢
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	☢☢☢☢

Variant 3: **Chronic cough lasting more than 8 weeks. Persistent symptoms despite initial clinical evaluation and empiric treatment. Initial imaging.**

Procedure	Appropriateness Category	Relative Radiation Level
Radiography chest	Usually Appropriate	☢
CT chest with IV contrast	Usually Appropriate	☢☢☢
CT chest without IV contrast	Usually Appropriate	☢☢☢
CT maxillofacial without IV contrast	May Be Appropriate	☢☢
Fluoroscopy biphasic esophagram	Usually Not Appropriate	☢☢☢
MRI heart function and morphology without and with IV contrast	Usually Not Appropriate	O
CT maxillofacial with IV contrast	Usually Not Appropriate	☢☢
CT chest without and with IV contrast	Usually Not Appropriate	☢☢☢
CT maxillofacial without and with IV contrast	Usually Not Appropriate	☢☢☢
V/Q scan lung	Usually Not Appropriate	☢☢☢
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	☢☢☢☢
SPECT or SPECT/CT MPI rest and stress	Usually Not Appropriate	☢☢☢☢

CHRONIC COUGH

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Summary of Literature Review

Introduction/Background

Chronic cough is defined by a duration lasting at least 8 weeks [1], often contributing to patient discomfort and altered psychosocial well-being [2]. The most common causes of chronic cough include smoking-related lung disease, upper airway cough syndrome (UACS), asthma, gastroesophageal reflux disease (GERD), and nonasthmatic eosinophilic bronchitis [1-3]. Cough can further be characterized by quality, that is productive or nonproductive. Conditions that may be associated with productive cough include bronchiectasis, chronic bronchitis, asthma, and immunodeficiencies [4-6]. There is varied opinion in the literature regarding the utility of cough productivity in the phenotypic stratification of chronic cough patients [5,7,8].

Cough is a protective reflex mediated by a complex network of afferent and efferent neuronal pathways [9]. Stimuli for cough can occur in the chest wall, airways, esophagus, larynx, and middle ear [10]. It is believed that a significant number of individuals with chronic cough may be suffering from cough hypersensitivity [11,12], in which the threshold for cough is lowered by repeated exposure to stimulus or inflammation [11-13]. There may be similarity in the neuronal hyperstimulation seen in chronic cough with that of chronic pain [14]. The etiology of chronic cough in some patients may be difficult to localize to an isolated source and is often multifactorial [15]. The complex pathophysiology, clinical presentation, and variable manifestations of chronic cough underscore the challenges faced by clinicians in the evaluation and management of these patients.

Varying guidelines and algorithms exist for the evaluation and management of chronic cough, driven by a thorough history and physical examination, empiric treatment, and often diagnosis by exclusion [1,15,16]. Standardized clinical algorithms have shown efficacy in the diagnosis and treatment of chronic cough [7,10,16,17]. Imaging plays a role in the evaluation, although there is lack of high-quality evidence guiding which modalities are useful and at what time point in the clinical evaluation they should be performed. Further research may be needed to evaluate which imaging modalities performed earlier in the clinical assessment are beneficial in long-term outcomes.

Special Imaging Considerations

Our literature review has identified several studies investigating thoracic ultrasound (US) in the evaluation of the noncardiac chest pain. Noncardiac thoracic US performed better than radiography in small prospective cohorts staged in the postoperative intensive care unit [18] and primary care setting [19], confidently identifying findings such as pneumothorax, pleural effusion, consolidation, and interstitial patterns of lung disease. US was shown to correlate well with high-resolution CT (HRCT) and pulmonary function test (PFT) abnormalities [20], and it performed well in several small studies of patients with known interstitial lung disease [21-23]. US may be prone to diminished specificity. For instance, Moazedi-Fuerst et al [24] showed that up to 12% of patients with normal HRCT studies had sonographic findings of an interstitial pattern based on B-lines and artifacts. Adequate US evaluation is operator dependent and requires experience to perform and interpret examination findings. To our knowledge, there is no relevant literature to support the use of thoracic US in the evaluation of chronic cough; however, it is included in this section for awareness and to promulgate future research into this particular topic.

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Low-dose chest CT (LDCT) has been clinically validated in the National Lung Screening Trial Research Team for early detection of lung cancer [25]. LDCT has been investigated for early detection of pulmonary infection in elderly patients with normal or equivocal chest radiographs. Park et al [26] showed that 49 out of 166 elderly patients presenting to the emergency room who had normal chest radiographs were subsequently diagnosed with acute respiratory infection from findings on LDCT. In a prospective case comparison, Christe et al [27] showed good correlation between standard dose (150 mAs) and low-dose (40 mAs) CT protocols for evaluating the majority of pulmonary abnormalities, including bronchiectasis, air trapping, and pleural disease. Investigators did identify a drop in sensitivity in low-dose scans for ground-glass nodules, reticulation, and mucus plugging [27]. Ultra-low-dose CT demonstrated 91% sensitivity and 100% specificity in identifying asbestos-related lung abnormalities in a prospective cohort of 55 asymptomatic persons with relevant exposure history [28]. To our knowledge, there is no relevant literature to support the use of LDCT in the evaluation of chronic cough, and further research into this topic may be warranted.

Initial Imaging Definition

Initial imaging is defined as imaging at the beginning of the care episode for the medical condition defined by the variant. More than one procedure can be considered usually appropriate in the initial imaging evaluation when:

- There are procedures that are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care)

OR

- There are complementary procedures (ie, more than one procedure is ordered as a set or simultaneously where each procedure provides unique clinical information to effectively manage the patient's care).

Discussion of Procedures by Variant

Variant 1: Chronic cough lasting more than 8 weeks. No known risk factors for lung cancer. Initial imaging.

Radiography Chest

Chest radiography is recommended by numerous pulmonary and thoracic societies for the evaluation of chronic cough [1,10,15,29], although the exact timing of imaging has varied between groups. The American College of Chest Physicians (ACCP) includes a recommendation for an initial chest radiograph in their chronic cough algorithm [1]. The evidence supporting chest radiography at initial evaluation of chronic cough is limited to case series, observational studies, and retrospective analysis. Initial evaluation with posteroanterior chest radiography has been included as part of two investigative case series using standardized clinical protocols for chronic cough [7,17]. Of the 131 patients evaluated, 49 chest radiographs were reported abnormal, with the final diagnosis of primary lung pathology other than asthma made in 29 patients, including 8 patients with bronchiectasis, 8 patients with interstitial lung disease, and 2 patients with neoplasm. The authors did not report the sensitivity or specificity of chest radiography in the setting of chronic cough; however, abnormal radiography was positively associated with underlying primary pulmonary pathology other than asthma (odds ratio 7.7) [7]. Ojoo et al [17] prospectively evaluated 112 patients with chronic cough in a similar standardized clinical investigative protocol. In this study, 7 radiographs (6.3%) were reported contributory to the final diagnosis. Of the 92 patients with diagnosis found at discharge, 12 (13%) patients had pathologies including bronchiectasis, interstitial lung disease, self-limiting cough, and 2 cases of lung cancer. Both of these studies reported clinical efficacy with standardized protocols utilizing initial chest radiography, with diagnosis achieved in 93% in the Kastelik et al study [7] and 82% in the Ojoo et al study [17]. The most commonly reported etiologies were reflux, asthma, postinfective or viral cough, and rhinitis, representing between 61% to 67% of final diagnosis, which were more common than bronchiectasis, interstitial lung disease, and neoplasm, which represents <13% to 18% of final diagnosis [7,17]. Both case series are limited by sample size, and both studies were performed out of referral centers, likely contributing to selection bias.

Retrospective analyses have been performed specific to chronic cough and normal chest radiography. Turner et al [16] retrospectively reviewed the medical records of 404 patients with chronic cough referred to specialty care who either had or subsequently were found to have a normal chest radiograph. Of the 266 patients who were given a diagnosis, 8 patients were found to have a diagnosis that could be made on imaging (4 with lower respiratory tract infection, 2 with malignancy, 1 with bronchiectasis, and 1 with pulmonary fibrosis). Although made explicit for the 2 cases with malignancy, it is only implied that the other 6 patients had normal chest radiography and that the diagnosis was made by other means (ie, chest CT). Additionally, the cases of malignancy were suspected on the

grounds of additional clinical features. Even in a referral setting, the authors suggest that a large majority of patients could be managed with simple clinically driven investigations, to include chest radiography. Truba et al [3] conducted a retrospective analysis of nonsmoking patients with chronic cough who had both a negative chest radiograph followed by a chest CT. The investigators found a relatively low negative predictive value of 64% for chest radiography, when they considered CT findings that were felt to be relevant to chronic cough. The most common CT findings included bronchiectasis, bronchial wall thickening, mediastinal lymphadenopathy, and interstitial abnormalities. Although specificity could be inferred from the provided data (~82%), the sensitivity of chest radiography is inherently not calculable. The authors suggested that chest radiography was not sensitive to exclude the majority of "relevant" findings; however, the selection of CT findings was based on a combination of literature review, expert opinion, and consensus. For instance, mediastinal lymphadenopathy, which was nearly 20% of the CT findings, was felt to be relevant. Additionally, the decision for CT evaluation was discretionary, and CT imaging was only performed once common causes were excluded, which provides basis for selection bias.

The diagnostic performance of chest radiography varies among the reviewed literature. In a systematic review of the literature, Piccazzo et al [30] reported a high negative predictive value for chest radiography in the evaluation of active and inactive tuberculosis. Abnormalities on chest radiography did have a lower specificity, and findings, which were equivalent the authors concluded, should prompt consideration for CT as this modality was shown to have better performance for both active and inactive tuberculosis. Colaci et al [31] prospectively evaluated 107 consecutive patients with systemic sclerosis with both radiography and HRCT. Their study showed strong correlation between radiographic and HRCT findings of interstitial lung disease, with strong association between cough symptoms and HRCT findings. Interstitial lung pattern and restrictive PFT was more commonly identified than airway involvement and obstructive disease. The authors, however, did not publish sensitivity or specificity for radiography [31]. The diagnostic performance of radiography for other patterns of lung disease may be worse. In a retrospective analysis of 236 patients with CT-proven bronchiectasis, Altenburg et al [32] reported that up to 34% of chest radiographs were reported unremarkable. As mentioned above, the most common CT findings in those patients with chronic cough with normal radiographs were in fact bronchiectasis (28%) and bronchial wall thickening (21%) [3]. The sensitivity of chest radiography for airway abnormalities was found to be 69% to 71% when referenced to helical CT in 70 patients with known airway abnormalities and lesions [33]. In a retrospective analysis of elderly emergency room patients who were evaluated for acute respiratory infection, Park et al [26] showed that chest radiographs were normal in 49 out of 166 confirmed cases on LDCT. Chest radiography was more often normal when LDCT identified ground-glass opacity (GGO), bronchial wall thickening, centrilobular nodules, and small and dependent consolidations. Chest radiography was also found to have poor correlation with chest CT for the presence of pulmonary opacities [34,35], with a positive predictive value of only 27% when compared with chest CT in a secondary analysis of a large retrospective cohort of 3,400 patients.

Limitations of chest radiography reflect superimposed soft-tissue structures, radiographic findings related to comorbidities, and limited contrast resolution. Unfortunately, there are no high-quality studies evaluating the clinical efficacy of chest radiography in the early evaluation of patients with chronic cough, and this may be an area of future investigation. Based on the available literature, there is a suggestion that initial evaluation of chronic cough with chest radiography is beneficial in the clinical setting. There does remain question regarding the sensitivity of chest radiography in this group [3], which is likely skewed toward early disease and airway abnormalities. This could potentially result in delayed diagnosis for a small percent of patients with chronic cough.

CT Chest

There is no high-quality evidence to support the use of chest CT in the initial evaluation of patients presenting with chronic cough. No studies have directly compared the utility of contrast-enhanced versus noncontrast-enhanced CT imaging in regard to chronic cough. Contrast-enhanced studies offer improved visualization of cardiopulmonary vasculature, mediastinal structures, and soft-tissue abnormalities [35], although MRI is developing a more consistent role for the latter. For the majority of studies, however, the noncontrast technique appears to be adequate. Chest CT is more sensitive than chest radiographs for the evaluation of most pulmonary abnormalities as well as mediastinal, cardiac, and chest wall findings, combining improved soft-tissue contrast and anatomical localization. This was demonstrated in a few small studies included in our literature review [3,32,36]. Chest CT is considered the reference standard for the noninvasive diagnosis of bronchiectasis [37] as well as of interstitial lung disease.

CT abnormalities have been described in patients with chronic cough. Truba et al [3] performed a retrospective analysis of patients with chronic cough with negative initial chest radiograph findings, reporting 21 out of 59 patients with CT abnormalities believed to be relevant to chronic cough. The authors identified bronchiectasis and

bronchial wall thickening as the two most commonly identified CT abnormalities (12% and 10%, respectively), with 3 patients showing interstitial lung pattern [3]. Hochhegger et al [38] compared chest CT findings between patients with chronic cough with chronic rhinosinusitis (CRS) (n = 59) and those without CRS (n = 64). Both groups had findings of bronchial wall thickening (57%–62%) and air trapping (31%–35%) on HRCT with a significantly higher prevalence of centrilobular nodules, atelectasis, GGO, and bronchiolectasis in those patients with clinical manifestations of CRS. Utilizing quantitative methods, bronchial wall thickening was significantly associated with cough symptoms in patients with chronic obstructive pulmonary disease (COPD) [39]. Youssef et al [36], in a small prospective case series of 36 consecutive patients with rheumatoid arthritis (RA), showed a significant association between cough symptoms and HRCT abnormalities.

Other studies showed a lack of association between cough symptoms and chest CT findings. Ooi et al [6] was unable to correlate respiratory symptom exacerbation (including cough symptoms) with HRCT findings of small airways abnormality, mosaic attenuation, and bronchial wall thickening in 60 patients with CT-proven bronchiectasis, although there was association between CT findings and sputum production and PFT abnormality. Wilsher et al [40], in a prospective analysis of 60 consecutive patients newly diagnosed with RA, demonstrated that bronchiectasis was prevalent in up to 48% of patients, despite only 30% of patients presenting with respiratory complaints. There was no association between the cough symptoms and bronchiectasis, although there was a statistically significant association for dyspnea symptoms.

Wide application of chest CT in symptomatic patient cohorts may not be diagnostically rewarding. In the STAMPEDE study (Study of Active Duty Military for Pulmonary Disease Related to Environmental Deployment Exposures), HRCT was noncontributory or normal in 48 of 49 imaged postdeployment military personnel with respiratory complaints [41]. The authors suggested reserving HRCT for indeterminate chest radiograph findings or those with abnormalities on PFT. Screening large populations utilizing chest CT may also reveal findings that are either nonrelevant or subclinical in relevance. In a retrospective analysis of CT findings from a large health screening study performed in South Korea, 9.1% of studied persons were found to have bronchiectasis, with only 57% of patients with bronchiectasis reporting any respiratory symptoms [4]. CT abnormalities were skewed toward elderly patients with up to 20% of subjects >70 years of age found to have bronchiectasis [4]. Winter et al [42] also showed a higher prevalence of CT abnormalities in asymptomatic nonsmoking elderly (≥65 years of age) patients when compared with younger volunteers. CT findings included both parenchymal (bands and ground glass) and airway findings, such as bronchiectasis and bronchial wall thickening.

The major pulmonary societies recommend noncontrast chest CT for the evaluation of chronic cough when the more common causes are excluded or empirically treated [1,10,15,29], and this is usually preceded by a chest radiograph. Of the studies evaluating the clinical management of patients with chronic cough, none utilized chest CT in the initial workup [3,7,16,17], and two studies specifically addressed a cohort of patients with normal chest radiography findings [3,16]. Kastelik et al [7] utilized a probability-based clinical algorithm in the prospective treatment of 131 patients presenting with cough lasting >8 weeks. All patients were initially evaluated with chest radiography and empirically treated based on the probability of underlying etiologies. Chest CT was performed in those patients with clinical suspicion of underlying disease (n = 29) as well as in those with indications or negative initial workup otherwise (n = 17). Of these, 26 out of 29 patients (positive predictive value of 90%) suspected of having underlying pulmonary disease were diagnosed and treated as appropriate; however, 17 patients in whom chest CT was performed without cause and as part of the algorithmic evaluation did not have findings relevant to their management. The authors concluded that chest CT should be performed only in selected patients and those with abnormal chest radiographs.

In another prospective observational study, Ojoo et al [17] evaluated 112 consecutive patients with chronic cough. All patients were evaluated with chest radiography. Chest CT was performed only based on clinical suspicion. The authors reported that 74 out of 81 patients managed clinically without the need for chest CT examination, suggesting chest CT would not have made a difference in these patients. It should be noted that both studies did identify primary pulmonary etiologies felt to be associated with chronic cough, of which bronchiectasis and interstitial lung disease were the two most common. In a retrospective cohort of patients with chronic cough referred to specialty care with normal chest radiographs, Turner et al [16] showed successful clinical management of 266 patients with minimal investigation and empiric treatment, requiring chest CT in 1 patient to diagnose bronchiectasis, 1 patient with pulmonary fibrosis, and 2 patients with malignancy. Future studies may be needed to better validate CT findings with clinical features in order to determine causation/association in the context of chronic cough. Lung patterns of disease and obvious abnormalities identified on CT will still be of clinical value, and an expected number of CT

abnormalities may be noncontributory to management. The role of chest CT in the initial evaluation of chronic cough remains indeterminate. The evidence suggests that wide application in all patients presenting with chronic cough may be of low clinical yield. Appropriate selection would likely improve the specificity of findings.

FDG-PET/CT Skull Base to Mid-Thigh

There is no relevant literature to support the use of fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG)-PET in the initial evaluation of chronic cough. FDG-PET/CT is not listed as an imaging option in the most recent ACCP guidelines on chronic cough [1]. FDG-PET utilizes a radiolabeled glucose analog to evaluate for upregulated metabolism in areas of infection, inflammation, and neoplasm [43].

MRI Chest

There is no relevant literature to support the use of thoracic MRI in the initial evaluation of chronic cough. MRI of the chest is not included in the clinical algorithms recommended by various pulmonary and thoracic societies [1,10,15,29]. Thoracic MRI (nonbreast, noncardiac, nonmusculoskeletal) is currently utilized for the evaluation of indeterminate findings on other imaging modalities, most commonly mediastinal and thymic [44], less often utilized for vascular, airway, and pulmonary parenchymal abnormalities. MRI offers improved soft-tissue contrast, with advanced sequences able to identify soft-tissue characteristics to the cellular level (ie, diffusion-weighted imaging and spectroscopy). Advanced techniques allow for calculation of total lung water density, which has been shown to correlate with disease severity in adult patients with cystic fibrosis [45]. With the addition of intravenous (IV) contrast, the vascular nature of an abnormality is exquisitely imaged and has been shown to be as accurate as contrast-enhanced CT for the evaluation for pulmonary embolism [35]. IV contrast also offers the evaluation of pulmonary perfusion [46]. Limitations of pulmonary MRI include low signal-to-noise ratio (especially with a normally aerated lung), low spatial resolution, and need for adequate breath-hold technique or respiratory gating [46]. Parenchymal lung abnormalities naturally increase cellular proton density and/or water content while displacing low signal gas, providing contrast for visualization [35]. Despite limitations, pulmonary MRI has been shown to have noninferior diagnostic quality when compared with CT [46,47]. Ohno et al [47] analyzed 85 consecutive patients with high-resolution pulmonary MR using ultrashort time to echo and compared findings with both standard CT and LDCT. The authors found equivalent diagnostic efficacy for all observed findings, noting decreased sensitivity and image quality when evaluating for emphysema, bronchiectasis, and reticular opacity. The authors concluded that based on their assessment, ultrashort time to echo pulmonary MR is equivalent to LDCT imaging [47].

There is no relevant literature evaluating IV contrast versus noncontrast MRI in the setting of chronic cough, and decisions may need to be made on a case-by-case basis. Investigational contrast agents may prove useful in the future. Hyperpolarized gas MRI is an example, which is currently FDA approved for investigational use [44,48]. Hyperpolarized Xe-129 gas MRI allows for improved contrast of the lung parenchyma with techniques allowing for the evaluation of anatomical and functional data [48]. These techniques are still in their infancy and will likely require future studies to evaluate their role in imaging in chronic cough. In 2014, Ackman et al [44] surveyed thoracic radiologists from the Society of Thoracic Radiology regarding utilization of nonvascular thoracic MRI. Respondents offered an insight into the underutilization of thoracic MRI. Challenges in implementing MRI into clinical practice were described, including ordering health care provider awareness, lack of training, and technical, as well as administration hurdle.

Variant 2: Chronic cough lasting more than 8 weeks. Increased risk for lung cancer. Initial imaging.

Radiography Chest

Chest radiography is often performed early in the investigation of chronic cough and is recommended by the ACCP [1]. There was no literature that addressed this modality in the setting of chronic cough with risk factors for lung cancer. In each of the available prospective case series evaluating standardized clinical protocols for chronic cough, there was a diagnosis of malignancy in 2 of 131 [7] and 2 of 122 [17] patients assessed, all of whom had initial chest radiography. Both studies reported that clinical and radiographic findings led to increased suspicion of malignancy. In a retrospective analysis of patients with chronic cough who had normal chest radiographs, 2 out of 266 diagnosis were determined to be malignant. Both patients had suspicious clinical findings, which prompted further evaluation with chest CT [16].

Cough has been shown to be a prevalent symptom in patients with lung cancer [49,50], with 57% consecutive patients with lung cancer reporting cough as a symptom (n = 223). The exact prevalence of malignancy in a population with chronic cough is not well documented and likely <1% to 2% from the small collection of case series

reviewed. Nevertheless, in the setting of elevated risk (ie, smoking and occupational exposure), the prevalence may be more significant.

The diagnostic performance of chest radiography has been reported, with variable results depending on the studied populations. Chest radiography detected significantly fewer pulmonary abnormalities than HRCT in 36 consecutive patients with RA. Although the authors did not detail the specific abnormalities that led to a false-negative study, the large majority of patients had interstitial pattern of lung disease [36]. In a case series of 107 patients with systemic sclerosis, chest radiography showed good correlation with HRCT findings ($r = 0.825$) [31]. In the setting of occupational exposure, Tutkun et al [51] performed HRCT on 74 asymptomatic welders whose chest radiographs were reported as "nonpathalogic." The investigators identified 27 patients with parenchymal changes, including nodular disease, GGO, parenchymal lines, and emphysematous changes. Chest radiography had low sensitivity (69%–71%) when compared with digital tomosynthesis and chest CT in a cohort of patients with a high prevalence of airway neoplasms and abnormality (91 airway lesions in 149 patients) [33]. In a chronic cough population of 97 patients with normal radiographs, Truba et al [3] reported a significant number of abnormalities identified on chest CT. Out of 128 abnormalities reported, 19 lesions were noncalcified solitary pulmonary nodules (1 nodule measuring >8 mm in size). In a large prospective randomized screening study, LDCT performed better than chest radiography for the detection of lung cancer and resulted in a 20% mortality reduction [25].

The role of chest radiography in the early evaluation of patients with chronic cough is largely founded in the exclusion of treatable and/or serious underlying pulmonary pathology. When extrapolating from the available evidence, there remains a question regarding the sensitivity of chest radiography for the detection of subclinical disease and early malignancy. In this setting, there may be a population of patients with chronic cough that may benefit from earlier use of advanced imaging. Future research into this topic may elucidate the specific features and clinical qualities that would provide risk stratification and entail appropriate imaging recommendation.

CT Chest

There is no relevant literature to support the use of chest CT in patients with chronic cough who have one or more high-risk factors for lung cancer. In nonsmoking adults, risk factors vary and include environmental pollutants, genetic variations, underlying chronic pulmonary disease, immunosuppression, and occupational exposures (ie, asbestos and silica) [52]. Cough has been shown to be a prevalent symptom in patients with lung cancer [49,50], 57% of a small cohort of consecutive patients with lung cancer (n = 223). However, the true prevalence of isolated cough (without any additional clinical features) in the setting of malignancy remains unknown. Some authors suggest this combination to be rare in the clinical setting of chronic cough [16]. In a retrospective analysis of patients with chronic cough who have normal chest radiographs, 2 out of 266 diagnoses were determined to be malignancy. Both patients had suspicious clinical findings, which prompted further evaluation with chest CT. It is also worth noting that both patients had a normal chest radiograph [16]. In prospective case series evaluating standardized clinical protocols for chronic cough, the prevalence of malignancy was found to be between 1% and 2% [7,17].

CT of the chest is recommended for the evaluation of suspected pulmonary neoplasm [15,53] and has been recommended for patients with chronic cough who are smokers or when chronic lung disease is clinically suspected [16,53]. Chest CT has been shown to be more sensitive than chest radiography for the detection of lung cancer in the National Lung Cancer Screening Trial [25], with significant overall mortality benefit. There is limited data regarding the differential imaging evaluation of patients with chronic cough with occupational exposures. In a small sample of male welders (n = 74) with a normal chest radiograph, HRCT identified 27 patients with micronodular disease, 5 patients with emphysematous changes, 3 patients with GGO, and 1 patient with pleural thickening [51], questioning the sensitivity of radiography for occupational disease. Red flags and concerning features are discussed by various authors and larger pulmonary societies [1,13,29], although our literature review did not identify studies directly evaluating CT of the chest in patients with chronic cough with elevated risk. Additionally, red flags in this setting have not been validated and shown to be predictive of malignancy.

In the setting of elevated lung cancer risk, there is no high-quality evidence supporting chest CT in patients with chronic cough. It is worth noting that in the few case series evaluating patients with chronic cough, malignancy was diagnosed in 1% to 2% of studied groups. This is a not an insignificant quantity and actually rivals case detection in both lung cancer and breast cancer screening. Furthermore, at least two of these reported malignancies were in the context of a normal chest radiograph. It is likely that the prevalence of malignancy in the setting of chronic cough is far lower, and these studies are likely biased by selection. Nevertheless, there may be a cohort of patients with chronic cough who would benefit from earlier chest CT, potentially leap-frogging weeks of sequential

therapeutic trials that may in fact delay diagnosis. Future research may be needed to evaluate which patients with chronic cough would gain from earlier evaluation with CT.

FDG-PET/CT Skull Base to Mid-Thigh

There is no relevant literature to support the use of FDG-PET/CT in the evaluation of chronic cough with increased risk factors for lung cancer. FDG-PET utilizes a radiolabeled glucose analog to evaluate for upregulated metabolism in areas of infection, inflammation, and neoplasm [43]. It is often utilized in the setting of solitary pulmonary nodules to allow for risk stratification. In the setting of known malignancy, FDG-PET is suitable for staging nodal and metastatic involvement. FDG-PET provides valuable input for further noninvasive testing and operative planning. In patients with chronic cough who have elevated risk factors for lung cancer, it is unlikely that FDG-PET would significantly add value over other imaging modalities, such as chest radiography or chest CT.

MRI Chest

There is no relevant literature to support the use of thoracic MRI in the evaluation of patients with chronic cough who have increased risk of lung cancer. No studies specific to chronic cough distinguished between contrast-enhanced and noncontrast MRI. In the setting of neoplasm of the chest wall or mediastinum, the addition of extracellular contrast agent would allow for differentiation of cystic and solid features and may add value in planning appropriate invasive testing. Additionally, vasculature is imaged well with the addition of contrast, and contrast-enhanced MRI has been shown to be nearly equivalent to contrast-enhanced CT for the evaluation for pulmonary embolism [29]. MRI was not evaluated in the two prospective clinical series evaluating the utility of a standardized clinical protocol for the evaluation of chronic cough [7,17]. MRI is also not explicitly recommended in the available practice guidelines for the evaluation of chronic cough by the ACCP [1]. Limitations of pulmonary MRI include low signal-to-noise ratio (especially with normally aerated lung), low spatial resolution, and need for adequate breath-hold technique or respiratory gating [46]. Based on our literature review, there is limited evidence evaluating the diagnostic quality of MRI for the evaluation of pulmonary abnormalities. Ohno et al [47] analyzed 85 consecutive patients with a high prevalence of pulmonary abnormality with high-resolution pulmonary MR using ultrashort time to echo and compared findings with both standard and LDCT acquisition. High-resolution MRI demonstrated excellent correlation with standard dose CT for mass or nodule, GGO, and lymphadenopathy. MRI demonstrated 89% sensitivity and 99% specificity for mass or nodule identification. The authors noted diminished imaging quality; however, this did not affect overall evaluation. The role of MRI in the setting of chronic cough and increased cancer risk remains unknown at this time. Future research in this setting may be warranted for certain populations.

Variant 3: Chronic cough lasting more than 8 weeks. Persistent symptoms despite initial clinical evaluation and empiric treatment. Initial imaging.

Radiography Chest

Regarding the utility of chest radiography in the context of failed initial evaluation or failed empiric treatment, it is likely, based on the reader's preference on clinical practice guidelines for chronic cough, that radiography has been performed. In fact, the majority of pulmonary societies, guidelines, authors, and other groups recommend at least consideration for chest radiography upon initial presentation. We did not come across recommendations for re-imaging after initial treatment, and as described for the above variants, advanced imaging may be more useful.

CT Chest

The most commonly identified etiologies reported for chronic cough are asthma, GERD, and UACS [1]. Prospective case series have shown clinical efficacy in diagnosing and managing chronic cough using standard clinical algorithms with minimal investigation [7,17]. When this has failed to result in diagnosis, or when empiric sequential treatment for the most common etiologies has failed to resolve symptoms, further investigative modalities and additional specialty referrals have been recommended. The ACCP and German Respiratory Society both recommend HRCT after an appropriate clinical evaluation and empiric trial has been performed [1,29]. HRCT is typically performed with multidetector helical CT, and the standard for performance can be reviewed in the ACR practice parameter for HRCT [54]. Briefly, thin-slice acquisition and high spatial resolution reconstruction algorithms allow for near-isotropic voxels. This gives the reader additional tools for a thorough evaluation of the imaged field, including multiplanar reformats and both maximum and minimum intensity projection postprocessed images. In the setting of chronic cough, however, the various modalities and specific protocol designs have not been adequately investigated and compared. It is unclear how much the added resolving power of HRCT adds to the clinical evaluation of patients with chronic cough. Contrast- and noncontrast-enhanced studies have also not been compared. The addition of contrast would allow for improved visualization of the mediastinum, chest wall, and soft

tissues. At least one investigative group reported that mediastinal lymphadenopathy could be a "relevant" finding in the evaluation of chronic cough [3], and the addition of contrast would make this finding more conspicuous; however, it is unlikely that clinically significant mediastinal lymphadenopathy would be overlooked on a noncontrast scan. Contrast also allows for adequate evaluation of blood pool structures and pulmonary vessels; however, our review did not identify reports of vascular etiology for chronic cough.

HRCT is considered the reference standard for the evaluation of bronchiectasis. Bronchiectasis has been identified as an etiology for chronic cough in up to 8% of patients in case series [2,7]. Although suspicion for bronchiectasis can be aided by clinical features [5], chest radiography has shown poor sensitivity for evaluation. Altenburg et al [32] reported that radiographic findings did not detect ectatic airways in up to 34% of patients reviewed. Bronchiectasis and bronchial wall thickening were identified in 27% and 21% of patients, respectively, referred to chest CT for the evaluation of chronic cough in whom radiographs were reportedly normal [3]. There remains variable association between identification of bronchiectasis and clinical features. Bronchiectasis has been found by chest CT in asymptomatic persons enrolled in a health survey screening setting [4], as well as in asymptomatic elderly persons [37]. Wilsher et al [40] evaluated 60 consecutive patients with newly diagnosed RA and were unable to demonstrate a correlation between cough symptoms and bronchiectasis, although association reached significance for dyspnea. Furthermore, bronchiectasis and bronchial wall thickening were identified in 48% and 58% of patients, respectively, with only 30% reporting any symptoms. Ooi et al [6] were unable to correlate the frequency of acute symptom exacerbation (including cough symptoms) and the degree of bronchial wall thickening in 60 consecutive patients with CT-proven bronchiectasis. In a large single-center prospective study, Grydeland et al [39] used quantitative analysis of bronchial wall thickening and compared findings between patients with COPD (n = 463) and those without COPD (n = 488). Airway wall thickening was found to be statistically associated with chronic cough in patients with COPD but did not reach significance in the non-COPD group.

Interstitial lung disease and pulmonary fibrosis have been reported as etiologies of chronic cough, although prevalence of diagnosed cases is variable, ranging between 0.4% and 8% of the reviewed case series [2,7,16,17]. Chest CT is considered the reference standard in the evaluation of interstitial lung disease. Although at least one study reported good correlation between chest radiography and chest CT in this setting [46], chest CT has been shown to be more sensitive than both chest radiography [31] and LDCT [27]. In 97 patients with chronic cough who also had normal chest radiographs, Truba et al [3] reported interstitial abnormalities in 4 patients. Association between cough symptoms and CT findings of interstitial lung disease has been variable. In a small prospective cohort of 36 patients with RA, cough was not found to be statistically associated with restrictive findings on either PFT or HRCT analysis [31]. In 107 consecutive patients with systemic sclerosis, cough was associated with HRCT findings [31].

In the setting of chronic cough after failed initial evaluation and/or empiric treatment, the limited evidence suggests a role for chest CT to identify underlying pulmonary disease. Although it remains unclear if HRCT or LDCT play a role, clinical features may stratify patients for appropriate imaging evaluation in order to balance diagnostic yield and dose considerations.

CT Maxillofacial

CT of the sinuses and maxillofacial structures offers improved visualization of the sinonasal anatomy, allowing for localization, characterization, and grading of sinonasal pathology. UACS is largely a conglomerate terminology for cough related to inflammation or irritation of the upper airways, which includes postnasal drip, allergic and nonallergic CRS, as well as laryngeal reflux. UACS is considered one of the more common causes of chronic cough [1,53]. Based on a few case series of patients with chronic cough, UACS/rhinitis prevalence ranged from 6% to 65% [2,7,17]. Guidelines for the evaluation of chronic cough by the ACCP places sinus imaging under consideration after initial clinical examination and chest radiography [1]. The clinical evaluation of UACS is not sensitive and often not specific [53], and features may go unrecognized even by endoscopy [12,55,56], creating an integral role for noninvasive imaging. Symptoms alone were found to have a sensitivity between 37% and 73% in a retrospective analysis of 126 patients who underwent CT imaging for the evaluation of CRS [57]. Furthermore, up to 35% of patients who were diagnosed with CRS had normal endoscopic findings [57]. Abrass et al [55] reviewed 100 patients with clinical findings suspicious of CRS, all with negative endoscopic evaluations. The investigators reported between 20% and 49% of studied individuals had positive findings on point-of-care CT of the sinuses, and the utilization of imaging allowed for a decrease in unnecessary antibiotic prescription. In a small retrospective case control study evaluating patients with CRS, Conley et al [56] showed increased clinical accuracy and a lower rate of unnecessary antibiotic use when cone-beam CT was used to evaluate the sinuses at initial office visit. In a

prospective study of 81 patients who were imaged with cone-beam sinus CT prior to dental implantation, Horwitz Berkun et al [58] showed a significant association between self-reported symptoms of cough and CT features of sinus osteal obstruction and sinus membrane thickening. However, the authors of this study did not collect questionnaire data pertaining to the duration of symptoms. The international consensus statement on allergy and rhinology recommends objective evidence (endoscopy or CT imaging findings) for the diagnosis of CRS [57,59]. The international statement does not include cough as one of the "cardinal" symptoms. It is unclear if chronic cough is a sole presenting symptom in cases of UACS. Associated symptoms, such as nasal congestion, sneezing, and anosmia, were seen in 16 of 17 patients with chronic cough diagnosed with UACS [16]. Based on limited available literature, there may be a role for sinonasal imaging in the evaluation of chronic cough in this setting.

FDG-PET/CT Skull Base to Mid-Thigh

There is no relevant literature to support the use of FDG-PET/CT in the evaluation of chronic cough. This imaging modality was not evaluated in limited case series evaluating patients with chronic cough, nor was it recommended in the available guidelines published by various societies and groups. FDG avidity has been correlated to sites of parenchymal abnormality in a small study of 36 patients with interstitial lung disease [43,60]. Yadav et al [61] showed increased FDG activity corresponding to HRCT abnormalities in 16 patients with known interstitial lung disease. Win et al [62] evaluated a small cohort of patients with idiopathic pulmonary fibrosis and demonstrated increased FDG activity in areas of the lung with and without HRCT abnormalities, suggesting increased sensitivity of PET for early inflammation. The limited literature is suggestive of an increased sensitivity of PET/CT to various inflammatory processes, so clearly there is a role in the evaluation and staging of malignancy. Future research may be needed to evaluate the role of PET/CT in cases of idiopathic chronic cough. One could speculate that a few inflammatory processes (ie, arteritis) with minimal imaging findings on more conventional modalities may demonstrate FDG uptake.

Fluoroscopy Biphasic Esophagram

There is no relevant literature to support the use of biphasic esophagram in the evaluation of chronic cough.

Biphasic esophagram is a real-time evaluation utilizing fluoroscopic technique with oral administration of a contrast agent. This description does not include a "modified swallow" barium study, which is often performed by or with the assistance of a speech therapist. The interpreting radiologist performing a contrast esophagram has the benefit of direct patient interaction and can modify examination parameters to evaluate for abnormality as indicated. The examination allows for both anatomical and physiologic assessment, specifically the evaluation of gastroesophageal reflux, anatomic pathology (webs, hiatal hernia, and stricture), and esophageal dysmotility. To this end, a single- or double-phase examination would suffice, as in the context of chronic cough, it is unclear if the evaluation of mucosal abnormality would contribute to diagnostic yield. There is an association between chronic cough and gastroesophageal reflux [63], although the exact mechanism remains unresolved, and causality has not been widely proven [64]. Case series have shown an association between GERD, esophageal abnormalities, and hiatal hernia with chronic aspiration [65], which may contribute to chronic cough. It is thought that reflux may contribute to cough mechanism via stimulation of a vagal-mediated cough reflex, via microaspiration, or through laryngeal reflux [64], with microaspiration playing less of a role than previously thought [66]. GERD is one of the more common etiologies for chronic cough [1]. In the reviewed case series of patients with chronic cough, reflux-associated chronic cough was prevalent in 22% to 29% of patients [7,17]. In a large systematic review of the literature, authors of the updated 2016 CHEST guidelines on the treatment of GERD in chronic cough identified variable prevalence of GERD as a cause, ranging from 2% to 86% [67]. Probability-based clinical diagnosis has shown efficacy in the setting of chronic cough [7]. In a prospective case series of 95 consecutive patients with chronic cough, the addition of swallowed contrast agent to a posteroanterior and lateral radiograph led to the identification of 12 patients with esophageal abnormality relevant to chronic cough. These included hiatal hernia, achalasia, neoplasm, and diverticulum. After appropriate therapy, chronic cough symptoms resolved in 11 out of 12 patients [68]. This study did not perform dynamic evaluation of esophageal motility, which is standard practice for a diagnostic esophagram. Gastroesophageal scintigraphy has demonstrated esophageal dysmotility in symptomatic patients even in the setting of absent reflux, suggesting that dysmotility may contribute to cough-like symptoms [69]. Limitations of barium esophagram include imaging in a limited time frame. Abnormalities such as reflux or dysmotility may not be imaged during the study. Irwin et al [63] evaluated 12 patients with chronic cough (>3 weeks by the author's definition) using multiple modalities. Out of the 11 patients with reflux identified by 24-hour esophageal monitoring, only 4 patients had abnormalities on barium esophagram to suggest GERD. From limited literature reviewed, the role of

barium esophagram in the setting of chronic cough remains unclear. It is possible that this imaging modality could function as a "bridge" to more invasive testing, such as 24-hour pH monitoring or endoscopy.

MRI Heart Function and Morphology Without and With IV Contrast

There is no relevant literature to support the use of MRI of the heart in the evaluation of chronic cough. This modality is not described for use in the most recent guidelines by ACCP on chronic cough [1]. The etiology of chronic cough in the setting of underlying heart disease could be related to venous congestion secondary to poor cardiac function, anatomic abnormality (left atrial dilatation), and congenital disease, inflammatory or infiltrative processes involving the myocardium and/or pericardium. We did not identify case series regarding isolated chronic cough in this setting, and it is likely that patients would also present with other clinical features such as chest pain and dyspnea. We refer the readers to the ACR Appropriateness Criteria® topics on "Chronic Chest Pain-High Probability of Coronary Artery Disease" [70], "Chronic Dyspnea-Noncardiovascular Origin" [71], and "Dyspnea–Suspected Cardiac Origin" [72] regarding these latter symptoms.

SPECT or SPECT/CT MPI Rest and Stress

There is no relevant literature supporting the use of single-photon emission CT (SPECT) or SPECT/CT myocardial perfusion imaging (MPI) rest and stress for the evaluation of chronic cough. MPI uses a radiolabeled perfusion agent to evaluate for reversible perfusion defects in the myocardium between a rest and stress condition. Stress can be achieved with exercise or pharmaceutical aid and myocardial perfusion can be performed with Tc-99m sestamibi or tetrofosmin. The addition of CT imaging offers the ability of attenuation correction and localization of unexpected sites of radiotracer uptake. This imaging modality has not been evaluated for isolated chronic cough to our knowledge and is unlikely to play a role without additional clinical features, such as dyspnea or chest pain. We refer the readers to the ACR Appropriateness Criteria® topics on "Chronic Chest Pain-High Probability of Coronary Artery Disease" [70], "Chronic Dyspnea-Noncardiovascular Origin" [71], and "Dyspnea–Suspected Cardiac Origin" [72] regarding these latter symptoms.

V/Q Scan Lung

There is no relevant literature supporting the use of ventilation-perfusion lung scan (V/Q) in the evaluation of chronic cough. Radiolabeled agents administered to the patient allow for physiologic imaging of pulmonary perfusion (Tc-99m macroaggregated albumin) and pulmonary ventilation (Tc-99m DTPA or Xe-133 gas). Protocols exist for perfusion-only evaluation in the appropriate context. The most common use for V/Q pulmonary imaging is in the evaluation of acute pulmonary embolism. We refer the readers to the ACR Appropriateness Criteria® topic on "Suspected Pulmonary Embolism" [73] regarding this diagnosis. Additionally, there is utility for the evaluation of chronic pulmonary embolism. Ventilation scans performed with Xe-133 gas can detect air trapping. None of the reviewed case series evaluating cohorts of patients with chronic cough identified a vascular etiology for chronic cough [2,7,16,17]. V/Q pulmonary scanning is not currently included in the ACCP chronic cough guidelines.

Summary of Recommendations

- **Variant 1**: Radiography chest is usually appropriate for the initial imaging of patients with chronic cough lasting >8 weeks with no known risk factors for lung cancer.
- **Variant 2**: Radiography chest is usually appropriate for the initial imaging of patients with chronic cough lasting >8 weeks and increased risk for lung cancer.
- **Variant 3**: Radiography chest or CT chest with IV contrast or CT chest without IV contrast is usually appropriate for the initial imaging of patients with chronic cough lasting >8 weeks with persistent symptoms despite initial clinical evaluation and empiric treatment. These procedures are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care), although following up a chest radiograph with a CT would be considered complementary if a concerning finding is discovered on the chest radiograph.

Supporting Documents

The evidence table, literature search, and appendix for this topic are available at https://acsearch.acr.org/list. The appendix includes the strength of evidence assessment and the final rating round tabulations for each recommendation.

For additional information on the Appropriateness Criteria methodology and other supporting documents go to www.acr.org/ac.

Appropriateness Category Names and Definitions

Appropriateness Category Name	Appropriateness Rating	Appropriateness Category Definition
Usually Appropriate	7, 8, or 9	The imaging procedure or treatment is indicated in the specified clinical scenarios at a favorable risk-benefit ratio for patients.
May Be Appropriate	4, 5, or 6	The imaging procedure or treatment may be indicated in the specified clinical scenarios as an alternative to imaging procedures or treatments with a more favorable risk-benefit ratio, or the risk-benefit ratio for patients is equivocal.
May Be Appropriate (Disagreement)	5	The individual ratings are too dispersed from the panel median. The different label provides transparency regarding the panel's recommendation. "May be appropriate" is the rating category and a rating of 5 is assigned.
Usually Not Appropriate	1, 2, or 3	The imaging procedure or treatment is unlikely to be indicated in the specified clinical scenarios, or the risk-benefit ratio for patients is likely to be unfavorable.

Relative Radiation Level Information

Potential adverse health effects associated with radiation exposure are an important factor to consider when selecting the appropriate imaging procedure. Because there is a wide range of radiation exposures associated with different diagnostic procedures, a relative radiation level (RRL) indication has been included for each imaging examination. The RRLs are based on effective dose, which is a radiation dose quantity that is used to estimate population total radiation risk associated with an imaging procedure. Patients in the pediatric age group are at inherently higher risk from exposure, because of both organ sensitivity and longer life expectancy (relevant to the long latency that appears to accompany radiation exposure). For these reasons, the RRL dose estimate ranges for pediatric examinations are lower as compared with those specified for adults (see Table below). Additional information regarding radiation dose assessment for imaging examinations can be found in the ACR Appropriateness Criteria® Radiation Dose Assessment Introduction document [74].

Relative Radiation Level Designations		
Relative Radiation Level*	**Adult Effective Dose Estimate Range**	**Pediatric Effective Dose Estimate Range**
O	0 mSv	0 mSv
☢	<0.1 mSv	<0.03 mSv
☢☢	0.1-1 mSv	0.03-0.3 mSv
☢☢☢	1-10 mSv	0.3-3 mSv
☢☢☢☢	10-30 mSv	3-10 mSv
☢☢☢☢☢	30-100 mSv	10-30 mSv
*RRL assignments for some of the examinations cannot be made, because the actual patient doses in these procedures vary as a function of a number of factors (eg, region of the body exposed to ionizing radiation, the imaging guidance that is used). The RRLs for these examinations are designated as "Varies."		

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