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Electromagnetic Navigation Bronchoscopy (ENB)

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Related Policies (if applicable)
None

Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

When flexible bronchoscopy alone, or with endobronchial ultrasound, are considered inadequate to accomplish the diagnostic or interventional objective, electromagnetic navigation bronchoscopy (ENB) **may be considered medically necessary** to**:**

- Establish a diagnosis of suspicious peripheral pulmonary lesion(s), or
- Place fiducial markers within lung tumor(s) prior to treatment.

Electromagnetic navigation bronchoscopy **is considered experimental, investigational and/or unproven** for use with flexible bronchoscopy for the diagnosis of mediastinal lymph nodes as well as all other uses not covered above.

Policy Guidelines

Bronchoscopists performing electromagnetic navigation bronchoscopy (ENB) require specific training in the procedure.

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 marker placement.

Background

Pulmonary Nodules

Pulmonary nodules are identified on plain chest radiographs, or chest computed tomography (CT) 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

Lung cancer is the leading cause of cancer-related death in the U.S., with an estimated 238,340 new cases and 127,070 deaths due to the disease in 2023. (1) The stage at which lung cancer is diagnosed has the greatest impact on prognosis. Localized disease confined to the primary site has a 60% relative 5-year survival but accounts for only 22% of lung cancer cases at diagnosis. (1, 2) Mortality increases sharply with advancing stage and metastatic lung cancer has a relative 5-year survival of 6%. (1) In addition to tumor stage, other factors such as age, sex, race/ethnicity, and performance status are independent prognostic factors for survival in patients with lung cancer. The average age at diagnosis is about 70 years and most people diagnosed with lung cancer are 65 years of age or older. The lifetime risk of lung cancer is approximately 1 in 16 for men and 1 in 17 for women, with an increased risk in people who smoke. Rates of lung cancer have been dropping among men over the past few decades, but only for about the last decade in women. Black men are about 12% more likely to develop lung cancer compared to White men, although Black men are less likely to develop small cell lung cancer when compared to White men. Among women, the rate of lung cancer is about 16% lower for Black versus White women.

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 are 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. (3-5)

Advances in technology may increase the yield of established diagnostic methods. Computed tomography (CT) 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 (EBUS) by radial probes, previously used in the perioperative staging of lung cancer, can also be used to locate and guide sampling of peripheral lesions. EBUS is reported to increase the diagnostic yield of flexible bronchoscopy to at least 82%, regardless of lesion size or location. (3)

Marker Placement

Another proposed enhancement to standard bronchoscopy is ENB. 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 ENB 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 guidewire inserted through the catheter.

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.

Two ENB systems are currently available, the SPiN Thoracic Navigation System (Veran Medical Technologies) and the superDimension™ navigation system (Medtronic).

Rationale

The medical policy was created in January 2009 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through June 4, 2024.

Medical policies 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. Medical policies assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these policies, and credible information on technical reliability is available from other sources.

Electromagnetic Navigation Bronchoscopy (ENB) to Aid Diagnosing Pulmonary Lesions

Clinical Context and Test Purpose

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

The following PICO was used to select literature to inform this policy.

Populations

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 a 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. Potential procedure-related adverse events include pneumothorax, bronchopulmonary hemorrhage, and respiratory complications.

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

Study Selection Criteria
For the evaluation of clinical validity of the ENB with flexible bronchoscopy, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores);
- Included a suitable reference standard;
- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described.

Several studies were excluded from the evaluation of the clinical validity because they did not use the marketed version of the test, did not include information needed to calculate performance characteristics, did not adequately describe the patient characteristics, or did not adequately describe patient selection criteria.

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
Sun et al. (2023) published a meta-analysis of the diagnostic value and safety of ENB for diagnosing peripheral pulmonary lesions suspected of cancer. (6) The analysis included 55 retrospective and prospective cohort studies (N=5,879). The authors reported that most of the literature included were deemed as unclear risk of bias because there were no suitable reference standards that were used across studies.

Folch et al. (2020) published a systematic review of the literature on the sensitivity and safety of ENB for diagnosing peripheral pulmonary lesions suspected of cancer. (7) Forty prospective and retrospective studies (N=3,342) were included in the analysis. Many of the included studies were single-center, single arm, and retrospective. Because most studies did not use a proper

reference standard, the authors reported that most studies had a higher or unclear risk of bias regarding patient selection, index test, and the reference standard. Most studies used the superDimension system.

A systematic review of the literature on the diagnostic yield and safety of ENB was published by Zhang et al. (2015). (8) Reviewers updated a systematic review by Gex et al. (2014) (9) with newer studies. The Zhang et al. (2015) 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 (N=971 patients), reported somewhat different outcomes (see Table 1).

Table 1. Meta-Analysis of Electromagnetic Navigation Bronchoscopy Performance

Outcomes	**Rate (95% Confidence Interval), %**			
	Sun et al. (2023) (6)	***Folch et al. (2020) (7)***	***Zhang et al. (2015) (8)***	***Gex et al. (2014) (9)***
Sensitivity for malignancy	0.77 (0.73 to 0.81)	77 (72 to 78) using random effects model; 76 (74 to 78) using fixed effect model	82 (79 to 85)	71.1 (64.6 to 76.8)
Specificity for malignancy	0.97 (0.93 to 0.99)	100 (99 to 100)	100 (98 to 100)	
Positive likelihood ratio	24.27 (10.21 to 57.67)	15.8 (10.3 to 24.2)	18.67 (9.04 to 38.55)	
Negative likelihood ratio	0.23 (0.19 to 0.28)	0.2 (0.1 to 0.3)	0.22 (0.15 to 0.32)	
Diagnostic odds ratio	104.19 (41.85 to 259.37)		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 et al. (2014), whereas the navigation success rate using ENB was generally very high, the diagnostic yield and negative predictive value (NPV) were relatively low. (9) Moreover, in Sun et al. (2023), Folch et al. (2020), and Zhang et al. (2015), the positive likelihood ratio was large, but the negative likelihood ratio suggested only a small decrease in the likelihood of disease following the test. (6-8) Neither Sun, Folch, or Zhang conducted 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 the 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 3.27% in Sun et al. (2023), 2% in Folch et al. (2020), 5.9% in Zhang et al. (2015), and 3.1% in Gex et al. (2014) (1.6% required chest tube placement for pneumothorax). (6-9) Zhang et al. (2015) stated that 2 of the pneumothoraxes were induced by transbronchial biopsy and the others were unrelated to the ENB procedure. Folch et al. (2020) also reported a risk of major and minor bronchopulmonary bleeding of 0.8% and 1%, respectively, and risk of acute respiratory failure of 0.6%. (7)

Randomized Controlled Trials

Eberhardt et al. (2007) published the only randomized controlled trial (RCT) to evaluate ENB for the diagnosis of pulmonary nodules. (10) This trial used surgical biopsy as a criterion standard confirmation of diagnosis. Patients were randomized to ENB only, endobronchial ultrasound (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 the 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 a 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 the 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.

Prospective Uncontrolled Studies

One key uncontrolled prospective, multicenter observational study is the NAVIGATE study. NAVIGATE is a prospective, multicenter (37 sites) analysis of outcomes in patients who received ENB in U.S. and European (EU) 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. Analyses of 1-month data on the first 1000 patients and 12-month data from the U.S. cohort have been published. (11, 12)

Khandhar et al. (2017) published a preplanned 1-month interim analysis of the first 1000 patients from the NAVIGATE study. (11) The analysis focused on safety outcomes; the primary endpoint 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 1 was deemed related to general anesthesia complications.

Folch et al. (2019) published 1-year results from the U.S. cohort of NAVIGATE (1215 patients at 29 sites). (12) This analysis included diagnostic outcomes as well as adverse events. Twelve-month follow-up was completed in 976 of 1215 (80.3%) patients. Navigation was successful, and tissue was obtained in 1092 of the 1157 patients who received ENB for lung lesion biopsy (94.4%). Of these 1092 biopsies, 44.3% diagnosed malignancy (484) and 55.7% (608) were negative. As of 12 months, 284 initially negative outcomes were considered true-negative and 220 were false-negative. The 12-month diagnostic yield was 72.9% and ranged from 66.4% to 75.4% assuming all deferred cases were false-negatives and true-negatives, respectively.

Most adverse events occurred within the first-month post-procedure and were previously reported in Khandhar et al. (2017). Overall, 4.3% of the patients had experienced pneumothorax. Pneumothorax requiring hospitalization or intervention (Common Terminology Criteria for Adverse Events [CTCAE] grade 2 or higher) occurred in 35 of 1215 patients (2.9%). Bronchopulmonary hemorrhage overall occurred in 2.5% of patients overall and CTCAE grade 2

or higher in 1.5%. Grade 4 or higher respiratory failure occurred in 0.7% of patients. There were 23 deaths at 12 months, none related to the ENB device. There was 1 anesthesia-related death 9 days post-procedure in a patient with multiple comorbidities.

Folch et al. (2022) published 2-year results from the EU and U.S. cohorts of NAVIGATE (1388 patients at 37 sites). (13) The 2-year mortality rate was 29% (403 of 1388 patients). Any-grade pneumothorax occurred in 4.7% of participants (7.4% EU; 4.3% U.S.) and grade 2 or higher pneumothorax occurred in 3.2% of participants (5.1% EU; 2.9% U.S.). The rate of any-grade bronchopulmonary hemorrhage was 2.7% (4% EU; 2.5% U.S.) and the rate of grade 2 or higher bronchopulmonary hemorrhage was 1.7% (2.3% EU; 1.6% U.S.). Navigation was successful and tissue was obtained in 1260 of the 1329 patients who received ENB for lung lesion biopsy (94.8%). At 2 years, of the 723 cases initially considered negative for malignancy, 285 were true-negative, 321 were false-negative, and 117 remained indeterminate. The diagnostic yield was 67.8% (range not provided) in the global cohort, 55.2% (range: 52.3% to 57.5%) in the EU cohort, and 69.8% (range: 63.3% to 72.6%) in the U.S. cohort. In the global EU and U.S. cohorts, sensitivity for malignancy was 62.6% (range: 55.1% to 62.6%), 44.7% (range: 41.7% to 44.7%), and 65.6% (range: 57.2% to 65.6%), whereas NPV was 47.0% (range: 39.4% to 55.6%), 34.6% (range: 31.9% to 39.8%), and 49.6% (range: 40.8% to 58.5%), respectively. In a univariate analysis of the global cohort, Hispanic or Latino ethnicity was associated with lower diagnostic yield (63%: range: 41% to 98%).

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

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). (14) 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. ENB was reserved for the most difficult patients. They tended to be poor or borderline candidates for surgery and transthoracic sampling. The procedure was planned for ENB whether or not eventually used and ENB was done only when the other approaches were inadequate. In this context, the "low yield" observed for ENB was actually high for this highly selected population. 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. In AQuiRE, ENB was reserved for the most difficult patients.

One prospective observational study has examined the sequential use of ENB; endobronchial ultrasound was used initially, with the addition of ENB when endobronchial ultrasound failed to reach or diagnose the lesion.

A study by Chee et al. (2013) included 60 patients with peripheral pulmonary lesions. (15) Patients either had a previous negative CT-guided biopsy or did not have 1 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.

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

A 2023 meta-analysis of 55 studies, a 2020 meta-analysis of 40 studies, and a 2015 meta-analysis of 17 studies of ENB reported a large pooled positive likelihood ratio but a small negative likelihood ratio. Similarly, a 2014 meta-analysis of 15 studies found that navigation success was high, but diagnostic yield (64.9; 95% confidence interval [CI], 59.2 to 70.3) and NPV (52.1; 95% CI, 43.5 to 60.6) were relatively low. The systematic reviews assessed the methodological quality of the evidence as low. Results from 2 large prospective multicenter uncontrolled studies, AQuiRE and NAVIGATE, provide information about test characteristics and safety of ENB. 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. In the U.S. cohort of the NAVIGATE study, the 2-year diagnostic yield was 69.8%. Overall, 4.3% of patients experienced pneumothorax, and grade 2 or higher pneumothorax occurred in 2.9% of patients. Bronchopulmonary hemorrhage occurred in 2.5% of patients overall and grade 2 or higher bronchopulmonary hemorrhage in 1.6% of patients. There were no deaths related to the ENB device.

Electromagnetic Navigation Bronchoscopy to Aid in the Diagnosis of Mediastinal Lymph Node(s)

Clinical Context and Test Purpose

The purpose of using ENB with flexible bronchoscopy in individuals who have enlarged mediastinal lymph nodes (MLNs) is to inform a decision whether to initiate treatment for lung cancer.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with enlarged MLNs.

Interventions

The test being considered is ENB with flexible bronchoscopy.

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. Potential procedure-related adverse events include pneumothorax, bronchopulmonary hemorrhage, and respiratory complications. 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.

Study Selection Criteria

For the evaluation of clinical validity of the ENB with flexible bronchoscopy, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores);
- Included a suitable reference standard;
- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described.

Several studies were excluded from the evaluation of the clinical validity because they did not use the marketed version of the test, did not include information needed to calculate performance characteristics, did not adequately describe the patient characteristics, or did not adequately describe patient selection criteria.

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 mediastinal lymph nodes (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. (16) 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 1 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.

Case Series

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 MLNs. (17) 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 MLNs 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.

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 in the Diagnosis of Mediastinal Lymph Node(s)
There is less published literature on ENB for diagnosing MLNs than for diagnosing pulmonary lesions. One RCT found higher sampling and diagnostic success with ENB-guided TBNA than with conventional TBNA. Endobronchial ultrasound, 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.

Electromagnetic Navigation Bronchoscopy to Aid in Placement of Fiducial Markers Prior to Treatment

Clinical Context and Therapy Purpose
The purpose of using ENB with flexible bronchoscopy in individuals who have lung tumors requiring placement of fiducial markers when flexible bronchoscopy alone or with endobronchial ultrasound are inadequate to place the markers near the pulmonary lesion(s) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations
The relevant population of interest is individuals with lung tumors requiring placement of fiducial markers prior to treatment when flexible bronchoscopy alone or with endobronchial ultrasound is inadequate to place the markers near the pulmonary lesion(s).

Intervention
The intervention of interest is ENB with the placement of fiducial markers.

The purpose of ENB 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. The guide catheter can be used to place fiducial markers. Markers are loaded in the proximal end of the catheter with a guidewire inserted through the catheter.

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.

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.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Evaluation of ENB as an aid to the 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 policy only evaluates the use of ENB to place fiducial markers; it does not evaluate the role of fiducial markers in radiotherapy.

Comparative Observational Study
Only one 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. (18) 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.

Noncomparative Observational Studies and Case Series

Several noncomparative observational studies and case series were identified. (11, 19-24) Studies with the largest sample sizes are described next.

Two publications from the NAVIGATE observational cohort study (described above) have reported preliminary outcomes in patients who had fiducial marker placement with ENB. (11, 25). In an interim analysis reported by Khandhar et al. (2017), 210 patients received 417 fiducial markers. (11) 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). Bowling et al. (2019) reported 1-month outcomes in 258 patients who had a total of 563 fiducial markers placed at 21 centers in the U.S. (25) Follow-up data were available for 255/258 patients (99.8%). Based on subjective operator assessment, fiducial markers were accurately placed in 99.2% of patients (256/258). Follow-up imaging occurred an average of 8.1 days post-procedure and showed that 239 of 254 markers remained in place (239/254). Fourteen patients (5.4%) experienced pneumothorax; in 8 patients (3.1%) the pneumothorax was rated CTCAE grade 2 or higher.

Bolton et al. (2015) retrospectively reported on ENB fiducial marker placement in 64 patients (68 lung lesions) for guiding stereotactic radiotherapy. (21) 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. (20) 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.

An advantage of ENB is that it allows the placement of pleural dye and/or fiducial markers in the same procedure as ENB-guided lung lesion biopsy, thereby reducing the need for a second

procedure and potentially reducing risks to the patient. For example, in NAVIGATE, all but 39 of the patients had lung lesion biopsy or pleural dye marking during the same procedure. (25) Patients being treated with targeted radiation are typically those with advanced respiratory disease who cannot undergo surgical resection. They are also more at risk for pneumothorax and resultant further complications. As the markers need to be near and not necessarily in a lesion, the accuracy advantage of a transthoracic approach is outweighed by the safety advantage of ENB over a transthoracic approach.

Section Summary: Electromagnetic Navigation Bronchoscopy to Aid in Placement of Fiducial Markers Prior to Treatment

There is only one 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 noncomparative observational studies and case series. In the largest series, a subgroup analysis of 258 patients from the NAVIGATE study, the subjective assessment of outcome was that 99.2% of markers were accurately placed and 94.1% were retained at follow-up (mean 8.1 days post-procedure). Pneumothorax of any grade occurred in 5.4% of patients, and grade 2 or higher pneumothorax occurred in 3.1%.

Summary of Evidence

For individuals who have suspicious peripheral pulmonary lesion(s) when flexible bronchoscopy alone or with endobronchial ultrasound are inadequate to sample the pulmonary lesion(s), the evidence includes meta-analyses, a randomized controlled trial (RCT), and uncontrolled prospective observational studies. Relevant outcomes are test accuracy and validity, other test performance measures, and treatment-related morbidity. A 2020 meta-analysis of 40 studies and a 2015 meta-analysis of 17 studies of electromagnetic navigation bronchoscopy (ENB) reported a large pooled positive likelihood ratio but a small negative likelihood ratio (0.2 to 0.22). Similarly, a 2014 meta-analysis of 15 studies found that navigation success was high, but diagnostic yield (64.9; 95% confidence interval [Cl], 59.2 to 70.3) and negative predictive value (52.1; 95% Cl, 43.5 to 60.6) were relatively low. The systematic reviews assessed the methodological quality of the evidence as low. Results from 2 large prospective multicenter uncontrolled studies, AQuiRE (American College of Chest Physicians Quality Improvement Registry, Evaluation, and Education) and NAVIGATE (Clinical Evaluation of superDimension Navigation System for Electromagnetic Navigation Bronchoscopy), provide information about test characteristics and safety of ENB. 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 endobronchial ultrasound. In the U.S. cohort of the NAVIGATE study, the 2-year diagnostic yield was 69.8%. Overall, 4.3% of patients experienced pneumothorax, and grade 2 or higher pneumothorax occurred in 2.9% of patients. Overall, bronchopulmonary hemorrhage occurred in 2.5% of patients, and grade 2 or higher bronchopulmonary hemorrhage in 1.6% of patients. There were no deaths related to the ENB device. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have enlarged mediastinal lymph nodes who receive ENB with flexible bronchoscopy, the evidence includes a RCT and case series. Relevant outcomes are test accuracy and validity, other test performance measures, and treatment-related morbidity. There is less published literature on ENB for diagnosing mediastinal lymph nodes than for diagnosing pulmonary lesions. One RCT identified found higher sampling and diagnostic success with ENB-guided transbronchial needle aspiration than with conventional transbronchial needle aspiration. EBUS, which has been shown to be superior to conventional transbronchial needle aspiration, 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. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have lung tumor(s) who need fiducial marker placement prior to treatment when flexible bronchoscopy alone or with endobronchial ultrasound are inadequate to place the markers near the pulmonary lesion(s), the evidence includes 1 comparative observational study and several noncomparative observational studies and case series. Relevant outcomes are health status measures and treatment-related morbidity. In the largest series, a subgroup analysis of 258 patients from the NAVIGATE study, the subjective assessment of outcome was that 99.2% of markers were accurately placed and 94.1% were retained at follow-up (mean 8.1 days post-procedure). Pneumothorax of any grade occurred in 5.4% of patients, and grade 2 or higher pneumothorax occurred in 3.1%. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Clinical Input (2019)

For individuals who have suspicious peripheral pulmonary lesion(s) who receive ENB with flexible bronchoscopy, clinical input supports this use and provides a clinically meaningful improvement in net health outcome and indicates this use is consistent with generally accepted medical practice in a subgroup of appropriately selected patients. Clinical input states that ENB is generally reserved for the most difficult patients, who are poor or borderline candidates for surgery and transthoracic sampling. In this context, the "low yield" observed in observational studies was actually high for this highly selected population. ENB, when used as an option in the armamentarium of the bronchoscopist, is a highly useful and low-risk modality for proper diagnosis and staging of lung cancer. For example, patients who are able to achieve a positive biopsy result through ENB benefit by getting a diagnostic result to appropriately guide treatment while avoiding transthoracic needle biopsy which has a 2 to 4 times higher risk of pneumothorax than a bronchoscopic biopsy approach.

For individuals who have enlarged mediastinal lymph node(s) who receive ENB with flexible bronchoscopy, clinical input does not support a clinically meaningful improvement in net health outcome and does not indicate this use is consistent with generally accepted medical practice. Clinical input states that mediastinal lymph node diagnosis was an early indication for ENB which has been largely replaced by endobronchial ultrasound. One could consider it in the uncommon scenario in which linear endobronchial ultrasound is not available and the patient is already having an ENB procedure for a peripheral nodule.

For individuals who have lung tumor(s) who need fiducial marker placement prior to treatment who receive ENB with flexible bronchoscopy, clinical input supports this use and provides a clinically meaningful improvement in net health outcome and indicates this use is consistent with generally accepted medical practice in a subgroup of appropriately selected patients. Clinical input states that the key advantage of ENB placement is the markedly reduced risk of pneumothorax compared to the transthoracic approach. Patients being treated with targeted radiation are typically those with advanced respiratory disease who cannot undergo surgical resection. They are also more at risk for pneumothorax and resultant further complications. As the markers need to be near and not necessarily in a lesion, the accuracy advantage of a transthoracic approach is outweighed by the safety advantage of ENB over a transthoracic approach.

Practice Guidelines and Position Statements

American College of Chest Physicians (ACCP)

In 2013, the ACCP updated its guidelines on the diagnosis of lung cancer. (26) Regarding electromagnetic navigation bronchoscopy, the guideline 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").

National Comprehensive Cancer Network (NCCN)

Current National Comprehensive Cancer Network (v.7.2024) practice guideline 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. (27)

- "Patients with central masses and suspected endobronchial involvement should undergo bronchoscopy.
- Patients with pulmonary nodules may benefit from navigational bronchoscopy (including robotic), 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."

Ongoing and Unpublished Clinical Trials

Some currently ongoing or unpublished trials that might influence this policy are listed in Table 2.

Table 2. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
Ongoing			

NCT05804786	Prospective Cohort of Diagnostic Bronchoscopy for Peripheral Lung Lesions	1240	July 2027
NCT05518669	mCBCT in Combination With ENB for the Diagnosis of PPNs	109	June 2024 (recruiting)
NCT04553809	Navigation Endobronchial Ultrasound (NEBULA)	200	Sept 2024 (recruiting)
NCT04730453	ENB-guided Ablation Therapy Combined With VATS in the Treatment of MPLC	30	Dec 2025 (recruiting)
NCT05662553	ENB Guided MWA Combined With VATS Versus Sequential Surgery for Synchronous Bilateral Multiple Primary Lung Nodules	172	Dec 2025 (recruiting)
Unpublished			
NCT01779388	Bronchoscopy Assisted by Electromagnetic Navigation (EMN) in the Diagnosis of Small Pulmonary Nodules	120	Dec 2021
NCT04194333	Cone Beam CT Guided Electromagnetic Navigational Bronchoscopy (CBCTENB)	180	Nov 2021

NCT: national clinical trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	31626, 31627
HCPCS Codes	A4648, C7509, C7510, C7511, C9751

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change

11/15/2024	Document updated with literature review. Coverage unchanged. Reference 6 added; others updated.
10/15/2023	Reviewed. No changes.
01/15/2023	Document updated with literature review. Coverage unchanged. References 1, 2, 6, and 12 added; others removed.
09/15/2021	Reviewed. No changes.
01/15/2021	Document updated with literature review. The following change was made to Coverage: Modified medically necessary criteria. Add/updated the following references: 8, 21, 22, and 23.
07/01/2019	Document updated with literature review. Coverage unchanged. References 3, 17, 20-21, 27-30, and 33 added.
10/15/2017	Reviewed. No changes.
01/01/2017	Document updated with literature review. Coverage unchanged.
07/15/2015	Reviewed. No changes.
10/15/2014	Document updated with literature review. The following coverage change was made: Electromagnetic navigation bronchoscopy (ENB) with or without fluoroscopic guidance may be considered medically necessary in adult patients for the evaluation of a solitary pulmonary nodule that is highly suspicious for malignancy and meets one of the criteria below: 1.) The solitary pulmonary nodule is deemed inaccessible by standard bronchoscopic methods or standard bronchoscopic methods have failed; 2.) More invasive diagnostic procedures pose an unacceptable risk to the patient (e.g., bullous lung disease, diffuse emphysema); 3.) Patients with an identified lung lesion(s) and a co-existing cancer in whom further determination of the lung lesion will impact staging of the primary tumor and thus impact the treatment plan; 4.) Placement of fiducial markers in patients who are not candidates for surgical intervention and who have elected to undergo radiation therapy. Use of electromagnetic navigation bronchoscopy (ENB) for any other indication is considered experimental, investigational, and/or unproven.
07/15/2011	Document updated with literature review. The following language change was made to the coverage statement: Electromagnetic navigation bronchoscopy is considered experimental, investigational and unproven for all indications.
01/01/2010	New medical document originating from SUR716.013bu. Bulletin converted to Medical policy new CPT codes added.
01/01/2009	New medical document