DISCLAIMER

Our medical policies are designed for informational purposes only and are not an authorization, explanation of benefits or a contract. Receipt of benefits is subject to satisfaction of all terms and conditions of the coverage. Medical technology is constantly changing, and we reserve the right to review and update our policies periodically.

POLICY

Handheld radiofrequency spectroscopy for intraoperative assessment of surgical margins during breast-conserving surgery is considered **investigational**.

POLICY GUIDELINES

There is no specific CPT code for this spectroscopic assessment. An unlisted CPT code that might be used is 19499 unlisted procedure breasts.

BENEFIT APPLICATION

BLUE CARD/NATIONAL ACCOUNT ISSUES

State or federal mandates (e.g., Federal Employee Program) may dictate that certain U.S. Food and Drug Administration–approved devices, drugs, or biologics may not be considered investigational, and thus these devices may be assessed only by their medical necessity.

BACKGROUND

As part of the treatment of localized breast cancer, breast-conserving surgery is optimally achieved by attaining tumor-free margins around the surgical resection site. Failure to achieve clear margins will often require additional surgery to re-excise breast tissue. Currently, histologic examination of excised tissues after completion of surgery is the only method to determine definitively whether clear margins were achieved. Intraoperative methods of assessing surgical margins, such as specimen imaging, frozen section pathology, and touch print cytology, are either not highly accurate, not commonly available, or require considerable time and resources.

The MarginProbe device uses radiofrequency spectroscopy to measure the dielectric properties of tissue into which it comes in contact. Cancer cells and normal breast tissues produce different signals. A handheld probe is applied to a small area of the lumpectomy specimen and analyzes whether the tissue is likely malignant or benign. The device gives a positive or negative reading for each touch. If any touch on a particular margin gives a positive reading, the margin is considered to be positive and more tissue should be re-excised if possible. The device can only be used on the main lumpectomy specimen; it
The Intervention undergoing The Patients The outcome The breast should if shows practice Breast Clinical MARGINPROBE outside assess The no make original MEDLINE This RATIONALE in intraoperative identification In REGULATORY STATUS thus intended cannot avoiding the need for a second procedure to excise more breast tissue.

In January 2013, MarginProbe® (Dune Medical Devices, Caesarea, Israel) was approved by the U.S. Food and Drug Administration through the premarket approval process as an adjunctive diagnostic tool for identification of cancerous tissue at the margins (≤1 mm) of the main ex vivo lumpectomy specimen after primary excision. It is indicated for intraoperative use in conjunction with standard methods (e.g., intraoperative imaging and palpation) for patients undergoing lumpectomy for previously diagnosed breast cancer. Food and Drug Administration product code: OEE.

RATIONALE

This evidence review was created in August 2013 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through December 11, 2017. The original review was informed by a 2013 TEC Assessment.¹

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.

MARGINPROBE FOR BREAST CANCER MARGIN DETECTION

Clinical Context and Test Purpose
Breast cancer outcomes can be optimized by a thorough excision of breast cancer. A standard surgical practice of surgeons is to remove more breast tissue if pathologic examination of the initial excision shows positive margins. The purpose of MarginProbe is to evaluate the resected specimen to determine if further excision is necessary during the initial lumpectomy. The targeting of additional resection should reduce re-excision rates, maintain a low cancer recurrence rates, and minimize the volume of breast tissue excised.

The question addressed in this evidence review is: Does use of MarginProbe improve the net health outcome for individuals undergoing lumpectomy for localized breast cancer or ductal carcinoma in situ (DCIS)?

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

Patients
The relevant populations of interest are patients with localized breast cancer or DCIS who are undergoing lumpectomy.

Interventions
The technology being considered is MarginProbe as an adjunct to standard assessment of margins.
Comparators
The following practice is currently being used: standard intraoperative assessment of margins. This can vary, however, in different settings and the incremental benefit of MarginProbe may vary according to what is considered the standard intraoperative assessment.

Outcomes
The short-term outcome of interest is the re-excision rate. However, the re-excision rate can only be considered a valid outcome if all other downstream outcomes (e.g., local recurrence rate, long-term cancer outcome) are either equivalent or in favor of MarginProbe. For example, if the use of MarginProbe results in lower re-excision rates, but local cancer recurrence rates are higher, the adequacy of the initial treatment must be questioned.

Timing
MarginProbe is used during breast cancer surgery, with outcomes of interest including immediate re-excision rate and long-term recurrence and survival rates after cancer detection.

Setting
The setting is the outpatient surgical center.

Simplifying Test Terms
There are 3 core characteristics for assessing a medical test. Whether imaging, laboratory, or other, all medical tests must be:

- Technically reliable
- Clinically valid
- Clinically useful.

Because different specialties may use different terms for the same concept, we are highlighting the core characteristics. The core characteristics also apply to different uses of tests, such as diagnosis, prognosis, and monitoring treatment.

Diagnostic tests detect presence or absence of a condition. Surveillance and treatment monitoring are essentially diagnostic tests over a time frame. Surveillance to see whether a condition develops or progresses is a type of detection. Treatment monitoring is also a type of detection because the purpose is to see if treatment is associated with the disappearance, regression, or progression of the condition.

Prognostic tests predict the risk of developing a condition in the future. Tests to predict response to therapy are also prognostic. Response to therapy is a type of condition and can be either a beneficial response or adverse response. The term predictive test is often used to refer to response to therapy. To simplify terms, we use prognostic to refer both to predicting a future condition or to predicting a response to therapy.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.
Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Pivotal Trial
The evidence evaluating the efficacy of MarginProbe comes from the pivotal trial that led to device approval by the U.S. Food and Drug Administration.² An earlier study (2008) evaluating its use did not use the same classification algorithm and may not represent the current performance of the device.³ The reviewed trial reported the most relevant patient outcomes available for evaluating MarginProbe with the largest number of patients, including a large proportion of U.S. patients. In addition to clinical outcomes, the trial permitted assessments of diagnostic test performance of MarginProbe, which will help inform judgments of its utility.

The pivotal trial (NCT00749931) compared surgical processes and short-term outcomes in patients undergoing lumpectomies for non-palpable breast malignancies whose excised tissue was and was not assessed using MarginProbe. The control strategy did not include intraoperative histologic techniques, but did include radiographic imaging of the main resection specimen in addition to inspection and palpation of the resection specimen. The pivotal trial was a multicenter (21 sites) randomized study of 596 patients assigned equally to both treatment arms. Enrolled patients met criteria described in Food and Drug Administration labeling, but all also had non-palpable lesions that required image-guided localization. Trial design was complex and included several steps in sequence in which additional shavings of breast tissue could be taken during the operation. The declared principal outcome of the trial was called complete surgical resection, in which positive margins were either re-excised or specifically noted if not re-excised. It was not necessary for the re-excision to result in a clear margin. This outcome is not fully clinically relevant.

For the principal outcome, surgeries using MarginProbe had a rate of successful surgical excision of 71.8% vs 22.4% for controls, with positive margin subjects as the denominator. The large magnitude of difference was statistically significant. However, this outcome was biased against the control group and included non-clinically relevant events as outcomes, such as positive margins not resected. The volume of tissue resected, on both a relative and an absolute scale, was greater in the MarginProbe group, but the trial only presents conclusions of a non-inferiority analysis without specifying the non-inferiority margin.

More clinically relevant outcomes included the proportion of patients with positive margins on final pathology after surgery, which was 31% for the MarginProbe group and 42% for the control group (p=0.008). Some patients with positive margins in the MarginProbe group did not have positive margins in their main specimen on final pathology. However, due to false-positive MarginProbe readings, additional shavings were taken, and cancer tissue was found at the margin. Without these additional shavings in response to MarginProbe assessment, these patients would have been considered to have clear margins. This occurrence reflects the uncertainty of final pathology in ascertaining whether all cancer tissue had been removed. The uncertainty complicated the comparison of outcomes between groups because a measure usually considered a poor outcome (e.g., positive margin), in this case, was not due to inadequate surgery but to inadvertent discovery of residual cancer due to false-positive MarginProbe readings.

Re-excision rates using all patients enrolled in the trial as the denominator showed about a 5% absolute reduction in the MarginProbe group (28.5% vs 23.8%), which was not statistically significant. The
decision to reoperate was based on surgeon judgment of patient and tumor characteristics and the totality of pathologic findings. The trial did not assess outcomes beyond the short-term re-excision rate; thus, it is unknown whether the lower re-excision rates resulted in at least equivalent local recurrence rates. Without knowing whether recurrence rate is at least equivalent, a lower re-excision rate could reflect inadequate initial surgery.

The trial also reported the diagnostic characteristics of MarginProbe. Of 1788 margins with final histopathology, MarginProbe readings were valid or not missing in 1750 samples. Three hundred twenty-seven margins were positive, and MarginProbe was positive in 246, for a sensitivity of 75%. Of 1423 negative margins on final pathology, MarginProbe was negative in 660, for a specificity of 46%. These performance characteristics showing moderate sensitivity and poor specificity are consistent with better-than-random capability of the device in detecting positive margins. Given the 19% (327/1750) prevalence of positive margins, the positive predictive value of a positive MarginProbe test for a margin is 24%. In another analysis (performed or requested by the Food and Drug Administration) in which the location of the positive margin was ignored and the test was considered positive if any margin tested positive, MarginProbe was 96% sensitive but only 9% specific. Although this test performance characteristic is less clinically relevant, the low specificity in this trial indicates that MarginProbe was positive for at least 1 margin in almost every patient in the trial, even though the prevalence of at least 1 positive margin was 52%.

**Systematic Reviews**
A 2014 systematic review of techniques used for intraoperative assessment of margins in breast-conserving therapy for DCIS concluded that larger studies are needed to determine whether MarginProbe has a role to play in breast-conserving surgery. This conclusion was based on the pivotal trial previously reviewed and earlier studies.

A systematic review by St John et al (2017) of intraoperative techniques to assess margins following breast conservation surgery identified 55 studies, 35 of which were included in meta-analysis. The primary end point was diagnostic accuracy of the various techniques, which was based on pooled sensitivity, specificity, and area under the receiver operating characteristic curve. Reviewers found only one prospective study on MarginProbe, which was found to have a diagnostic accuracy of 68.2%, based in part on sensitivity (71.4%) and specificity (67.7%). Re-excision rates were a secondary outcome: of 57 patients in the MarginProbe study, 15.8% required re-excision during the initial surgery. Because there was only 1 study on the MarginProbe, it was not included in the meta-analysis. Other intraoperative techniques included in meta-analysis had pooled specificity ranging from 81% to 96%, depending on the modality, and pooled sensitivity ranging from 53% to 91%. The meta-analysis was limited by heterogeneity between studies in methodology and varying criteria for diagnosis and assessment of margins. A number of studies identified for the review could not be included in meta-analysis because of missing raw data.

**Nonrandomized Studies**
In 2014, Thill et al reported on final results of a 2011 cohort study of MarginProbe in DCIS. Forty-two (76%) of 55 patients enrolled from the general screening population at 3 centers in Germany were eligible for analysis. Patients underwent preoperative wire localization followed by breast-conserving surgery, with intraoperative assessment of the excised specimen by MarginProbe, radiograph, and paraffin-embedded pathologic review. MarginProbe also was used on additional shavings. Outcome measures were re-excision rate compared with a historical control rate of 39% and “procedure success,” defined as (1) negative margins after breast-conserving surgery and (2) early identification of an
extended lesion, with conversion to mastectomy rather than re-excision. Criteria for re-excision defined a negative margin of 5 mm. The historical cohort comprised 67 patients with DCIS who underwent breast-conserving surgery by the same surgeons involved in the study during the year before enrollment began. Because information about patient selection and baseline data were not provided for either cohort, it is unknown how comparable the 2 cohorts were. Re-excision rate was 17%, a statistically significant difference from the historical control rate (p=0.018) with MarginProbe, and “procedure success” occurred in 24 (57%) of 42 patients. Sensitivity was 57% (95% confidence interval [CI], 48% to 66%) and specificity was 50% (95 CI, 42% to 58%). It is possible that the observed reduction in the re-excision rate was due to an increased incidence of mastectomies.

A 2015 retrospective, multicenter, before-after study found a reduction in re-excision procedures from 26% to 10% after introduction of Margin Probe. Investigators reviewed case records of 4 surgeons in 3 centers who used individual (non-standardized), routine lumpectomy methods including criteria for re-excision (186 cases before MarginProbe; 165 cases with MarginProbe). For each surgeon, re-excision rates using MarginProbe were compared with those from a historical set, comprising a consecutive series of cases shortly before each surgeon started using MarginProbe. With the device, there were 28 cases in which the margin on the main specimen was clear, but the corresponding shaving contained cancer. Three (1.8%) of 165 patients in the “after” group underwent mastectomy; mastectomy rate in the “before” group was not reported. Performance characteristics (e.g., sensitivity, specificity) of Margin Probe cannot be calculated from these data. Other study limitations included lack of baseline description of the control (“before”) group, potential confounding by secular trends over time, and lack of recurrence outcomes.

A retrospective single-center study by Blohmer et al (2016) compared the use of MarginProbe in 150 patients with a historical control group of 172 patients. The 2 groups had approximately similar proportions of patients with invasive breast cancer and DCIS. The historical control group underwent gross pathology examination and radiogram of the specimen as standard intraoperative procedures. The principal outcome of the study was re-excision rate. In patients for whom MarginProbe was used, the re-excision rate was 14.6%; in the historical control group, it was 29.7%. Nothing in the study assessed the performance of MarginProbe, the criteria for re-excision, or long-term patient outcomes. The difference in the amount of breast tissue removed between strategies was not reported.

A retrospective single-center study by Coble et al (2017) compared the use of MarginProbe in 137 patients with a historical control group of 199 patients. The 2 groups had approximately similar demographic characteristics and proportions with invasive breast cancer and DCIS. The historical control group underwent standard lumpectomy followed by additional shavings taken circumferentially from all aspects of the cavity. The principal outcome of the study was re-excision rate. For procedures using MarginProbe, the re-excision rate was 6.6%; in the historical control group, the rate was 15.1%. The total volume of tissue (main specimen plus additional shavings) removed was also less in the MarginProbe cases (78 cm³ vs 116 cm³; p= 0.002).

Kupstas et al (2017) retrospectively reviewed charts of patients from a single center who were treated with MarginProbe during lumpectomy for invasive carcinoma and DCIS; 120 patients were intraoperatively assessed using standard of care, and 120 patients were intraoperatively assessed using the MarginProbe device. Reviewers found an improvement in the device group for the primary outcome, re-excision rate (9.2% of patients treated with MarginProbe required re-excision surgery vs 18.2% of those treated with standard of care; p=0.039). Included in this re-excision group were those who needed a second lumpectomy—5.8% (n=7) of the device group vs 15% (n=18) of the standard care group (p=0.020). The study population differed in initial specimen volume; the device group was with
significantly smaller breast volume on average (p=0.032). It also differed in the number of shavings required, as those in the device group tended to receive 1.5 more shavings than their counterparts. The final mean volume of removed tissue was comparable between the device group (53.6 mL) and the standard of care group (53.5 mL; p=0.974). Study limitations included the absence of long-term outcomes.

**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 randomized controlled trials.

No evidence was identified supporting the long-term utility of MarginProbe when used to assess surgical margins during lumpectomy for localized breast cancer or DCIS.

**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.

Current evidence does not support the clinical validity of MarginProbe, hence a chain of evidence cannot be constructed.

**Section Summary: Clinically Useful**
Although these nonrandomized retrospective studies showed a reduction in re-excision rate when using MarginProbe compared with historical controls, they were not rigorously controlled. Moreover, re-excision rate is an intermediate outcome that is only valid if long-term patient outcomes (eg, recurrence rate) are equivalent between MarginProbe and the alternative strategy. The available randomized controlled trial comparing short-term outcomes for patients undergoing breast surgery for nonpalpable breast malignancies managed with and without MarginProbe reported moderate sensitivity and low specificity, and did not find significant differences in re-excision rates between the 2 trial arms.

**SUMMARY OF EVIDENCE**
For individuals who have localized breast cancer or DCIS undergoing breast-conserving surgery (lumpectomy) who receive handheld radiofrequency spectroscopy for intraoperative assessment of surgical margins (e.g., MarginProbe), the evidence includes a randomized trial, several historical control studies, and a systematic review. Relevant outcomes are change in disease status and morbidity events. In the randomized trial, histologic examination of surgical margins was not used in the control arm; the outcome measure (complete surgical resection) was not directly clinically relevant and was biased against the control arm; and patient follow-up was insufficient to assess local recurrence rates. The difference in re-excision rates between the 2 trial arms was not statistically significant. Diagnostic characteristics of the device showed only moderate sensitivity and poor specificity; thus, the device will miss some cancers and provide frequent false-positive results. Although several historical control studies have shown lower re-excision rates among patients in whom MarginProbe was used, the studies lacked adequate rigor to demonstrate whether the outcomes are attributable to MarginProbe. The studies did not report recurrence outcomes, which is important for assessing adequacy of resection. A randomized
Handheld Radiofrequency Spectroscopy for Intraoperative Assessment of Surgical Margins During Breast-Conserving Surgery

A trial that assesses recurrence rates is required to evaluate whether the net health outcome improves with handheld radiofrequency spectroscopy compared with standard intraoperative surgical margin evaluation, including histologic techniques. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

Current National Comprehensive Cancer Network guidelines for breast cancer (v.3.2017) do not include recommendations for intraoperative assessment of surgical margins using radiofrequency spectroscopy for ductal carcinoma in situ or invasive breast cancer.\(^{14}\)

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

MEDICARE NATIONAL COVERAGE

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

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might impact this review are listed in Table 1.

Table 1. Summary of Key Trials

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<td>NCT02774785</td>
<td>Reducing Re-excisions After Breast Conserving Surgery: A Randomized Controlled Trial Comparing the MarginProbe Device in Addition to Standard Operating Procedure Versus Standard Operating Procedure Alone in Preventing Re-excision</td>
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<td>NCT02406599(^a)</td>
<td>MarginProbe® System U.S. Post-Approval Study Protocol CP-07-001</td>
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<td>Jan 2019</td>
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NCT: national clinical trial.
\(^a\) Denotes industry-sponsored or cosponsored trial.

REFERENCES


CODES

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