

# CLINICAL GUIDELINE:

## IMAGING UTILIZATION Lower Respiratory Disease



Physician Clinical Integration  
Network, LLC

### Scope

According to a survey conducted by the U.S. Census Bureau, 9.1% of adults residing in the United States and the District of Columbia have asthma, 6.6% have been diagnosed with COPD, and 13.4% report a diagnosis of chronic lung disease [3]. Bacterial pneumonia accounted for 8% of deaths in the United States in 2014 [4].

The primary reason patients seek medical attention is for respiratory signs and symptoms, including dyspnea, with chest X-ray (CXR) as the most commonly performed radiologic procedure (Table 1-5) [1]. This guideline focuses on the symptoms of dyspnea (the most common subjective symptom) and the four major lower respiratory diseases: asthma, chronic obstructive pulmonary disease (COPD), acute respiratory illness, and interstitial lung disease [1].

With the rise in immunodeficiency syndromes related to HIV, AIDS, cancers treated with chemotherapy, transplantations, and patients with an already impaired immune system (i.e., diabetes, alcoholism, COPD), establishing a definitive diagnosis can be challenging for the primary care provider. Since there is an increased risk of morbidity and mortality, information is presented to address this population (Tables 6 & 7) [2].

### Guidance

The PCIN Quality Committee and its designees reviewed the available information in the medical literature and societal guidelines on the evaluation, management and appropriate use of imaging for adult patients (>18 years) presenting with lower respiratory disease in the Primary Care and Emergency Department setting, as well as information derived from their clinical practice to devise these guidelines.

#### Population Included

- Adults (> 18 years)
  - Immunocompromised patients
  - Those presenting with initial respiratory symptoms

#### Exclusions

- Pediatric patients
- Pregnant females

### Recommendations

- ✓ A focused history and physical examination should be performed on all patients presenting with a chief complaint of lower respiratory disease (prior to any radiographic procedure).
- ✓ Immunocompromised patients should have a CXR performed in a timely manner due to increased risk of morbidity and mortality.
- ✓ A CXR should be the initial diagnostic study performed on patients presenting with symptoms of lower respiratory disease.
- ✓ A CT scan/HRCT should be considered if the correlation made between the presenting symptoms, clinical assessment, CXR, and other tests requires a more definitive diagnosis.
- ✓ MRI is not the diagnostic procedure of choice in patients presenting with lower respiratory disease symptoms.
- ✓ The American College of Radiology's (ACR) "Appropriate Use Criteria" should be utilized for dyspnea and Acute Respiratory Illness in Immunocompetent Patients (Tables 1-7).

## Rationale

### Assessment and Evaluation of Patients Presenting with Lower Respiratory Disease Symptoms

A thorough assessment and evaluation of a patient presenting with lower respiratory symptoms is imperative in determining the need for radiologic procedures extending past a chest radiograph. A history focused on the severity, rate of worsening, and presence or absence of risk factors and other symptoms is crucial in determining if there is a cardiovascular and/or a pulmonary origin. The chest radiograph coupled with laboratory testing usually result in a specific diagnosis; however, a chest CT or MRI is useful in identifying specific disease characterizations [1].

Initial clinical assessment for patients with a suspected diagnosis of acute respiratory illness includes symptoms of cough, sputum production, chest pain, and/or dyspnea (with or without fever) (Tables 1-5). The risk of morbidity and mortality is heightened in immunocompromised patients, warranting more aggressive testing (Tables 6 & 7) [2].

### Asthma

CXR is the initial radiographic procedure used in patients presenting with asthma symptoms. While useful in determining the cause of wheezing in asthma patients (i.e., hyperinflation and bronchovascular changes), the CXR is valuable in the diagnosis of other diseases, such as pneumonia. Clinical correlation remains essential in the primary diagnosis of asthma. CT scans can be used to support the diagnosis of asthma and in determining air trapping and bronchodilator response. Because wheezing is not always indicative of asthma, CT scans can eliminate possible etiologies such as tracheal tumors, foreign bodies, pneumonia, and other conditions mimicking asthma. High-resolution CT (HRCT) scans demonstrate finer details such as air trapping, measurable bronchial wall thickening, atelectasis, centrilobular nodules due to mucous plugging, and acinar nodules due to low-grade inflammatory changes [6]. In severe asthmatics, the chest CT is useful in the diagnosis of diseases associated with asthma, such as allergic bronchopulmonary aspergillosis, eosinophilic pneumonia, and eosinophilic granulomatosis with polyangiitis [7]. In a study of 35 patients with severe airway obstruction, Lucidarme et al, determined that air trapping may permit detection of airway obstruction in patients with clinically suspected asthma even when pulmonary function tests are normal [5].

### Chronic Obstructive Pulmonary Disease/Emphysema

While the CXR is readily available and less expensive, the CT is the standard modality for objective visualization, providing more discrete imaging and clinical correlation of emphysema, airway disease, and more recently, pulmonary vascular disease [7]. The CT scan is useful in determining type, extent, and distribution of emphysema and identifying early changes of COPD. The expiratory CT image reflects airflow limitation related to dyspnea associated with COPD [1]. Other considerations such as optical coherence tomography (OCT) offers the ability to image airway wall structures at a higher resolution, creating 3D images of the airway for improved diagnostics, while the MRI details lung structure and function [8].

Due to the limited contrast resolution of the CXR, focal areas of increased lucency, due to presence of lung destruction, can be difficult to identify. The CT scan, specifically the HRCT scan with contrast, can detect areas of abnormally low attenuation in comparison to surrounding normal lung parenchyma. The most compelling studies focus on the accuracy of the CT and HRCT identifying the correlation between CT score and pathological specimens invitro [9].

### Acute Respiratory Illness

To ensure patients presenting with an acute respiratory illness are treated appropriately, clinicians must distinguish between those attributed by a viral infection vs. bacterial pneumonia.

The Global Initiative for Chronic Obstructive Lung Disease's (GOLD) standard for diagnosis of bacterial pneumonia is an upright posteroanterior and lateral CXR [2]. The need for a CXR is reliant on the following factors: illness severity, presence of fever, clinical exam, patient age, lab results indicating leukocytosis and/or other risk factors. However, according to the Infectious Diseases Society of America and the American Thoracic Society, "a demonstrable infiltrate by chest radiograph or other imaging technique...is required for the diagnosis of pneumonia" [4].

Specific characteristics of various pathogens can assist the physician in the initial treatment with antibiotics, while specific imaging appearances can be instrumental in the evaluation of treatment (antibiotics) (Table 8). A CXR may confirm the diagnosis of



pneumonia, while the CT scan may be used as a lead to causative pathogens, to exclude noninfectious pneumonia or to reveal underlying diseases [10].

### Interstitial Lung Disease

Radiologic images provide supportive diagnostic information in correlation with laboratory testing and physical examination. A posteroanterior CXR will assist the physician in identifying patterns suggestive of interstitial lung disease (ILD) and/or complications, as well as diseases mimicking ILD. Comparison to previous CXRs helps determine if the ILD is acute or chronic [11]. A reticular pattern is the most common radiographic abnormality, although nodular or mixed patterns are not uncommon. Honeycombing is usually an indication of a poor prognosis [12]. An abdominal CT scan will provide images inclusive of the lower lung regions, thorax, and cervical spine. HRCT of the thorax is instrumental and has become a standard diagnostic tool. Lack of pulmonary parenchymal changes on the HRCT virtually excludes a diagnosis of ILD (Table 9) [11].

### References

1. McComb, B L. Ravenel, J F. Steiner, R M. Chung, J H. Ackman, J B. Carter, B. Colletti, P M. Crabtree, T D. de Groot, P M. Iannettoni, M D. Jokerst, C. Maldonado, F. Kanne, J P (2018). ACR appropriateness criteria Chronic Dyspnea Noncardiovascular Origin. Journal of the American College of Radiology. Retrieved from [https://www.jacr.org/article/S1546-1440\(18\)31157-8/fulltext](https://www.jacr.org/article/S1546-1440(18)31157-8/fulltext)
2. American College of Radiology. (2019). ACR appropriateness criteria acute respiratory illness in immunocompromised patients, pdf. Retrieved from: <https://acsearch.acr.org/docs/69447/Narrative/>
3. American Lung Association. Methodology: Estimated Prevalence and Incidence of Lung Disease, 2019. Retrieved from <https://www.lung.org/our-initiatives/research/monitoring-trends-in-lung-disease/estimated-prevalence-and-incidence-of-lung-disease/methodology.html>
4. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44 Suppl 2:S27-72
5. Lucidarme O, Coche E, Cluzel P, et al. Expiratory CT scans for chronic airway disease: correlation with pulmonary function test results. AJR Am J Roentgenol. 1998 Feb. DOI:10.2214/ajr.170.2.9456933
6. Grimm L. (2016). Asthma Imaging. Retrieved from <https://emedicine.medscape.com/article/353436-overview#showall>
7. Ash S, Diza A. (2017). The role of imaging in the assessment of severe asthma. Curr Opin Pulm Med. 2017 Jan; 23(1): 97–102. doi: 10.1097/MCP.0000000000000341
8. Washko R. (2010). Diagnostic Imaging in COPD. Semin Respir Crit Care Med. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4334134/>
9. Muller N L, Coxson H. (2002). Chronic obstructive pulmonary disease, 4: Imaging the lungs in patients with chronic obstructive pulmonary disease. Thorax. Retrieved from: <https://thorax.bmj.com/content/thoraxjnl/57/11/982.full.pdf>
10. Nambu A, Ozawa K, Kobayashi N, Tago M. (2014). Imaging of community-acquired pneumonia: Roles of imaging examinations, imaging diagnosis of specific pathogens and discrimination from noninfectious diseases. World Journal of Radiology. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4209424/>
11. Meyer K. (2014). Diagnosis and management interstitial lung disease. Translational Respiratory Medicine. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4215823/>
12. King T E. (2019). Approach to the adult with interstitial lung disease: Diagnostic testing. Retrieved from: <https://www.uptodate.com/contents/approach-to-the-adult-with-interstitial-lung-disease-diagnostic-testing>



## Appendix

### Table 1

Chronic Dyspnea. Unclear Etiology. Initial Imaging.

Procedure	Appropriateness Category	Comments
Radiography chest	Usually Appropriate	Guides further imaging decisions
CT chest without IV contrast	May Be Appropriate (Disagreement)	
CT chest with IV contrast	May Be Appropriate	
CT chest without and with IV contrast	Usually Not Appropriate	
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	
MRI chest without and with IV contrast	Usually Not Appropriate	
MRI chest without IV contrast	Usually Not Appropriate	
Ultrasound chest	Usually Not Appropriate	

McComb, B L. Ravenel, J F. Steiner, R M. Chung, J H. Ackman, J B. Carter, B. Colletti, P M. Crabtree, T D. de Groot, P M. Iannettoni, M D. Jokerst, C. Maldonado, F. Kanne, J P (2018). ACR appropriateness criteria Chronic Dyspnea Noncardiovascular Origin. Journal of the American College of Radiology. Retrieved from [https://www.jacr.org/article/S1546-1440\(18\)31157-8/fulltext](https://www.jacr.org/article/S1546-1440(18)31157-8/fulltext)

### Table 2

Chronic Dyspnea. Suspected Chronic Obstructive Pulmonary Disease (COPD). Initial Imaging.

Procedure	Appropriateness Category	Comments
Radiography chest	Usually Appropriate	Guide to comorbidities, complications and alternative diagnoses
CT chest without IV contrast	May Be Appropriate	
CT chest with IV contrast	May Be Appropriate	
MRI chest without and with IV contrast	Usually Not Appropriate	
MRI chest without IV contrast	Usually Not Appropriate	
Ultrasound chest	Usually Not Appropriate	
CT chest without and with IV contrast	Usually Not Appropriate	
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	

McComb, B L. Ravenel, J F. Steiner, R M. Chung, J H. Ackman, J B. Carter, B. Colletti, P M. Crabtree, T D. de Groot, P M. Iannettoni, M D. Jokerst, C. Maldonado, F. Kanne, J P (2018). ACR appropriateness criteria Chronic Dyspnea Noncardiovascular Origin. Journal of the American College of Radiology. Retrieved from [https://www.jacr.org/article/S1546-1440\(18\)31157-8/fulltext](https://www.jacr.org/article/S1546-1440(18)31157-8/fulltext)



**Table 3****Chronic Dyspnea. Suspected Interstitial Lung Disease. Initial Imaging.**

Procedure	Appropriateness Category	Comments
CT chest without IV contrast	Usually Appropriate	Consider including expiratory or prone imaging
Radiography chest	Usually Appropriate	
CT chest with IV contrast	May Be Appropriate (Disagreement)	
MRI chest without and with IV contrast	Usually Not Appropriate	No established clinical role
MRI chest without IV contrast	Usually Not Appropriate	
Ultrasound chest	Usually Not Appropriate	
CT chest without and with IV contrast	Usually Not Appropriate	Consider if predisposed to ILD
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	Marker of disease extent and severity in sarcoidosis, reveals inflammatory activity or severity/prognosis of ILD

McComb, B L. Ravenel, J F. Steiner, R M. Chung, J H. Ackman, J B. Carter, B. Colletti, P M. Crabtree, T D. de Groot, P M. Iannettoni, M D. Jokerst, C. Maldonado, F. Kanne, J P (2018). ACR appropriateness criteria Chronic Dyspnea Noncardiovascular Origin. Journal of the American College of Radiology. Retrieved from [https://www.jacr.org/article/S1546-1440\(18\)31157-8/fulltext](https://www.jacr.org/article/S1546-1440(18)31157-8/fulltext)

**Table 4****Chronic Dyspnea. Suspected Disease of the Pleura or Chest Wall. Initial Imaging.**

Procedure	Appropriateness Category	Comments
Radiography chest	Usually Appropriate	Limited in determining exact location (i.e., parenchymal, pleural or extrapleural)
CT chest with IV contrast	Usually Appropriate	Superior to CXR to determine extent
CT chest without IV contrast	Usually Appropriate	Superior to CXR to determine extent
MRI chest without and with IV contrast	May Be Appropriate (Disagreement)	Contrast used to determine soft-tissue relationships
MRI chest without IV contrast	May Be Appropriate	
Ultrasound chest	May Be Appropriate (Disagreement)	
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	For staging of mesothelioma and pleural metastatic disease
CT chest without and with IV contrast	Usually Not Appropriate	

McComb, B L. Ravenel, J F. Steiner, R M. Chung, J H. Ackman, J B. Carter, B. Colletti, P M. Crabtree, T D. de Groot, P M. Iannettoni, M D. Jokerst, C. Maldonado, F. Kanne, J P (2018). ACR appropriateness criteria Chronic Dyspnea Noncardiovascular Origin. Journal of the American College of Radiology. Retrieved from [https://www.jacr.org/article/S1546-1440\(18\)31157-8/fulltext](https://www.jacr.org/article/S1546-1440(18)31157-8/fulltext)

**Table 5****Chronic Dyspnea. Suspected Diaphragm Dysfunction. Initial Imaging.**

Procedure	Appropriateness Category	Comments
Radiography chest	Usually Appropriate	For position of diaphragm
Fluoroscopy chest	Usually Appropriate	More accurate for diaphragmatic motion
MRI chest without and with IV contrast	May Be Appropriate	For position of diaphragm
MRI chest without IV contrast	May Be Appropriate	For position of diaphragm
Ultrasound chest	May Be Appropriate	For diagnosis of neuromuscular disorders of the diaphragm
CT chest with IV contrast	Usually Not Appropriate	
CT chest without and with IV contrast	Usually Not Appropriate	
CT chest without IV contrast	Usually Not Appropriate	

McComb, B L. Ravenel, J F. Steiner, R M. Chung, J H. Ackman, J B. Carter, B. Colletti, P M. Crabtree, T D. de Groot, P M. Iannettoni, M D. Jakerst, C. Maldonado, F. Kanne, J P (2018). ACR appropriateness criteria Chronic Dyspnea Noncardiovascular Origin. Journal of the American College of Radiology. Retrieved from [https://www.jacr.org/article/S1546-1440\(18\)31157-8/fulltext](https://www.jacr.org/article/S1546-1440(18)31157-8/fulltext)

**Table 6****Acute Respiratory Illness in Immunocompetent Patients with Negative Physical Examination, Normal Vital Signs, and No Other Risk Factors. Initial Imaging.**

Procedure	Appropriateness Category	Comments
Radiography chest	Usually Appropriate	
CT chest with IV contrast	Usually Not Appropriate	
CT chest without and with IV contrast	Usually Not Appropriate	
CT chest without IV contrast	Usually Not Appropriate	
MRI chest without and with IV contrast	Usually Not Appropriate	
MRI chest without IV contrast	Usually Not Appropriate	
Ultrasound chest	Usually Not Appropriate	

American College of Radiology. (2019). ACR appropriateness criteria acute respiratory illness in immunocompromised patients, pdf. Retrieved from: <https://acsearch.acr.org/docs/69447/Narrative/>

**Table 7****Acute Respiratory Illnesses in Immunocompetent Patients with Positive Physical Examination, Abnormal Vital Signs, Organic Brain Disease, or Other Risk Factors. Initial Imaging.**

Procedure	Appropriateness Category	Comments
Radiography chest	Usually Appropriate	
Ultrasound chest	May Be Appropriate	
CT chest with IV contrast	Usually Not Appropriate	
CT chest without and with IV contrast	Usually Not Appropriate	
CT chest without IV contrast	Usually Not Appropriate	
MRI chest without and with IV contrast	Usually Not Appropriate	
MRI chest without IV contrast	Usually Not Appropriate	

American College of Radiology. (2019). ACR appropriateness criteria acute respiratory illness in immunocompromised patients, pdf. Retrieved from: <https://acsearch.acr.org/docs/69447/Narrative/>



**Table 8**

<b>Specific Imaging Findings of Representative Pathogens for Community-Acquired Pneumonia</b>	
<b>Pathogens</b>	<b>Specific Imaging Appearances</b>
Streptococcus Pneumoniae	Alveolar/Lobar Pneumonia
Mycoplasma Pneumoniae	Bronchopneumonia with wall thickening of the central bronchi
Chlamydophila Pneumoniae	Infectious bronchiolitis with bronchial dilation
Legionella Pneumophila	Sharply marinated peribronchial consolidations within ground-glass opacities
Varicella-Zoster	Scattered nodules with a random distribution
Tubercle Bacillus	Tree-in-bud appearance with finer and denser branching opacities than those of bronchopneumonia caused by common bacteria (post primary tuberculosis)
Cryptococcus Neoformans	Multiple nodules/masses with or without cavities in the same pulmonary lobe
Pneumocystis Jirovecii	Bilateral patchy ground-glass opacities with a geographic distribution
<b>Particular Clinical Conditions Related to Community-Acquired Pneumonia</b>	
<b>Pathophysiological Conditions</b>	<b>Imaging Findings</b>
Aspiration Pneumonia	Bronchopneumonia or patchy ground-glass opacities at the dependent parts of the lung (S2, S1+2, S6 and S10), intrabronchial materials
Sinobronchial Syndrome	Centrilobular or peribronchial nodules with bronchial wall thickening and bronchiectasis, and mucus in the bronchi, findings of paranasal sinusitis
Pneumonia on a Background of Pulmonary Emphysema	Consolidation with pseudocavities or pseudo honeycombing, emphysema of the surrounding lung (easier to see at a narrower window and lower level settings and with a thinner section), delayed resolution
<b>Representative Differential Diagnoses of Community-Acquired Pneumonia</b>	
<b>Condition</b>	<b>Discriminators from Community-Acquired Pneumonia</b>
Non-Infectious Pneumonia	
Cryptogenic Organizing Pneumonia	Relatively chronic clinical course (often for more than one month), evidence of organization (concavity of the opacities, traction bronchiectasis, clear visualization of peripheral air bronchograms, or mild parenchymal distortion), reversed halo sign
Chronic Eosinophilic Pneumonia	Bilateral nonsegmental consolidations with peripheral predominance
Lipoid Pneumonia	Presence of fat within the consolidation on both visual assessment and computed tomography value measurement
Neoplasm	Lack of inflammatory response on laboratory data, chronic clinical course
Mucinous Invasive Adenocarcinoma	Bulging contour, stretching or thinning of bronchi, cavities
Malignant Lymphoma	Infiltrative spread around the consolidation (halo sign, galaxy sign or thickening of surrounding vessels, etc.)

Nambu A, Ozawa K, Kobayashi N, Tago M. (2014). Imaging of community-acquired pneumonia: Roles of imaging examinations, imaging diagnosis of specific pathogens and discrimination from noninfectious diseases. World Journal of Radiology. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4209424/>

**Table 9**

Imaging Modality	Pattern	Consistent ILD Diagnoses, Mimics of ILD, and/or Complications of ILD
<b>Routine CXR</b>	Hilar Lymphadenopathy	Sarcoidosis, Silicosis, CBD, Infection, Malignancy
	Septal Thickening	CHF, Malignancy, Infection, PVOD
	Lower Lung Zone Predominance	IPF, Asbestosis, DIP, CTD, NSIP
	Mid/Upper Lung Zone Predominance	Sarcoidosis, Silicosis, Acute HP, LCH, CBD, AS, Chronic EP
	Peripheral Lung Zone Predominance	COP, Chronic EP, IPF
	Honeycomb Change	IPF, Asbestosis, Chronic HP, Sarcoidosis, Fibrotic NSIP, CTD
	Small Nodules	Sarcoidosis, HP, Infection
	Cavitating Nodules	PAG, Mycobacterial Infection, CA
	Migratory or Fluctuating Opacities	HP, COP, DIP
	Pneumothorax	PLCH, LAM, Neurofibromatosis, TS
	Pleural Involvement	Asbestosis, CTD, Acute HP, Malignancy, Sarcoidosis, Radiation Fibrosis
	Kerley B Line Prominence	Lymphangitic Carcinomatosis, CHF
<b>HRCT</b>	Nodules	Sarcoidosis HP, CBD, Pneumoconiosis, RA, Malignancy
	Septal Thickening	Edema, Malignancy, Infection, Drug Toxicity, PVOD
	Cyst Formation	LAM, LCH, LIP, DIP, SS
	Reticular Lines	IPF, Asbestosis, Chronic EP, Chronic HP, CTD, NSIP
	Traction Bronchiectasis	IPF, other End-Stage Fibrosis
	Honeycomb Change	IPF, Chronic EP and HP, Asbestosis, Sarcoidosis
	Ground-Glass Opacity	AIP, Acute EP, PAP, Chronic EP, COP, Lymphoma, Sarcoidosis, NSIP, Infection, Hemorrhage
<p><b>Abbreviations:</b>  <b>AIP</b>=Acute Interstitial Pneumonia; <b>AS</b>=Ankylosing Spondylitis; <b>CA</b>=Cancer; <b>CBD</b>=Chronic Beryllium Diseases; <b>CHF</b>=Congestive Heart Failure; <b>COP</b>=Cryptogenic Organizing Pneumonia; <b>CTD</b>=Connective Tissue Disease; <b>DIP</b>=Desquamative Interstitial Pneumonia; <b>EP</b>=Eosinophilic Pneumonia; <b>HP</b>=Hypersensitivity Pneumonitis; <b>IPF</b>=Idiopathic Pulmonary Fibrosis; <b>LAM</b>=Lymphangioleiomyomatosis; <b>LCH</b>=Langerhans Cell Histiocytosis; <b>LIP</b>=Lymphoid Interstitial Pneumonia; <b>NSIP</b>=Non-Specific Interstitial Pneumonia; <b>PAG</b>=Polyangiitis with Granulomatosis; <b>PAP</b>=Pulmonary Alveolar Proteinosis; <b>PLCH</b>=Pulmonary Langerhans Cell Histiocytosis <b>PVOD</b>=Pulmonary Veno-Occlusive Disease; <b>RA</b>=Rheumatoid Arthritis; <b>SS</b>=Sjogren’s Syndrome; <b>TS</b>=Tuberous Sclerosis</p>		

Meyer K. (2014). Diagnosis and management interstitial lung disease. Translational Respiratory Medicine. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4215823/>

*Approved: 11/15/2019*