I. POLICY

Handheld radiofrequency spectroscopy for intraoperative assessment of surgical margins during breast-conserving surgery is considered investigational as there is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

II. PRODUCT VARIATIONS

This policy is applicable to all programs and products administered by Capital BlueCross unless otherwise indicated below.

FEP PPO*
*Refer to FEP Medical Policy Manual MP-7.01.140 Handheld Radiofrequency Spectroscopy for Intraoperative Assessment of Surgical Margins during Breast-Conserving Surgery. The FEP Medical Policy manual can be found at: www.fepblue.org

III. DESCRIPTION/BACKGROUND

Breast-conserving surgery as part of the treatment of localized breast cancer is optimally achieved by attaining margins around the surgical resection that are free from tumor cells. MarginProbe® 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.

Breast-conserving surgery as part of the treatment of localized breast cancer is optimally achieved by attaining margins around the surgical resection that are free from tumor cells. 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. Intra-operative 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.

MarginProbe® is a device based on the principles of dielectric spectroscopy that characterizes tissue that the device comes in contact with. 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 to be 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.

Regulatory Status

In January 2013, MarginProbe® received PMA approval from the Food and Drug Administration (FDA). The Dune MarginProbe®™ System is an adjunctive diagnostic tool for identification of cancerous tissue at the margins (≤ 1mm) of the main ex-vivo lumpectomy specimen following primary excision and is indicated for intraoperative use in conjunction with standard methods (such as intraoperative imaging and palpation) for patients undergoing lumpectomy for previously diagnosed breast cancer.

IV. RATIONALE

Evidence evaluating the efficacy of MarginProbe® comes from the pivotal trial that led to Food and Drug Administration (FDA) approval. 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 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 (NCT00749931) compared surgical processes and short-term outcomes in patients in whom MarginProbe® was used versus patients in whom margin probe was not used. The control strategy did not include intraoperative histologic techniques but did include radiographic imaging of the main resection specimen in addition to inspection and palpation of the resection specimen. The pivotal trial was a multicenter (21 sites) randomized trial of 596
patients assigned equally to the 2 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. Thus, this outcome is not fully clinically relevant.

For the principal outcome, 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 was biased against the control group and included nonclinically relevant events as outcomes, such as positive margins not resected. Volume of tissue resected, on both a relative and an absolute scale, was greater in the MarginProbe® group, but the study 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 1 margin in almost every patient in the trial, even though the prevalence of at least 1 positive margin was 52%.

A 2014 systematic review 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. This conclusion was based on the pivotal trial reviewed above and earlier studies.

In 2014, Thill et al reported final results of a cohort study of MarginProbe® in DCIS. Forty-two (76%) of 55 patients enrolled from the general screening population at 3 centers in Germany were eligible for analysis. Patients underwent preoperative wire localization followed by breast-conserving surgery, with intraoperative assessment of the excised specimen by MarginProbe®, radiograph, and paraffin-embedded pathologic review. MarginProbe® also was used on additional shavings. Outcome measures were re-excision rate compared with a historical control rate of 39% and “procedure success,” defined as (1) negative margins after breast-conserving surgery and (2) early identification of an extended lesion, with conversion to mastectomy rather than re-excision. Criteria for re-excision defined a negative margin of 5 mm. The historical cohort comprised 67 patients with DCIS who underwent breast-conserving surgery by the same surgeons involved in the study during the year before enrollment began. Because information about patient selection and baseline data were not provided for either cohort, it is unknown how comparable the 2 cohorts were. Re-excision rate was 17%, a statistically significant difference from the historical control rate (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 randomized trial that assesses recurrence is required to demonstrate improvement in net health outcome with MarginProbe®.

A 2015 retrospective, multicenter, before-after study found a reduction in re-excision procedures from 26% to 10% after introduction of Margin Probe®. Investigators reviewed case records of 4 surgeons in 3 centers who used individual (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.

**Ongoing and Unpublished Clinical Trials**
Some currently unpublished trials that might impact this review are listed in Table 1.

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td>MarginProbe® System U.S. Post-Approval Study Protocol CP-07-001</td>
<td>440</td>
<td>Jan 2019</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

Denotes industry-sponsored or cosponsored trial.

**Summary of Evidence**
The evidence for the use of handheld radiofrequency spectroscopy for intraoperative assessment of surgical margins (i.e., MarginProbe®) in patients with breast cancer or ductal carcinoma in situ (DCIS) who are undergoing breast-conserving surgery (lumpectomy) includes 1 randomized trial, 2 observational studies, and 1 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. A subsequent cohort study in women with DCIS showed poor sensitivity and specificity and suggested that more mastectomies may be performed with MarginProbe®. A retrospective before-after study examined re-excision rates rather than recurrence outcomes. A randomized trial that assesses recurrence is required to evaluate whether net health outcome is improved with MarginProbe® compared with standard intraoperative surgical margin evaluation, including histologic techniques. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Practice Guidelines and Position Statements**

**National Comprehensive Cancer Network**
Current National Comprehensive Cancer Network guidelines for breast cancer (v.2.2015) do not include recommendations for intraoperative assessment of surgical margins using radiofrequency spectroscopy for either DCIS or invasive breast cancer.\(^{10}\)

**U.S. Preventive Services Task Force Recommendations**
Not applicable.

Medicare National Coverage
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

V. DEFINITIONS

N/A

VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member’s contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

VII. DISCLAIMER

Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.
There is no specific CPT code for this Spectroscopic assessment.

Investigational therefore not covered:

<table>
<thead>
<tr>
<th>CPT Codes®</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>19499</td>
<td></td>
</tr>
</tbody>
</table>

IX. REFERENCES

X. **Policy History**

<table>
<thead>
<tr>
<th>Policy Number</th>
<th>Issue Date</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CAC 11/25/14</td>
<td>Consensus review. References and rationale updated. No changes to the policy statements. FEP variation added to refer to the FEP medical policy manual.</td>
</tr>
<tr>
<td></td>
<td>CAC 11/24/15</td>
<td>Consensus review. No change to policy statements. References and rationale updated. Coding reviewed.</td>
</tr>
<tr>
<td></td>
<td>CAC 9/27/16</td>
<td>Consensus. No change to policy statements. References and rationale updated. Variation reformatted. Coding reviewed.</td>
</tr>
</tbody>
</table>

*Health care benefit programs issued or administered by Capital BlueCross and/or its subsidiaries, Capital Advantage Insurance Company®, Capital Advantage Assurance Company® and Keystone Health Plan® Central. Independent licensees of the BlueCross BlueShield Association. Communications issued by Capital BlueCross in its capacity as administrator of programs and provider relations for all companies.*