Endobronchial Ultrasound for Diagnosis and Staging of Lung Cancer

Policy Number: 6.01.58  Last Review: 08/2018
Origination: 08/2015  Next Review: 08/2019

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for Endobronchial Ultrasound for Diagnosis and Staging of Lung Cancer when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Endobronchial ultrasound guidance with transbronchial needle biopsy may be considered medically necessary for the evaluation of peripheral pulmonary lesions in patients with suspected lung cancer when the following criteria are met:

- Tissue biopsy of the peripheral pulmonary lesion is required for diagnosis (see Considerations section)
- The peripheral pulmonary lesion is not accessible using standard bronchoscopic techniques

Endobronchial ultrasound guidance with transbronchial needle biopsy is considered medically necessary for mediastinal staging in patients with diagnosed lung cancer when the following criteria are met:

- The patient is suitable and willing to undergo specific treatment for lung cancer, with either curative or palliative intent (see Considerations section)
- Tissue biopsy of abnormal mediastinal lymph nodes seen on imaging is required for staging and specific treatment planning (see Considerations section)
- Abnormal lymph nodes seen on imaging are accessible by EBUS-TBNA biopsy

When Policy Topic is not covered
Endobronchial ultrasound is considered not medically necessary for diagnosis and staging of lung cancer when the above criteria are not met.

Endobronchial ultrasound is considered investigational for all other indications.
Considerations

Diagnosis and Staging Guidelines
The American College of Chest Physicians has published comprehensive evidence-based clinical practice guidelines for the diagnosis(1) and staging(2) of lung cancer. Key elements of those guidelines relevant to this Policy are outlined next.

The general approach to patients who are suspected of having lung cancer begins with a comprehensive history and physical examination. Imaging studies will include a CT scan of the chest and a whole body PET (positron emission tomography) or PET-CT study to seek extrathoracic lesions. A patient’s suitability and desire for curative treatment of a proven lung cancer is the chief consideration in choosing among subsequent management options. These factors in turn will guide the approach to establishing a diagnosis and staging the disease, as follow:

1. Some individuals may prefer no treatment, particularly those with life-limiting comorbid conditions. In such individuals, neither surgical biopsy nor staging is justified. Aggressive surveillance using serial CT may be used to monitor symptoms for palliation.

2. Two categories of patients, who could potentially benefit from curative surgical resection based on the presence of a solitary, locally confined pulmonary lesion and documented absence of extrathoracic metastatic disease, will not proceed to surgery for completely different reasons.
   a. One group would be considered ineligible for surgery due to sufficiently impaired cardiopulmonary function or other comorbidity that precludes general anesthesia.
   b. A second group of individuals would otherwise be eligible for curative surgery but for personal reasons refuse surgical resection.

For either category of patients listed above, surgical diagnostic and staging procedures are contraindicated. Their options include functional imaging (PET, PET-CT, magnetic resonance imaging), CT scan surveillance, and needle-based nonsurgical biopsy, including guided bronchoscopic procedures such as EBUS.

3. Patients who are candidates for curative surgical resection by virtue of documented (PET, PET-CT) absence of distant metastatic lesions, locally confined single tumors, and otherwise sound physical condition are eligible for any type of diagnostic and staging procedure.

4. In patients suspected of having lung cancer based on radiographic imaging (CT), functional imaging (PET, PET-CT) and clinical findings (signs and symptoms of lung cancer), a presumptive diagnosis must be confirmed, preferably by the least invasive method, as dictated by the patient’s presentation and desire for definitive treatment.
5. For patients with extensive mediastinal infiltration of tumor and no distant metastases, it is suggested that radiographic (CT) assessment of the mediastinal stage is usually sufficient without invasive confirmation.

6. In patients with discrete mediastinal lymph node enlargement (and no distant metastases) with or without PET uptake in mediastinal nodes, invasive staging of the mediastinum is recommended over staging by imaging alone.

### Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals: ▪ With peripheral pulmonary lesions and suspected lung cancer</td>
<td>Interventions of interest are: ▪ Endobronchial ultrasound– guided transbronchial needle aspiration for diagnosis</td>
<td>Comparators of interest are: ▪ Flexible bronchoscopy with transbronchial needle aspiration ▪ Transthoracic (percutaneous) needle aspiration using computed tomography guidance ▪ Mediastinoscopy ▪ Surgical lung biopsy</td>
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<td>Relevant outcomes include: ▪ Test accuracy ▪ Test validity ▪ Morbid events</td>
</tr>
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Endobronchial ultrasound (EBUS) is a technique that enhances standard flexible bronchoscopy by providing an ultrasound-generated image of the lungs beyond the airway walls, extending to peribronchial structures and distal peripheral lung lesions. The purpose of EBUS is to allow navigation to distal regions of the lungs and facilitate biopsy of suspected cancerous lesions, especially for peripheral pulmonary nodules. Another intended use of EBUS is to examine and biopsy the mediastinal lymph node regions as part of staging for non-small-cell lung cancer (NSCLC). Both techniques use transbronchial needle aspiration (TBNA) of lesions to obtain tissue samples.

The evidence for EBUS-guided TBNA (EBUS-TBNA) for diagnosis in individuals with peripheral pulmonary lesions and suspected lung cancer includes a recent systematic review and meta-analysis and 2 small randomized trials. Relevant outcomes are test accuracy, test validity, and morbid events. The body of evidence supports a conclusion that EBUS-TBNA has diagnostic performance characteristics for solitary pulmonary lesions similar to those of traditional flexible bronchoscopy with transthoracic needle aspiration. The evidence also indicates that the safety profile of EBUS-TBNA may be better than with other techniques, as reflected by pneumothorax and chest tube insertion rates. The evidence is
sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for EBUS-TBNA for staging individuals with lung cancer and mediastinal lymph nodes seen on imaging includes multiple systematic reviews and meta-analyses. Relevant outcomes are test accuracy, test validity, and morbid events. Evidence supports a conclusion that EBUS-TBNA exhibits test performance characteristics similar to other needle-based methods used to stage the mediastinum in patients diagnosed with lung cancer. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

**Background**

Individuals who are suspected of having lung cancer may present with widely differing signs and symptoms that are related to the type of cancer (e.g., NSCLC vs small-cell lung cancer [SCLS]), its location within the lung, and the stage of disease (i.e., localized, locoregionally advanced, metastatic). All 3 of the major parameters of type, location, and stage will dictate subsequent management of the cancer, determining whether it is primarily surgical or requires systemic chemotherapy. Early diagnosis of lung cancer is essential because of the uniformly poor prognosis when cancer is diagnosed later in the disease course.

Approximately 75% to 80% of newly diagnosed lung cancers are NSCLC. The clinical presentation and findings on CT or fluoro(18)-2-deoxyglucose (FDG) PET scan of the chest typically permit a presumptive diagnosis of lung cancer and differentiation between NSCLC and SCLC. If SCLC is suspected based on radiographic characteristics and other clinical findings, a diagnosis is made by whatever means is easiest (sputum cytology, thoracentesis if an accessible pleural effusion is present, fine-needle aspiration [FNA] of a supraclavicular node, etc.). However, the diagnosis of suspected NSCLC is usually dictated by the stage of the disease. NSCLC can present with extensive infiltration of the mediastinum, defined as a mass with no visible lymph nodes, or it may present as a solitary pulmonary nodule that may be bronchogenic or peripheral. In any patient with suspected NSCLC, the diagnosis should be established by the method that has the most favorable risk-benefit ratio.

**Diagnosis of Peripheral Pulmonary Nodules**

Solitary pulmonary lesions are typically identified on plain chest radiographs or chest CT scans, often incidentally. Although most of these nodules will be benign, some will be cancerous. Peripheral lung lesions and solitary pulmonary nodules (most often defined as asymptomatic nodules <6 mm) are more difficult to evaluate than larger, centrally located lesions. There are several options for diagnosis; however, none of the methods is ideal for safely and accurately diagnosing malignant disease in all patients. Sputum cytology is the least invasive approach. Reported sensitivity rates are relatively low and vary widely across studies, and sensitivity is even lower for peripheral lesions. Sputum cytology, however, has a high specificity, and a positive test may obviate the need for more invasive testing.
Flexible bronchoscopy, a minimally invasive procedure, is the most common approach to evaluating pulmonary nodules. The sensitivity of flexible bronchoscopy for diagnosing bronchogenic carcinoma has been estimated at 88% for central lesions and 78% for peripheral lesions.\textsuperscript{2} For small peripheral lesions less than 1.5 cm in diameter, the sensitivity may be as low as 10%, due to the inability to reach into smaller bronchioles.

Transthoracic (percutaneous) needle aspiration (TNA), using CT guidance, can be performed for peripheral nodules that are beyond the reach of traditional bronchoscopy. The diagnostic accuracy of TNA tends to be as high or higher than that of flexible bronchoscopy for peripheral lesions; the sensitivity and specificity are both greater than 90%.\textsuperscript{2} A disadvantage of TNA is that a pneumothorax may occur in as many as 15% of patients, although this number can range from 1% to 15%. About 1% to 7% will require insertion of a chest tube. PET scans are also highly sensitive for evaluating pulmonary nodules, yet may miss small lesions less than 1 cm in size. Surgical lung biopsy is the criterion standard for diagnosing pulmonary nodules but is an invasive procedure that is not indicated for all patients.

**Staging of Lung Cancer: Assessment of Mediastinal Involvement**

The stage of a lung cancer (its extent through the body) at diagnosis will directly impact the management approach for each patient.\textsuperscript{3,4} The first step in staging is to identify whether the patient has distant metastatic disease (M stage) or the tumor is confined to the chest; this will determine if treatment should be aimed at palliation or at potential cure, respectively. If the primary tumor is confined (T stage), determining whether the mediastinal lymph nodes (N stage) are involved is a crucial factor in guiding therapy.

As for diagnostic procedures, there are a number of options for mediastinal staging. The choice of a noninvasive or invasive staging method is dictated by the patient’s condition and whether he or she can tolerate or will elect surgery. Thus, staging procedures may be based on noninvasive imaging methods (ie, CT or PET, or combined PET-CT), or may be fully invasive, such as mediastinoscopy—a surgical procedure that is performed under general anesthesia and is regarded as the reference standard for staging lung cancer.\textsuperscript{3}

Recent advances in technology have led to enhancements that may increase the yield of established needle-based diagnostic methods that represent a third approach between noninvasive and surgical procedures.\textsuperscript{1} CT scanning equipment can be used to guide flexible bronchoscopy and bronchoscopic transbronchial needle biopsy but has the disadvantage of exposing the patient and staff to radiation.

**Endobronchial Ultrasound With Transthoracic Needle Aspiration**

Among its potential applications, endobronchial ultrasound (EBUS) using ultrasound probes, can be used to locate and guide sampling of pulmonary lesions and mediastinal lymphadenopathy.
EBUS uses 2 distinct types of transducers that have specific uses: radial probe and convex probe.

A radial probe EBUS comprises a 20- or 30-MHz rotating transducer to provide high-resolution 360° radial images. The probe is inserted into the airways via a standard therapeutic bronchoscope. With the use of an ultrathin bronchoscope combined with radial probe EBUS through a guide sheath, an endoscopist can reach and visualize the sixth- to eighth-generation bronchi, whereas a traditional bronchoscope can only reach the fourth-generation bronchi. The use of radial probe EBUS imaging allows the physician to verify visually that a lesion has been reached and to maintain position in the periphery to allow a needle biopsy to be performed for diagnosis. These probes do not allow real-time imaging during biopsy. For biopsy or tissue sampling, the target area is located by radial probe EBUS; the radial probe is subsequently retracted and is replaced with a biopsy or sampling device.

Convex probe EBUS transducers are adjustable within a frequency range of 5 to 12 MHz. Such transducers are incorporated into the structure of a dedicated bronchoscope and provide real-time pie-slice sector views of 50° to 60° parallel to the axis of the bronchoscope. Convex probe EBUS with transbronchial needle aspiration (EBUS-TBNA) also can be used for staging the mediastinal nodes. The curved linear probe technology allows real-time visualization and needle aspiration of a lesion. Because EBUS-TBNA of the mediastinal nodes may be performed under conscious sedation, it may be used in patients who are not surgical candidates but for whom accurate staging is needed to guide choice among systemic treatments, particularly targeted systemic agents such as tyrosine kinase inhibitors.

**Regulatory Status**
A number of instruments are commercially available to perform EBUS-TBNA for diagnosis and staging of lung cancer. All have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process and are shown in Table 1.

<table>
<thead>
<tr>
<th>Device Name</th>
<th>Manufacture</th>
<th>Date Cleared</th>
<th>510(k)</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVIS EXERA Bronchofibervideoscope, Olympus BF type UC160F-OL8 bronchoscope and its diagnostic ultrasound transducer</td>
<td>Olympus Medical Systems</td>
<td>Aug 2004</td>
<td>K042140</td>
<td>To provide real-time endoscopic US imaging and US-guided FNA, including the upper airways and tracheobronchial tree</td>
</tr>
<tr>
<td>EU-M60 EUS EXERA Endoscopic Ultrasound Center</td>
<td>Olympus Medical Systems</td>
<td>Dec 2004</td>
<td>K04327</td>
<td>To acquire and to display high-resolution and high-penetration, real-time endoscopic US B-mode 2D and 3D images, including the upper airways and tracheobronchial tree</td>
</tr>
<tr>
<td>Instrument Name</td>
<td>Manufacturer</td>
<td>Date of Approval</td>
<td>Category</td>
<td>Description</td>
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<tr>
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<tr>
<td>XBF-UC180F-DT8 Ultrasonic Bronchofibervideoscope and the ALOKA SSD-Alfa 5/10 Ultrasound System</td>
<td>Olympus Medical Systems</td>
<td>Jul 2007</td>
<td>K070983</td>
<td>To provide real-time endoscopic US imaging and US-guided FNA including the upper airways and tracheobronchial tree</td>
</tr>
<tr>
<td>SonoTip® II EBUS-TBNA Needle System</td>
<td>Medi-Globe</td>
<td>May 2009</td>
<td>K091257</td>
<td>For US-guided FNA of submucosal and extraluminal lesions of the tracheobronchial tree</td>
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<tr>
<td>EchoTip® Ultra High Definition Endobronchial Ultrasound Needle</td>
<td>Cook Medical</td>
<td>Jan 2010</td>
<td>K093195</td>
<td>For use in conjunction with an EBUS endoscope to gain access to and sample submucosal and extramural lesions within or adjacent to the tracheobronchial tree through the accessory channel of an EUS for FNA</td>
</tr>
<tr>
<td>PENTAX Ultrasound Video Bronchoscope EB-1970UK + HI VISION Preirus endoscopic ultrasound</td>
<td>PENTAX Medical</td>
<td>Apr 2014</td>
<td>K131946</td>
<td>To provide optical visualization of, ultrasonic visualization of, and therapeutic access to, the pulmonary tract including but not restricted to the nasal passages, pharynx, larynx, trachea, bronchial tree (including access beyond the stem), and underlying areas</td>
</tr>
<tr>
<td>SonoTip® Pro and Pro Flex EBUS-TBNA Needle System</td>
<td>Medi-Globe</td>
<td>May 2014</td>
<td>K133763</td>
<td>Intended for US-guided FNA of submucosal and extraluminal lesions of the tracheobronchial tree and gastrointestinal tract (eg, lymph nodes, abnormal tissue in the mediastinum)</td>
</tr>
<tr>
<td>Expect™ Pulmonary Endobronchial Ultrasound Transbronchial Aspiration Needle</td>
<td>Boston Scientific</td>
<td>Nov 2015</td>
<td>K151315</td>
<td>For use with EBUS endoscopes for US-guided FNA of the submucosal and extramural lesions of the tracheobronchial tree</td>
</tr>
</tbody>
</table>

EBUS: endobronchial ultrasound; EUS: endoscopic ultrasound; FDA: Food and Drug Administration; FNA: fine-needle aspiration; TBNA: transbronchial needle aspiration; US: ultrasound.

**Rationale**

This evidence review was created in November 2014 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through July 21, 2017.

Assessment of a diagnostic technology typically focuses on 3 categories of evidence: (1) technical reliability (test-retest reliability or interrater reliability); (2) clinical validity (sensitivity, specificity, and positive and negative predictive value) in relevant populations of patients; and (3) clinical utility (ie, demonstration that the diagnostic information can be used to improve patient outcomes).
Diagnosis of Lung Cancer

Clinical Context and Test Purpose
The question addressed in this evidence review is whether there is sufficient evidence that endobronchial ultrasound–guided transbronchial needle aspiration (EBUS-TBNA) used to diagnose lung cancer improves the net health outcome compared with standard bronchoscopic techniques. The primary question of interest to the review is as follows: Is EBUS-TBNA as or more accurate than standard techniques and does it offer fewer harms? Whether any improvement in accuracy leads to improved survival outcomes is also of interest, but, due to the lack of published data, that question is not a focus of the review.

The following PICOTS were used to select literature to inform this review.

Patients
The relevant populations of interest are individuals with peripheral pulmonary lesions and suspected lung cancer.

Interventions
The intervention of interest is EBUS-TBNA.

Comparators
Because EBUS is intended as an adjunct to standard bronchoscopic techniques, the primary comparator is flexible bronchoscopy with TBNA. EBUS-TBNA can also be compared with other methods for determining whether peripheral pulmonary lesions (PPLs) are cancerous: transthoracic (percutaneous) needle aspiration using computed tomography (CT) guidance for lesions outside the reach of traditional bronchoscopy, mediastinoscopy, or surgical lung biopsy.

Outcomes
Outcomes of interest for diagnostic accuracy include test accuracy, test validity (eg, sensitivity, specificity) and potential harms of testing (eg, pneumothorax and chest tube insertion rates). The primary outcomes of interest for clinical utility are overall mortality and lung cancer–specific mortality. In the absence of direct evidence on mortality impacts, a chain of evidence can be constructed that addresses the likely impact on mortality.

Timing
EBUS-TBNA would be performed after PPLs were identified or when a prior less invasive test was inconclusive.

Setting
The test would be performed in a specialty care setting.

Technical Reliability
A number of instruments are commercially available to perform EBUS-TBNA, and the technical reliability of these devices has been evaluated by the Food and Drug Administration as part of the 510(k) process.
Clinical Validity

Systematic Reviews
A substantial body of literature exists on the use of radial probe EBUS to diagnose lung cancer in individuals with solitary pulmonary nodules or lesions. Several systematic reviews of the literature have been published including 2 reviews by the American College of Chest Physicians (ACCP).\textsuperscript{1,2} The ACCP reviews indicated that, in general, most of the evidence comes from small retrospective or prospective studies, plus 2 randomized controlled trials (RCTs).

In 2017, Ali et al published a systematic review and meta-analysis of studies on the accuracy of radial probe EBUS for diagnosing PPLs.\textsuperscript{8} Reviewers searched the literature through September 2016 and included studies that met the following criteria: (1) used radial probe EBUS for PPLs; (2) diagnoses were confirmed histologically or by close clinical follow-up for at least 6 months; and (3) enrolled at least 20 patients.

Fifty-seven studies reporting on 7872 lesions met the eligibility criteria. The pooled data on diagnostic yield, using 54 studies, was 70.6\% (95\% confidence interval [CI], 68.0\% to 73.1\%). In a subgroup analysis of 25 prospective studies with a total of 2920 lesions, the pooled diagnostic yield was 72.3\% (95\% CI, 67.5\% to 76.8\%). In the 28 studies that reported diagnostic yield separately by lesion size, pooled diagnostic yield was 60.5\% (95\% CI, 56.6\% to 64.4\%) for lesions 2 cm or smaller and 75\% (95\% CI, 72.1\% to 79.2\%) for lesions greater than 2 cm. The overall complication rate in the 57 studies included in the Ali meta-analysis was 2.8\%. There was a total of 160 reported complications, 82 pneumothoraces, 61 bleeds, and 17 cases of pneumonia.

The performance of radial probe EBUS in the Ali meta-analysis appears to be at least as high as flexible bronchoscopy for peripheral nodules as reported in an ACCP meta-analysis (diagnostic sensitivity, 33\% for lesions <2 cm, 62\% for lesions >2 cm, 57\% for all peripheral lesions).\textsuperscript{1}

A 2017 systematic review and meta-analysis by Ye et al focused on fluoroscopy guidance.\textsuperscript{9} Reviewers identified 4 studies comparing EBUS plus fluoroscopy-guided transbronchial biopsy (TBB) and conventional fluoroscopy-guided TBB to diagnosis PPLs. (Three of the 4 studies were included in the Ali meta-analysis; the Ye analysis had a different focus.) The studies included a total of 461 patients. In a pooled analysis, the overall diagnostic accuracy was significantly higher in the EBUS-TBB group than in the conventional TBB group (odds ratio [OR], 2.21; 95\% CI, 1.42 to 3.44; p<0.001).

Randomized Controlled Trials
Two small randomized trials were identified that evaluated EBUS: one compared its use with TBB and the other, with conventional fluoroscopy-guided flexible bronchoscopy. In the RCT by Paone et al (2005), patients with identified peripheral lung lesions suspicious as malignancy who could undergo a complete clinical
diagnostic follow-up (n=293) were enrolled in the trial and randomized to EBUS-TBB (n=97) or TBB (n=124). Patients for whom biopsies were not diagnostic underwent more invasive procedures to obtain a final diagnosis, and a complete follow-up was possible in 206 patients (87 EBUS-TBB, 119 TBB). Lung cancer was diagnosed in 61 patients in the EBUS-TBB group and in 83 patients in the TBB group. The sensitivity of EBUS (78.7%) was significantly higher than TBB (55.4%; p=0.004). The specificity was 100% in both groups. Overall, the accuracy was 85% in the EBUS group and 69% in the TBB group (p=0.007). The analysis of a subset of patients with lesions greater than 3 cm showed no significant difference in diagnostic ability between the 2 procedures. A considerable decline in TBB sensitivity (31%) and accuracy (50%; p<0.000) was observed in lesions less than 3 cm, while EBUS-TBB sensitivity (75%) and diagnostic yield (83%; p=0.001) were maintained. A similar difference was observed when the sensitivity of the 2 procedures was compared in lesions less than 2 cm (23% vs 71%, p<0.001).

An RCT by Fielding et al (2012) aimed to determine diagnostic, complication, and patient tolerability rates of EBUS with a guide sheath (EBUS-GS) and CT-guided percutaneous core biopsy for peripheral lung lesions among patients with visible lesions suspicious of malignancy. Patients with lesions greater than 1 cm diameter on CT were randomized to EBUS-GS biopsy or CT-guided biopsy. Patients with severe chronic obstructive airway disease, lesions touching visceral pleura or hilum, and patients with symptoms needing bronchoscopic evaluation were excluded. Among 64 participants, 57 completed the study.

Diagnostic sensitivity was 67% (22/33 cases) for EBUS-GS and 78% (19/24 cases) for CT-guided biopsy (p>0.1). In those with negative results, 9 patients in the EBUS group had a CT-guided biopsy as a crossover, seven of which were diagnostic. In the CT group, four had crossover EBUS-GS, three of which were diagnostic. When both initial and crossover procedures were evaluated, sensitivity for malignancy was 17 (74%) of 23 for EBUS-GS and 23 (88%) of 26 (p>0.1).

For lesions less than 2 cm, a CT-guided biopsy had a significantly better diagnostic yield (80% vs 50%, p=0.05). In EBUS-GS cases, for lesions with an air bronchogram, sensitivity was 89%. Pneumothorax and intercostal catheter insertion was performed in 3 and 2 cases, respectively, for EBUS, and 10 and 3 cases for CT-guided biopsy (p=0.02 for pneumothorax). Nine unexpected admissions occurred after CT-guided biopsy compared with three after EBUS-GS.

**Clinical Utility**

**Direct Evidence**
Direct evidence of clinical utility of EBUS-TBNA is provided by studies that have compared health outcomes for patients managed with EBUS-TBNA with an alternative approach to lung cancer diagnosis (e.g., flexible bronchoscopy plus TBNA). Preferred evidence comes from RCTs. No RCTs or other controlled studies reporting on longer term health outcomes (i.e., mortality) were identified.
Chain of Evidence
A chain of evidence for the clinical utility of EBUS-TBNA as an adjunct to standard bronchoscopy for the diagnosis of lung cancer is based on an examination of the data on diagnostic accuracy and an examination of harms associated with various diagnostic methods.

The available evidence supports a conclusion that EBUS-TBNA has diagnostic performance characteristics for solitary pulmonary lesions similar to those of traditional flexible bronchoscopic techniques with transthoracic needle biopsy. The evidence also indicates that the safety profile of EBUS-TBNA may be less risky than other techniques, as reflected by pneumothorax and chest tube insertion rates. For example, as found by Fielding et al (2012) (discussed above), although CT-guided biopsy had higher yields in lesions less than 2 cm, EBUS-GS had better tolerability and fewer complications. The evidence does not establish that 1 technique is better than the others. Thus, the chain of evidence suggests that EBUS-TBNA can improve the net health outcome (ie, has a similar benefit to alternative techniques with less harm).

Section Summary: Diagnosis of Lung Cancer
Evidence from 2017 meta-analysis of 57 studies and from 2 RCTs supports a conclusion that EBUS-TBNA has diagnostic performance characteristics for solitary pulmonary lesions similar to those of traditional flexible bronchoscopic techniques with transthoracic needle biopsy. The available evidence also indicates that the safety profile of EBUS-TBNA may be better than other techniques (eg, CT-guided biopsy). This evidence does not establish that any technique is better than the others. The choice of technique for biopsy depends on a number of factors, including the size and location of the lesion(s) and the risks of the planned procedure.

Staging of Lung Cancer
Clinical Context and Test Purpose
The question addressed in this evidence review is whether there is sufficient evidence that EBUS-TBNA used for lung cancer staging improves the net health outcome compared with standard bronchoscopic techniques. Specifically, is EBUS-TBNA as or more accurate than standard techniques and does it have fewer harms?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant populations of interest are individuals with lung cancer and mediastinal lymph nodes seen on imaging.

Interventions
The intervention of interest is EBUS-TBNA.
Comparators
Because EBUS is intended as an enhancement to standard bronchoscopic techniques, the primary comparator is flexible bronchoscopy with TBNA. EBUS-TBNA can also be compared with other methods for staging lung cancer which include PET, transthoracic needle aspiration using CT guidance and mediastinoscopy.

Outcomes
Outcomes of interest for diagnostic accuracy include test accuracy, test validity (eg, sensitivity, specificity) and potential harms of testing (eg, pneumothorax and chest tube insertion rates). The primary outcomes of interest for clinical utility are overall mortality and lung cancer–specific mortality.

Timing
EBUS-TBNA would be performed after lung cancer is diagnosed.

Setting
The test would be performed in a specialty care setting.

Technical Reliability
A number of instruments are commercially available to perform EBUS-TBNA, and the technical performance of these devices has been evaluated by the Food and Drug Administration as part of the 510(k) process.

Clinical Validity
In 2013, ACCP published a systematic review with pooled analyses that provided a comprehensive resource for noninvasive and invasive methods to stage the mediastinum, including EBUS-based techniques. Table 2 summarizes the pooled test performance characteristics for a number of staging procedures drawn from the ACCP evidence review.

### Table 2. Pooled Performance Characteristics of Techniques Used to Stage the Mediastinum in Patients With Lung Cancer

<table>
<thead>
<tr>
<th>Technique</th>
<th>N</th>
<th>Cancer Prevalence, %</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
</tr>
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<tbody>
<tr>
<td>CT with contrast enhancement</td>
<td>7368</td>
<td>30</td>
<td>55</td>
<td>81</td>
<td>58</td>
<td>83</td>
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<tr>
<td>PET alone</td>
<td>4105</td>
<td>28</td>
<td>80</td>
<td>88</td>
<td>75</td>
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<td>PET-CT</td>
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<td>22</td>
<td>62</td>
<td>90</td>
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<td>Traditional mediastinoscopy</td>
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<td>33</td>
<td>78</td>
<td>(100)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>(100)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>91</td>
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<td>Video-assisted mediastinoscopy</td>
<td>995</td>
<td>31</td>
<td>89</td>
<td>(100)&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Mediastinal lymphadenectomy</td>
<td>386</td>
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<td>81</td>
<td>(100)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>(100)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>91</td>
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<td>Video-assisted thoracic surgery</td>
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<td>(100)&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Transthoracic needle aspiration (percutaneous)</td>
<td>215</td>
<td>84</td>
<td>94</td>
<td>(100)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>(100)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NR&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
The data in the table would suggest that the grouping of imaging techniques as a whole does not perform as well as the invasive techniques overall. Within the invasive grouping, there seems to be little apparent difference in terms of performance characteristics. Traditional surgical mediastinoscopy has long been considered the criterion standard for staging the mediastinum in patients diagnosed with lung cancer; variants of it are used in specific cases (eg, when the cervical approach does not provide information specific to certain node stations). Mediastinoscopy is indicated mainly for patients who would be candidates for curative surgical resection. The less invasive guided needle-based methods are suitable for nonsurgical candidates or those who refuse surgery, yet require staging to plan specific systemic therapy or radiotherapy. They appear to have very similar performance characteristics based on the ACCP analyses, including EBUS-TBNA.

A more recent systematic review, published in 2015 by Ge et al, compared EBUS-TBNA with mediastinoscopy for the mediastinal staging of lung cancer. Reviewers included studies with at least 10 patients that used either EBUS-TBNA or mediastinoscopy to stage mediastinal lymph nodes in patients with suspected or confirmed lung cancer. Ten studies with 999 EBUS patients and 7 studies with 915 mediastinoscopy patients were included. Due to the extremely low rate of false positive results, reviewers assumed that all positive results were true positives. Thus, they only pooled analyses of sensitivity (with no false positives, the specificity would be 100%). For the EBUS-TBNA studies, the pooled sensitivity was 83% (95% CI, 79% to 87%); for mediastinoscopy, it was 86% (95% CI, 82% to 90%). The difference in sensitivity was not statistically significant (p=0.632). Seventeen complications, including 2 pneumothoraces, 2 cases of perioperative bleeding, one esophagus injury, and one wound infection, occurred in the mediastinoscopy group and only 4 minor injuries occurred in the EBUS-TBNA group. A limitation of the literature and the systematic review is that studies were not head-to-head comparisons of staging techniques.

**Clinical Utility**

**Direct Evidence**

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with EBUS-TBNA compared with an alternative approach to lung cancer diagnosis (eg, flexible bronchoscopy plus TBNA).
Preferred evidence comes from RCTs. No RCTs or other controlled studies were identified.

**Chain of Evidence**
A chain of evidence of the clinical utility of EBUS-TBNA for the staging of lung cancer is based on an examination of the EBUS-TBNA data on diagnostic accuracy and harms associated with various staging techniques. The evidence underlying the pooled accuracy for mediastinal staging is less than optimal. The literature review for staging did not identify any RCT evidence to compare EBUS guidance with any other needle-based technique. There are differences among the patient populations and the use of reference standard confirmation of node positivity. The evidence summarized herein supports a conclusion that EBUS-TBNA exhibits test performance characteristics similar to other needle-based methods used to stage the mediastinum in patients diagnosed with lung cancer. Although EBUS-TBNA could be used in patients who are surgical candidates and plan to undergo surgery, it also may be suitable for those who are not eligible for curative resection—or for those who refuse to undertake major surgery but still require staging for planning systemic or radiotherapy. A major advantage of EBUS-based methods is that they can be performed on an outpatient basis under limited sedation if necessary, and thus would be less invasive and less risky than traditional mediastinoscopy. Thus, the chain of evidence suggests that EBUS-TBNA may be more beneficial in certain situations.

**Section Summary: Staging of Lung Cancer**
The literature review on use of EBUS-TBNA for staging did not identify any RCT evidence that compared EBUS guidance with any other needle-based technique. The evidence summarized herein from systematic reviews of observational studies supports a conclusion that EBUS-TBNA exhibits test performance characteristics similar to other needle-based methods used to stage the mediastinum in patients diagnosed with lung cancer. Although it could be used in patients who are surgical candidates and plan to undergo surgery, it also may be suitable for those who are not eligible for curative resection or refuse to undertake major surgery but still require staging for planning systemic or radiotherapy. A major advantage of EBUS-based methods is that they are less invasive and less risky than traditional mediastinoscopy.

**Summary of Evidence**
For individuals who have peripheral pulmonary lesions and suspected lung cancer who receive EBUS-TBNA for diagnosis, the evidence includes a recent systematic review and meta-analysis and 2 small randomized trials. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and morbid events. Evidence supports a conclusion that EBUS-TBNA has diagnostic performance characteristics for solitary pulmonary lesions similar to those of traditional flexible bronchoscopy with transthoracic needle aspiration. The evidence also indicates that the safety profile of EBUS-TBNA may be better than the profile of other techniques, as reflected by pneumothorax and chest tube insertion rates. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.
For individuals who have lung cancer and mediastinal lymph nodes seen on imaging who receive EBUS-TBNA for staging, the evidence includes systematic reviews and meta-analyses. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and morbid events. Evidence from systematic reviews of observational studies supports a conclusion that EBUS-TBNA exhibits test performance characteristics similar to other needle-based methods used to stage the mediastinum in patients diagnosed with lung cancer. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements

National Comprehensive Cancer Network
National Comprehensive Cancer Network guidelines on non-small-cell lung cancer (v.8.2017) state:

“The least invasive biopsy with the highest yield is preferred as the first diagnostic study....
Patients with suspected nodal disease should be biopsied by EBUS [endobronchial ultrasound], EUS [endoscopic ultrasound], navigational bronchoscopy or mediastinoscopy.”

American College of Chest Physicians
The American College of Chest Physicians (ACCP) has offered a number of evidence-based guidelines on the use of EBUS-guided needle aspiration of pulmonary lesions for diagnosis of lung cancer and mediastinal staging of patients diagnosed with lung cancer (see Table 3). A separate guideline and expert panel report (2016) has addressed the technical aspects of EBUS-guided transbronchial needle aspiration and its use outside the setting of lung cancer.

Table 3. ACCP Guidelines on Use of EBUS to Diagnose and Stage Lung Cancer

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis of peripheral pulmonary nodules</strong></td>
<td></td>
</tr>
<tr>
<td>“2.3.2. In patients suspected of having lung cancer, who have extensive infiltration of the mediastinum based on radiographic studies and no evidence of extrathoracic metastatic disease (negative PET scan), it is recommended that the diagnosis of lung cancer be established by the least invasive and safest method (bronchoscopy with TBNA, endobronchial ultrasound-guided needle aspiration [EBUS-NA], endoscopic ultrasound-guided needle aspiration [EUS-NA], transthoracic needle aspiration [TTNA], or mediastinoscopy).”</td>
<td>1C</td>
</tr>
<tr>
<td>“3.3.2.1. In patients suspected of having lung cancer, who have a peripheral lung nodule, and a tissue diagnosis is required due to uncertainty of diagnosis or poor surgical candidacy, radial EBUS is recommended as an adjunct imaging modality.”</td>
<td>1C</td>
</tr>
<tr>
<td>Staging of the mediastinum in patients diagnosed with lung cancer</td>
<td></td>
</tr>
<tr>
<td>“4.4.4.3. In patients with high suspicion of N2,3 involvement, either by discrete mediastinal lymph node enlargement or PET uptake (and no distant metastases), a</td>
<td>1B</td>
</tr>
</tbody>
</table>
needle technique (endobronchial ultrasound [EBUS]-needle aspiration [NA], EUS-NA or combined EBUS/EUS-NA) is recommended over surgical staging as a best first test....

Remark: In cases where the clinical suspicion of mediastinal node involvement remains high after a negative result using a needle technique, surgical staging (eg, mediastinoscopy, video-assisted thoracic surgery [VATS], etc) should be performed.”

PET: positron emission tomography.

**U.S. Preventive Services Task Force Recommendations**
No U.S. Preventive Services Task Force recommendations for endobronchial ultrasound have been identified.

**Medicare National Coverage**
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

**Ongoing and Unpublished Clinical Trials**
Some currently unpublished trials that might influence this review are listed in Table 4.

**Table 4. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00559611</td>
<td>Endobronchial Ultrasound Versus Mediastinoscopy in Patients With Non-Small Cell Lung Cancer (NSCLC)</td>
<td>100</td>
<td>Oct 2018</td>
</tr>
<tr>
<td>NCT02719847</td>
<td>Additive Value of Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration (EBUS-TBNA) for Staging Non-Small Cell Lung Cancer in Patients Evaluated for Stereotactic Body Radiation Therapy</td>
<td>150</td>
<td>Mar 2020</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

**References**

Billing Coding/Physician Documentation Information

31652  Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with endobronchial ultrasound (EBUS) guided transtracheal and/or transbronchial sampling (eg, aspiration[s]/biopsy[ies]), one or two mediastinal and/or hilar lymph node stations or structures (New code 1/1/2016)
31653  Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with endobronchial ultrasound (EBUS) guided transtracheal and/or transbronchial sampling (eg, aspiration[s]/biopsy[ies]), 3 or more mediastinal and/or hilar lymph node stations or structures (New code 1/1/2016)
31654  Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with transendoscopic endobronchial ultrasound (EBUS) during bronchoscopic diagnostic or therapeutic intervention(s) for peripheral lesion(s) (List separately in addition to code for primary procedure[s]) (New code 1/1/2016)

ICD-10 Codes
C34.00- C34.92  Malignant neoplasm of bronchus and lung code range
C78.00- C78.39  Secondary malignant neoplasm of respiratory organs code range
D02.20- D02.22  Carcinoma in situ of bronchus and lung code range
D14.30- D14.32  Benign neoplasm of bronchus and lung code range
D38.1  Neoplasm of uncertain behavior of trachea, bronchus and lung
**D49.1** Neoplasm of unspecified behavior of respiratory system  
**J98.4** Other disorders of lung  

CPT 31620 deleted as of 12/31/15.

**Additional Policy Key Words**  
N/A

**Policy Implementation/Update Information**  
8/1/15  New Policy. Endobronchial ultrasound is medically necessary for diagnosis and staging of lung cancer when criteria are met.  
8/1/16  No policy statement changes.  
8/1/17  No policy statement changes.  
8/1/18  No policy statement changes.

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