

7.01.140 Handheld Radiofrequency Spectroscopy for Intraoperative Assessment of Surgical Margins During Breast-Conserving Surgery			
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Section:	7.0 Surgery	Page:	Page 1 of 15

## Policy Statement

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

**NOTE:** Refer to [Appendix A](#) to see the policy statement changes (if any) from the previous version.

## Policy Guidelines

The following code is specific to radiofrequency spectroscopy:

- **0546T:** Radiofrequency spectroscopy, real time, intraoperative margin assessment, at the time of partial mastectomy, with report

## Description

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. Handheld radiofrequency spectroscopy for intraoperative assessment of surgical margins (e.g., MarginProbe) is intended to increase the probability that the surgeon will achieve clear margins in the initial procedure, thus avoiding the need for a second surgery to excise more breast tissue.

## Related Policies

- N/A

## Benefit Application

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

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

## Regulatory Status

In December 2012, MarginProbe® (Dune Medical Devices, Caesarea, Israel) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process as an adjunctive diagnostic tool for identification of cancerous tissue at the margins ( $\leq 1$  mm) of the main ex vivo lumpectomy specimen after primary excision (P110014). 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. FDA product code: OEE.

## Rationale

### 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.<sup>1</sup> Failure to achieve clear margins will often require additional surgery to re-excite 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.

A device to detect positive margins should have a high sensitivity, indicating the ability to accurately detect any tumor found in the margins, ideally above 95%. While specificity is less important, excess false-positive margin detection would lead to additional unnecessary tissue removal. A new device should have a specificity at least matching current standard best practices, estimated at 85%.<sup>2</sup>

The MarginProbe is an intraoperative device which 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 cannot be used on shavings or in the lumpectomy cavity of the patient's breast. Use of MarginProbe is intended to increase the probability that the surgeon will achieve clear margins in the initial surgery, thus avoiding the need for a second procedure to excise more breast tissue.

### Literature Review

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

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

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

### Handheld Radiofrequency 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. Handheld radiofrequency spectroscopy (for example, MarginProbe) evaluates the resected specimen to determine if further excision is necessary during the initial

lumpectomy. The use of handheld radiofrequency spectroscopy should reduce re-excision rates, maintain low cancer recurrence rate, and minimize the volume of breast tissue excised.

The following PICO was used to select literature to inform this review:

### ***Populations***

The relevant population of interest is patients with localized breast cancer or ductal carcinoma in situ (DCIS) who are undergoing lumpectomy.

### ***Interventions***

The technology being considered is handheld radiofrequency spectroscopy (for example, MarginProbe) as an adjunct to standard assessment of margins.

### ***Comparators***

The following practice is currently being used: standard intraoperative assessment of margins such as inspection, palpation, intraoperative imaging, and intraoperative histologic examination. The technique used can vary by institution and surgeon. The incremental benefit of handheld radiofrequency spectroscopy (for example, 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 long-term outcomes (e.g., local recurrence rate, long-term cancer outcome) are either equivalent or in favor of handheld radiofrequency spectroscopy (e.g., MarginProbe). For example, if the use of handheld radiofrequency spectroscopy results in lower re-excision rates, but local cancer recurrence rates are higher, the adequacy of the initial treatment must be questioned.

A handheld radiofrequency spectroscopy 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.

## **Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

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

## **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).

## **Review of Evidence**

### **Pivotal Trial**

The evidence evaluating the efficacy of MarginProbe comes from the pivotal trial by Allweis et al (2008) that led to device approval by the U.S. Food and Drug Administration (FDA).<sup>4,5,6,7</sup> 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 inform judgments of its utility.

The pivotal trial, MarginProbe, a Device for Intraoperative Assessment of Margin Status in Breast Conservation Surgery (NCT00749931) compared surgical processes and short-term outcomes in patients undergoing lumpectomies for nonpalpable breast malignancies whose excised tissue was and was not assessed using MarginProbe. In both arms, surgeons could use standard of care intraoperative methods such as palpation, specimen imaging, and gross and/or microscopic pathology assessments. 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 FDA labeling, but all also had nonpalpable 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 principal outcome of the trial was 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% versus 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 nonclinically 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 noninferiority analysis without specifying the noninferiority 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 ( $p=.008$ ). 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 not 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 FDA) 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%.

Geha et al. (2020) reported single-center results for the Columbia cohort ( $n = 46$ ).<sup>8</sup> Following conventional lumpectomy and intraoperative assessment, margins in 23 patients were additionally evaluated with MarginProbe. Data were collected until the earliest of the following events: 2 months after last surgery, conversion to mastectomy, or initiation of chemotherapy. The re-excision rate in the device group was significantly lower compared to control (4.3% vs. 34.8%;  $p=.022$ ). The authors hypothesize that the device re-excision rate at their study site was lower than previously reported for the multicenter trial due to a higher number of patients with DCIS in the device group (30%) compared to control (8%) who were surgically-managed with thicker tissue shavings in the case of device-reported margin involvement. Long-term excision and local recurrence rates were not reported for this cohort.

### Systematic Reviews

A systematic review by Butler-Henderson et al (2014) 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.<sup>9</sup> 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 a meta-analysis.<sup>10</sup> The primary endpoint 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 1 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. The MarginProbe study was not included in the meta-analysis. Other intraoperative techniques included in the 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 the meta-analysis because of missing raw data.

A systematic review by Gray et al (2018) on intraoperative margin management in breast-conserving surgery identified 5 articles involving radiofrequency spectroscopy in a literature search conducted in July 2016.<sup>11</sup> The evidence for MarginProbe showed a 70% specificity. Higher false-positive rates result in higher volumes of tissue removal. When the authors considered the improved positive margin detection balanced with the limited specificity, they concluded that the routine use of MarginProbe was not recommended (grade 2B recommendation).

A systematic review with meta-analysis by Rossou et al (2023) evaluated re-excision rates in studies of patients undergoing breast-conserving surgery for non-palpable DCIS or invasive breast cancer with intraoperative use of MarginProbe.<sup>12</sup> The authors included data from 4 RCTs and 8 nonrandomized studies comprising 2680 patients. Re-excision was reported in a mean of 10.93% ( $\pm 5.49\%$ ) of patients whose evaluation included MarginProbe compared with 25.8% ( $\pm 10.12\%$ ) of patients whose evaluation did not include use of MarginProbe ( $p=.001$ ). Calculated mean specificity and sensitivity were 63.47% and 69.07%, respectively. Other clinical outcomes were not analyzed.

### Nonrandomized Studies

Thill et al (2014) reported on final results of a 2011 cohort study of MarginProbe in patients with DCIS.<sup>13,14</sup> 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 ( $p=.018$ ) 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 retrospective, multicenter, before-after study by Sebastian et al (2015) found a reduction in re-excision procedures from 26% to 10% after introduction of MarginProbe.<sup>15</sup> Investigators reviewed case records of 4 surgeons in 3 centers who used individual (nonstandardized), 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; the mastectomy rate in the "before" group was not reported. Performance characteristics (e.g., sensitivity, specificity) of MarginProbe 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.<sup>16</sup> 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%. The study did not describe the criteria for re-excision or include long-term patient outcomes. The difference in the amount of breast tissue removed between strategies was also 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.<sup>17</sup> 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 cm<sup>3</sup> vs. 116 cm<sup>3</sup>;  $p=.002$ ).

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.<sup>18</sup> 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;  $p=.039$ ). Included in this re-excision group were those who needed a second lumpectomy 5.8% ( $n=7$ ) of the device group versus 15% ( $n=18$ ) of the standard care group ( $p=.020$ ). The study population differed in initial specimen volume. The device group was with significantly smaller breast volume on average ( $p=.032$ ). 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;  $p=.974$ ). A study limitation included the absence of long-term outcomes.

Gooch et al (2019) retrospectively reviewed charts of patients ( $n=341$ ) from a single center who underwent breast-conserving surgery with the aid of the MarginProbe device during lumpectomy from 2013 to 2017 to elucidate the relationship between mammographic breast density and positive lumpectomy margins.<sup>19</sup> A main lumpectomy specimen served as the index lesion assessed via the device. The final margin status was defined as the conclusion of the surgery, taking into account any additional margins excised after removal of the main specimen with the aid of the MarginProbe device. Mammographic breast density was not correlated with the likelihood of a final positive margin ( $p=.4564$ ). Higher mammographic breast density was associated with younger age ( $p<.0001$ ) and lower body mass index ( $p<.0001$ ). The MarginProbe device identified 135 margin-positive main specimens. Final margins were positive in 34 (25.2%) patients and negative in 101 (74.8%) patients. The MarginProbe device identified 206 margin-negative main specimens. Final margins were positive in 17 (8.3%) and negative in 189 (91.7%) patients. These findings correspond to a sensitivity of 66.7% and a specificity of 65.2%. Positive margins on the main lumpectomy specimen were correlated with larger tumor size ( $p<.001$ ), more advanced disease stage at diagnosis ( $p=.0247$ ), the presence of a palpable mass ( $p=.0010$ ), and an increased likelihood of subsequent re-excision ( $p=.0002$ ). The overall re-excision rates were 11.3% and 8.0% for patients with BI-RADS category ratings of A-B or C-D, respectively.

A prospective single-center study by LeeVan et al (2020) compared the use of MarginProbe for breast-conserving surgery in 60 patients with a historical control group.<sup>20</sup> Intraoperative margin assessment was performed with a surgical standard operating procedure consisting of specimen radiography and gross pathological examination. Re-excision surgery was defined as a return to the operating table for a subsequent procedure. However, criteria for re-excision surgery were not provided. While 8 patients (13.3%) had a final close or positive margin on pathology following use of MarginProbe, only 4 patients consented to re-excision surgery, yielding a re-excision rate of 6.6%. Four patients declined re-excision in favor of whole breast irradiation. Although this result was statistically lower compared to the historical re-excision rate of 8.6% ( $p<.01$ ), the authors concluded that this difference was not clinically meaningful. The sensitivity, specificity, negative predictive value, and positive predictive value for the use of MarginProbe were 67%, 60%, 16%, and 94% respectively, which was similar to standard protocol alone. Long-term outcomes and complete demographic characteristics for each group were not reported.

Cen et al (2021) published a retrospective review of patients in a single center's institutional breast cancer database who received both neoadjuvant chemotherapy and breast-conserving surgery ( $N=61$ ) between 2010 and 2018.<sup>21</sup> Median patient age was 51.8 years and the study population had diverse representation (White 43%, Black or African American 17%, Hispanic 24%, and Asian 17%). A complete response was achieved for 19 (31.1%) patients. Of the remaining 42 patients, 9 (21%) had margins that required re-excision. While the use of MarginProbe was associated with a lower re-excision rate (6% vs. 31%, respectively), this difference was not statistically significant. Long-term outcomes were not reported.

Hoffman et al (2022) conducted a prospective cohort study of patients undergoing breast-conserving surgery with the use of MarginProbe ( $N=48$ ) in a single-center general surgery department between 2018 and 2019.<sup>22</sup> Of the 48 patients included in the study, there were 51 total tumors analyzed. Out of 306 margins (in 51 tumors), 4 were not assessed by MarginProbe. MarginProbe correctly identified 3 of 13 positive margins; it also read 97 false positive readings of 289 true negative margins. These findings correspond to a sensitivity of 23.1% (95% CI, 5.0% to 53.8%), specificity of 66.4% (95% CI, 60.7% to 71.9%), positive predictive value of 3.0% (95% CI, 0.6% to 8.5%), and negative predictive value of 95.1% (95% CI, 91.1% to 97.6%).

Key limitations in relevance, design, and conduct of the identified studies are summarized in Tables 1 and 2.

**Table 1. Study Relevance Limitations**

Study	Population <sup>a</sup>	Intervention <sup>b</sup>	Comparator <sup>c</sup>	Outcomes <sup>d</sup>	Duration of Follow-Up <sup>e</sup>
Thill et al (2014) <sup>13</sup>				1. Re-excision rate is an intermediate outcome  3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values)	1. Long-term outcomes not reported
Sebastian et al (2015) <sup>15</sup>				1. Re-excision rate is an intermediate outcome  3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values)	1. Long-term outcomes not reported
Blohmer et al (2016) <sup>16</sup>				1. Re-excision rate is an intermediate outcome  3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values)	1. Long-term outcomes not reported
Coble et al (2017) <sup>17</sup>				1. Re-excision rate is an intermediate outcome  3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values)	1. Long-term outcomes not reported
Kupstas et al (2017) <sup>18</sup>				1. Re-excision rate is an intermediate outcome  3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values)	1. Long-term outcomes not reported
Gooch et al (2019) <sup>19</sup>				1. Re-excision rate is an intermediate outcome	1. Long-term outcomes not reported
LeeVan et al (2020) <sup>20</sup>				1. Re-excision rate is an intermediate outcome	1. Long-term outcomes not reported
Cen et al (2021) <sup>21</sup>				1. Re-excision rate is an intermediate outcome  3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values)	1. Long-term outcomes not reported
Hoffman et al (2022) <sup>22</sup>					1. Long-term outcomes not reported

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear;



4. Study population not representative of intended use.

<sup>b</sup> Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

<sup>c</sup> Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3.

Not compared to other tests in use for same purpose.

<sup>d</sup> Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4.

Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described

(excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).

<sup>e</sup> Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

**Table 2. Study Design and Conduct Limitations**

Study	Selection <sup>a</sup>	Blinding <sup>b</sup>	Delivery of Test <sup>c</sup>	Selective Reporting <sup>d</sup>	Data Completeness <sup>e</sup>	Statistical <sup>f</sup>
<b>Thill et al (2014)<sup>13</sup></b>	1. Information about patient selection and baseline data were not provided for either cohort					
<b>Sebastian et al (2015)<sup>15</sup></b>	1. There is a lack of baseline selection and description of the control group					
<b>Blohmer et al (2016)<sup>16</sup></b>			3. Did not describe the criteria for re-excision			
<b>Coble et al (2017)<sup>17</sup></b>						
<b>Kupstas et al (2017)<sup>18</sup></b>						
<b>Gooch et al (2019)<sup>19</sup></b>						
<b>LeeVan et al (2020)<sup>20</sup></b>	1. Complete demographic characteristic information and selection criteria for each group were not reported		3. Did not describe the criteria for re-excision			
<b>Cen et al (2021)<sup>21</sup></b>			3. Did not describe the criteria for re-excision			
<b>Hoffman et al (2022)<sup>22</sup></b>	1. Complete demographic characteristic information and selection criteria for each group were not reported					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).

<sup>b</sup> Blinding key: 1. Not blinded to results of reference or other comparator tests.

<sup>c</sup> Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.

<sup>d</sup> Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

<sup>e</sup> Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.

<sup>f</sup> Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

### **Clinically Useful**

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or 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 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: Handheld Radiofrequency for Breast Cancer Margin Detection**

Although the nonrandomized 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 (e.g., recurrence rate) are equivalent between MarginProbe and the alternative strategy. The single RCT comparing short-term outcomes for patients undergoing breast surgery for nonpalpable breast malignancies managed with and without MarginProbe reported no significant difference in re-excision rates between the 2 trial arms. In addition, both the sensitivity and specificity rates for the MarginProbe were lower than those for the current standard best practices.

### **Supplemental Information**

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

### **Practice Guidelines and Position Statements**

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

### **American Society of Breast Surgeons**

In 2015, the most current version of the American Society of Breast Surgeons performance and practice guidelines for breast-conserving surgery mention that specimens should be submitted for margin assessment either intraoperatively or post-surgically, depending on each institution's protocol. A recommendation for a specific margin assessment method over another was not made.<sup>23</sup>

In 2017, the American Society of Breast Surgeons issued a consensus guideline for breast cancer lumpectomy margins, providing an algorithm for re-excision surgery after lumpectomy or breast conservation for invasive or in-situ breast cancer. Margin definitions and treatment recommendations are based on inked specimen edges and do not include recommendations for the intraoperative assessment of surgical margins via radiofrequency spectroscopy.<sup>24</sup>

### National Comprehensive Cancer Network

Current (v. 5.2023 ) National Comprehensive Cancer Network guidelines for breast cancer do not include recommendations for intraoperative assessment of surgical margins using radiofrequency spectroscopy for ductal carcinoma in situ or invasive breast cancer.<sup>25</sup>

### 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 ongoing and unpublished trials that might impact this review are listed in Table 3.

**Table 3. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
<i>Unpublished</i>			
NCT02774785	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	127	Feb 2021 (completed)
NCT02406599 <sup>a</sup>	MarginProbe® System U.S. Post-Approval Study Protocol CP-07-001	440	Nov 2021
NCT00625417	Optical Spectroscopy in Evaluating Tumor Margins in Patients Who Have Undergone Surgery for Breast Tumors	180	December 2021

NCT: national clinical trial.

<sup>a</sup> Denotes industry-sponsored or cosponsored trial.

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## Documentation for Clinical Review

- No records required

## Coding

*This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.*

*The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.*

Type	Code	Description
CPT®	0546T	Radiofrequency spectroscopy, real time, intraoperative margin assessment, at the time of partial mastectomy, with report
HCPCS	None	

## Policy History

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

Effective Date	Action
11/26/2014	BCBSA Medical Policy adoption
05/01/2016	Policy revision without position change
04/01/2017	Policy revision without position change
04/01/2018	Policy revision without position change
04/01/2019	Policy revision without position change
04/01/2020	Annual review. No change to policy statement. Literature review updated.
04/01/2021	Annual review. No change to policy statement. Policy guidelines and literature review updated.
04/01/2022	Annual review. No change to policy statement. Policy guidelines and literature review updated.
04/01/2023	Annual review. No change to policy statement. Literature review updated.
04/01/2024	Annual review. No change to policy statement. Literature review updated.

## Definitions of Decision Determinations

**Medically Necessary:** Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished

primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

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

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

### Prior Authorization Requirements and Feedback (as applicable to your plan)

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

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at [www.blueshieldca.com/provider](http://www.blueshieldca.com/provider).

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: [MedPolicy@blueshieldca.com](mailto:MedPolicy@blueshieldca.com)

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

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	AFTER
<p>Handheld Radiofrequency Spectroscopy for Intraoperative Assessment of Surgical Margins During Breast-Conserving Surgery 7.01.140</p> <p>Policy Statement:</p> <p>I. Handheld radiofrequency spectroscopy for intraoperative assessment of surgical margins during breast-conserving surgery is considered <b>investigational</b></p>	<p>Handheld Radiofrequency Spectroscopy for Intraoperative Assessment of Surgical Margins During Breast-Conserving Surgery 7.01.140</p> <p>Policy Statement:</p> <p>I. Handheld radiofrequency spectroscopy for intraoperative assessment of surgical margins during breast-conserving surgery is considered <b>investigational</b>.</p>