AMERICAN COLLEGE OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE

OCCUPATIONAL INTERSTITIAL LUNG DISEASE

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SUMMARY OF RECOMMENDATIONS

The Evidence-based Practice Interstitial Lung Disease Panel's recommendations are based on critically appraised higher quality research evidence and on expert consensus observing First Principles when higher quality evidence was unavailable or inconsistent (see Methodology). The reader is cautioned to utilize the more detailed indications, specific appropriate diagnoses, temporal sequencing, preceding testing or conservative treatment, and contraindications that are elaborated in more detail for each test or treatment in the body of this Guideline in using these recommendations in clinical practice or medical management. These recommendations are not simple "yes/no" criteria.

All ACOEM guidelines include analyses of numerous interventions, whether or not FDA-approved. For non-FDA-approved interventions, recommendations are based on the available evidence; however, this is not an endorsement of their use. In addition, many of the medications recommended are utilized off-label. (For example, anti-epileptic agents have been used off-label since the 1960s to treat chronic pain.)

Recommendations are made under the following categories:

- Strongly Recommended, "A" Level
- Moderately Recommended, "B" Level
- Recommended, "C" Level
- Insufficient-Recommended (Consensus-based), "I" Level
- Insufficient-No Recommendation (Consensus-based), "I" Level
- Insufficient-Not Recommended (Consensus-based), "I" Level
- Not Recommended, "C" Level
- Moderately Not Recommended, "B" Level
- Strongly Not Recommended, "A" Level

CT Scans	High-Resolution Computed Tomography for the Diagnosis of Asbestosis	Strongly Recommended, Evidence (A)
	High-Resolution Computed Tomography for the Diagnosis of Chronic Beryllium Disease	Strongly Recommended, Evidence (A)
	High-Resolution Computed Tomography for the Diagnosis of Coal Workers' Pneumoconiosis	Strongly Recommended, Evidence (A)
	High-Resolution Computed Tomography for the Diagnosis of Silicosis	Moderately Recommended, Evidence (B)
DLCO	Carbon Monoxide Diffusing Capacity for the Diagnosis of Occupational Lung Disease	Recommended, Evidence (C)
Lavage	Bronchoalveolar Lavage for the Diagnosis of Occupational Lung Disease Caused by Asbestos	Recommended, Evidence (C)
Spirometry	Spirometry for Occupational ILD Diagnosis and Surveillance	Moderately Recommended, Evidence (B)
Sputum Samples	Sputum Sampling for the Diagnosis of Occupational Lung Disease Caused by Asbestos	Recommended, Evidence (C)
Treatment	Exposure Assessment for the Management of Occupational ILD	Recommended, Insufficient Evidence (I)
	Pharmacological Treatment for the Management of Occupational ILD	Recommended, Insufficient Evidence (I)

Walk Test	6-Minute Walk Test to Monitor Treatment Response or Disease Progression	Recommended, Evidence (C)
X-rays	Posterior-Anterior (PA) and Lateral Chest Radiographs for the Diagnosis of Other Occupational ILDs (including but not limited to chronic beryllium disease, hypersensitivity pneumonitis, and hard metal disease)	Recommended, Insufficient Evidence (I)
	Posterior-Anterior (PA) and Lateral Chest Radiographs for the Diagnosis of Asbestosis	Moderately Recommended, Evidence (B)
	Posterior-Anterior (PA) and Lateral Chest Radiographs for the Diagnosis of Coal Workers' Pneumoconiosis	Moderately Recommended, Evidence (B)
	Posterior-Anterior (PA) and Lateral Chest Radiographs for the Diagnosis of Silicosis	Moderately Recommended, Evidence (B)

OVERVIEW

These guidelines and recommendations are intended to guide the clinician in an evidence-based approach to occupational lung diseases. The guidelines focus on the "traditional" inorganic dust-related diseases (e.g., silicosis, asbestosis, and coal workers' pneumoconiosis (CWP)). They do not cover the immunologically mediated diseases such as chronic beryllium disease (CBD) or hypersensitivity pneumonitis (HP). Written recommendations for each topic have been researched and developed. Although clinical medicine remains both a science and an art, occupational exposure history, presentation, and diagnostic screening test results form the foundation for diagnosis and treatment plans.

Interstitial lung diseases (ILDs) are a heterogeneous group of more than 100 diseases that inflame and/or scar the lung parenchyma and which are classified together because of similar clinical, roentgenographic, physiologic, and/or pathologic features.[1-3] Although the etiology of many ILDs is currently unknown, those that are occupationally-induced are preventable.[4, 5]

The term "Occupational ILD" describes diverse pathophysiologies that are analogous to those that occur with non-occupational ILD. Occupational ILD can be similar to non-occupational ILD from a functional viewpoint. Both have progressive fibrotic changes and may share common physiologic sequelae. Although both ILD and occupational ILD may have common structural abnormalities, and be similar physiologically, there are critical differences in the processes that lead to the fibrosis (i.e., exposures) which may affect the clinical findings.[6] According to the National Occupational Exposure Survey, there are millions of workers potentially exposed to substances known to cause occupational ILD.

Occupational lung disease is often classified into several different categories, of which occupational ILD is one of the main categories and obstructive airways diseases such as, work-related asthma and occupational chronic obstructive pulmonary disease (COPD) is another. However, because most occupational dusts are not homogeneous in size, they may deposit and trigger inflammatory effects in airways, as well as, alveoli. Inflammatory responses may result in airflow limitation in both large and small airways with changes in lung volumes as the lung parenchymal tissue becomes stiffened and scarred.[7, 8]

ILD describes disorders affecting the lung interstitium, or fabric of connective tissue that supports the many pulmonary structures, surrounds the air spaces, provides the microscopic separation of blood from air with minimal impedance to diffusion, serves as a conduit and fluid

channel for lymphatic drainage and the migration of immune cells, and collects and sequesters a fraction of insoluble particles that deposit in the lung.[9] Acute injury to the interstitium is manifested mostly by edema and inflammation, while chronic injury is characterized by fibrosis, the end stage of chronic inflammation. ILD sometimes referred to as "pulmonary fibrosis" or "interstitial fibrosis" is a group of chronic, generally irreversible conditions manifested by a vigorous immune and/or inflammatory response and exuberant fibroblast activity that results in excessive collagen deposition.[10, 11]

There is often some degree of overlap in which exposures that cause ILD may also affect airways. For example, exposures triggering hypersensitivity pneumoconiosis may also affect airways and interstitium (e.g., many dust exposures result in airway inflammation).[5]

Occupationally-related ILDs fall into four often clinically overlapping categories:

- *Pneumoconiosis* is defined as the non-neoplastic reaction of the lungs to inhaled mineral or organic dusts and the resultant alteration of pulmonary tissue structure.[4, 11] Hundreds of types of pneumoconioses have been identified, but only three are common and, therefore, reasonably feasible for guidelines: silicosis, asbestosis, and CWP.[4, 12] In these conditions, the radiological characteristics result from the accumulation of inflammatory and fibrotic responses triggered by dust deposition.

- *Hypersensitivity Pneumonitis* (HP), also called extrinsic allergic alveolitis, is a large family of disorders of immune response to inhaled antigens or low-molecular weight chemicals, often associated with granulomatous pathological changes.[4] Agents include animal proteins, plant proteins, bacteria, fungi, and diisocyanates. HPs tend to be highly specific to occupation or environmental settings. In agricultural workers, the most common HP is an immune response to spores of a thermophilic actinomycete bacteria and is often called "farmer's lung." Farmer's lung is one of the most frequent forms of HP but there are many others including Bird fancier's lung, hot tub lung, humidifier lung, and mushroom picker's disease.[13]

- *Other Granulomatous Diseases* are chronic immune and foreign-body responses to antigens in the lung (which may be dusts and, therefore, also considered pneumoconioses). Prominent examples include beryllium (beryllium disease) or, rarely, to cobalt in cemented tungsten carbide (hard metal disease).[14-17] The tissue response is mediated by immune mechanisms and may not localize to an area of dust accumulation. This may manifest in systemic, body-wise disease manifestations. These disorders are uncommon, problems develop at different exposure levels in different people, and the clinical presentations are variable.

- *Diffuse Interstitial Fibrosis* is a response to severe lung injury including irritant inhalation injury (e.g., diffuse alveolar injury related to nitrogen oxides). Diffuse interstitial fibrosis should be distinguished from more common idiopathic interstitial fibrosis either of the "usual interstitial pneumonia" or the "nonspecific interstitial pneumonia" types. Advanced forms of all of the occupational ILDs may have a similar clinical presentation to diffuse interstitial fibrosis.

Occupational ILDs have varied latency periods, usually years in the case of pneumoconioses (e.g., 20-40 years for asbestos[197-199]; 6-10 years for beryllium[200]), and present predominantly or exclusively with pulmonary manifestations. There are few exceptions where extra-pulmonary

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symptoms and signs may develop (e.g., rare cases of beryllium disease, silica-associated autoimmune disease or renal disease).[4, 18]

IMPACT

Although the prevalences of pneumoconioses in the United States have declined, especially after institution of modern dust regulations and changes in industry practices, they and other occupational ILDs remain a substantial risk in the U.S. workforce. Silicosis is still the most common occupational disease worldwide with estimates of "3,600-7,300 cases per year in the United States from 1987 to 1996."[28] Silicosis currently causes approximately 150 annual deaths in the United States. Asbestosis continues to be seen as a legacy disease in older workers. Occasional new cases of asbestosis are seen in younger workers, for example, those engaged in insulation removal without proper preventive measures including respiratory protection, engineering controls (e.g., exhaust ventilation) and work practices (e.g., wet processes).[29] CWP, which was disappearing for decades, has been rising in prevalence in recent years.[30, 31] Other ILDs (e.g., flock workers' lung and indium lung) tend to be localized due to specific, regional occupations and are not generally monitored closely. Certain surveillance information is available through National Institute for Occupational Safety and Health (NIOSH) reports and trends in work-related lung diseases from the Work-Related Lung Disease (WoRLD) Surveillance System (available at: www2.cdc.gov/drds/WorldReportData/).

ETIOLOGIC AGENTS

Occupational ILDs are most commonly associated with mineral and metal dusts, fibers, organic dusts and persistent antigens, reactive low molecular-weight compounds that act as antigens when inhaled into the lungs, and toxic gases that cause deep lung injury. While most of these ILDs are rare outside of occupational settings, some may occur with sufficient non-occupational exposures in uncontrolled settings (e.g., hobbies). Pharmaceuticals are especially known for triggering ILD in non-occupational settings. Table 1 contains potential examples of exposures that may increase risk of occupational ILDs if there is sufficient frequency, intensity and duration of exposures, especially if not well controlled. Latency is also an important issue, which can be many years in the case of some ILDs (e.g., asbestos).

Table 1. Etiologic Agents for Occupational ILDs*

Exposure Category	Agents	Industries	Example Processes
Inorganic mineral dusts			
Non-fibrous	Crystalline silica Silicates (including talc, kaolin, diatomaceous earth, mica, mixed dusts)	Mining, oil and gas, construction, foundry, pottery, manufacturing	Drilling, mining, excavating, abrasive blasting, grinding, cutting
Fibrous	Asbestos, mineral fibers	Power plant, foundry, demolition	Removal of old asbestos-containing construction materials (e.g., insulation)
Carbonaceous	Coal, graphite	Mining, electricity generation and storage, metals	Coal mining/ handling, battery manufacture, pencil making
Metals	Beryllium, tin, cobalt, indium, barium	Nuclear, aircraft, tools, electronics	Machining, grinding, smelting, metal product manufacturing

Toxic and inflammatory	PVC fumes, paraquat, diisocyanates	Plastics, chemicals	Construction, freezer/refrigerator insulation, weed killing
Organic dusts	Fungi, bacteria, plant and animal proteins	Wood and food products, animal rearing, farming	Cleaning, water sprays, shredding

*All listed exposures may have increased risk of occupational ILDs where there is sufficient frequency, intensity and duration of exposures, and especially if not well controlled.

Adapted from Redlich CA. Pulmonary fibrosis and interstitial lung diseases. In: Harber P, Schenker MB, Balmes JR (eds). *Occupational and Environmental Respiratory Diseases*. St. Louis: Mosby; 1996:216-7; and Bonura E, Rom WN. Chapter 13: Occupational lung diseases. In: Schraufnagel, DE (ed). *Breathing in America: Diseases, Progress, and Hope. American Thoracic Society*. 2010. Available at: https://www.thoracic.org/patients/patient-resources/breathing-in-america/ .

MINERALS AND METALS[1]

Although there are hundreds of dusts that may produce a pneumoconiosis after excessive exposure, only five are both reasonably common exposures and frequently associated with disease especially in poorly controlled settings: 1) silica; 2) asbestos; 3) coal mine dust; 4) beryllium; and 5) "hard metal" (an alloy of steel, tungsten, and cobalt).[4] Additional metals associated with ILD such as indium continue to be recognized.[32]

- **Silica.** This includes crystalline silicon dioxide, but excludes glass and other amorphous forms of silica. At least 1.7 million U.S. workers are exposed to respirable crystalline silica in a variety of industries and occupations, including construction, sandblasting, and mining. Exposure to sufficient respirable silica leads to silicosis, an irreversible disease. Silicosis also increases risk for lung cancer, pulmonary tuberculosis, autoimmune disease, renal disease, and airways diseases.[33] Some evidence suggests there may be risk of lung cancer absent silicosis, although at much lower levels of risk than among those with silicosis.[201, 202]

- **Asbestos.** Asbestos is the term for six otherwise distinct and mostly unrelated silicate mineral fibers that are particularly used for heat resistant applications. Chrysotile ("white" or serpentine asbestos) is reportedly responsible for the great majority of asbestosis cases worldwide, mostly from insulation installation and removal. Asbestos insulation removal is currently the most common exposure setting. Prior exposures were more widespread and included shipbuilding, manufacturing, end use of asbestos-containing products (e.g., tiling and roofing materials)[34-38] and mining. Other forms that may be encountered include amosite ("brown" asbestos), crocidolite ("blue" asbestos), anthophyllite ("green" asbestos"), actinolite, and tremolite (a potential contaminant of chrysotile and vermiculite).[36-38] All forms of asbestos are reported causes of asbestosis and malignancies.[21, 38] As well, the fibrous zeolites (erionite and mordenite) have similar properties, cause disorders identical to "classic" asbestosis, and are most frequently encountered in mining and tunneling, especially in the western United States, Turkey, and central Asia.

- **Coal Mine Dust.** Coal dust is a mixture of carbon and complex organic materials and minerals, including variable amounts of silica and silicates. In general, the higher the

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[1]In this section, and throughout this Guideline, it is assumed that there must be sufficient frequency, intensity, and duration of exposure to cause the ILD. This text is omitted from the documented in each discussion of each exposure to allow for the text to be sufficiently succinct to be readable.

compaction and energy content or "rank" of the coal (roughly, anthracite > bituminous > lignite) and the higher the silica content, the greater is the milligram potency of mine dust in causing CWP ("black lung") and the more severe the disease (with or, usually, without accompanying silicosis). CWP is a distinct disease, distinguishable pathologically from silicosis, although the two may occur together particularly in miners who drilled or cut through rock. CWP differs histologically from silicosis in the morphology of the lesion.

- **Beryllium.** Beryllium (Be) is a strong, lightweight, heat-resistant metal used in high-performance alloys such as aviation brakes and in the nuclear industry. Beryllium dust causes a granulomatous disorder that in its chronic from is virtually identical to sarcoidosis.[39]

- **"Hard Metal."** This is generally a descriptor of a steel alloy rich in cobalt (Co) and tungsten (W). It is encountered in machining and metalworking. Cobalt may produce an asthma-like condition of variable airways obstruction against a background of pneumoconiosis. Hard metal exposure is associated with giant cell interstitial pneumonia (GIP), one of the more unusual ILDs that may present with a distinct tissue reaction identifiable on biopsy.

ORGANIC RESPIRABLE DUSTS

Inhalation of organic dust with antigenic properties may lead to development of HP. Mold spores, dust containing bird droppings, animal-derived dusts, and grain dust are the most common sources of antigen. Historically, farmers' lung, caused by the antigen of a thermophilic actinomycete, was a common cause of HP. Common contemporary inhalation exposures include antigenic organic materials resulting from renovation of buildings (especially demolition or exposing damp interior walls), exposure to contaminated water or persistently wet spaces (humidifiers, hot tubs, saunas, and unventilated showers), and handling birds. Many responsible antigens are either associated with microorganisms, mostly fungi and actinomycetes, or bird-derived proteins, with occasional cases arising from sensitization to other animals (such as furrier's lung), insects (such as miller's lung, the antigen to which is a wheat weevil protein), amoebae (humidifier lung), and pesticide powder (pyrethrum HP). There are many other dusts associated with HP.[40]

LOW MOLECULAR WEIGHT SENSITIZING CHEMICALS

Antigens formed by reactive chemicals that bind to proteins and persist in the body may also cause HP. A history of skin or inhalation exposure to paints, foams, or plastics containing materials such as diisocyanates, trimellitic anhydride, epoxy resins, or "Bordeaux mixture" (a pesticide made from copper sulfate used in vineyards) may suggest the diagnosis.

TOXIC CAUSES OF OCCUPATIONAL ILD (GASES)

Exposure to irritant or oxidant gases of low solubility that penetrate to deep lung tissues (e.g., nitrogen dioxide, ozone, and phosgene) or ionizing radiation with sufficient injury may cause diffuse fibrosis with honeycombing on chest imaging. Usually this fibrosis occurs weeks after an acute pneumonitis that may include pulmonary edema. It may also progress to bronchiolitis obliterans. In addition to inhalation exposure, paraquat toxicity associated with suicide ingestion, may result in hyperacute ILD. The mechanism is purely toxic and results in rapidly proliferative fibrosis, for which lung transplant may be the only therapeutic option.

OTHER PARTICULATE DUSTS

Respirable dusts that result in interstitial lung disease are also believed to have potential non-specific irritant effects including bronchitis, chronic cough, and sneezing (large particle size) If these irritant effects are severe, there is believed to be potential for accelerated loss of lung function with obstructive disease.

COMPLICATIONS AND COMORBIDITIES

Chronic bronchitis, defined by chronic sputum production, is common among workers exposed to silica. It has been reported that exposure to silica at levels below those associated with simple silicosis has been associated with chronic airflow limitation and/or mucus hypersecretion and/or pathologic emphysema.[19] Several studies have suggested that patients with silicosis have increased risk for lung cancer. However, it is not clear whether silica exposure in the absence of silicosis carries increased risk for lung cancer and if so, at what dose. The International Agency for Research on Cancer (IARC) reclassified silica as a Group I substance ("carcinogenic to humans") in October 1996.[19]

Silicosis may also progress to massive, accreted fibrotic zones in the lung ("conglomerative silicosis") that result in respiratory failure, pulmonary hypertension, and cor pulmonale with right heart failure. Silica exposure is associated with a variety of systemic and pulmonary conditions.[18]

Comorbid exposures and conditions are common (e.g., different exposures capable of producing ILD, as well as smoking and other exposures that may impair lung function) and may result in challenging medical evaluations and management. Thus, a worker may have been exposed to various combinations of dust exposures (e.g., silica and coal dust; silica and beryllium). Similarly, a worker can have both dust-related interstitial lung disease and chronic aspiration pneumonitis. Individuals with asbestosis experience variable rates of disease progression, ranging from mild to severe respiratory impairment. Persistent and progressive dyspnea and wheezing are associated with accelerated loss of ventilatory capacity.[20]

Pleural thickening, in the form of discreet pleural plaques (calcified or uncalcified) or diffuse pleural thickening, is most common and characteristic of prior asbestos exposures. These findings help to identify past asbestos exposures, including when overt parenchymal disease is not evident. Non-malignant asbestos-related pleural effusion may also be an early manifestation in some cases. Asbestos exposure is associated with an increased risk for lung cancer (with far greater risk, or interaction, with smoking), mesothelioma (involving pleural or peritoneal serosal membranes), laryngeal and colon cancer.[21] Pneumothoraces have also been reported to spontaneously occur.[22]

Coal workers' pneumoconiosis (CWP) is often associated with bronchitis and some degree of airways obstruction. CWP may progress to large intrathoracic fibrotic masses, usually visible on chest x-rays in the upper and mid lung fields ("progressive massive fibrosis"), which are associated with severe respiratory impairment. CWP is associated with an elevated risk of autoimmune disorders, principally rheumatoid arthritis (aka, "Caplan's syndrome"). Thus, workers with CWP may have associated autoimmune disorders and develop systemic clinical manifestations.[23]

HP often begins with wheezing and airways obstruction. Untreated and unmanaged, it may progress to respiratory insufficiency and profound impairment. Pigeon breeders' lung famously is associated with clubbing, unlike most hypersensitivity pneumonitides.[24]

Hard metal disease is an immune-mediated pneumoconiosis associated with airway hyper-reactivity. It is often accompanied by cobalt-induced reversible airways disease. Clinical presentations typically include recurring, severe episodes of bronchospasm, with this entity sometimes called "hard metal asthma."[25]

Giant cell interstitial pneumonia is a rare disorder associated with cobalt in cemented tungsten carbide (hard metal disease)[26] Giant cell interstitial pneumonia is a pathological diagnosis in which interstitial fibrosis is accompanied by activated macrophages that fill alveoli and is part of a dysfunctional foreign body reaction.[27]

INITIAL ASSESSMENT

The general approach to diagnosing occupationally-related ILD involves satisfying four general criteria[2]:
1. Evidence of structural lesion consistent with the interstitial process (e.g. fibrosis);
2. Awareness of epidemiological or workplace studies with evidence of an agent-disease relationships;
3. Evidence of exposure to an agent(s) known to cause occupational ILD (e.g., asbestos), including sufficient dose and latency to cause the disease; and
4. Exclusion of alternative diagnoses as less likely (e.g., chronic aspiration/swallowing dysfunction, prior radiotherapy, chemotherapy, systemic rheumatological disorders).

In practice, evidence of a structural lesion is usually demonstrated by chest x-ray followed generally by high-resolution CT (HRCT) scan of the chest and lungs. Consideration of alternative diagnoses may require additional clinical tests and even biopsy. Biopsies are rarely necessary for the positive diagnosis of occupational ILD. Serological testing may be needed for beryllium disease. Clinical determination of causation by a particular agent may be satisfied by the occupational history and these initial steps. Conclusive evidence of causation may in some cases require considerably greater investigation (see Work-Relatedness Guideline).

MEDICAL HISTORY

The occupational history is usually specific for occupational ILD. Identification of a past, significant exposure usually suggests the diagnosis. Yet, in addition to describing the most recent work, it is essential to describe prior work due to the long latencies associated with some exposures. Patients with ILD of all types usually present with shortness of breath and cough. Unfortunately, those clinical symptoms are nonspecific and may be of limited value for recognition, diagnosis, and confirmation of either non-occupational or occupational ILD without additional objective testing. The presence of a comorbid condition that is associated with interstitial disease such as rheumatologic, autoimmune, inflammatory bowel, connective tissue disease (aka, collagen-vascular disorders), or drug reactions may render occupational causes less likely. However, in the case of some pneumoconioses, there may be confounding autoimmune pathology that may be related to work exposures. CWP and silicosis, in particular,

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[2]Two of the steps to determine work-relatedness are not generally needed for the initial assessment (Validity of Testimony and Conclusions).

are associated with an increased incidence of rheumatoid arthritis and, in the case of silicosis, systemic sclerosis, autoimmune vasculitis, and nephropathy.

Occupational ILD affects both sexes and workers of all ethnic backgrounds, although most are men due to the occupational distributions and pneumoconioses are much more prevalent in some racial/ethnic populations presumably due to greater exposures.[41, 42] While genetic factors have been identified and associated with immune mediated pneumoconioses, heredity has not been demonstrated to play a major role in ILD.[26]

The time since first exposure (latency) to development of clinically apparent ILD varies by exposure, but some generalizations can be made. Pneumoconioses typically become clinically apparent over a period of years, exceptions are rare and include accelerated silicosis and CWP associated with high exposure levels. In HP, sensitization may occur in the first few weeks after beginning exposure, yet in others, it may be delayed for months or years. The acute, predominant airways symptoms of HP or acute beryllium disease develop in a sensitized individual over days to weeks and progress over weeks to interstitial inflammation and ultimately to fibrosis, but may rarely also be hyperacute or sudden in onset, similar to some eosinophilic pneumonias or some drug-induced pneumonitis.

Differential diagnosis of an acute influenza-like or febrile disorder should include HP in a patient with a history of exposure to inhaled antigens. However, it may also suggest rheumatological or autoimmune lung disease and infection (mycoplasma, Legionella spp., or, rarely, diffuse mycosis) as a cause of interstitial disease, the latter especially in a host with a compromised immune system. A history of exposure to birds should also raise the possibility of other diseases including psittacosis.

While there are no well-established risk factors for development of HP, personal susceptibility may play a role. Personal risk factors may play an important role in idiopathic interstitial fibrosis (usual interstitial pneumonia), which has a strong genetic component; a small subset of sarcoidosis are thought to be familial. Tuberous sclerosis, neurofibromatosis, and metabolic diseases affecting the lung, such as Gaucher's disease, are hereditary but are individually rare. Other genetic impacts and interactions are not well defined.

INTERVIEW QUESTIONS

Symptoms of occupational ILD most commonly include dyspnea, with variable cough (including recurrent attacks of bronchitis with phlegm production), wheezing and chest tightness. In addition to a standard medical history, the following questions may be considered:[11] (See also General Approach to Initial Assessment and Documentation and Initial Approaches to Treatment Guidelines).

1. **What do you hope to accomplish during this visit?**[43]
2. **What are your symptoms?**
   - What are your symptoms? Do you have cough, coughing up blood, shortness of breath, shortness of breath on exertion, or wheezing? Do you have chest pain? Pain when you take a deep breath?
   - When did these symptoms first occur?
   - When did these symptoms first occur relative to the beginning of your work in that location? In that department? In that work cell?
   - How frequently do symptoms occur?

- Is there a pattern to your symptoms?
    - Are the symptoms worse at work?
    - Do they improve when you are away from work such as on weekends, nighttime (off-shift) or holidays or vacations?
    - Is there a seasonal pattern to your symptoms? What time of year are they the worst?
- How frequent and severe are your symptoms? Have your pulmonary symptoms included throat tightness, difficulty with inspiration or expiration, harsh sounds, cough, or sputum production?
- Did a physician or healthcare provider ever document your lung function?
- Do you have a history of past lung disease? Describe the prior frequency of symptoms, treatment with medication and response to medications.
- Do you have a history of allergy? Anaphylaxis?
- Did the symptoms begin after a one-time, high-level workplace inhalation exposure to an irritant gas, fume, smoke or vapor?
- What medications do you take? Did you start taking a medication before your symptoms started? Do you think that any of your medications affect your symptoms?
- Do others at work have the same symptoms you have?

2. **How did your condition develop?**
   PAST:
- Have you had previous similar episodes before your current job?
- What past treatment(s) did you receive for these symptoms?
- Were the treatments effective?
- Who was your doctor?

   CAUSE:
- What do you think caused the problem?
- If work-related, how do you think it is related to work?

   OCCUPATIONS AND OUTSIDE ACTIVITIES (Lifetime):
- What do you do for work?
- Describe your current occupation and specific work activities including shift, hours, duration, days worked per week. (Subjects working 6 days a week or more may not have enough time away from work to symptomatically improve.)
- What were your prior jobs and what were the dust exposures have you had in each of your prior jobs (e.g., silica, coal, asbestos)? Describe each prior job including specific activities. Describe if there is a history of similar symptoms.
- List any chemicals or substances including gas, fumes, vapors, dusts, or aerosols that you work with. Do you have any possible exposures at home or during leisure activities?
- List any "secondary jobs" or concurrent occupations that may involve exposure to chemicals or substances including gas, fumes, vapors, dusts, or aerosols.
- What is the work area's room size, specific ventilation, other co-worker reports, exhaust hoods, remodeling, and recent change in processes? Are there Material Safety Data Sheets and industrial hygiene reports available?
- Were there changes in work processes in the period preceding the onset of symptoms?[3]
- Does your employer provide protective equipment at work, such as masks or respirators? How often do you use them? Are they required? When were you last fit tested?

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[3]Symptoms of cough or dyspnea that develop or worsen after a worker starts a new job or after new materials are introduced on a job are suggestive (a substantial period – from months to years – can elapse between initial exposure and development of symptoms).

- Are your symptoms constant or do they come and go?
- Does anything seem to make the problem worse or better? Do symptoms develop within minutes of specific activities or exposures at work?
- Describe when your symptoms first started? Was there an event at the time the symptoms started?
- Have your symptoms changed over time since then? How?
- Do your symptoms limit your work performance and if so, how?
- Describe your living environment including any hobbies, crafts, pets, family members who work with chemicals, family members who smoke, living near an industrial plant, or living near congested traffic area.[4, 44]

NON-OCCUPATIONAL ACTIVITIES:
- What is your lifetime exposure to tobacco? Second-hand exposure?
- What has your lifetime exposure been to other inhaled substances, marijuana, hookah, spice, etc?
- What are your leisure activities (e.g., woodworking, gardening, welding etc.)?
- Do you have a second job (moonlighting)?

3. **How do these symptoms limit you?**
- Are there any activities that you can no longer perform?
- Do you feel very short of breath during exercise?
- Do you feel more short of breath when doing normal daily activities?
- How long have your activities been limited?

4. **Do you have other medical problems?**
- Do you have headaches, fatigue, malaise, weight loss, changes in appetite, fever, physical abilities and exercise intolerance?
- Do you have any autoimmune, connective tissue, infectious, or metabolic diseases?
- Do you have any allergies?
- Do you have any other respiratory diseases or conditions?
- Do you have problems with swallowing and/or esophageal dysfunction?
- Do you smoke? Does someone else in your environment smoke?
- Do you use other drugs, including marijuana?
- Do you have diabetes, kidney disease, or HIV/AIDS?
- Have you ever had cancer? Radiation therapy? Chemotherapy?

PHYSICAL EXAMINATION

Other references provide detailed guidance on pulmonary examination.[45, 46] In general, an occupational pulmonary physical examination should include the following elements:
- Vital signs, including measured respiratory rate.
- Overall functional abilities, including ease of movement, walking and changing positions while assessing breathlessness.
- Assessment of respiratory status with quiet respirations (e.g., rate, depth, use of accessory muscles, nasal flaring).
- Inspection for stigmata of pulmonary disease as well as potential etiologies including mucous membrane abnormalities, nasal polyps/swelling, clubbing (asbestosis, idiopathic pulmonary fibrosis, some hypersensitivity pneumonitides), nasal crease line, and anterior-posterior diameter. While of limited sensitivity, clubbing, if present, may be useful in the diagnosis of asbestosis and idiopathic pulmonary fibrosis (IPF).

- Palpation primarily for chest wall abnormalities, tracheal deviation or tactile fremitus.
- Percussion for resonance to identify aeration, diaphragm level, suggestion for fluid interface or consolidation.
- Auscultation for inspiration to expiration ratio, adventitious breath sounds including crackles, wheeze (often a secondary manifestation of HP and a primary manifestation of eosinophilic pneumonia) and pleural rubs, as well as timing, location and persistence of lung findings.
- Cardiac examination with attention to findings of cor pulmonale and heart failure.
- Dermal examination for signs of disease, i.e., erythema nodosum (sarcoidosis).[11]

DIAGNOSTIC APPROACH

The diagnoses of silicosis, asbestosis and CWP are typically made clinically, based on occupational history of sufficient exposure with appropriate latency, objective radiographic evidence (chest radiograph and/or HRCT), assessment of pulmonary function (including consistent changes in ventilatory capacity, static lung volumes or gas-exchange), and consideration of alternative differential diagnoses. While some reviews have recommended a surgical biopsy for diagnosis of non-occupational ILD, in the setting of an appropriate clinical presentation, several studies have established the diagnosis of ILD by HRCT at 70%.[11]

The diagnosis of most occupational ILDs may be suggested when the patient belongs to a group at high risk. The diagnosis is usually made from the combination of occupational exposure history and imaging studies, often a chest x-ray alone. The most common challenges in differential diagnosis include: 1) distinguishing between occupational interstitial disease and idiopathic pulmonary fibrosis, 2) identifying the responsible agent in a case of mixed-dust pneumoconiosis or HP, 3) identifying the agent when the history is unclear, and 4) differentiating between sarcoidosis and beryllium disease, generally using immunologic testing.

In a worker with a typical clinical picture (including exposure history, latency, and radiographic presentation), lung biopsy is rarely needed to provide a diagnosis of occupational ILD. Pathologic examination of lung tissue may at times be required in atypical settings, particularly to exclude treatable non-occupational disorders or malignancy. As in non-occupational settings, by using an interdisciplinary approach, including HRCT, to reach a diagnosis results in a lung biopsy being rarely helpful unless clinical or radiographic features are inconclusive or atypical.[11]

DIAGNOSTIC RECOMMENDATIONS

SPIROMETRY

Spirometry is an integral part of the evaluation of all patients with lung disease and should generally be done on all patients presenting with persistent or recurrent respiratory symptoms. Recommendations summarized below refer to the spirometry findings and how such findings can be utilized to make a diagnosis or to monitor ILD.

Spirometry is the most commonly performed of the pulmonary function tests (PFTs). Since spirometry is often the only PFT performed in the occupational setting, it is frequently simply called a "PFT." Spirometry measures the volumes and rates of flow during forced exhalation after a maximal inhalation. In the occupational setting, a calibrated volume or flow measuring device is used to monitor ventilatory function and to identify existing or incipient lung disorders involving the

airways, lungs, and chest wall.[47, 48] The forced vital capacity (FVC) reflects the capacity of the lung to hold air after a maximal inspiration and is the primary initial screening indicator of the presence of possible restrictive impairment. The FVC is reduced, or "restricted," when compliance of the lung is decreased, or when chest wall expansion or neuromuscular function are limited. Though the FVC may also be reduced in airway diseases that result in airway closure and trapping air in the lungs, the FVC reduction usually will not be accompanied by an equal reduction in the FEV_1, so the ratio of FEV_1/FVC is reduced in purely obstructive disorders. In contrast, in a purely restrictive disorder, both FVC and FEV_1 are reduced by a similar degree, yielding a normal or high FEV_1/FVC ratio.[49-51]

In interpreting the results of spirometry, it is important to consider all aspects of the worker's health, including exposures, smoking status, and other conditions including adiposity that may affect the results. Spirometry patterns are generally not specific for any one type or cause of occupational ILD. However, spirometry provides important information regarding the functional status of the lungs, and is useful in initial assessment, evaluating prognosis, and monitoring the effectiveness of exposure controls and other therapeutic interventions. Spirometry is used for several distinct purposes: 1) routine surveillance testing to identify workers requiring more detailed evaluation; 2) as a key component in the diagnosis of occupational and other ILDs; 3) as a factor in considering work ability and appropriate assignments; 4) for monitoring course over time; and 5) as part of the assessment of compensable impairment. The appropriate criteria should be selected for each case.

Recommendation: Spirometry for Occupational Interstitial Lung Disease Diagnosis and Surveillance
Spirometry is moderately recommended in the diagnostic work-up and monitoring of individuals at risk of occupationally related interstitial lung diseases and in surveillance programs in conjunction with other diagnostic testing.

> *Strength of Evidence* **– Moderately Recommended, Evidence (B)**
> *Level of Confidence* **– High**

Indications – Diagnostic: Patients with history and/or chest radiography consistent with ILD and workplace exposure consistent with plausible etiologies (e.g., worker complaining of chronic or intermittent cough, shortness of breath, or decreased physical abilities).[52] Reliable results may not be achieved in the presence of symptomatic upper or lower respiratory infections or painful disorders of the chest or mouth. [49] Thus, spirometry should generally be postponed if there has been recent surgery, respiratory infections, or recent cardiac problems.

Indications – Surveillance: For workers in occupations with exposures that are either known or thought to be associated with development of occupational ILD, the American College of Occupational and Environmental Medicine (ACOEM), NIOSH and the American Thoracic Society (ATS) currently recommend that a decrement in FEV_1 over time that is at least 15% more than that expected due to aging should trigger further medical evaluation of the worker.[47, 50] Computerized software is available to calculate trends over time, such as NIOSH's Spirola.[203] Such longitudinal evaluation should only be undertaken when spirometry tests are of adequate technical quality. It is recommended to perform periodic serial spirometry testing to assist in earlier determination of pulmonary decline.[47-49, 53]

Harms – Minimal.

Benefits – Provide physiologic evidence for occupational ILD, and differentiate between obstructive and restrictive patterns of lung function. Identification of those who need further testing with lung volumes (e.g., total lung volume).

Technique – Diagnostic spirometry testing should be performed using recommended equipment and procedures by an appropriately trained technician in accordance with recommendations or requirements of Occupational Safety and Health Administration (OSHA), NIOSH, and Mine Safety and Health Administration (MSHA). When diagnostic spirometry is abnormal, testing should first be repeated on another occasion, if possible, to ensure that a worker was maximally inhaling, blasting out hard, and exhaling fully during the test. If results remain abnormal, short term reversibility of the spirometry results should be assessed, most often by repeating the spirometry testing after the individual has undergone a standardized short-acting bronchodilator inhalation protocol. ACOEM recommends numerous quality controls, including that when performing occupational spirometry, technicians strive to meet ATS/ERS criteria for a valid test, that is, recording three or more acceptable curves, with the largest FVC and largest FEV_1 repeated to within 0.15 L (150 mL).[50] Once a satisfactory test has been recorded for the worker, diagnostic interpretation may compare his/her largest results with normal ranges derived from appropriate similar populations.[49, 54, 55]

Interpretation – There are several steps in the interpretation of spirometry testing performed as part of the evaluation of workers at risk of occupational ILD. First, the interpreter must review and comment on test quality and determine whether within and between manoeuvre acceptability criteria were met. If the test is considered adequate for interpretation, then assess reference values (often called normal or predicted values) against which to compare the worker's results must be selected based on studies of asymptomatic and otherwise healthy persons of similar age, height, gender, and race/ethnicity. For workers in the U.S., ACOEM,[50] American Thoracic Society/European Respiratory Society (ATS/ERS),[56] OSHA,[51] and *AMA Guides to the Evaluation of Permanent Impairment*[57] recommend the use of reference values from the National Health and Nutrition Examination Survey (NHANES) III study, which included large numbers of subjects of varying race/ethnicities.[50] Measured worker results are compared to the NHANES III predicted/normal values that are specific for the tested individual's age, gender, self-reported race/ethnicity, and measured height. Normative values differ for African-Americans.[204,205] For Asian Americans, for whom there are no NHANES III reference values at this time, the worker's FVC and FEV_1 results should be compared to race-adjusted reference values. These adjusted values are obtained by determining the reference values (i.e., the predicted value and the Lower Limit of the Normal (LLN)) for a Caucasian of the same age, height, and gender and then multiplying those FVC and FEV_1 predicted and LLN values by a scaling factor of 0.88.[50, 51, 58] If this correction is omitted for Asian Americans, workers may be erroneously labeled with restrictive impairments. No other groups at this time are recognized as needing race-adjustment of reference values.

Since 1991, the ATS (1991, 2005), and more recently ACOEM (2000, 2011) and OSHA (2013) have recommended interpreting test results using two steps after verifying adequate test quality. The first measurement to be assessed is the FEV_1/FVC. If the worker's measured ratio is below the predicted LLN ratio, the worker has airways obstruction. The severity of obstruction is assessed by comparing the worker's measured FEV_1 to the appropriate predicted or reference value. Percent of predicted is calculated, with decreasing values indicating worsening severity of obstruction.

The second step in interpretation of results is to assess the worker's vital capacity relative to the normal range for individuals with the worker's characteristics. Percent predicted values for FVC

are also used clinically to assess restrictive ventilatory impairment (e.g., in various workers' compensation systems). Since the FVC is the measure of vital capacity obtained from the spirometric forced expiratory maneuver, the measured FVC is compared to the lower limit of normal for the worker's FVC. If the results fall below the lower limit, it is interpreted as having possible restrictive impairment and may need further tests of pulmonary function and/or imaging studies to confirm a true restrictive impairment. Severity of a possible restrictive impairment also may be assessed using percent of predicted FEV_1 as recommended by the ATS/ERS – "Mild: FEV_1 >70% of predicted, Moderate: FEV_1 60-69% of predicted, Moderately Severe: FEV_1 50-59% of predicted, Severe: FEV_1 35-49% of predicted, Very Severe: FEV_1 <35% of predicted."[56]

Current ATS/ERS recommendations determine the severity of impairment based solely upon reduction in the FEV_1 as a percent of predicted since this measurement will decrease along with FVC in moderate to severe restrictive impairment. However, this approach may not entirely reflect the impact of the occupational ILD disease process on the individual's functional status.[56]

ILD is also defined by lung volumes (including, e.g., total lung volume), not merely spirometry. If spirometry is abnormal and ILD is suspected, measurement of lung volumes is typically performed to confirm a reduction in volume consistent with ILD.

The absence of both an obstructive and restrictive impairment pattern indicates normal pulmonary function. The presence of both obstructive and restrictive patterns indicates a mixed pattern.

While findings consistent with asthma are not typical of ILD (e.g., bronchodilator responsiveness, which is a short-term reversibility of the spirometry results consistent with the duration of the bronchodilator's effectiveness), it may be assessed to evaluate mixed disease, most often by repeating the spirometry testing after undergoing a standardized short-acting bronchodilator inhalation protocol. The pattern and severity should be reported for the results obtained both before and after inhaled bronchodilator, as well as the magnitude and significance of any change from pre-bronchilator values.

For examinees who have previously completed spirometry, changes in test results are evaluated over time. Interpretation of spirometry values over time takes into account the magnitude of the loss, the number and variability of the earlier results, and the duration of follow-up. When appropriate methods are used, longitudinal interpretation may facilitate early detection of important disease processes and provide objective correlation with changes in reported respiratory symptoms over time.[20, 47, 58]

Although spirometry provides information regarding the functional status of the lungs, spirometry patterns are generally not specific for any one type or cause of occupational ILD. Borderline normal, indeterminate, or unusual patterns of impairment may also be noted. Those patterns or any spirometry results that appear inconsistent with other clinical findings, may require either repeated testing and/or referral to a pulmonary specialist. Current treatments which may affect lung function should be recorded. Because healthy workers often have above average lung function, earlier tests may provide a subsequently useful comparison value, which is uniquely appropriate to the tested individual.

Rationale for Recommendation
There are 11 moderate-quality studies specific to the diagnosis and management of occupational ILD that use spirometry for diagnostic testing. Other evidence-based guidelines

address spirometry testing for the diagnosis and management of general ILD.[49] Leung et al. reported radiographic findings paralleled more severe findings on spirometry (FVC <80%). They also reported that 56% of patients with a diagnosis of silicosis had normal spirometry.[52] Wang et al. reported a decrease in FVC, FEV_1, and FEV_1/FVC among refractory workers with radiographic silicosis that was attributed to the emphysema and hyperinflation associated with silica exposure.[59] Miller et al. evaluated workers exposed to asbestos in insulation and smoking habits. They reported a decrease in spirometry values compared to the general population, and associated the decrements with both smoking and exposure to asbestos.[60] Kilburn et al. reported significant differences in spirometric values in smokers exposed to asbestos and non-smokers with asbestosis compared to unexposed controls.[61] Barnhart et al. stressed the importance in considering both restrictive and obstructive lung disease when monitoring with spirometry.[62] In several studies, spirometry in combination with history and chest radiography aided in the diagnosis of lung disease in workers, but workers with abnormal chest radiography may often still have normal spirometric testing results.[63-65] Kilburn et al. reported relatively normal spirometric values in non-smoking shipyard workers with 1/1 International Labour Office (ILO) classification on chest radiographs.[65]

Spirometry is not invasive, has few adverse effects, and is low to moderate cost. Thus, it is highly recommended, although the evidence base is moderate, as part of a diagnostic workup and monitoring of occupational ILDs.

Evidence for the Use of Spirometry
There are 11 moderate-quality diagnostic studies incorporated into this analysis.[7, 52, 59-67] There are 7 other studies in Appendix 2.[47, 48, 54, 68-71]

CHEST RADIOGRAPHS

Chest radiographs are part of the usual evaluation of patients with respiratory symptoms. They historically have been used to investigate the relationship between exposure to respirable particles (dusts) and disease,[72] and are widely used for diagnosing and monitoring ILD. Chest radiographs show opacities which represent the accumulation of dust and the body's reaction to the exposure.[73-77] Of the ILDs, some have more easily identifiable lesions supporting a diagnosis with radiographic testing than others. Many diseases require consideration of clinical findings, occupational history, and radiographic findings for the diagnosis.[78, 79] Silicosis and CWP, while distinct diseases, have similar radiographic appearances that generally necessitate a well-focused occupational history to help differentiate between the two disorders.

Radiographs should be interpreted by a physician with ***appropriate training, experience, and skills*** in interpretation of radiographs for diagnosis of ILD. To document the patterns and severity of radiographic appearances of pneumoconiosis, radiographs are often interpreted according to the International Labour Organization (ILO) classification.[80] The size, shape and number of the opacities recorded using the ILO classification system have been shown to be related to the amount and composition of dust retained in the lung.[73, 74, 81-85] Comparison of radiographic appearances with associated pathology and lung dust content in a group of coal workers have been reported.[73] ILO classification of pneumoconiosis is recommended for worker screening and epidemiological purposes.[80, 86]

Recommendation: Posterior-Anterior (PA) and Lateral Chest Radiographs

Chest radiographs – posterior-anterior (PA) and lateral – are recommended for the diagnosis of occupational interstitial lung disease based on the following criteria.

1. **Diagnosis of silicosis, asbestosis, or coal workers' pneumoconiosis (CWP).**

   > *Strength of Evidence* – **Moderately Recommended, Evidence (B)**
   > *Level of Confidence* – **High**

2. **Other occupational ILD – including but not limited to chronic beryllium disease (CBD), HP, and hard metal disease.**

   > *Strength of Evidence* – **Recommended, Insufficient Evidence (I)**
   > *Level of Confidence* – **Moderate**

Performed – Chest radiographs should be performed by trained technicians and according to the ACR-SPR Practice Guidelines for the performance of chest radiography.[87] Physicians who interpret chest radiographs for diagnosis or medical surveillance of occupational lung disease should have appropriate training, experience, and skills. The International Labor Organization's criteria are the most widely used criteria for radiograph interpretation in the context of pneumoconiosis and require specific training and certification, which in the United States is certification as a B-reader administered by NIOSH.[80, 86, 206] Interpretation of the radiographs includes numerous standardized ratings to include separate ratings for interstitial changes, size/shape of opacities, and pleural disease.

Indications – To assist in the diagnosis of ILD in workers.[88, 89]

Harms – Small amount of radiation exposure 0.1mSV.[87] Not as sensitive or specific as HRCT, which has a central role in the evaluation of ILD (see HRCT recommendations below).

Benefits – Provides structural anatomic information about the lung parenchyma and pleura that informs the differential diagnosis of occupational ILD and also provides information about the extent of involvement and progression of disease.

Advantages and Limitations – Chest radiographs are widely available and relatively inexpensive. Radiographs may assist in the diagnosis of occupational lung diseases, but cases will often need additional testing and history.[85, 88, 89]

Rationale for Recommendations
Chest radiographs are effective in identifying ILD; however, they are less sensitive and less specific than CT scans (see below). There are studies evaluating the use of chest radiographs in diagnosis of occupational ILDs. The majority of the high and moderate quality studies are done in populations exposed to coal, silica, and asbestos.

Paris et al. reported the use of total lung capacity (TLC) in combination with high exposure, basilar crackles on exam and positive x-ray findings for diagnosing asbestosis to a sensitivity of 76% and specificity of 57%.[90] A study comparing PA x-rays to autopsy results in veterans exposed to asbestos recommended x-ray in the diagnosis of pleural plaques.[91] Ruckley et al. compared chest x-rays within four years of death to the autopsy lung tissue in coal miners reported important correlations in the type of lesions seen on x-ray and the degree of exposure. They also reported that certain types of opacities (p in the ILO classification) are more common in miners with emphysema. However, they also reported that up to 45% of patients with evidence of simple pneumoconiosis had no findings on x-ray.[73] In 1987, a follow-up study also

reported fibrotic lesions in lungs in x-rays classified as normal.[75] Another study in coal workers reported benefit in using x-rays in the diagnosis of CWP, but also reported that x-rays often missed lesions if they were less than 3-5mm in diameter.[92] Other studies of coal miners also reported a strong correlation between ILO readings and dust burden in lung tissue.[77] Other studies also reported findings on x-ray and comparisons to other diagnostic tests and recommended x-rays in the diagnosis of ILDs.[64, 81-83, 88, 93-95] Sun et al. published data on silicosis that supports the use of both x-ray and high resolution CT scans (HRCT).[96]

Evidence for the Use of Chest Radiographs
There are 4 high-[90-92, 96] and 13 moderate-quality[64, 73-75, 77, 81, 86, 88, 93-95, 97, 98] studies incorporated into this analysis. There is 1 low-quality study in Appendix 2.[83]

HIGH-RESOLUTION COMPUTED TOMOGRAPHY (HRCT) SCANS

Since the late 1980s, CT scans have been used in diagnosis of ILD. Contemporary practice is to use high resolution CT scanning (HRCT) for pulmonary evaluation. Several studies have reported both greater sensitivity and specificity compared to chest x-ray in detecting both parenchymal and airway changes.[99-110] However, with the newer technologies, it is becoming more difficult to separate between subnormal radiological findings that may occur in normal working populations, especially as the working population ages and these findings must be evaluated in context of exposures and other comorbidities. Although grading systems for HRCT have been proposed, there is currently no widely adopted counterpart to the ILO Classification system for chest x-rays.

Although useful in diagnosis of occupational ILD, HRCT is not considered an essential part of the evaluation if there are existing radiographs documenting occupational ILD consistent with the worker's exposure. On the other hand, if there are atypical features, subtle abnormalities on routine radiography, and/or competing causes for the findings, then an HRCT may be quite helpful in confirming or excluding a diagnosis of occupational ILD. HRCT also has a role in screening for lung cancer.

Recommendation: High-Resolution CT Scan
High-resolution CT scans are recommended for the diagnosis of occupational interstitial lung disease based on the following criteria:

1. **Diagnosis of coal workers' pneumoconiosis, asbestosis, or chronic beryllium disease.**

   Strength of Evidence **– Strongly Recommended, Evidence (A)**
   Level of Confidence – **High**

2. **Diagnosis of silicosis.**

   Strength of Evidence **– Moderately Recommended, Evidence (B)**
   Level of Confidence – **High**

Performed – CT scans should be performed by trained technicians and according to the American College of Radiology (ACR) guidelines. Readers of CT scans for occupational lung disease should have appropriate training and experience. They are generally performed in the supine position, but prone imaging may be of use in certain circumstances, for example, detection of subtle peripheral and/or basilar findings.[102] There is also evidence to support scanning the entire thorax in patients with asbestosis to look for apical disease.[111]

Indications – Generally considered the diagnostic test for evaluation of ILD.[106] HRCT scanning is strongly recommended when the findings make occupational ILD reasonably likely and when the chest radiograph alone is insufficient. If there are atypical features, subtle abnormalities on routine radiography, and/or competing causes for the findings, then an HRCT may be especially helpful in confirming or excluding a diagnosis of occupational ILD.

Harms – Spurious findings resulting in performance of invasive studies that carry inherent risks (e.g., thoracotomy, biopsy).[87]

Benefits – Provides detailed information regarding structural parenchymal and pleural changes to support differential diagnosis of occupational ILD. May potentially lead to diagnosis of other (e.g., neoplastic) lung findings.

Advantages and Limitations – CT scans are moderately costly and have increased radiation exposure compared to chest radiography.[112] Many of the findings on CT scan may also be related to other health conditions, such as idiopathic pulmonary fibrosis; therefore, the findings must be considered in context with clinical history and work-related exposures. HRCT may demonstrate patterns of structural abnormality that may permit specific categorization of occupational ILD particularly as silicosis, with a high degree of diagnostic certainty.

Rationale for Recommendations
There are 5 high- and 8 moderate-quality studies evaluating the use of HRCT scans in the diagnosis of occupational ILDs. Many of the studies did not include baseline smoking status, which may make drawing conclusions more difficult.

Gamsu et al. conducted HRCT scans both in the prone and supine positions at maximal inspiration. They compared HRCT scan results to biopsy results and chest radiography. They reported greater specificity of asbestosis diagnosis with at least two findings on HRCT scan.[102] Several other moderate-quality studies reported greater sensitivity by HRCT scan compared to chest radiography in the detection of abnormalities associated with a diagnosis of asbestosis.[100, 103, 107, 109] Collins et al. reported that HRCT scans may detect CWP at earlier stages than chest radiography, but that the workers with HRCT findings and normal chest radiographs did not have any physiological abnormalities.[106] Gevenois et al. also reported greater detection of abnormalities on HRCT compared to chest radiography in low grade CWP.[99] Other studies also reported HRCT detecting more findings compared to chest radiography in worker's exposed to coal dust.[105]

Evidence for the Use of HRCT
There are 5 high-[99, 102, 104, 106, 113] and 9 moderate-quality[100, 101, 103, 105, 107, 111, 112, 114, 115] studies incorporated into this analysis.

MAGNETIC RESONANCE IMAGING (MRI) OF THE CHEST

There is no recommendation regarding the role of MRI of the lung in the diagnosis of occupational lung disease. MRI is not currently used as a primary diagnostic tool for occupational ILD.

PET/CT SCANS OF THE CHEST

PET/CT scans are beyond the scope of this guideline. These are generally used in cases with questions of mass lesions or invasion of chest wall and not used either for surveillance or first-line diagnosis of occupational ILD. They may be used to evaluate cases of cancer, including cancer associated with ILD.

CARBON MONOXIDE DIFFUSING CAPACITY (DL$_{CO}$)

DL$_{CO}$ is a measurement of carbon monoxide transfer from inspired gas to pulmonary capillary blood. DL$_{CO}$ is a product of two measurements during breath holding at full inhalation, carbon monoxide uptake from the alveolar gas space, and the accessible alveolar volume. The single-breath diffusion capacity testing is a common method for measuring diffusing capacity of the lung.[103, 116, 117] The lung volume during breath holding is measured simultaneously by dilution of a non-absorbable gas such as helium or methane.[118] DL$_{CO}$ measures CO transfer from the inspired air to the pulmonary capillary blood and this includes all the following steps:

1. Bulk flow delivery of CO to the airways and alveolar spaces;
2. Mixing and diffusion of CO in the alveolar ducts, air sacs and alveoli;
3. Transfer of CO across the gaseous to liquid interface of the alveolar membrane;
4. Mixing and diffusion of CO in the lung parenchyma and alveolar capillary plasma;
5. Diffusion across the red cell membrane and within the interior of the red blood cell; and
6. Chemical reaction with constituents of blood hemoglobin.[119]

DL$_{CO}$ has long been used in the diagnosis of lung disease in both the non-occupational and occupational setting. It has been reported to be a sensitive indicator of gas exchange, being abnormal in patients with ILD, pulmonary vascular lung disease, and emphysema.[120] However, although DL$_{CO}$ may be a useful test for assessing the presence of ILD in general, it is not diagnostic for any specific type of ILD. The measurement of carboxyhemoglobin (COHb) levels and hemoglobin (Hb) concentrations for adjustment of DL$_{CO}$ results is important for correct interpretation of both individual and group studies of DL$_{CO}$ and should be performed whenever possible.[121, 122]

Recommendation: Carbon Monoxide Diffusing Capacity (DL$_{CO}$)
Carbon monoxide diffusing capacity is recommended for use in diagnosing occupational lung disease.

>   *Strength of Evidence* – **Recommended, Evidence (C)**
>   *Level of Confidence* – **High**

Performed – DL$_{CO}$ should be performed according to the ATS/ERS statement published in 2005. Standardized predicted values are required.[207, 208] Correction for hemoglobin should be included. It is recommended that at least two DL$_{CO}$ tests should be performed and the average reported. It is recommended that the two measurements for the DL$_{CO}$ agree within 10%.[119] It is important to assess smoking status because smoking increases baseline levels of CO, causing increased back-pressure and carboxyhemoglobin.[119]

Indications – DL$_{CO}$ may be used to help in diagnosing gas exchange abnormalities in patients with lung disease.[123]

Harms – None.

Benefits – Accurate assessment of gas exchange abnormalities in patients with lung disease.

Advantages and Limitations – DL_{CO} may be affected by different diseases and exposures (Table 4). These must be considered when interpreting the test results.

Table 4. Diseases /Conditions Associated with Alterations in DL_{CO}

Diseases/Conditions that Decrease DL_{CO}
• Reduced effort or respiratory muscle weakness
• Thoracic deformity preventing full inflation
• Anemia
• Pulmonary emboli
• Hb binding changes (e.g., HbCO, increased Fl, O_2)
• Valsalva maneuver
• Lung resection
• Emphysema
• Interstitial lung disease (e.g., IPF, sarcoidosis)
• Chronic beryllium disease (CBD)
• Pulmonary edema
• Pulmonary vasculitis
• Pulmonary hypertension
Diseases/Conditions that Increase DL_{CO}
• Polycythemia
• Left to right shunt
• Pulmonary hemorrhage
• Asthma
• Exercise
• Hb binding changes
• Muller maneuver
• Supine position
• Obesity

Adapted from MacIntyre N, Crapo R, Viegi G. Stadardization of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J*. 2005;26:720-35. Additional source: Pappas GP, Newman LS. Early pulmonary physiologic abnormalities in beryllium disease. *Am Rev Respir Dis*. 1993;148:661-6.

Rationale for Recommendations
Eterovic et al. reported good correlation between changes in DL_{CO} values and asbestos-related lung disease.[103] Dujic et al. reported DL_{CO} value changes may precede radiographic evidence of asbestos-related lung disease and pleural/parenchymal lung disease.[124] Abejie et al. reported a decrease in DL_{CO} values in employees exposed to asbestos fibers without evidence of asbestosis on chest radiographs and even larger decreases in employees with findings consistent with asbestosis on chest radiographs.[125]

Evidence for the Use of DL_{CO}
There are 6 moderate-quality studies incorporated into this analysis.[103, 124-128]

SPUTUM SAMPLES AND BRONCHOALVEOLAR LAVAGE (BAL)

If insufficient clinical objective evidence is obtained from physical examination, chest radiographs and spirometry, additional testing including biological sampling may be indicated to

confirm the diagnosis of occupational ILD. The following discussion includes specific indications for biological sampling for each major category of occupational ILD.

Bronchoalveolar lavage (BAL) has been suggested as a potentially important diagnostic tool in the evaluation of exposure to asbestos and other occupational lung diseases.[129-131] This method of testing has been used in the diagnosis of lower respiratory tract disease prior to the use of HRCT of the chest.[132]

Collection of sputum is simpler, less invasive and less expensive than BAL.[133] Sputum collection is done by having the patient cough to attempt to produce sputum from deep within the lungs. It is recommended that each sample be at least 15mL to help increase the sensitivity of the sample.

Inhaled asbestos fibers that are coated with iron-containing mucoprotein and imbedded in lung tissue are referred to as asbestos bodies (AB). Ferruginous bodies (FB) result from the deposition of an iron-rich protein layer at the cell-particle interface of any type of fiber and when asbestos is verified they are called asbestos bodies.[134] Ferruginous/asbestos bodies are detectible by light microscopy, whereas asbestos fibers are detected with electron microscopy.

Recommendation: Bronchoalveolar Lavage
Bronchoalveolar lavage is recommended as an aid for the diagnosis of occupational lung disease caused by asbestos.

1. **Diagnosis of asbestos-related occupational interstitial lung disease.**

> *Strength of Evidence* **– Recommended, Evidence (C)**
> *Level of Confidence* – **Low**

Performed – BAL should be performed according to the ATS guidelines on performance of BAL for ILD.[132]

Indications – To assist in the diagnosis of occupationally-related asbestos interstitial lung disease.[129, 132, 135, 136]

Harms – Low incidence of paroxysmal coughing, vomiting, syncope.

Benefits – Support for diagnosis (though not required given modern testing i.e., HRCT).

Advantages and Limitations – Smoking is an important confounder in the assessment of BAL fluid (BALF) as it may interfere with cellular profiles of the lavage. BAL has been reported to be more beneficial in diagnosing occupational lung disease in non-smoking populations.[132] Presence of specific fibers or dusts in asbestos exposure, coal or silica does not discriminate well between exposure and disease.[132] The type of asbestos fiber may also influence the results with reports of less ABs found with chrysotile exposure.[133, 137] Differences in sampling, preparation and counting techniques, definitions of reference populations and expression of results have previously caused major difficulties in comparing results from different laboratories.[138]

Rationale for Recommendation
Teschler et al. reported a greater sensitivity with BAL compared to sputum among a selected sample group.[133] Vathesatogkit et al. reported more FBs detected in the BALF of exposed

versus unexposed subjects, and also reported a decrease in spirometry and DL_{CO} in subjects with FBs in their BALF.[130]

BAL is a high-cost procedure with moderate risk of adverse events, but has fewer adverse events also costing less when compared to open lung biopsy. Therefore, it is recommended in select cases.

Recommendation: Sputum Sampling
Sputum, both induced and spontaneous, is recommended as an aid for the diagnosis of occupational lung disease caused by asbestos.

1. **Diagnosis of asbestos-related occupational interstitial lung disease.**

> *Strength of Evidence* **– Recommended, Evidence (C)**
> *Level of Confidence* – **Low**

Harms – Paroxysmal coughing, vomiting, syncope.

Benefits – Support for diagnosis (though not current given modern imaging techniques such as HRCT).

Rationale for Recommendation
Sputum has been less reliable than BAL samples largely because of inability to obtain quality specimens.[134] However, sputum has the advantages of being a noninvasive and less expensive method when compared to BAL, thoracoscopic or open lung biopsy. Overall, the sensitivity of identifying asbestos bodies in sputum is poor but specificity is reportedly high.[135, 139, 140]

Collection of sputum is simpler when compared to BAL and biopsy. It is also less expensive and has fewer adverse effects. ABs in sputum is considered a highly specific marker of asbestos exposure, but it is considered insensitive.[133, 141] In a study of 11,000 sputum samples from the general population, no false-positive samples were reported.[142] Sulotto et al. reported ABs found in workers exposed to both chrysotile and amphibole fibers, while there was no direct correlation between ABs in sputum samples and asbestos-related disease.[141]

Evidence for the Use of Bronchial Alveolar Lavage (BAL) and Sputum
There are 4 moderate-quality studies on BAL[130, 133, 137, 143] and 4 moderate-quality studies on sputum incorporated into this analysis.[135, 139-141] There is 1 low-quality study and 2 other studies in Appendix 2.[129, 131, 134]

TREATMENT OVERVIEW
Management of workers diagnosed with occupational ILD consists of the coordinated use of five strategies:

1. General management of restrictive lung disease due to interstitial fibrosis.
2. Specific management of the underlying disease.
3. Specific management of comorbidities.
4. Prevention of further loss of lung function and major complications.
5. Evaluation of work capacity and fitness for duty.

The *general management of restrictive lung disease due to interstitial fibrosis* primarily consists of avoiding further exposures and supporting oxygenation. This includes use of supplemental oxygen if desaturation is documented during exertion or sleep. In advanced or rapidly

progressive cases, evaluation for lung transplantation should be performed. ILD, as it advances, is often associated with a chronic dry cough, which may require suppression, particularly when it interferes with sleep. Smoking cessation is indicated.

Fibrosis associated with pneumoconioses and autoimmune processes tends to progress through stages, ultimately reaching a similar "end stage" condition characterized by restrictive disease, pulmonary hypertension, cor pulmonale, congestive heart failure, and lung infections due to loss of host defense mechanisms. Extensive fibrosis, which may occur following recovery from diffuse alveolar damage by toxic inhalation, is refractory to direct management.

Specific management of the underlying disease is more critical for a good outcome than general management of fibrotic lung disease. Systemic glucocorticosteroids (aka "steroids") may be effective when used judiciously in HP and beryllium disease. Steroids are rarely used for other pneumoconiosis, although some modest improvements have been documented (e.g., in silicosis, asbestosis, and CWP). Yet adverse effects of steroids are considerable.[144, 145]

Treatment options that may be proposed for rheumatologic ILD (e.g., systemic sclerosis), such as cytotoxic drugs or immunotherapy, are not known to have any benefit in occupational ILD or idiopathic ILD.

Bronchodilators and inhaled corticosteroids may have a role in the presence of an accompanying airways effect, as in HP, cobalt-induced asthma, or dust-related airway diseases. Among fibrotic lung diseases, asbestosis and IPF are associated with a high rate of lung cancer. Although it has not been validated in asbestosis specifically, this screening modality (and possibly others in the future) may also reasonably be considered in cases of asbestosis.[146]

Screening for colon cancer has been recommended for patients with asbestosis.[22] Silicosis also confers a risk for lung cancer, but not as great as asbestosis and without known risk for other malignancies. Screening with helical high-resolution CT scanning has been recommended for cigarette smokers, who are a high-risk group.

Specific management of comorbidities is important in occupational ILD, particularly for silicosis. Silicosis is sometimes complicated by opportunistic infections, particularly tuberculosis and atypical mycobacteria. The resulting "silicotuberculosis" may be refractory to management and may require highly individualized and prolonged multi-drug treatment. Coexisting airways disease is managed with standard treatment approaches.

Preventing further loss of lung function by preventing respiratory comorbidity is essential, as the natural history of occupational ILD is an accelerated decline in lung function, often with sporadic incremental drops due to decompensation and exacerbation following which the patient usually does not return to baseline. This naturally includes smoking cessation. (See also Cornerstones of Disability Prevention and Management Guideline). Patients with ILD require immunization against pneumococcal pneumonia and influenza. Respiratory infections are recommended to be treated aggressively, with a low threshold for hospitalization if the ILD is advanced.

Pulmonary rehabilitation may be effective even in the complex settings of occupational respiratory diseases (e.g., asthma), providing sustained improvement of functional capacity, preventing deconditioning, and reducing health care utilization.[147, 148] No studies have made direct comparisons between different systems of rehabilitation.[149]

Preventing further loss of lung function by avoiding provocative exposures is essential and has implications for fitness for duty in work that involves airborne exposures. Smoking, of any variety, including exposure to sidestream smoke, should be strictly avoided, as the resulting respiratory irritation further compromises lung function. Avoidance of airway irritants, including fragrances, alcohols and aldehydes, solvents, and dusts may help some patients to preserve lung function, prevent episodes of shortness of breath, and to reduce the propensity to cough. On the other hand, low-level exposure, when easily tolerated by the patient, is not necessarily a contraindication to continued work, although as discussed below, monitoring is recommended to assure early recognition of disease acceleration or cardiopulmonary complications.

Evaluation of work capacity and fitness for duty is an important function when the patient is capable of working. A fitness-for-duty evaluation should be performed with detailed knowledge of workplace exposures. The worker should be identified as fit for duty, fit for duty with accommodation, or unfit for duty. Workers who are thought to be fit for duty with accommodation should have the recommended work limitations identified in as much detail as necessary to support an appropriate job placement (i.e., "light duty" is not sufficient). Patients who are unfit for duty should generally be further evaluated using their state's system and/or the relevant edition of the American Medical Association's *AMA Guides to the Evaluation of Permanent Impairment*, which provides detailed guidance on respiratory impairment,[iv] or the relevant guidelines for state or federal programs (e.g., reference the extensive procedures specified in the Code of Federal Regulations (CFR).[(150)]

Medical removal is a strategy used to permit an individual to avoid further exposures that might lead to progression or resulting in earlier impairment. "Medical removal" is the decision to move a worker to an alternative work assignment in order to protect them from a potential occupational hazard. It applies when the worker is believed to be unusually susceptible to exposure levels below existing occupational exposure limits (usually the OSHA or MSHA permissible exposure limits (PELs) or NIOSH-recommended exposure limits (RELs)) and ongoing potential exposures are judged to represent an excessive health risk to the individual. Workers who have developed evidence of pneumoconiosis, particularly with fewer than 20 years of exposure, may be particularly susceptible and should be considered for recommending medical removal. Whenever medical removal is contemplated due to the recognition of an occupational disease, it is essential to concurrently analyze ongoing exposures in the applicable working environments, and to identify potential explanations for the failure of primary protection.

If a worker has minor impairment(s) and when current exposures have been consistently shown to be well-controlled during all tasks, there may be no compelling rationale for medical removal. In such cases, it is reasonable for the affected worker to continue working in the assignment if both the worker and the employer will carefully avoid sporadic conditions that have potential for exposure at greater than minimal acceptable levels. In such instances, it is important to monitor dust levels and control measures as well as periodically reevaluate the worker's health.

For affected workers, participation in professionally administered personal respiratory protection programs may be especially useful under mildly dusty conditions, near the PEL, or in moderately dusty conditions near the PEL where there is no spillover of dust and dust levels are low where workers wear their respirators. Respirators may not be completely protective in cases of exposure to high airborne particulate levels. Additionally, periodic medical monitoring is important for individuals with symptoms or findings of occupational lung effects who continue to experience workplace exposures. Progressing ILD may make the worker intolerant of respirators, especially when moderately severe or worse, due to the increased work of breathing

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[iv]States have adopted a wide range of editions of the *AMA Guides to the Evaluation of Permanent Impairment*.

and increased dead space.[151] Therefore, queries about compliance to be sure that the worker is not removing the respirator during work for reasons of communication, discomfort, or health (e.g., expectoration), thus defeating its purpose.

Maintenance of work capacity and fitness for duty through exercise is important to prevent deconditioning. This is also important for patients who are unfit for work so that they may retain capacity for activities of daily living. Pulmonary rehabilitation programs, as for COPD and asthma, have not been shown to have a benefit for restrictive lung disease. However, in cases of mixed disease or when depression or lack of adherence is an issue, participation in rehabilitation programs may provide motivation, peer support, and better monitoring and control of comorbid conditions, such as airways disease.

TREATMENT RECOMMENDATIONS

PHARMACOLOGICAL TREATMENT

Recommendation: Pharmacological Treatment Management of Occupational Interstitial Lung Disease

It is recommended that the pharmacological treatment of occupational interstitial lung disease follow established guidelines for treatment of interstitial lung disease (152, 153).

> *Strength of Evidence* – **Recommended, Insufficient Evidence (I)**
> *Level of Confidence* – **Moderate**

Pharmacologic Treatment of Occupational ILD
The goal of pharmacologic treatment of occupational ILD primarily addresses symptoms and limitations. It cannot reduce fibrosis. The pharmacologic treatment of occupational ILD does not differ from the treatment of ILD that is not work related. Workers with clinical findings consistent with a given type of occupational ILD should be referred to a physician with training and experience in medical management of that condition.

Rationale – Existing guidelines from the American Thoracic Society provide evidence-based treatment recommendations for interstitial lung disease [1].

Evidence – A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: glucocorticoids, steroids, corticosteroids, adrenal cortex hormones; interstitial lung disease, sarcoidosis, pneumonitis, asbestosis, idiopathic pulmonary fibrosis; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, and not adolescents. We found and reviewed 322 articles in PubMed, 6126 in Scopus, 53 in CINAHL, 48 in Cochrane Library, 12800 in Google Scholar, and 4 from other sources[†]. We considered for inclusion 9 from PubMed, 3 from Scopus, 1 from CINAHL, 4 from Cochrane Library, 0 from Google Scholar, and 4 from other sources. Of the 21 articles considered for inclusion, 2 randomized trials and 4 systematic studies met the inclusion criteria.

[†] The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an

additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens, then the remaining articles are not reviewed due to a lack of relevancy.

EXPOSURE ASSESSMENT

Recommendation: Management of Occupational ILD (Exposure Assessment)
It is recommended that an exposure assessment be completed for workers diagnosed with occupational interstitial lung disease.

> *Strength of Evidence* **– Recommended, Insufficient Evidence (I)**
> *Level of Confidence* – **Moderate**

Benefits – Accurate identification of etiologic agents for occupational ILD and provision of data to support evidence-based decision making regarding personal protective equipment and return to work.

Exposure Assessment for Workers with Occupational ILD
Exposure data from industrial hygiene surveys and Safety Data Sheets (formerly known as Material Safety Data Sheets) and other sources such as area or personal monitoring data should be reviewed and considered for each worker diagnosed with occupational ILD. It is recommended that those evaluating workers with occupational ILD should request this information from the worker's employer(s) rather than relying solely on the worker's self-reported exposures (e.g., Safety Data Sheets; personal or area quantified industrial hygiene exposure data). Additional data such as medical surveillance records from periodic examinations performed in compliance with OSHA standards may also be available for review to support past evaluation of pulmonary status.

Rationale for Recommendations
Exposure assessment data are necessary to determine past and present exposures to specific agents, to ascertain the degree of respiratory hazards that exist, and to identify appropriate personal protective equipment to reduce exposure. In addition, as continued occupational exposure to certain agents such as beryllium would not be advisable for workers who have developed occupational ILD, identification of this exposure is essential for fitness for duty/return to work decision-making. The ability of a worker to use appropriate personal protective equipment to protect from further exposure is dependent upon pulmonary function and the physical demands of the job. Generally speaking, workers with severe to very severe respiratory impairment may not have sufficient inspiratory capacity to work while wearing respirators that increase the work of breathing (such as half-or full-face filtering respirators), and likewise may not be able to perform the functions of an occupation requiring moderate physical activity.

6-MINUTE WALK TEST AND DISTANCE-SATURATION PRODUCT

The 6-minute walk test (6MWT) is described as a prognostic tool for patients with various pulmonary diseases, although this is not a diagnostic test.[152-162] The test measures the distance a patient can walk on a flat, hard surface in a period of 6 minutes. Results provide objective measurement of the pulmonary system, as well as the cardiovascular, musculoskeletal, and nervous systems. The distance-saturation product (DSP) is the product of the distance walked during the 6MWT and the lowest oxygen saturation during the test.[155] This

has been reported to be a more reliable indicator of prognosis with lung disease than either parameter alone.[153]

The 6MWT is relatively inexpensive to perform, and is accessible in most clinical settings. Current studies support that the 6MWT is useful in research settings to evaluate grouped data, and in individuals with non-occupational ILD. The 6MWT may be useful for monitoring individuals with ILD, to assess individual performance over time. The presence of peripheral vascular disease, muscle weakness, deconditioning, and nutritional status are other important determinants of functional performance that may impact the results of the 6MWT. Although the 6MWT result correlates with performance, it may not provide sufficient information to assess maximum exercise performance. The 6MWT is not a substitute for maximal exercise testing, and thus may not provide sufficient information for decision-making regarding an individual worker's functional ability to perform the duties of a specific occupation or position, or for determination of impairment.[159, 161-181] Therefore, referral to a physician with skills and expertise in evaluating workers with ILD is generally indicated for assessment for fitness for duty for moderately strenuous jobs, particularly if the ILD is more than mild.

Recommendation: 6-Minute Walk Test
The 6-minute walk test is recommended in individuals with interstitial lung disease as a means to monitor response to treatment or progression of the disease.

> *Strength of Evidence* **– Recommended, Evidence (C)**
> *Level of Confidence* **– Moderate**

Technique – The walking course should be 30 meters or more. The corridor should be marked off every 3 meters. Treadmills are not recommended as the patient cannot pace themselves and studies have reported significant differences between treadmill 6MWT and hallway 6MWT.[152, 182] Pulse oximetry is optional for the 6MWT but required for DSP testing. It is recommended to use both the walking distance and the body weight as it has been shown to correlate closer with lung function, anaerobic threshold, and maximal oxygen uptake.[183, 184] It is recommended that the patient walk alone, including pushing their own oxygen tank as this more accurately represents their independent function.[187]

Absolute contraindications for the 6MWT include:
1. History of unstable angina.
2. Heart attack within the previous month.

Relative contraindications for the 6MWT include:
1. Resting tachycardia (>120 beats/minute)
2. Uncontrolled hypertension.[152, 185]

Reasons for immediately stopping the test are chest pain, intolerable dyspnea, leg cramps, staggering, excessive diaphoresis, and pale or ashen appearance.[152, 185] An example of a reference equation for the 6-minute walk distance in healthy adults is "6MWD pred = 218+(5.14 x height (cm)-5.32 x age (years)) – 1.8 x height (cm)) + (51.31 x sex) where sex = 1 for males, 0 for females."[188] Other gender-specific reference equations are also available.[187]

Criteria and Standards for Use – To be used as a measure of functional capacity targeted at people with at least moderately to severe impairment from lung disease. The 6-minute walk distance has variability based on age, gender, ethnicity, and height and weight in patients without any disease.[157, 186, 188] It has been recommended that the six minute walk distance be interpreted as a percentage of the predicted value much like spirometry.[184, 186]

Indications – To measure the response to medical interventions in patients with moderate to severe heart or lung disease. It may also be used as a measure of functional status of patients as well as a predictor of morbidity and mortality.[152, 189]

Harms – Potential dyspnea, rare myocardial infarctions.

Benefits – Assessment of exercise tolerance to inform fitness for duty and return to work decisions, relative ease of performance in a clinical setting.

Advantages and Limitations – The 6MWT is a more realistic test for testing the patient's ability to perform daily activities. Changes in 6 minute walk distance after therapeutic interventions correlate with subjective improvements in dyspnea.[152, 168] The walk distance increases with repeated testing which can confound treatment monitoring with ongoing testing.[173] The 6MWT does not diagnose the cause of dyspnea on exertion or evaluate the causes or mechanisms of exercise limitation.[154] The 6MWT in occupationally related ILDs is not well studied. The 6MWT is relatively easy to perform, low cost, with minimal risk and therefore, has been recommended for evaluation and treatment of occupationally-related ILDs.

A change in distance walked >54m has been reported to be clinically significant.[158, 185, 190] A 6-minute walk distance of <350m in COPD patients has been reported to predict mortality.[191] A total distance under 200 meters is consistent with poor functional capacity, while a total distance of under 350 meters is consistent with low functional capacity and a higher risk of complications.[194]

Rationale for Recommendations
There are 5 moderate-quality studies in non-occupationally-related ILD. These studies suggest that the 6MWT with saturations help monitor treatment response and assess mortality risks in patients with at least moderate lung disease.

Evidence for the Use of the 6-Minute Walk Test
There are 5 moderate-quality studies incorporated into this analysis.[153, 156, 162, 168, 193] There are 2 low-quality studies and 6 other studies in Appendix 2.[154, 157, 160, 161, 171, 186, 187, 194]

FLOWCHART FOR WORK DISPOSITION DETERMINATIONS FOR WORKERS WITH OCCUPATIONAL ILD

Review data on clinical and functional status
- Symptoms
- Pulmonary function tests
- 6-minute walk test

↓

Review data on occupational exposures, physical and exertional demands of the job, engineering controls, and available personal protective equipment (PPE) resources

↓

Is PPE program adequately protective for the specific job tasks and exposures? — **No** →

Yes ↓

Does continuing to do same tasks risk clinically important worsening (given PPE program)? — **Yes** →

No ↓

Does worker have functional capability to safely and effectively participate in PPE program and perform job duties?

Yes ← Medical clearance; continue environmental and health monitoring as appropriate

No → No clearance at this time; consider additional functional testing and /or referral

ALGORITHM 1. DIAGNOSTIC TESTING OF OCCUPATIONAL INTERSTITIAL LUNG DISEASE

Does the working-age adult report persistent cough, dyspnea, paroxysmal cough, and/or exercise intolerance?

—Yes→ **Obtain medical and occupational histories, including occupational and environmental exposures to potential agents.**

→ **Are symptoms consistent with diagnosis of occupational ILD?**

- No → **Consider EKG, Exercise Tolerance Test to evaluate for cardiac disease**
- Yes → **Is there evidence of exposure?**
  - No → **Refer to primary healthcare provider and/or pulmonologist for evaluation for non-occupational pulmonary**
  - Yes or Uncertain → **Request Exposure Data (e.g., Material Safety Data Sheets, industrial hygiene monitoring data), accident/spill reports,**

↓

Perform physical exam with attention to pulmonary system, (crackles, wheezing, cyanosis, clubbing). Consider pulse oximetry. Obtain spirometry and chest radiograph (PA and lateral) with interpretation by a physician with training and expertise in chest radiography.

↓

Findings consistent with asthma?

- Yes → **Refer to Occupational/Work-related Asthma Guideline**
- No → **Findings consistent with occupational ILD?**
  - No → **Additional work-up as suggested or refer for appropriate evaluation. Exit algorithm.**
  - Yes → **Additional work-up as suggested and/or refer to pulmonologist for further evaluation as appropriate. Consider chest CT, etiology-specific testing, full Pulmonary Function Tests with DL_{CO2}.**

Consider HRCT, full pulmonary function tests, DL_{CO}

APPENDIX 1. CHEST RADIOGRAPHS

The International Labour Organization (ILO) pneumoconioses classification system provides specific ratings for opacity size, shape and number seen on routine chest radiographics, and is most commonly used globally and in the United States.[81] It is a descriptive method that standardizes the interpretation and reporting of both the type and degree of changes on chest x-ray. However, it does not provide diagnostic criteria for the pneumoconioses.

The Coal Workers' X-Ray Surveillance Program was established under the Federal Coal Mine Health and Safety Act of 1969 (P.L. 91-173), which was amended by the Federal Mine Safety and Health Act of 1977 [30 USC 843]. In 2014, the MSHA extended coverage to surface, as well as, underground miners. Currently, mandatory x-rays include the following:

- An initial chest x-ray within 6 months of beginning employment,
- Another chest x-ray 3 years after the initial examination,
- A third chest x-ray 2 years following the second one if a miner is still engaged in underground coal mining and if the second chest x-ray shows evidence of category 1 or higher pneumoconiosis according to the ILO classification.[197]

In addition to these mandatory chest x-rays, mine operators are required to offer an opportunity for periodic, voluntary chest x-rays approximately every 5 years. The chest x-rays obtained under the Coal Workers' X-Ray Surveillance Program are submitted to and become the property of NIOSH.

APPENDIX 2: LOW-QUALITY/SUPPLEMENTARY STUDIES

The following low-quality/supplementary studies were reviewed by the Evidence-based Practice Interstitial Lung Disease Panel to be all inclusive, but were not relied upon for purpose of developing this document's guidance because they were not of high quality due to one or more errors (e.g., lack of defined methodology, incomplete database searches, selective use of the studies and inadequate or incorrect interpretation of the studies' results, etc.), which may render the conclusions invalid. ACOEM's Methodology requires that only moderate- to high-quality literature be used in making recommendations.[198]

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