BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Endobronchial Ultrasound for Diagnosis and Staging of Lung Cancer

Policy #: 576
Category: Surgical

Latest Review Date: October 2018
Policy Grade: B

Background:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

Description of Procedure or Service:

Endobronchial ultrasound (EBUS) is an imaging technique for adjunctive use with standard flexible bronchoscopy. It provides 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 facilitate navigation to distal regions of the lungs and biopsy of peripheral pulmonary nodules; especially suspected cancerous lesions. Another intended use of EBUS is to localize and facilitate biopsy of the mediastinal lymph nodes as part of staging for non-small-cell lung cancer. Both techniques primarily use transbronchial needle aspiration of lesions to obtain tissue samples.

Lung Cancer

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 three 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 computed tomography (CT) or a fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET) scan of the chest will 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 the least invasive (e.g., sputum cytology, thoracentesis if an accessible pleural effusion is present, fine-needle aspiration of a supraclavicular node). The diagnostic technique to evaluate suspected NSCLC is usually dictated by the apparent 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 ≤ 8 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. 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%. 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. 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, whether or not he or she can tolerate or will elect surgery. Thus, staging procedures may be based on noninvasive imaging (i.e., CT or PET, or combined PET-CT) methods, or 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.

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. 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.

Policy:

Effective for dates of service on and after February 23, 2015:

Blue Advantage will treat **endobronchial ultrasound guidance with transbronchial needle biopsy** as a **covered benefit** for the **evaluation of peripheral pulmonary lesions in patients with suspected lung cancer** when **BOTH** of the following criteria are met:

- Tissue biopsy of the peripheral pulmonary lesion is required for diagnosis; **AND**
- The peripheral pulmonary lesion is not accessible using standard bronchoscopic techniques

Blue Advantage will treat **endobronchial ultrasound guidance with transbronchial needle biopsy** as a **covered benefit** for **mediastinal staging in patients with diagnosed lung cancer** when **ALL** of the following criteria are met:

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

Blue Advantage will treat **endobronchial ultrasound** as a **non-covered benefit for diagnosis and staging of lung cancer when the above criteria are not met**.

Blue Advantage will treat **endobronchial ultrasound for all other indications** as a **non-covered benefit** and as **investigational**.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue

Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

The most recent literature review was updated through July 12, 2018.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Diagnosis of Lung Cancer

Clinical Context and Test Purpose

The purpose of endobronchial ultrasound–guided transbronchial needle aspiration (EBUS-TBNA) in patients who have pulmonary lesions and suspected lung cancer is to isolate and biopsy the lesions in order to diagnose and stage detected cancers.

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 most significant 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 (e.g., sensitivity, specificity) and potential harms of testing (e.g., 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 PPLs were identified or when a prior less invasive test was inconclusive.

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

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

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). 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. 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 was 2.8%. There were a total of 160 reported complications, 82 pneumothoraxes, 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).

A systematic review and meta-analysis by Ye et al (2017) focused on fluoroscopy guidance. Reviewers identified 4 studies (total N=461 patients). In a pooled analysis, the overall diagnostic accuracy was significantly higher in the EBUS transbronchial biopsy (TBB) group than in the conventional TBB group (odds ratio, 2.21; 95% CI, 1.42 to 3.44; p<0.001).

In 2018, Han et al published a systematic review and meta-analysis comparing radial EBUS and CT-guided transthoracic needle biopsy for the diagnosis of pulmonary lesions 3 centimeters or smaller. Twenty-four studies were identified, 9 for EBUS (813 procedures) and 15 for CT (3463 procedures). The pooled diagnostic yield was 75% for EBUS and 93% for CT. For pulmonary lesions 2 centimeters or smaller, the pooled diagnostic yield was 66% and 92% for EBUS and CT, respectively. Complications were less common for EBUS than for CT; only 10 cases of pneumothorax were reported for EBUS while 660 were reported for CT. The review was limited by the following: (1) all EBUS studies were conducted in the same country, (2) study quality was not uniform, (3) different imaging tools were used in the CT group, and (4) possible study selection bias.

ACCP has published 2 reviews. The ACCP reviews indicated that, in general, most of the evidence comes from small retrospective or prospective studies, plus 2 randomized controlled trials (RCTs).

Tables 1 and 2 summarize the characteristics and results of systematic reviews assessing the clinical validity studies using EBUS to diagnose lung cancer.

Table 1. Characteristics of Systematic Reviews Assessing the Clinical Validity of R-EBUS for Diagnosing Lung Cancer

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Han et al (2018)	2000-2016	24	Patients with small PLs	4249 (24-795)	Prospective, Retrospective	NR
Ali et al (2017)	2002-2016	57	Patients receiving R-EBUS for diagnosing PPLs	7872 lesions (20-815 lesions)	Prospective, Retrospective	NR
Ye et al (2017)	2004-2014	4	Patients with PPLs referred for diagnostic bronchoscopy or R-EBUS- guided bronchoscopy	461 (92-145)	Prospective, Retrospective	NR

NR: not reported; PL: pulmonary lesion; PPL: peripheral pulmonary lesion; R-EBUS: radial endobronchial ultrasound.

Table 2. Results of Systematic Reviews Assessing of Radial EBUS for Diagnosing Lung Cancer

Study	Diagnostic Yield, %	Diagnostic Yield PLS≤2cm, %	Overall Complication Rate, %	Pneumothorax, n/N(%)
Han et al (2018)				
EBUS	75	66		10/815 (1.23)
95% CI	69 to 80	55 to 76		
Computed Tomography	93	92		660/3434 (19.23)
95% CI	90 to 96	88 to 95		
Ali et al (2017)				
	70.6	60.5	2.8	
95% CI	68 to 73.1	56.6 to 64.4		
Ye et al (2017)				
Odds Ratio	2.183	5.045		
95% CI	1.368 to 3.485	2.063 to 12.337		
p	0.001	<0.001		

CI: confidence interval; EBUS: endobronchial ultrasound.

Randomized Controlled Trials

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 or 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 two 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).

Two small randomized trials were conducted that evaluated EBUS: one compared its use with TBB and the other, with conventional fluoroscopy-guided flexible bronchoscopy. A RCT by Fielding et al (2012) aimed to determine the diagnostic, complication, and patient tolerability rates of EBUS with a guide sheath EBUS 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 guide sheath EBUS biopsy or CT-guided biopsy. Diagnostic sensitivity was 67% (22/33 cases) for guide sheath EBUS biopsy 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, 4 had crossover EBUS biopsy, 3 of which were diagnostic. When both initial and crossover procedures were evaluated, sensitivity for malignancy was 17 (74%) of 23 for EBUS biopsy and 23 (88%) of 26 for CT-guided biopsy (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 biopsy cases, for lesions with an air bronchogram, sensitivity was 89%. Pneumothorax and intercostal

catheter insertion were 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 3 after guided sheath EBUS biopsy.

Tables 3 and 4 summarize the characteristics and results of RCTs assessing the clinical validity studies using EBUS to diagnose lung cancer.

Table 3. Characteristics of RCTs Assessing the Clinical Validity of EBUS for Diagnosing Lung Cancer

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Fielding et al (2012)	Australia	1	2007-2011	Patients with PPLs >1 cm	EBUS-GS (n=33)	CT-guided biopsy (n=31)
Paone et al (2005)	Italy	1	2001-2003	Patients with PPLs	EBUS-TBB (n=87)	TBB (n=119)

CT: computed tomography; EBUS-GS: EBUS-guide sheath; EBUS-TBB: endobronchial ultrasound-driven transbronchial biopsy; PPL: peripheral pulmonary lesion; RCT: randomized controlled trial; TBB: transbronchial biops

Table 4. Results of RCTs Assessing the Clinical Validity of EBUS for Diagnosing Lung Cancer

				Sensitivity for PPLs <2	Sensitivity for PLLs	Diagnostic Yield for PPLs	Pneumothorax,
Study	Sens, %	Spec, %	Acc, %	cm, %	<3 cm, %	<2 cm, %	n/N (%)
Fielding et al (2012)							
EBUS-GS	74					50	3 (8.1)
CT-guided biopsy	88					80	10 (30.3)
p	NR					0.05	0.02
Paone et al (2005)							
EBUS-TBB	78.7	100	85	71	75		
TBB	55.4	100	69	23.3	30.7		
p	0.004	NR	0.007	<0.001	0.001		

Acc: accuracy; CI: confidence interval; CT: computed tomography; EBUS-GS: guide sheath endobronchial ultrasound; EBUS-TBB: endobronchial ultrasound-driven transbronchial biopsy; PPL: peripheral pulmonary lesion; RCT: randomized controlled trial; Sens: sensitivity; Spec: specificity.

The purpose of the gaps tables (see Tables 5 and 6) is to display notable gaps identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement

Table 5. Relevance Gaps

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Fielding et al (2012)					1. Follow-up duration not clear; perhaps 1-3 d
Paone et al (2005)			5. Complications (e.g., pneumothorax, chest tube insertions) not reported		1. Follow-up duration not reported

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. [a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 6. Study Design and Conduct Gaps

Study	Allocation	Blinding	Selective Reporting	Data Completeness	Power	Statistical
Fielding et al (2012)	1.Unclear if allocation was concealed from patients	1.No blinding was performed		2.7/64 (10.9%) did not complete the study		
Paone et al (2005)	1. Unclear if allocation was concealed from patients	1. Physicians performing procedures could not be blinded		2.15/221 (6.8%) patients lost to follow up and others unavailable, making treatment groups uneven (87 vs 119)		

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
a Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
b Blinding key: 1. Not blinded to results of reference or other comparator tests.
c Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
d Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
e Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
f Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are interventional studies, the preferred evidence would be from RCTs.
No RCTs or other controlled studies reporting on longer term health outcomes (i.e., mortality) were identified.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

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 (i.e., has a similar benefit to alternative techniques with less harm).

Section Summary: Diagnosis of Lung Cancer
Evidence from 3 meta-analyses and 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 (e.g., 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 purpose of EBUS-TBNA in patients who have lung cancer is to biopsy the lesions in order to stage the disease.

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 (e.g., sensitivity, specificity) and potential harms of testing (e.g., 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.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

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.

El-Osta et al (2018) published a meta-analysis evaluating EBUS-TBNA for nodal staging of non-small-cell lung cancer with radiologically normal mediastinum. Thirteen studies were included, with a total of 1905 patients (range, 57-258 patients). Sensitivity was 49.5%, negative predictive value was 93.0%, and diagnostic odds ratio was 5.069. The meta-analysis was limited by (1) major heterogeneity across included studies, (2) publication bias, (3) a lack of essential data in some studies, and (4) size, location, and histology of tumor were not considered due to inconsistent reporting.

Tables 7 and 8 summarize the characteristics and results of systematic reviews assessing the clinical validity studies using EBUS to stage lung cancer.

Table 7. Characteristics of Systematic Reviews Assessing the Clinical Validity of EBUS-TBNA for Staging Lung Cancer

Study	Dates	Trials	Participants	N (Range)	Design	Duration
El-Osta et al (2018)	2006-2017	13	Patients receiving EBUS-TBNA to detect NSCLC with no radiologic mediastinal involvement	1905 (57-258)	Prospective, Retrospective	**NR**
Ge et al (2015)	2003-2014	16	Patients with suspected or confirmed lung cancer	1914 (18-216)	Prospective, Retrospective	**NR**

EBUS-TBNA: endobronchial ultrasound–guided transbronchial needle aspiration; NR: not reported; NSCLC: non-small-cell lung cancer.

Table 8. Results of Systematic Reviews Assessing the Clinical Validity of EBUS-TBNA for Staging Lung Cancer

Study	Sensitivity, %	Complications, n/N (%) NPV, %	Diagnostic Odds Ratio
El-Osta et al (2018)			
EBUS-TBNA	49.5	93.0	5.069
95% CI	36.4 to 62.6	90.3 to 95.0	4.212 to 5.925
Ge et al (2015)			
EBUS-TBNA	0.83	4/999 (0.4)	
95% CI	0.79 to 0.87	NR	
Mediastinoscopy	0.86	17/915 (1.9)	
95% CI	0.82 to 0.90	NR	

CI: confidence interval; NPV: negative predictive value; NR: not reported.

In 2013, ACCP published a systematic review conducted by Silvestri et al (2013), with pooled analyses that provided a comprehensive resource for noninvasive and invasive methods to stage the mediastinum, including EBUS-based techniques. Table 9 summarizes the pooled test

performance characteristics for a number of staging procedures drawn from the ACCP evidence review.

Table 9. Pooled Performance Characteristics of Techniques Used to Stage the Mediastinum in Patients with Lung Cancer

Technique	N	Cancer Prevalence, %	Sensitivity, %	Specificity, %	PPV, %	NPV, %
CT with contrast enhancement	7368	30	55	81	58	83
PET alone	4105	28	80	88	75	91
PET-CT	2014	22	62	90	63	90
Traditional mediastinoscopy	9267	33	78	(100)[a]	(100)[a]	91
Video-assisted mediastinoscopy	995	31	89	(100)[a]	(100)[a]	92
Mediastinal lymphadenectomy	386	34	81	(100)[a]	(100)[a]	91
Video-assisted thoracic surgery	246	63	99	(100)[a]	(100)[a]	96
Transthoracic needle aspiration (percutaneous)	215	84	94	(100)[a]	(100)[a]	NR[b]
TBNA	2408	81	78	(100)[a]	(100)[a]	77
Esophageal EUS-guided needle aspiration	2443	58	89	(100)[a]	(100)[a]	86
Real-time EBUS-TBNA	2756	58	89	(100)[a]	(100)[a]	91

CT: computed tomography; EBUS-TBNA: endobronchial ultrasound–guided transbronchial needle aspiration; EUS: endoscopic ultrasound; NPV: negative predictive value; NR: not reported; PET: positron emission tomography; PPV: positive predictive value.
a. Technically, the specificity and positive predictive value cannot be assessed in those studies reporting 100% values because a positive result was not followed by an additional criterion standard test.
b. All patients had mediastinal disease.

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 (e.g., 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.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs or other controlled studies were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

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 reviews and meta-analyses 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.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

National Comprehensive Cancer Network guidelines on non-small-cell lung cancer (v.6.2018) state:

"The least invasive biopsy with the highest yield is preferred as the first diagnostic study…. Patients with peripheral (outer one-third) nodules may benefit from navigational bronchoscopy, radial EBUS [endobronchial ultrasound], or transthoracic needle aspiration (TTNA)…. Patients with suspected nodal disease should be biopsied by EBUS, 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 cancer1 and mediastinal staging of patients diagnosed with lung cancer (see Table 1). 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 1. Guidelines on Use of Endobronchial Ultrasound to Diagnose and Stage Lung Cancer

Recommendation	Grade
Diagnosis of peripheral pulmonary nodules	
"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)."	1C
"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."	1C
Staging of the mediastinum in patients diagnosed with lung cancer	
"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 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 (e.g., mediastinoscopy, video-assisted thoracic	1B

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.

Key Words:
Endobronchial Ultrasound, EBUS, Transbronchial needle biopsy, TBNA, lung cancer, Olympus Medical Systems EU-M60 EUS Exera, EVIS EXERA Bronchofibervideoscope, ATL HDI 5000 Ultrasound System, Olympus BF type UC160F-OL8 bronchoscope, ALOKA SSD-Alpha 5/10 Ultrasound System, Olympus Medical Systems XBF-UC180F-DT8 Ultrasonic Bronchofibervideoscope, PENTAX Ultrasound Video bronchoscope EB-1970UK + HI VISION Preirus endoscopic ultrasound, Medi-Globe SonoTip® II EBUS-TBNA Needle System, Cook EchoTip®, Medi-Globe SonoTip® Pro and Pro Flex EBUS-TBNA

Approved by Governing Bodies:
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 2.

Table 2. FDA-Cleared Instruments Used to Perform EBUS-TBNA

Device Name	Manufacture	Date Cleared	510(k)	Indications
EVIS EXERA Bronchofibervideoscope, Olympus BF type UC160F-OL8 bronchoscope and its diagnostic ultrasound transducer	Olympus Medical Systems	Aug 2004	K042140	To provide real-time endoscopic US imaging and US-guided FNA, including the upper airways and tracheobronchial tree
EU-M60 EUS EXERA Endoscopic Ultrasound Center	Olympus Medical Systems	Dec 2004	K04327	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
XBF-UC180F-DT8 Ultrasonic Bronchofibervideoscope and the ALOKA SSD-Alpha 5/10 Ultrasound System	Olympus Medical Systems	Jul 2007	K070983	To provide real-time endoscopic US imaging and US-guided FNA including the upper airways and tracheobronchial tree
SonoTip® II EBUS-TBNA Needle System	Medi-Globe	May 2009	K091257	For US-guided FNA of submucosal and extraluminal lesions of the tracheobronchial tree
EchoTip® Ultra High Definition Endobronchial Ultrasound Needle	Cook Medical	Jan 2010	K093195	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

PENTAX Ultrasound Video Bronchoscope EB-1970UK + HI VISION Preirus endoscopic ultrasound	PENTAX Medical	Apr 2014	K131946	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
SonoTip® Pro and Pro Flex EBUS-TBNA Needle System	Medi-Globe	May 2014	K133763	Intended for US-guided FNA of submucosal and extraluminal lesions of the tracheobronchial tree and gastrointestinal tract (e.g., lymph nodes, abnormal tissue in the mediastinum)
Expect™ Pulmonary Endobronchial Ultrasound Transbronchial Aspiration Needle	Boston Scientific	Nov 2015	K151315	For use with EBUS endoscopes for US-guided FNA of the submucosal and extramural lesions of the tracheobronchial tree

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

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply.
FEP: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:

CPT Codes:

31652 Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with endobronchial ultrasound (EBUS) guided transtracheal and/or transbronchial sampling (e.g. aspiration[s]/biopsy[ies], one or two mediastinal and/or hilar lymph node stations or structures. **(Effective 01/01/2016)**

31653 with endobronchial ultrasound (EBUS) guided transtracheal and/or transbronchial sampling (e.g. aspiration[s]/biopsy[ies], 3 or more mediastinal and/or hilar lymph node stations or structures. **(Effective 01/01/2016)**

31654 with transendoscopic endobronchial ultrasound (EBUS) during bronchoscopic diagnostic or therapeutic intervention(s) for peripheral lesion(s) **(Effective 01/01/2016)**

Previous Coding:

31620 Endobronchial ultrasound (EBUS) during bronchoscopic diagnostic or therapeutic intervention(s) (List separately in

addition to code for primary procedure[s]) (**Deleted effective 01/01/2016**)

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