7.01.122	Electromagnetic Navigation Bronchoscopy		
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Section:	7.0 Surgery	**Page:**	Page 1 of 17

Policy Statement

Electromagnetic navigation bronchoscopy is considered **investigational** for **any** of the following procedures:

- For use with flexible bronchoscopy for the diagnosis of pulmonary lesions and mediastinal lymph nodes
- For the placement of fiducial markers

Policy Guidelines

Coding:
There are specific CPT codes that describe electromagnetic navigation bronchoscopy procedures:

- **31626:** Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with placement of fiducial markers, single or multiple
- **31627:** Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with computer-assisted, image-guided navigation (List separately in addition to code for primary procedure[s])

***Note**: Code 31627 is an add-on used with CPT codes 31615, 31622-31631, 31635, 31636, and 31638-31643. Code 31627 includes 3-dimensional reconstruction, so it should not be reported with codes 76376 and 76377.

Description

Electromagnetic navigation bronchoscopy (ENB) is intended to enhance standard bronchoscopy by providing a 3-dimensional roadmap of the lungs and real-time information about the position of the steerable probe during bronchoscopy. The purpose of ENB is to allow navigation to distal regions of the lungs, so that suspicious lesions can be biopsied and to allow fiducial markers placement.

Related Policies

- Endobronchial Ultrasound for Diagnosis and Staging of Lung Cancer
- Molecular Testing in the Management of Pulmonary Nodules
- Stereotactic Radiosurgery and Stereotactic Body Radiotherapy

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

In 2004, the superDimension/Bronchus™ inReach™ system (superDimension) was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. The system includes planning and navigation software, a disposable extended working channel, and a disposable steerable guide. The FDA-cleared indication is for displaying images of the tracheobronchial tree that aids physicians in guiding endoscopic tools in the pulmonary tract. The device is not intended as an endoscopic tool; it does not make a diagnosis; and it is not approved for pediatric use. As of June 2016, the current version of the product is the Medtronic SuperDimension Navigation System (Medtronic).

In 2009, the ig4™ EndoBronchial system (Veran Medical) was cleared for marketing by the FDA through the 510(k) process. The system was considered to be substantially equivalent to the inReach™ system and is marketed as the SPiN Thoracic Navigation System™.

In April 2018, LungVision (Body Vision Medical) was cleared for marketing by the FDA through the 510(k) process (K172955).). The FDA determined that this device was substantially equivalent to existing devices for use "segment previously acquired 3D CT [computed tomography] datasets and overlay and register these 3D segmented data sets with fluoroscopic live X-ray images of the same anatomy in order to support catheter/device navigation during pulmonary procedure". FDA product code: EOQ.

Several other navigation software-only systems have been cleared for marketing by the FDA through the 510(k) process. They include:

- In 2008, the LungPoint® virtual bronchoscopic navigation (VPN) system (Broncus Technologies).
- In 2010, the bf-NAVI VPN system (Emergo Group).

FDA product codes: JAK, LLZ.

Rationale

Background
Pulmonary Nodules
Pulmonary nodules are identified on plain chest radiographs, or chest computed tomography scans. Although most nodules are benign, some are cancerous, and early diagnosis of lung cancer is desirable because of the poor prognosis when it is diagnosed later.

Diagnosis
The method used to diagnose lung cancer depends on a number of factors, including lesion size, shape, location, as well as the clinical history and status of the patient. 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 diagnosing malignant disease, but none of the methods is ideal. Sputum cytology is the least invasive approach. Reported sensitivity rates are relatively low and vary widely across studies; sensitivity is 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 an established approach to evaluate 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 (<1.5 cm in diameter), the sensitivity may be as low as 10%. The diagnostic accuracy of transthoracic needle aspiration for solitary pulmonary nodules tends to be higher than that of bronchoscopy; the sensitivity and specificity are both approximately 94%. A disadvantage of transthoracic needle aspiration is that a pneumothorax develops in 11% to 25% of patients, and 5% to 14% require insertion of a chest tube. Positron emission tomography scans are also highly sensitive for evaluating

pulmonary nodules yet may miss lesions less than 1 cm in size. A lung biopsy is the criterion standard for diagnosing pulmonary nodules but is an invasive procedure.[1-3]

Advances in technology may increase the yield of established diagnostic methods. Computed tomography scanning equipment can be used to guide bronchoscopy and bronchoscopic transbronchial needle biopsy but have the disadvantage of exposing the patient and staff to radiation. Endobronchial ultrasound by radial probes, previously used in the perioperative staging of lung cancer, can also be used to locate and guide sampling of peripheral lesions. Endobronchial ultrasound is reported to increase the diagnostic yield of flexible bronchoscopy to at least 82%, regardless of lesion size or location.[1]

Marker Placement

Another proposed enhancement to standard bronchoscopy is electromagnetic navigation bronchoscopy. Electromagnetic navigation bronchoscopy enhances standard bronchoscopy by providing a 3-dimensional roadmap of the lungs and real-time information about the position of the steerable probe during bronchoscopy. The purpose of electromagnetic navigation bronchoscopy is to allow navigation to distal regions of the lungs. Once the navigation catheter is in place, any endoscopic tool can be inserted through the channel in the catheter to the target. This includes insertion of transbronchial forceps to biopsy the lesion. Also, the guide catheter can be used to place fiducial markers. Markers are loaded in the proximal end of the catheter with a guide wire inserted through the catheter.

Literature Review

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.

Electromagnetic Navigation Bronchoscopy to Aid Diagnosing Pulmonary Lesions

Clinical Context and Test Purpose

The purpose of using electromagnetic navigation bronchoscopy (ENB) with flexible bronchoscopy in patients who have suspicious peripheral pulmonary lesions is to confirm a diagnosis of lung cancer and to initiate treatment.

The question addressed in this evidence review is: Does use of ENB with flexible bronchoscopy improve health outcomes in individuals with suspicious peripheral pulmonary lesions?

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

Patients

The relevant population of interest is individuals with suspicious peripheral pulmonary lesions.

Interventions

The test being considered is ENB with flexible bronchoscopy.

Comparators

The following tests are currently being used: flexible bronchoscopy only, computed tomography (CT) –guided needle biopsy, and endobronchial ultrasound (EBUS) with flexible bronchoscopy.

Outcomes
The general outcomes of interest are the accurate identification of cancerous lesions and reduction in disease-related morbidity and mortality. Potentially harmful outcomes are those resulting from false-positive or false-negative test results. False-positive test results can lead to unnecessary treatment. False-negative test results can lead to failure to initiate therapy.

Timing
The time frame for evaluating performance of the test varies the time from the initial CT scan to an invasive diagnostic procedure to up to 2 years, which would be the typical follow-up needed for some lung nodules.

Setting
ENB is administered in the outpatient setting by cancer specialists.

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 systematic review of the literature on the diagnostic yield and safety of ENB was published by Zhang et al (2015).[4] Reviewers updated a systematic review by Gex et al (2014)[5] with newer studies. The Zhang review included prospective and retrospective studies of patients with peripheral nodules confirmed by a radiographic evaluation that had more than 10 patients and reported the diagnostic yield of ENB for peripheral lung nodules or lesions. Seventeen studies with 1161 lung nodules or lesions in 1106 patients met the eligibility criteria. Reviewers used the Quality Assessment of Diagnostic Accuracy Studies tool to evaluate the methodologic quality of selected studies, and overall quality was poor. None compared ENB with surgery, and, in almost all studies, reviewers reported it was uncertain whether the selected patients were representative of the population that would undergo ENB in an actual clinical setting.

Results of pooled analyses are reported in Table 1. True-positive findings are those in which ENB biopsy yielded a definitive malignant diagnosis. True negatives were defined as benign findings on ENB biopsy, confirmed by follow-up procedures. The Gex et al (2014) systematic review, which included 15 studies (total N=971 patients), reported somewhat different outcomes (see Table 1).

Table 1. Meta-Analysis of Electromagnetic Navigation Bronchoscopy Performance

Outcomes	Rate (95% Confidence Interval), %	
	Zhang et al (2015)[4]	**Gex et al (2014)[5]**
Sensitivity for malignancy	82 (79 to 85)	71.1 (64.6 to 76.8)
Specificity for malignancy	100 (98 to 100)	
Positive likelihood ratio	18.67 (9.04 to 38.55)	
Negative likelihood ratio	0.22 (0.15 to 0.32)	
Diagnostic odds ratio	97.36 (43.75 to 216.69)	
Navigation success		97.4 (95.4 to 98.5)
Diagnostic yield		64.9 (59.2 to 70.3)
Accuracy for malignancy		78.6 (72.8 to 83.4)
Negative predictive value		52.1 (43.5 to 60.6)
Negative predictive value of intermediate benign results		78.5 (53.1 to 92.1)

As reported by Gex, whereas the navigation success rate using ENB was generally very high, the diagnostic yield and NPV were relatively low. Moreover, in Zhang et al (2015), the positive likelihood ratio was large, but the negative likelihood ratio (0.22) suggested only a small decrease in the likelihood of disease following the test. (Zhang did not conduct a pooled analysis of diagnostic yield.) As stated at the beginning of this section, the evidence of particular interest is whether the test can correctly identify patients who do not have malignancy (i.e., high NPV or low negative likelihood ratio). Studies included in the meta-analyses were limited because surgical biopsy was not used as the criterion standard; it is unclear whether follow-up was long enough to confirm ENB diagnoses.

The pneumothorax rate following ENB was 5.9% in Zhang et al (2015) and 3.1% in Gex et al (2014) (1.6% required chest tube placement for pneumothorax). Zhang stated that 2 of the pneumothoraxes were induced by transbronchial biopsy and the others were unrelated to the ENB procedure.

Randomized Controlled Trials

Eberhardt et al (2007) published the only randomized controlled trial (RCT) to evaluate ENB for the diagnosis of pulmonary nodules.[6] This trial used surgical biopsy as a criterion standard confirmation of diagnosis. Patients were randomized to ENB only, EBUS only, or the combination of ENB and EBUS. Whereas ENB is designed to help navigate to the target but cannot visualize the lesion, EBUS is unable to guide navigation but enables direct visualization of the target lesion before the biopsy. The trial included 120 patients with evidence of peripheral lung lesions or solitary pulmonary nodules and who were candidates for elective bronchoscopy or surgery. In all 3 arms, only forceps biopsy specimens were taken, and fluoroscopy was not used to guide the biopsies. The primary outcome was diagnostic yield, defined as the ability to yield a definitive diagnosis consistent with clinical presentation. If transbronchial lung biopsy did not provide a diagnosis, patients were referred for surgical biopsy. The mean size of the lesions was 26 mm.

Two patients who did not receive a surgical biopsy were excluded from the final analysis. Of the remaining 118 patients, 85 (72%) had a diagnostic result via bronchoscopy, and 33 required a surgical biopsy. The diagnostic yield by intervention group was 59% (23/39) with ENB only, 69% (27/39) with EBUS only, and 88% (35/40) with ENB plus EBUS; the yield was significantly higher in the combined group. The NPV for malignant disease was 44% (10/23) with ENB only, 44% (7/16) with EBUS only, and 75% (9/12) with combined ENB and EBUS. Note that the number of cases was small, and thus the NPV is an imprecise estimate. Moreover, the trialists stated that the yield in the ENB only group was somewhat lower than in other studies; they attributed this to factors such as the use of forceps for biopsy (rather than forceps and endobronchial brushes, which would be considered standard) and/or an improved diagnosis using a criterion standard. The pneumothorax rate was 6%, which did not differ significantly across the 3 groups.

Uncontrolled Studies

Key uncontrolled studies not included in the meta-analyses are described next, focusing on prospective multicenter studies.

Khandhar et al (2017) published a preplanned 1-month interim analysis of the NAVIGATE study.[7] NAVIGATE is a prospective multicenter (N=37) analysis of outcomes in patients who received ENB in U.S. and European centers. The study has broad inclusion criteria, including all adults who were candidates for ENB based on physician discretion, guideline recommendations, and institutional protocol. Participating physicians needed to have previous experience with ENB. The 1-month analysis of the first 1000 patients focused on safety outcomes; the primary end point was pneumothorax. Most of the first 1000 patients (n=964 [96%]) had ENB for evaluation of lung lesions. Any grade pneumothorax occurred in 49 (4.9%) of 1000 patients and pneumothorax of grade 2 or higher occurred in 32 (3.2%) patients. The rate of bronchopulmonary hemorrhage was 2.3%. There were 23 deaths by the 1-month follow-up, none was considered related to the ENB device, but one was deemed related to general anesthesia complications. Diagnostic

outcomes will be reported at the 12- and 24-month analyses; the authors noted that the follow-up time was insufficient at 1 month to verify true positives and true negatives.

The American College of Chest Physicians has established a registry of bronchoscopies performed for the diagnosis of peripheral lung nodules or masses to evaluate the diagnostic yield of different approaches in clinical practice, which may differ from findings in the clinical trial setting. Data from this registry, called AQuiRE (American College of Chest Physicians Quality Improvement Registry, Evaluation, and Education), were published by Ost et al (2016).[8] The primary outcome of this analysis was the diagnostic yield of bronchoscopy, defined as the ability to obtain a specific malignant or benign diagnosis. Bronchoscopy was diagnostic in 312 (53.7%) of 581 peripheral lesions. Diagnostic yield was 63.7% for bronchoscopy with no EBUS or ENB, 57.0% with EBUS alone, 38.5% with ENB alone, and 47.1% with ENB plus EBUS. Complications occurred in 13 (2.2%) of 591 patients. Pneumothorax occurred in 10 (1.7%) patients, 6 of whom required chest tubes. Pneumothorax rates were not reported for bronchoscopy with and without ENB.

Two prospective observational studies have examined the sequential use of ENB; EBUS was used initially, with the addition of ENB when EBUS failed to reach or diagnose the lesion. A study by Chee et al (2013) included 60 patients with peripheral pulmonary lesions.[9] Patients either had a previous negative CT-guided biopsy or did not have one due to technical difficulties. An attempt was first made to identify the lesion using peripheral EBUS and, if not identified, then an ENB system was used. Nodules were identified by EBUS alone in 45 (75%) of 60 cases. ENB was used in 15 (25%) cases, and in 11 (73%) of these cases the lesion was identified. Peripheral EBUS led to a diagnosis in 26 cases and ENB in an additional 4 cases, for a total diagnostic yield of 30 (50%) of 60 cases. In this study, the extent of improved diagnosis with ENB over EBUS alone was not statistically significant (p=0.125). The rate of pneumothorax was 8% (5/60 patients); the addition of ENB did not alter the pneumothorax rate.

Steinfort et al (2016) published findings on 236 patients with 245 peripheral pulmonary lesions who underwent bronchoscopy.[10] EBUS and virtual bronchoscopy were used initially, and ENB was performed when EBUS could not locate the lesion or when rapid onsite cytologic evaluation could not be successfully performed. A total of 188 (77%) of 245 lesions were localized with EBUS and virtual bronchoscopy. ENB was used in the remaining 57 cases, and lesion localization was achieved in an additional 17 cases (29.8% of those undergoing ENB). The addition of ENB increased the localization rate from 77% to 85.3%.

The rapid onsite cytologic evaluation was diagnostic for 138 (71%) of the 188 lesions reached with EBUS and virtual bronchoscopy. Thus, the diagnostic yield of EBUS plus virtual bronchoscopy was 134 (54.7%) of 245 lesions. An additional 9 (15.8%) of 57 ENB procedures were diagnostic, improving the overall diagnostic yield from 54.7% to 58.4%. However, the authors noted that, in only 4 of the 9 procedures, was the diagnostic outcome attributable to the accurate localization of the image with ENB. The authors did not conduct statistical analyses of diagnostic yield with EBUS vs EBUS with ENB.

Section Summary: Clinically Valid

The evidence on ENB for diagnosis of pulmonary lesions includes meta-analyses, an RCT, and a number of observational studies. A recent meta-analysis, which included 17 studies, reported a large pooled positive likelihood ratio but a modest negative likelihood ratio. Similarly, a 2014 meta-analysis with 15 studies found that navigation success was high, but diagnostic yield and NPV were relatively low. A high NPV or a small negative likelihood ratio is desirable because it indicates that patients who test negative would not need additional interventions. Both meta-analyses judged the quality of published studies to be low. The single RCT found higher diagnostic yield when both ENB and EBUS were used compared with either intervention alone but did not include a group without either ENB or EBUS.

Most observational studies had small sample sizes. Two large prospective multicenter uncontrolled studies. An analysis of more than 500 patients included in the AQuiRE registry found

a diagnostic yield of ENB that was lower than in other studies, and lower than bronchoscopy without ENB or EBUS. An interim analysis of the NAVIGATE study focused on safety outcomes in the first 1000 patients at 1 month. The rate of pneumothorax of any grade was 4.9%, and the rate of grade 2 or higher was 3.2%. The data are also insufficient to identify potential patient selection criteria. The meta-analyses identified lack of clear selection criteria as a key potential bias in the published literature.

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 were identified that evaluated health outcomes for the use of ENB.

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.

Because the clinical validity of ENB cannot be established, a chain of evidence cannot be constructed.

Section Summary: Electromagnetic Navigation Bronchoscopy to Aid Diagnosing Pulmonary Lesions
The most recent meta-analysis, which included 17 studies, reported a large pooled positive likelihood ratio but a modest negative likelihood ratio. Similarly, a 2014 meta-analysis with 15 studies found that navigation success was high, but diagnostic yield and NPV were relatively low. A high NPV or a small negative likelihood ratio is desirable because it indicates that patients who test negative would not need additional interventions. Both meta-analyses judged the quality of published studies to be low. The single RCT found higher diagnostic yield when both ENB and EBUS were used compared with either intervention alone, but did not include a group without either ENB or EBUS.

Most of the observational studies had small sample sizes. There are 2 large prospective multicenter uncontrolled studies. An analysis of more than 500 patients included in the AQuiRE registry found a diagnostic yield of ENB that was lower than in other studies, and lower than bronchoscopy without ENB or EBUS. An interim analysis of the NAVIGATE study focused on safety outcomes in the first 1000 patients at 1 month. The rate of pneumothorax of any grade was 4.9% and the rate of grade 2 or higher was 3.2%.

The data are also insufficient to identify potential patient selection criteria. The meta-analyses identified lack of clear selection criteria as a key potential bias in the published literature. A chain of evidence cannot be constructed to support a finding that ENB improves health outcomes for those with pulmonary lesions.

ENB to Aid in the Diagnosis of Mediastinal Lymph Node(S)
Clinical Context and Test Purpose
The purpose of using ENB with flexible bronchoscopy in patients who have enlarged mediastinal lymph nodes (MLNs) is to inform a decision whether to initiate treatment for lung cancer.

The question addressed in this evidence review is: Does use of ENB improve health outcomes in individuals with enlarged MLNs?

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

Patients
The relevant population of interest is individuals with enlarged MLNs.

Comparators
The following tests are currently being used: flexible bronchoscopy only, CT-guided needle biopsy, and EBUS with flexible bronchoscopy.

Outcomes
The general outcomes of interest are the accurate identification of MLNs and reduction in disease-related morbidity and mortality. Potentially harmful outcomes are those resulting from false-positive or false-negative test results. False-positive test results can lead to unnecessary treatment. False-negative test results can lead to failure to initiate.

Timing
The time frame for outcomes measures varies from short-term development of invasive procedure-related complications to long-term procedure-related complications, disease diagnosis, or overall survival.

Setting
ENB is administered in the outpatient setting by cancer specialists.

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).

Randomized Controlled Trials
One RCT was identified on ENB for the diagnosis of MLN. The trial, reported by Diken et al (2015), included 94 patients with mediastinal lymphadenopathy with a short axis greater than 1 cm on CT and/or increased uptake on positron emission tomography.[11] Patients were randomized to conventional transbronchial needle aspiration (TBNA; n=50) or ENB-guided TBNA (n=44). All samples were evaluated by a blinded cytopathologist. Sampling success was defined as the presence of lymphoid tissue in the sample, and diagnostic success was the ability to make a diagnosis using the sample. Diagnoses were confirmed by one of several methods such as mediastinoscopy, thoracotomy, or radiologic follow-up. Final diagnoses were sarcoidosis (n=29), tuberculous lymphadenitis (n=12), non-small-cell lung cancer (n=20), small-cell lung cancer (n=12), benign lymph node (n=5), and others (n=5). Sampling success was 82.7% in the ENB group and 51.6% in the conventional TBNA group ($p<0.001$); diagnostic success was 72.8% in the ENB group and 42.2% in the conventional TBNA group ($p<0.001$). When samples were stratified by MLN size, both sampling success and diagnostic success were significantly higher with ENB than with conventional TBNA in MLNs 15 mm or less and more than 15 mm. The trialists noted that, although EBUS-guided TBNA has been shown to have higher diagnostic yields than conventional TBNA, EBUS was not compared with ENB because it was not available at the institution in Turkey conducting the study. No pneumothorax or other major adverse events were reported for either group.

Uncontrolled Studies
No large uncontrolled studies were identified that focused on ENB for the diagnosing of MLN. A series by Wilson et al (2007) included both patients with suspicious lung lesions and enlarged MLN.[12] There was no consistent protocol for confirming the diagnosis, although the authors stated that most patients were followed for confirmation of diagnosis. ENB was used to locate, register, and navigate to the lesions. Once navigation was completed, fluoroscopic guidance was used to verify its accuracy and to aid in the biopsy or TBNA. Sixty-seven (94%) of 71 MLN were successfully reached, and tissue samples for biopsy were obtained from all of them. The primary study outcome was the diagnostic yield on the day of the procedure; this was obtained for 64 (96%) of 67 of the lymph nodes reached.

Section Summary: Clinically Valid
There is less published literature on ENB for diagnosing MLN than for diagnosing pulmonary lesions. One RCT identified found higher sampling and diagnostic success with ENB-guided TBNA than with conventional TBNA. EBUS, which has been shown to be superior to conventional TBNA, was not used as the comparator. The RCT did not report the diagnostic accuracy of ENB for identifying malignancy, and this was also not reported in uncontrolled studies.

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 were identified that evaluated health outcomes for the use of ENB.

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.

Because the clinical validity of ENB cannot be established, a chain of evidence cannot be constructed.

Section Summary: ENB to Aid in the Diagnosis of Mediastinal Lymph Node(s)
A chain of evidence cannot be constructed to support a finding that ENB improves health outcomes for those with MLNs There is less published literature on ENB for diagnosing MLN than for diagnosis of pulmonary lesions. One RCT identified found higher sampling and diagnostic success with ENB-guided TBNA than with conventional TBNA. EBUS, which has been shown to be superior to conventional TBNA, was not used as the comparator. The RCT did not report diagnostic accuracy of ENB for identifying malignancy, and this was also not reported in uncontrolled studies.

ENB to Aid in Placement of Fiducial Markers Prior to Treatment
Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The RCT is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Clinical Context and Test Purpose
The purpose of using ENB with flexible bronchoscopy in patients who have lung tumors requiring placement of fiducial markers is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does use of ENB improve health outcomes in individuals with lung tumors requiring placement of fiducial markers?

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

Patients
The relevant population of interest is individuals with lung tumors requiring placement of fiducial markers.

Comparators
The following practice is currently being used: placement of fiducial markers using CT or ultrasound guidance.

Outcomes
The general outcomes of interest are a reduction in surgical complications compared with other surgical techniques.

Timing
The time frame for outcomes measures varies from short-term development of invasive procedure-related complications to long-term procedure-related complications, disease progression, or overall survival.

Setting
ENB is used as an adjunct to surgery in the outpatient setting by cancer specialists.
Evaluation of ENB as an aid to placement of fiducial markers involves searching for evidence that there are better clinical outcomes when ENB is used to place markers than when fiducials are placed using another method or when no fiducial markers are used. This review only evaluates the use of ENB to place fiducial markers; it does not evaluate the role of fiducial markers in radiotherapy.

Only 1 study was identified that compared fiducial marker placement using ENB with another method of fiducial marker placement; it was not randomized. This study, by Kupelian et al (2007), included 28 patients scheduled for radiotherapy for early-stage lung cancer.[13] Follow-up data were available for 23 (82%) patients; 15 had markers placed transcutaneously under CT or fluoroscopic guidance, and 8 patients had markers placed transbronchially with ENB. At least 1 marker was placed successfully within or near a lung tumor in all patients. The fiducial markers did not show substantial migration during treatment with either method of marker placement. The only clinical outcome reported was the rate of pneumothorax; 8 of 15 patients with transcutaneous placement developed a pneumothorax, 6 of whom required chest tubes. In

contrast, none of the 8 patients with transbronchial placement developed pneumothorax. This study had a small sample size and a substantial dropout rate.

Several case series were identified.[7,14-19] Studies with the largest sample sizes are described next. In the interim analysis of the NAVIGATE study (described above), 1000 patients received ENB, 210 of whom received 417 fiducial markers.[7] The subjective operator assessment of accurate placement of the fiducial markers was 208 (99%) in the 210 patients and 192 (94%) of 205 fiducial markers were retained at follow-up imaging. The timing of follow-up imaging was not specified. ENB-related adverse events included 8 (4%) cases of pneumothorax (grade ≥2), 3 cases of respiratory failure (grade ≥4), and a single bronchopulmonary hemorrhage (grade 1).

Bolton et al (2015) retrospectively reported on ENB fiducial marker placement in 64 patients (68 lung lesions) for guiding stereotactic radiotherapy.[16] A total of 190 fiducial markers were placed, 133 in upper-lobe lesions and 57 markers in lower-lobe lesions. The rate of marker retention (the study's primary end point) was 156 (82%) of 190. Retention rate, by lobe, ranged from 68 (80%) of 85 in the right upper lobe to 10 (100%) of 10 in the right middle lobe. Complications included 3 (5%) unplanned hospital admissions, 2 cases of respiratory failure, and 2 cases of pneumothorax.

Schroeder et al (2010) reported findings from a prospective study with 52 patients who underwent placement of fiducial markers using ENB.[15] All patients had peripheral lung tumors; 47 patients had inoperable tumors and 5 patients refused surgery. Patients were scheduled to receive tumor ablation using the stereotactic radiosurgery, which involved fiducial marker placement. The procedures were considered successful if the markers remained in place without migration during the timeframe required for radiosurgery. A total of 234 fiducial markers were deployed. Radiosurgery planning CT scans were performed between 7 and 14 days after fiducial marker placement. The planning CT scans showed that 215 (99%) of 217 coil spring markers and 8 (47%) of 17 linear markers remained in place, indicating a high success rate for coil spring markers. Three patients developed pneumothorax; 2 were treated with chest tubes, and 1 received observation only.

Section Summary: ENB to Aid in Placement of Fiducial Markers Prior to Treatment
There is only 1 study comparing ENB with another method of fiducial marker placement, and only 8 patients in that study who had markers placed with ENB had data available. There are several case series. In the largest series, an interim analysis of the NAVIGATE study, the subjective assessment of outcome was that 99% were accurately replaced and 94% were retained at follow-up. Comparative data are needed to conclude the safety and efficacy of ENB for fiducial marker placement.

Summary of Evidence
For individuals who have suspicious peripheral pulmonary lesion(s) who receive ENB with flexible bronchoscopy, the evidence includes meta-analyses, an RCT, and a number of observational studies. Relevant outcomes are test accuracy and validity, other test performance measures, and treatment-related morbidity. For ENB, a high negative predictive value or small negative likelihood ratio is desirable because it indicates that patients who test negative would not need additional interventions. A recent meta-analysis reported a large pooled positive likelihood ratio but a modest negative likelihood ratio. Similarly, a 2014 meta-analysis found that navigation success was high, but diagnostic yield and negative predictive value were relatively low. Both meta-analyses judged the quality of published studies to be low. The single RCT found higher a diagnostic yield when both ENB and EBUS were used, compared with either intervention alone but did not include a group without ENB or EBUS. Most uncontrolled studies had small sample sizes. In the AQuiRE registry study, which included more than 500 patients receiving ENB in practice, diagnostic accuracy was lower than in other studies. A large multicenter uncontrolled study is underway. Known as NAVIGATE, an interim analysis of the first 1000 patients reported a 4.9% rate of pneumothorax of any grade and 3.2% rate for pneumothorax of grade 2 or higher. Findings for diagnostic accuracy from NAVIGATE are not yet available. Current data are insufficient to identify potential patient selection criteria or to determine the diagnostic

accuracy of ENB when used in clinical practice. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have enlarged MLNs who receive ENB with flexible bronchoscopy, the evidence includes an RCT and observational studies. Relevant outcomes are test accuracy and validity, other test performance measures, and treatment-related morbidity. The RCT found higher sampling and diagnostic success with ENB-guided TBNA than with conventional TBNA. EBUS, which has been shown superior to conventional TBNA, was not used as the comparator. The RCT did not report the diagnostic accuracy of ENB for identifying malignancy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have lung tumor(s) who need fiducial marker placement prior to treatment who receive ENB with flexible bronchoscopy, the evidence includes a controlled study and several uncontrolled studies. Relevant outcomes are other test performance measures, health status measures, and treatment-related morbidity. The controlled study compared markers placed transcutaneously under computed tomography or fluoroscopic guidance or transbronchially with ENB. However, data were only available for 8 patients who had markers placed with ENB. Several case series were identified, but comparative data are needed to conclude the safety and efficacy of ENB for fiducial marker placement. In the largest series, an interim analysis of the NAVIGATE study, the subjective assessment of outcome was that 99% were accurately replaced and 94% were retained at follow-up. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information
Practice Guidelines and Position Statements

National Comprehensive Cancer Network
Current National Comprehensive Cancer Network (v.4.2018) practice guidelines on non-small-cell lung cancer state that the strategy for diagnosing lung cancer should be individualized and the least invasive biopsy with the highest diagnostic yield is preferred as the initial diagnostic study.[20]

- "Patients with central masses and suspected endobronchial involvement should undergo bronchoscopy.
- Patients with peripheral (outer one-third) nodules may benefit from navigational bronchoscopy, radial EBUS [endobronchial ultrasound], or transthoracic needle aspiration….
- Patients with suspected nodal disease should be biopsied by EBUS, EUS [endoscopic ultrasound], navigation biopsy, or mediastinoscopy."

American College of Chest Physicians
The American College of Chest Physicians (2013) updated its guidelines on the diagnosis of lung cancer.[21] Regarding electromagnetic navigation bronchoscopy, the guidelines stated: "In patients with peripheral lung lesions difficult to reach with conventional bronchoscopy, electromagnetic navigation guidance is recommended if the equipment and the expertise are available." The College noted that the procedure can be performed with or without fluoroscopic guidance and has been found to complement radial probe ultrasound. The strength of evidence for this recommendation was grade 1C ("strong recommendation, low- or very-low-quality evidence").

British Thoracic Society
The British Thoracic Society (2011) published guidelines on advanced diagnostic and therapeutic flexible bronchoscopy in adults.[22] The guidelines included the following recommendation: "Electromagnetic bronchoscopy may be considered for the biopsy of peripheral lesions or to guide transbronchial needle aspiration for sampling mediastinal lymph nodes." This was a grade D recommendation, meaning that it was based on nonanalytic studies (e.g., case series, expert opinion) or data extrapolated from observational studies.

U.S. Preventive Services Task Force Recommendations

Not applicable.

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 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02410837[a]	NAVIGATE: Clinical Evaluation of superDimension™ Navigation System for Electromagnetic Navigation Bronchoscopy™	2500	Dec 2019
NCT01779388	Bronchoscopy Assisted by Electromagnetic Navigation (EMN) in the Diagnosis of Small Pulmonary Nodules	120	Dec 2019

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

IE
The following services may be considered investigational.

Type	Code	Description
CPT®	31626	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with placement of fiducial markers, single or multiple
	31627	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with computer-assisted, image-guided navigation (List separately in addition to code for primary procedure[s])
HCPCS	A4648	Tissue marker, implantable, any type, each
	C9751	Bronchoscopy, rigid or flexible, transbronchial ablation of lesion(s) by microwave energy, including fluoroscopic guidance, when performed, with computed tomography acquisition(s) and 3-d rendering, computer-assisted, image-guided navigation, and endobronchial ultrasound (ebus) guided transtracheal and/or transbronchial sampling (e.g., aspiration[s]/biopsy[ies]) and all mediastinal and/or hilar lymph node stations or structures and therapeutic intervention(s) ***(Code effective 1/1/2019)***
ICD-10 Procedure	0BB38ZX	Excision of Right Main Bronchus, Via Natural or Artificial Opening Endoscopic, Diagnostic
	0BB38ZZ	Excision of Right Main Bronchus, Via Natural or Artificial Opening Endoscopic
	0BB48ZX	Excision of Right Upper Lobe Bronchus, Via Natural or Artificial Opening Endoscopic, Diagnostic
	0BB48ZZ	Excision of Right Upper Lobe Bronchus, Via Natural or Artificial Opening Endoscopic
	0BB58ZX	Excision of Right Middle Lobe Bronchus, Via Natural or Artificial Opening Endoscopic, Diagnostic
	0BB58ZZ	Excision of Right Middle Lobe Bronchus, Via Natural or Artificial Opening Endoscopic
	0BB68ZX	Excision of Right Lower Lobe Bronchus, Via Natural or Artificial Opening Endoscopic, Diagnostic
	0BB68ZZ	Excision of Right Lower Lobe Bronchus, Via Natural or Artificial Opening Endoscopic
	0BB78ZX	Excision of Left Main Bronchus, Via Natural or Artificial Opening Endoscopic, Diagnostic
	0BB78ZZ	Excision of Left Main Bronchus, Via Natural or Artificial Opening Endoscopic
	0BB88ZX	Excision of Left Upper Lobe Bronchus, Via Natural or Artificial Opening Endoscopic, Diagnostic
	0BB88ZZ	Excision of Left Upper Lobe Bronchus, Via Natural or Artificial Opening Endoscopic
	0BB98ZX	Excision of Lingula Bronchus, Via Natural or Artificial Opening Endoscopic, Diagnostic
	0BB98ZZ	Excision of Lingula Bronchus, Via Natural or Artificial Opening Endoscopic
	0BBB8ZX	Excision of Left Lower Lobe Bronchus, Via Natural or Artificial Opening Endoscopic, Diagnostic
	0BBB8ZZ	Excision of Left Lower Lobe Bronchus, Via Natural or Artificial Opening Endoscopic
	0BBC8ZX	Excision of Right Upper Lung Lobe, Via Natural or Artificial Opening Endoscopic, Diagnostic
	0BBC8ZZ	Excision of Right Upper Lung Lobe, Via Natural or Artificial Opening Endoscopic
	0BBD8ZX	Excision of Right Middle Lung Lobe, Via Natural or Artificial Opening Endoscopic, Diagnostic

Type	Code	Description
	0BBD8ZZ	Excision of Right Middle Lung Lobe, Via Natural or Artificial Opening Endoscopic
	0BBF8ZX	Excision of Right Lower Lung Lobe, Via Natural or Artificial Opening Endoscopic, Diagnostic
	0BBF8ZZ	Excision of Right Lower Lung Lobe, Via Natural or Artificial Opening Endoscopic
	0BBG8ZX	Excision of Left Upper Lung Lobe, Via Natural or Artificial Opening Endoscopic, Diagnostic
	0BBG8ZZ	Excision of Left Upper Lung Lobe, Via Natural or Artificial Opening Endoscopic
	0BBH8ZX	Excision of Lung Lingula, Via Natural or Artificial Opening Endoscopic, Diagnostic
	0BBH8ZZ	Excision of Lung Lingula, Via Natural or Artificial Opening Endoscopic
	0BBJ8ZX	Excision of Left Lower Lung Lobe, Via Natural or Artificial Opening Endoscopic, Diagnostic
	0BBJ8ZZ	Excision of Left Lower Lung Lobe, Via Natural or Artificial Opening Endoscopic
	0BBK8ZX	Excision of Right Lung, Via Natural or Artificial Opening Endoscopic, Diagnostic
	0BBK8ZZ	Excision of Right Lung, Via Natural or Artificial Opening Endoscopic
	0BBL8ZX	Excision of Left Lung, Via Natural or Artificial Opening Endoscopic, Diagnostic
	0BBL8ZZ	Excision of Left Lung, Via Natural or Artificial Opening Endoscopic
	0BBM8ZX	Excision of Bilateral Lungs, Via Natural or Artificial Opening Endoscopic, Diagnostic
	0BBM8ZZ	Excision of Bilateral Lungs, Via Natural or Artificial Opening Endoscopic
	0BJK8ZZ	Inspection of Right Lung, Via Natural or Artificial Opening Endoscopic
	0BJL8ZZ	Inspection of Left Lung, Via Natural or Artificial Opening Endoscopic

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
04/30/2015	BCBSA Medical Policy adoption	Medical Policy Committee
08/01/2016	Policy revision without position change	Medical Policy Committee
08/01/2017	Policy revision without position change	Medical Policy Committee
08/01/2018	Policy revision without position change	Medical Policy Committee
02/01/2019	Coding update	Administrative Review

Definitions of Decision Determinations

Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.