Electromagnetic Navigation Bronchoscopy

Policy Number: 7.01.122  Last Review: 9/2019

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for Electromagnetic Navigation Bronchoscopy when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Electromagnetic navigation bronchoscopy may be considered medically necessary for individuals with either suspicious peripheral pulmonary lesion(s) or with lung tumor(s) who need fiducial marker placement prior to treatment when flexible bronchoscopy alone or with endobronchial ultrasound are considered inadequate to accomplish the procedure.

When Policy Topic is not covered
Electromagnetic navigation bronchoscopy is considered investigational for use with flexible bronchoscopy for the diagnosis of mediastinal lymph nodes as well as all other uses not covered above.

Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>▪ With suspicious peripheral pulmonary lesion(s) when flexible bronchoscopy alone or with endobronchial ultrasound are inadequate to sample the pulmonary</td>
<td>▪ Electromagnetic navigation bronchoscopy with flexible bronchoscopy</td>
<td>▪ Computed tomography-guided needle biopsy</td>
<td>▪ Test accuracy</td>
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<td>▪ Other test performance measures</td>
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<td>▪ Treatment-related morbidity</td>
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<td>Interventions</td>
<td>Comparators</td>
<td>Outcomes</td>
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<td><strong>Comparators of interest are:</strong></td>
<td><strong>Relevant outcomes include:</strong></td>
</tr>
<tr>
<td>▪ With enlarged mediastinal lymph node(s)</td>
<td>▪ Electromagnetic navigation bronchoscopy with flexible bronchoscopy</td>
<td>▪ Flexible bronchoscopy only</td>
<td>▪ Test accuracy</td>
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<td></td>
<td></td>
<td>▪ Computed tomography-guided needle biopsy</td>
<td>▪ Test validity</td>
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<tr>
<td></td>
<td></td>
<td>▪ Endobronchial ultrasound with flexible bronchoscopy</td>
<td>▪ Other test performance measures</td>
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<td>▪ With lung tumor(s) who need fiducial marker placement prior to treatment when flexible bronchoscopy alone or with endobronchial ultrasound are considered inadequate to accomplish the procedure</td>
<td>▪ Electromagnetic navigation bronchoscopy with placement of fiducial markers</td>
<td>▪ Placement of fiducial markers using computed tomography</td>
<td>▪ Health status measures</td>
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<td></td>
<td>▪ Treatment-related morbidity</td>
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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.

The following conclusions are based on a review of the evidence, including but not limited to, published evidence and clinical expert opinion, solicited via BCBSA’s Clinical Input Process.

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, and uncontrolled observational studies. A 2015 meta-analysis of
17 studies of ENB reported a large pooled positive likelihood ratio but a small negative likelihood ratio (0.22; 95% confidence interval 0.15 to 0.32). Similarly, a 2014 meta-analysis of 15 studies found that navigation success was high, but diagnostic yield (64.9; 95% confidence interval 59.2 to 70.3) and negative predictive value (52.1; 95% confidence interval 43.5 to 60.6) were relatively low. Both systematic reviews assessed the methodological quality of the evidence as low. Results from two 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 endobronchial ultrasound (EBUS). In the US cohort of the NAVIGATE study, the 12-month diagnostic yield was 72.9%. Overall, 4.3% of patients experienced pneumothorax, and pneumothorax requiring hospitalization or intervention occurred in 35 of 1215 patients (2.9%). Bronchopulmonary hemorrhage overall occurred in 2.5% of patients overall and Common Terminology Criteria for Adverse Events grade 2 or higher in 1.5%. There were no deaths related to the ENB device. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported through clinical input supports that this use provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice. 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 2-4 times higher risk of pneumothorax than a bronchoscopic biopsy approach. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have enlarged mediastinal lymph nodes who receive ENB with flexible bronchoscopy, the evidence includes a randomized controlled trial and observational studies. The 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 randomized controlled trial 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 randomized controlled trial did not report the diagnostic accuracy of ENB for identifying malignancy, and this was also not reported in uncontrolled studies. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported through clinical input is not generally supportive of a clinically meaningful improvement in net health outcome. Mediastinal lymph nodes diagnosis was an early indication for ENB which has been largely replaced by EBUS. One could
consider it in the uncommon scenario in which linear EBUS is not available and the patient is already having an ENB procedure for a peripheral nodule. 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 when flexible bronchoscopy alone or with endobronchial ultrasound are inadequate to place the markers near the pulmonary lesion(s), the evidence includes one comparative observational study and several case series. The 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 postprocedure). Pneumothorax of any grade occurred in 5.4% of patients, and grade 2 or higher pneumothorax occurred in 3.1%. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported through clinical input supports that this use provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice. 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. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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.\textsuperscript{1,2,3}

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.\textsuperscript{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 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 evidence review was created in November 2009 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through May 29, 2019.

The following conclusions are based on a review of the evidence, including but not limited to, published evidence and clinical expert opinion, solicited via BCBSA’s Clinical Input Process.

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 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 the use of ENB with flexible bronchoscopy improve health outcomes in individuals with suspicious peripheral pulmonary lesions?

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

**Patients**  
The relevant population of interest are individuals with suspicious peripheral pulmonary lesions.

**Interventions**  
The test being considered is ENB with flexible bronchoscopy.

ENB is administered in the outpatient setting by experienced bronchoscopists

**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.

**Technically Reliable**  
Assessment of technical reliability focuses on specific tests and operators and requires a 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 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 (total n=971 patients), reported somewhat different outcomes (see Table 1).

**Table 1. Meta-Analysis of Electromagnetic Navigation Bronchoscopy Performance**

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<th>Outcomes</th>
<th>Rate (95% Confidence Interval), %</th>
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<tr>
<td>Sensitivity for malignancy</td>
<td>82 (79 to 85)</td>
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<tr>
<td>Specificity for malignancy</td>
<td>100 (98 to 100)</td>
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<tr>
<td>Positive likelihood ratio</td>
<td>18.67 (9.04 to 38.55)</td>
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<td>Negative likelihood ratio</td>
<td>0.22 (0.15 to 0.32)</td>
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<td>Diagnostic odds ratio</td>
<td>97.36 (43.75 to 216.69)</td>
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<tr>
<td>Navigation success</td>
<td>97.4 (95.4 to 98.5)</td>
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<tr>
<td>Diagnostic yield</td>
<td>64.9 (59.2 to 70.3)</td>
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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. 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 (ie, 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 5.9% in Zhang et al (2015) and 3.1% in Gex et al (2014) (1.6% required chest tube placement for pneumothorax). Zhang et al (2015) 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. 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 three 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

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<thead>
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<th>Accuracy for malignancy</th>
<th>78.6 (72.8 to 83.4)</th>
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<td>Negative predictive value</td>
<td>52.1 (43.5 to 60.6)</td>
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<td>Negative predictive value of intermediate benign results</td>
<td>78.5 (53.1 to 92.1)</td>
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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 three groups.

**Uncontrolled Studies**

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

NAVIGATE is a prospective, multicenter (n=37 sites) 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. Analyses of 1-month data on the first 1000 patients and 12-month data from the U.S. cohort have been published.\(^7,8\) Twelve-month follow-up of the European cohort and two-year follow-up are ongoing.

Khandhar et al (2017) published a preplanned 1-month interim analysis of first 1000 patients from the NAVIGATE study.\(^7,8\) 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 one was deemed related to general anesthesia complications.

Folch et al (2019) published one-year results from the U.S. cohort of NAVIGATE (1215 patients at 29 sites).\(^8\) 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 Khandar 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 one anesthesia-related death nine days post-procedure in a patient with multiple comorbidities.

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). 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 ten (1.7%) patients, six of who required chest tubes. Pneumothorax rates were not reported for bronchoscopy with and without ENB. In AQuiRE, ENB was reserved for the most difficult patients.

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. 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. EBUS and virtual bronchoscopy were used initially, and ENB was performed when EBUS could not locate the lesion or when rapid on-site 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 on-site 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.

**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 Diagnosing Pulmonary Lesions**
A 2015 meta-analysis of 17 studies of ENB reported a large pooled positive likelihood ratio but a small negative likelihood ratio (0.22; 95% confidence interval [CI] 0.15 to 0.32). Similarly, a 2014 meta-analysis of 15 studies found that navigation success was high, but diagnostic yield (64.9; 95% CI 59.2 to 70.3) and NPV (52.1; 95% CI 43.5 to 60.6) were relatively low. Both systematic reviews assessed the methodological quality of the evidence as low. Results from two 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 12-month diagnostic yield was 72.9%. Overall, 4.3% of patients experienced pneumothorax, and pneumothorax requiring hospitalization or intervention 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%. There were no deaths related to the ENB device. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported through clinical input supports that this use provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice. 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 two to four times higher risk of pneumothorax than a bronchoscopic biopsy approach. Further details from clinical input are included in the Clinical Input section and the Appendix.

**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 MLNs is to inform a decision whether to initiate treatment for lung cancer.

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

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

**Patients**
The relevant population of interest are individuals with enlarged MLNs.

**Interventions**
The test being considered is ENB with flexible bronchoscopy.

ENB is administered in the outpatient setting by experienced bronchoscopists.

**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.

**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires a 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. 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. 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.

**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 MLN(s)**
There is less published literature on ENB for diagnosing MLN than for diagnosing pulmonary lesions. One RCT 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. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported through clinical input is not generally supportive of a clinically meaningful improvement in net health outcome. MLN diagnosis was an early indication for ENB which has been largely replaced by EBUS. One could consider it in the uncommon scenario in which linear EBUS is not available and the patient is already having an ENB procedure for a peripheral nodule. Further details from clinical input are included in the Clinical Input section and the Appendix.

**ENB to Aid in Placement of Fiducial Markers Prior to Treatment**
Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the 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 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 technology, two domains are examined: the relevance, and 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 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 question addressed in this evidence review is: Does the use of ENB improve health outcomes in individuals with lung tumors requiring placement of fiducial markers?

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

**Patients**
The relevant population of interest are individuals with lung tumors requiring fiducial marker 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 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. 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.

ENB is used as an adjunct to surgery in the outpatient setting by experienced bronchoscopists.
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.

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 review only evaluates the use of ENB to place fiducial markers; it does not evaluate the role of fiducial markers in radiotherapy.

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. 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 transbrachially with ENB. At least one 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 eight patients with transbrachial placement developed pneumothorax. This study had a small sample size and a substantial dropout rate.

Several case series were identified. Studies with the largest sample sizes are described next.

Two publications from the ongoing NAVIGATE observational cohort study (described above) have reported preliminary outcomes in patients who had fiducial marker placement with ENB. In an interim analysis reported by Khandhar et al (2017), 210 patients received 417 fiducial markers. 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 one-month outcomes in 258 patients who had a total of 563 fiducial markers placed at 21 centers in the U.S. 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 postprocedure and showed that 239 of 254 markers remained in place (239/254). Fourteen patients (5.4%) experienced pneumothorax; in eight 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. 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 endpoint) 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 three (5%) unplanned hospital admissions, two cases of respiratory failure, and two cases of pneumothorax.

Schroeder et al (2010) reported findings from a prospective study with 52 patients who underwent placement of fiducial markers using ENB. 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; two were treated with chest tubes, and one 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. 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: ENB 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 eight patients in that study who had markers placed with ENB had data available. There are several 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 postprocedure). Pneumothorax of any grade occurred in 5.4% of patients, and grade 2 or higher pneumothorax occurred in
3.1%. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported through clinical input supports that this use provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice. 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. Further details from clinical input are included in the Clinical Input section and the Appendix.

**Summary of Evidence**

The following conclusions are based on a review of the evidence, including but not limited to, published evidence and clinical expert opinion, solicited via BCBSA’s Clinical Input Process.

For individuals who have suspicious peripheral pulmonary lesion(s) when flexible bronchoscopy alone or with endobronchial ultrasound is inadequate to sample the pulmonary lesion(s), the evidence includes meta-analyses, an RCT, and uncontrolled observational studies. A 2015 meta-analysis of 17 studies of ENB reported a large pooled positive likelihood ratio but a small negative likelihood ratio (0.22; 95% CI 0.15 to 0.32). Similarly, a 2014 meta-analysis of 15 studies found that navigation success was high, but diagnostic yield (64.9; 95% CI 59.2 to 70.3) and NPV (52.1; 95% CI 43.5 to 60.6) were relatively low. Both systematic reviews assessed the methodological quality of the evidence as low. Results from two 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 12-month diagnostic yield was 72.9%. Overall, 4.3% of patients experienced pneumothorax, and pneumothorax requiring hospitalization or intervention 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%. There were no deaths related to the ENB device. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported through clinical input supports that this use provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice. 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 2-4 times higher risk of pneumothorax than a bronchoscopic biopsy approach. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have enlarged MLNs who receive ENB with flexible bronchoscopy, the evidence includes an RCT and observational studies. 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. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported through clinical input is not generally supportive of a clinically meaningful improvement in net health outcome. MLN diagnosis was an early indication for ENB which has been largely replaced by EBUS. One could consider it in the uncommon scenario in which linear EBUS is not available and the patient is already having an ENB procedure for a peripheral nodule. 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 when flexible bronchoscopy alone or with endobronchial ultrasound is inadequate to place the markers near the pulmonary lesion(s), the evidence includes one comparative observational study and several case series. The 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 postprocedure). Pneumothorax of any grade occurred in 5.4% of patients, and grade 2 or higher pneumothorax occurred in 3.1%. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported through clinical input supports that this use provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice. 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. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**CLINICAL INPUT**
Objective
In 2019, clinical input was sought to help determine whether the use of INTERVENTION for POPULATION would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice.

Respondents
Clinical input was provided by the following specialty societies and physician members identified by a specialty society or clinical health system:

- Combined response from American Thoracic Society (ATS) and American College of Chest Physicians (CHEST)

Clinical input provided by the specialty society at an aggregate level is attributed to the specialty society. Clinical input provided by a physician member designated by a specialty society or health system is attributed to the individual physician and is not a statement from the specialty society or health system. Specialty society and physician respondents participating in the Evidence Street® clinical input process provide a review, input, and feedback on topics being evaluated by Evidence Street. However, participation in the clinical input process by a specialty society and/or physician member designated by a specialty society or health system does not imply an endorsement or explicit agreement with the Evidence Opinion published by BCBSA nor any Blue Plan.

Clinical Input Responses
ATS: American Thoracic Society; CHEST: American College of Chest Physicians

Additional Comments:
- “In summary, 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 patients.” (ATS and CHEST)
- “While standard flexible bronchoscopy has a lower overall yield than ENB, the trained bronchoscopist can determine standard bronchoscopy is adequate for sampling and only use the more advanced technology for the more challenging cases. This also applies to the improved yield with radial probe ultrasound-guided sampling of peripheral nodules. The added step of ENB, is by definition, needed in the more difficult patient who cannot be accommodated by the plain or ultrasound-guided bronchoscopy. In fact, the nonrandomized database studies actually demonstrate that with the selective use of ENB, the "low yield" is actually quite high for such a select patient population.

As committee members participated in the AQuiRE database (1), we can speak to actual experience. 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 (Note: planning is neither billable or reimbursable) and ENB was done only when the other approaches were inadequate.
Example: If the patient had suspicious lymph nodes and a suspicious nodule, convex probe (scope based) EBUS would be done first. If the diagnosis was made, no sampling of the nodule was required. If the lesion still needed sampling and was reachable by fluoroscopy or radial probe ultrasound, no ENB was done. Therefore, the ‘low yield’ quoted for ENB must be taken in context of the most challenging cases and is in fact quite remarkable.” (ATS and CHEST)

- “A properly selected procedure for the diagnosis of lung cancer requires consideration of both diagnosis and staging in the fewest possible procedures. Combining bronchoscopic techniques moves to the needed diagnostic steps and minimizes risks, without requiring additional procedures. Too often, patients undergo a CT guided biopsy with the associated risks, and then need to have a mediastinal staging procedure. Allowing the use of the proper bronchoscopic techniques, which may include ENB, saves steps, complications and costs in these challenging patients (3.4).” (ATS and CHEST)
- For Enlarged Mediastinal Nodes: “This was an early indication for ENB which has been largely replaced by EBUS. One could consider it in the uncommon scenario in which linear EBUS is not available and the patient is having a procedure for a peripheral nodule in any case.” (ATS and CHEST)
- “Fiducial markers are needed in some situations for targeted radiation therapy and localization for VATS resection. The lung moves during breathing, and proper targeting of tumors while accounting for respiratory variation minimizes damage to uninvolved tissue, particularly with stereotactic radiation therapy. A fiducial marker can be placed with bronchoscopic guidance or percutaneously. ENB has been shown to be an accurate and safe way to deploy fiducial markers of several different kinds (5).

When needed, placement can be done as a standalone procedure or at the same time as a diagnostic procedure (6). The key advantage to ENB placement is the markedly reduced risk of pneumothorax compared to the transthoracic approach. Realize that the 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 far outweighed by the safety advantage of ENB over a transthoracic approach.” (ATS and CHEST)

See Appendix for additional clinical input details and references cited in quotations above, which are included in response to Question 6.

SUPPLEMENTAL INFORMATION
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.
In response to requests, while this policy was under review in 2019, clinical input on the use of electromagnetic navigation bronchoscopy was received from 2 specialty society respondents offering a combined society-level response on behalf of both organizations, including input from physicians with academic medical center affiliations.

Evidence from clinical input is integrated within the Rationale section summaries and the Summary of Evidence.

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.22.

- "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.23. 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.24. 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 (eg, 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 ongoing trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<td>Dec 2019</td>
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<td>NCT03628222</td>
<td>Transbronchial Lung Biopsy Guided by Electromagnetic Navigation Bronchoscopy: A Prospective, Randomized, Multicenter, Superiority Study</td>
<td>226</td>
<td>Oct 2019</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.


REFERENCES
Billing Coding/Physician Documentation Information

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))

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 (eg, aspiration[s]/biopsy[ies]) and all mediastinal and/or hilar lymph node stations or structures and therapeutic intervention(s)

ICD-10 Codes

C34.00- C34.92 Malignant neoplasm of bronchus and lung code range

Code 31627 is an add-on code that is used in conjunction with CPT codes 31615, 31622, 31623, 31624, 31625, 31626, 31627, 31628, 31629, 31630, 31631, 31635, 31636, 31638, 31640, 31641 and 31643. Code 31627 includes 3-dimensional reconstruction so it should not be reported with codes 76376 and 76377.

Additional Policy Key Words

N/A

Policy Implementation/Update Information

1/1/10 New policy; considered investigational.
9/1/10 Policy statement added to consider use for the placement of fiducial markers as investigational.
9/1/11 No policy statement changes.
9/1/12 No policy statement changes.
9/1/13 No policy statement changes.
9/1/14 No policy statement changes.
9/1/15 No policy statement changes.
9/1/16 No policy statement changes.
9/1/17 No policy statement changes.
9/1/18 No policy statement changes.
9/1/19 Populations for peripheral pulmonary lesions and fiducial marker placement revised to specify subgroups of patients for whom flexible bronchoscopy alone or with endobronchial ultrasound are inadequate. Updated those indications to medically necessary.
State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.