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## Medical Policy



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**\*Current Policy Effective Date: 7/1/25**  
(See policy history boxes for previous effective dates)

### **Title: Handheld Radiofrequency Spectroscopy and Computer-aided fluorescence imaging During Breast-Conserving Surgery (e.g., MarginProbe, LumiSystem)**

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#### **Description/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 of definitively determining 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>1</sup>

MarginProbe® is an intraoperative device which uses radiofrequency spectroscopy that measures 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 resected surgical specimen and analyzes the tissue as to whether it is likely malignant or benign. During the operation, the surgeon touches the MarginProbe® device to each surface of the biopsy specimen. The device gives a reading of positive or negative for each touch. If any one of the touches on a particular margin gives a positive reading, the margin is considered positive and should be re-excised if possible. The device can only be used on the main lumpectomy specimen and cannot be used on shavings or in the lumpectomy cavity in the

patient's breast. Use of the MarginProbe® device is intended to increase the probability that the surgeon will achieve clear margins in the initial operation, thus avoiding the need for a second surgery to excise more breast tissue.

LumiSystem (Lumicell Inc.) is computer aided fluorescence imaging used to assist the intraoperative detection of cancerous tissue within the resection cavity following removal of the primary specimen during lumpectomy. LumiSystem is comprised of LUMISIGHT™ (pegulicianine), Lumicell™ Direct Visualization System (DVS), and proprietary software. Pegulicianine, is an optical imaging agent that is administered by intravenous injection 2 to 6 hours prior to imaging. It is optically inactive until it is cleaved by enzymes that are present in higher levels within and around tumor cells. Once cleaved, pegulicianine produces a fluorescent signal that is detected by the DVS. Areas with suspected residual cancer are highlighted on the computer screen, enabling the surgeon to identify areas in need of additional resection.

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## **Regulatory Status**

In January 2013, MarginProbe® received premarket approval (PMA) approval from FDA. The Dune MarginProbe®™ System is 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. 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. In 2016, MarginProbe® received FDA premarket approval on modifications which made the device compliant with the European Union's Restriction of Hazardous Substances requirements. Additional modifications included an updated results display screen and improved CPU. PMA product code: OEE.

Both the Lumicell Direct Visualization System and Lumisight (pegulicianine) were initially approved by the U.S. Food and Drug Administration (FDA) on April 17, 2024, under P230014 and NDA 214511, respectively. There have been 3 supplements to P230014 related to suppliers and sterilization procedures.

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## **Medical Policy Statement**

Handheld radiofrequency spectroscopy for intraoperative assessment of surgical margins during breast-conserving surgery is considered experimental/investigational. The evidence is insufficient to determine that the technology results in an improvement in net health outcome.

Computer-aided fluorescence imaging for intraoperative detection of cancerous tissue within the resection cavity during breast conserving surgery is considered experimental/investigational. The evidence is insufficient to determine that the technology results in an improvement in net health outcome.

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## **Inclusionary and Exclusionary Guidelines**

N/A

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**CPT/HCPCS Level II Codes** *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

**Established codes:**

N/A

**Other codes (investigational, not medically necessary, etc.):**

19499            0546T            0945T            A9615

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**Rationale**

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.

**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 practice of surgeons is to re-excise breast tissue if pathologic examination of tissue shows positive margins. Handheld radiofrequency spectroscopy (e.g., MarginProbe) evaluates the resected specimen to determine if further excision is necessary during the initial lumpectomy. The use of a handheld radiofrequency spectroscopy should reduce re-excision rates, maintain low cancer recurrence rate, and minimize the volume of breast tissue excised.

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

**Populations**

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

**Interventions**

The intervention of interest is use of 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 a handheld radiofrequency spectroscopy (e.g., 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, such as local recurrence rate or long-term cancer outcome, are either equivalent or in favor of MarginProbe®. If, for example, use of MarginProbe® results in lower re-excision rates, but local cancer recurrence rates are higher, the adequacy of initial treatment must be questioned.

A handheld radiofrequency spectroscopy (e.g., 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.

### **Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

- a. Comparative controlled prospective trials were sought, with preference for RCTs;
- b. In the absence of such trials, comparative observational studies were sought, with preference for prospective studies.
- c. To assess longer term outcomes and adverse effects, single-arm studies that capture longer periods of follow up and/or larger populations were sought.
- d. 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**

Evidence evaluating the efficacy of MarginProbe® comes from the pivotal trial by Allwels et al (2008) that led to Food and Drug Administration (FDA) approval.<sup>3-6</sup> An earlier study evaluating its use did not use the same classification algorithm and may not represent the current performance of the device. The reviewed trial reported the most relevant patient outcomes available for evaluating.<sup>5</sup> MarginProbe® with the largest number of patients, including a large proportion of U.S. patients. In addition to clinical outcomes, the trial allows assessments of diagnostic test performance of MarginProbe®, which will help inform judgments of its utility.

The pivotal trial, MarginProbe, a device for intraoperative assessment of margin status in breast conservation surgery 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 trial of 596 patients assigned equally to the two treatment arms. Enrolled patients met criteria described in FDA labeling, but also all 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 declared principal outcome of the trial was called complete surgical resection, in which positive margins were either re-excised or

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 of complete surgical resection, MarginProbe® showed a rate of 71.8% versus 22.4% for controls, with positive margin subjects as the denominator, which is a large magnitude of difference and statistically significant. However, this outcome is biased against the control group and includes non-clinically relevant events as outcomes, such as positive margins that were not resected. The volume of tissue resected on both a relative and absolute scale were greater in the MarginProbe® group, but data analysis 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% in the control group ( $p=0.008$ ). Some patients with positive margins in the MarginProbe® group did not have positive margins in their main specimen. 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 a clear margin.

This occurrence reflects the uncertainty of final pathology in trying to ascertain whether all cancer tissue has been removed. It complicates the comparison of outcomes between the 2 groups because a measure usually considered a poor outcome such as a positive margin, in this case, is not due to inadequate surgery but 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 outcome of re-excision rate; thus, it is unknown whether the lower re-excision rate 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. Three hundred twenty-seven margins were positive, and MarginProbe® was positive in 246, for a sensitivity of 75.2%. Of 1423 negative margins, MarginProbe® was negative in 660, for a specificity of 46.4%. 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 (apparently performed or requested by FDA) in which the location of the positive margin was ignored, and the test was considered positive if any margin tested positive, MarginProbe® was 96.3% sensitive but only 8.9% specific. Although this test performance characteristic is less clinically relevant, the low specificity in this trial indicates that MarginProbe® was positive for at least one margin in almost every patient in the trial, even though the prevalence of at least one positive margin was 52%.

Geha et al (2020) reported single-center results for the Columbia cohort ( $n = 46$ ).<sup>7</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%;  $P = 0.022$ ). 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 2014 systematic review by Butler-Henderson et al (2014) of techniques used for intraoperative assessment of margins in breast conserving therapy for ductal carcinoma in situ (DCIS) concluded that larger studies are needed to determine whether MarginProbe® has a role to play in breast-conserving surgery.<sup>8</sup> This conclusion was based on the pivotal trial reviewed above and earlier studies.

A 2017 systematic review by St John et al of intraoperative techniques to assess margins following breast conservation surgery identified 55 studies, 35 of which were included in meta-analysis.<sup>9</sup> 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 (AUROC). 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.

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>10</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).

### **Nonrandomized Studies**

In 2014, Thill et al reported final results of a cohort study of MarginProbe® in DCIS.<sup>11,12</sup> Forty-two (76%) of 55 patients enrolled from the general screening population at three 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 two cohorts were. Re-excision rate was 17%, a statistically significant difference from the historical control rate (Fisher exact test,  $p=0.018$ ), and “procedure success” occurred in 24 (57%) of 42 patients. Sensitivity was 57% (95 CI, 48% to 66%), and specificity was 50% (95 CI, 42% to 58%). It is possible that the observed reduction in the reduced 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>13</sup> Investigators reviewed case records of four surgeons in three centers who used individual (nonstandardized), routine lumpectomy methods including criteria for re-excision ( $n=186$  cases before MarginProbe®;  $n=165$  cases with MarginProbe®). For each surgeon, re-excision rates with the use of MarginProbe® were compared with those from a historical set, comprising a consecutive series of cases from a time period shortly before each surgeon started using MarginProbe®. With use of 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 and specificity) of MarginProbe® cannot be calculated from these data. Other study limitations include lack of baseline description of the control (“before”) group, potential confounding by secular trends over time, and lack of recurrence outcomes.

A 2016 retrospective single center study by Blohmer et al compared the use of MarginProbe® in 150 patients to a historical control group of 172 patients.<sup>14</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 the re-excision rate. In patients in whom MarginProbe® was used, the re-excision rate was 14.6%; in the historical control group the re-excision rate 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 is not reported.

A 2017 retrospective single center study by Coble et al compared the use of MarginProbe® in 137 patients to a historical control group of 199 patients.<sup>15</sup> The 2 groups of patients had approximately similar demographic characteristics and proportions of patients with invasive breast cancer and DCIS. The historical control group underwent a standard lumpectomy procedure followed by additional shavings taken circumferentially from all aspects of the cavity. The principal outcome of the study was the re-excision rate. In patients in whom MarginProbe® was used, the re-excision rate was 6.6%; in the historical control group the re-excision rate was 15.1%. The total volume of tissue (main specimen plus additional shavings) removed was also less in the MarginProbe® cases (78 cc versus 116 cc,  $p=0.0023$ ).

Kupstas et al (2017) retrospectively reviewed charts of patients from a single center who were treated with MarginProbe® during lumpectomy for invasive and ductal carcinoma in situ; 120 patients were intraoperatively assessed using standard of care, and 120 patients were intraoperatively assessed using the MarginProbe® device.<sup>16</sup> Reviewers found an improvement in the device group for the primary outcome, re-excision rate: 9.2% of patients who were treated with MarginProbe® required re-excision surgery, compared with 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 the initial specimen volume; the device group was significantly smaller 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 and standard of care group: respectively, 53.6 mL (standard deviation, 38.5) and 53.5 mL (standard deviation, 32.0;  $p=0.974$ ). Limitations to this study include 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>17</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 ( $p=0.4564$ ). Higher mammographic breast density was associated with younger age ( $p<0.0001$ ) and lower body mass index ( $p<0.0001$ ). 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 ( $p<0.001$ ), more advanced disease stage at diagnosis ( $p=0.0247$ ), the presence of a palpable mass ( $p=0.0010$ ), and an increased likelihood of subsequent re-excision ( $p=0.0002$ ). 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>18</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% ( $P < 0.01$ ), the authors conclude that this difference is not clinically meaningful. The sensitivity, specificity, NPV, and PPV for the use of MarginProbe was 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.

Gen 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>19</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% versus 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. [20](#). 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) <a href="#">11</a>				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) <a href="#">13</a>				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) <a href="#">14</a>				1. Re-excision rate is an intermediate outcome  3. Key clinical validity outcomes not reported	1. Long-term outcomes not reported

				(sensitivity, specificity and predictive values)	
Coble et al (2017) <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
Kupstas et al (2017) <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
Gooch et al (2019) <sup>17</sup>				1. Re-excision rate is an intermediate outcome	1. Long-term outcomes not reported
LeeVan et al (2020) <sup>18</sup>				1. Re-excision rate is an intermediate outcome	1. Long-term outcomes not reported
Cen et al (2021) <sup>19</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>20</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>
Thill et al (2014) <sup>11</sup>	1. Information about patient selection and baseline data were not provided for either cohort					
Sebastian et al (2015) <sup>13</sup>	1. There is a lack of baseline selection and description of the control group					
Blohmer et al (2016) <sup>14</sup>			3. Did not describe the criteria for re-excision			
Coble et al (2017) <sup>15</sup>						
Kupstas et al (2017) <sup>16</sup>						
Gooch et al (2019) <sup>17</sup>						
LeeVan et al (2020) <sup>18</sup>	1. Complete demographic characteristic information and selection criteria for each group were not reported		3. Did not describe the criteria for re-excision			
Cen et al (2021) <sup>19</sup>			3. Did not describe the criteria for re-excision			
Hoffman et al (2022) <sup>20</sup>	1. Complete demographic characteristic					

	information and selection criteria for each group were not reported					
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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, 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: 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 randomized controlled trial 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.

## LumiSystem

### Clinical Context and Test Purpose

The use of the LumiSystem to reduce re-excision rates, maintain low cancer recurrence rate, and minimize the volume of breast tissue excised.

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

### **Populations**

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

### **Interventions**

The intervention of interest is use of LumiSystem 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 the LumiSystem 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, such as local recurrence rate or long-term cancer outcome, are either equivalent or in favor of the LumiSystem.

### **Review of Evidence**

Smith et al (2020) assessed the LumiSystem for real-time, intraoperative detection of residual tumor in breast lumpectomy cases.<sup>21</sup> Breast lumpectomy cavity walls and excised specimens were assessed with the LUMImaging System after 1 mg/kg intravenous LUM015, a protease-activatable fluorescent agent. Fluorescence at potential sites of residual tumor in lumpectomy cavity walls was evaluated intraoperatively with a sterile hand-held probe, with real-time predictive results displayed on a monitor intraoperatively, and later correlated with histopathology. In vivo lumpectomy cavities and excised specimens were imaged after LUM015 injection in 45 women undergoing breast cancer surgery. Invasive ductal and lobular cancers and intraductal cancer (DCIS) were included. A total of 570 cavity margin surfaces in 40 patients were used for algorithm development. Image analysis and display took approximately 1 s per 2.6-cm-diameter circular margin surface. All breast cancer subtypes could be distinguished from adjacent normal tissue. For all imaged cavity surfaces, sensitivity for tumor detection was 84%. Among 8 patients with positive margins after standard surgery, sensitivity for residual tumor detection was 100%; 2 of 8 were spared second surgeries because additional tissue was excised at sites of LUM015 signal. Specificity was 73%, with some benign tissues showing elevated fluorescent signal. The authors have made note that several factors may have contributed to creating false positive readings and other factors affected the systems performance.

Lanahan et al (2021) reported on the LumiSystem's impact on surgical workflow and performance across patient and tumor types.<sup>22</sup> The authors performed IRB-approved, prospective, non-randomized studies in breast cancer lumpectomy procedures. The LUM Imaging System uses LUM015, a protease-activated fluorescent imaging agent that identifies residual tumor in the surgical cavity walls. Fluorescent cavity images were collected in real-time and analyzed using system software. Cavity and specimen images were obtained in 55

patients injected with LUM015 at 0.5 or 1.0mg/kg and in 5 patients who did not receive LUM015. All tumor types were distinguished from normal tissue, with mean tumor: normal (T:N) signal ratios of 3.81-5.69. T:N ratios were 4.45 in non-dense and 4.00 in dense breasts ( $p = 0.59$ ) and 3.52 in premenopausal and 4.59 in post-menopausal women ( $p = 0.19$ ). Histopathology and tumor receptor testing were not affected by LUM015. Falsely positive readings were more likely when tumor was present  $< 2$  mm from the adjacent specimen margin. LUM015 signal was stable in vivo at least 6.5 h post injection, and ex vivo at least 4 h post excision. The authors concluded that intraoperative use of the LUM Imaging System detected all breast cancer subtypes with robust performance independent of menopausal status and breast density. There was no significant impact on histopathology or receptor evaluation.

Hwang et al (2022), in a pilot feasibility study, collected safety and initial efficacy data on the LumiSystem when used to identify residual cancer in the tumor bed of female patients undergoing breast conserving surgery (BCS).<sup>23</sup> This prospective single-arm open-label study was conducted as a nonrandomized multicenter controlled trial at 16 academic or community breast centers across the US. Female patients 18 years and older with newly diagnosed primary invasive breast cancer or ductal carcinoma in situ DCIS undergoing BCS were included, excluding those with previous breast cancer surgery and a history of dye allergies. Of 283 consecutive eligible patients recruited, 234 received a pegulicianine injection and were included in the safety analysis; of these, 230 were included in the efficacy analysis. Of 234 female patients enrolled (median [IQR] age, 62.0 [55.0-69.0] years), 230 completed the trial and 1 patient with a history of allergy to contrast agents had an anaphylactic reaction and recovered without sequelae. Correlation of pFGS with final margin status on a per-margin analysis showed an improvement in sensitivity over standard pathology assessment of the main lumpectomy specimen (69.4% vs 38.2%, respectively). On a per-patient level, the false-negative rate of pFGS was 23.7% (9 of 38), and sensitivity was 76.3% (29 of 38). Among 32 patients who underwent excision of pFGS-guided shaves, pFGS averted the need for re-excision in 6 (19%).

Smith et al (2023) assessed margin status with or without pegulicianine fluorescence-guided surgery (pFGS) for stages 0 to 3 breast cancers in a prospective trial.<sup>24</sup> Patients were randomly assigned 10:1 to pFGS or control groups, thus randomization was not designed to provide a control group for evaluating device performance, but to prevent surgeons from performing smaller than standard lumpectomies in anticipation of pFGS assistance. In patients undergoing pFGS, additional pFGS-guided cavity margins were excised at sites of pegulicianine signal. The authors evaluated three coprimary end points: the percentage of patients for whom pFGS-guided margins contained cancer, sensitivity, and specificity. Overall, 406 patients received 1.0 mg/kg intravenous pegulicianine followed by lumpectomy. Among 392 patients randomly assigned, 316 had invasive cancers, and 76 had in situ cancers. In 27 of 357 patients undergoing pFGS, pFGS-guided margins removed tumor left behind after standard lumpectomy, 22 from cavity orientations deemed negative on standard margin evaluation. Second surgeries were avoided by pFGS in 9 of 62 patients with positive margins. On per-margin analysis, pFGS specificity was 85.2%, and sensitivity was 49.3%. Pegulicianine administration was stopped for adverse events in six patients. Two patients had grade 3 serious adverse events related to pegulicianine. The authors concluded that the use of pFGS in breast cancer surgery met prespecified thresholds for removal of residual tumor and specificity but did not meet the prespecified threshold for sensitivity.

## SUMMARY OF EVIDENCE

For individuals who have localized breast cancer or ductal carcinoma in situ 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 (relapse rates) and morbid events (re-excision rates). In the randomized trial, histologic examination of surgical margins was not employed 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 have frequent false-positive results. Although several historical control studies show a lower re-excision rate among patients in whom MarginProbe® was used, the studies are not adequately rigorous to demonstrate whether the outcomes are attributable to use of MarginProbe®. The studies do not report recurrence outcomes, which is an important outcome for assessing adequacy of resection. A randomized trial that assesses recurrence rates is required to evaluate whether the net health outcome is improved 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.

For individuals who have localized breast cancer or ductal carcinoma in situ undergoing breast-conserving surgery (lumpectomy) who receive computer-aided fluorescence imaging (LumiSystem) for intraoperative assessment of surgical margins, the evidence includes a three cross sectional studies and one cohort study. These studies do not report on local recurrence rates or long-term cancer outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

## Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 3.

**Table 3. Summary of Key Trials**

<b>NCT No.</b>	<b>Trial Name</b>	<b>Planned Enrollment</b>	<b>Completion Date</b>
<i>Ongoing</i>			
<i>Unpublished</i>			
NCT02406599 <sup>a</sup>	MarginProbe® System U.S. Post-Approval Study Protocol CP-07-001	440	Nov 2021 (active, not recruiting)
NCT00625417	Optical Spectroscopy in Evaluating Tumor Margins in Patients Who Have Undergone Surgery for Breast Tumors	180	Nov 2023 (recruiting)
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)

NCT: national clinical trial

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

## SUPPLEMENTAL INFORMATION

## PRACTICE GUIDELINES AND POSITION STATEMENTS

### National Comprehensive Cancer Network

Current National Comprehensive Cancer Network guidelines for breast cancer (version 2. 2025) do not include recommendations for intraoperative assessment of surgical margins using radiofrequency spectroscopy or computer-aided fluorescence imaging for either DCIS or invasive breast cancer.<sup>25</sup>

### American Society of Breast Surgeons

The most current version of the American Society of Breast Surgeons' performance and practice guidelines for breast-conserving surgery (2015) mention that specimens should be submitted for margin assessment either intraoperatively or post-surgery, depending on each institution's protocol. A recommendation for one margin assessment method over another was not made.<sup>26</sup>

In 2024, the American Society of Breast Surgeons issued a resource guideline for breast cancer surgery margins for re-excision surgery after lumpectomy or breast conservation for invasive or in-situ breast cancer.<sup>27</sup> The guideline does not include recommendations for the intraoperative assessment of surgical margins via radiofrequency spectroscopy or computer-aided fluorescence imaging.<sup>27</sup>

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## Government Regulations

### National/Local:

There is no national or local coverage determination on this topic.

*(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)*

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## Related Policies

- Optical Coherence Tomography of the Breast and/or Axillary Lymph Nodes

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*The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through March 2025, the date the research was completed.*

### Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
7/1/15	4/21/15	5/8/15	Joint policy established
7/1/16	4/19/16	4/19/16	Routine maintenance
7/1/17	4/18/17	4/18/17	Updated rationale and reference sections (add # 10 & 11). Policy status unchanged.
7/1/18	4/17/18	4/17/18	Routine policy update added reference #7. No changes in policy status.
7/1/19	4/16/19		Routine policy maintenance. Added references 1, 9 and 17. No change in policy status.
7/1/20	4/14/20		Routine policy maintenance. Added references #16. No change to policy status.
7/1/21	4/20/21		Routine policy maintenance, added references #7 and 18. No change in policy status.
7/1/22	4/19/22		Routine policy maintenance added reference #19. No change in policy status.
7/1/23	4/18/23		Routine policy maintenance added reference #20, no change in policy status. Vendor managed: N/A. (ds)
7/1/24	4/16/24		Routine policy maintenance. No change in policy status. Vendor managed: N/A (ds)
7/1/25	4/15/25		Added LumiSystem to policy as E/I, Codes 0945T & A9615 added as E/I, updated rationale, references 21-24 added. No change in policy status. Vendor managed: N/A (ds)

Next Review Date: 2<sup>nd</sup> Qtr. 2026

## BLUE CARE NETWORK BENEFIT COVERAGE

### POLICY:

#### HANDHELD RADIOFREQUENCY SPECTROSCOPY AND COMPUTER-AIDED FLUORESCENCE IMAGING DURING BREAST-CONSERVING SURGERY (E.G. MARGINPROBE, LUMISYSTEM)

##### I. Coverage Determination:

<b>Commercial HMO (includes Self-Funded groups unless otherwise specified)</b>	Not covered.
<b>BCNA (Medicare Advantage)</b>	See government section.
<b>BCN65 (Medicare Complementary)</b>	Coinsurance covered if primary Medicare covers the service.

##### II. Administrative Guidelines:

N/A