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

[N] = No product variation, policy applies as stated
[Y] = Standard product coverage varies from application of this policy, see below

[N] Capital Cares 4 Kids
[N] PPO
[N] HMO
[N] SeniorBlue HMO
[N] SeniorBlue PPO

[N] Indemnity
[N] SpecialCare
[N] POS
[N] FEP PPO

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
<table>
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<th>Policy Title</th>
<th>Handheld Radiofrequency Spectroscopy for Intraoperative Assessment of Surgical Margins during Breast-Conserving Surgery</th>
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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. 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.

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 FDA documents describing the clinical trial that led to FDA approval. (2) The trial has not yet been published in a peer-reviewed journal as of May 2013. An earlier study evaluating its use did not use the same classification algorithm and may not represent the current performance of the device. (3) The reviewed study reports 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 study allows assessments of diagnostic test performance of MarginProbe®, which will help inform judgments of its utility.

The pivotal study 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 of the resection specimen. The pivotal study was a multicenter (21 sites) randomized study of 596 patients assigned equally to the two arms of the study.

Patients enrolled in the study met criteria mentioned in the FDA labeling, but also all had non-palpable lesions that required image-guided localization. The study design was complex and included several steps in the study 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 and appears to be biased against the control arm of the study.

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. Volume of tissue resected on both a relative and absolute scale were greater in the MarginProbe® group, but the data analysis only presents conclusions of a non-inferiority analysis. The non-inferiority margin for the normalized total tissue volume was not specified.

More clinically relevant outcomes include 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=0.0082). Some patients with positive margins in the MarginProbe® group arise from subjects that did not have positive margins in their main specimen. However, due to false positive MarginProbe® readings, additional shavings were undertaken in which cancer tissue was found at the margin. Without these additional shavings taken 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 two 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 study 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 re-operate was based on judgment of the surgeon.
based on patient and tumor characteristics and the totality of pathologic findings. The study does not assess outcomes beyond the short-term outcome of the re-excision rate; thus it is unknown if the lower re-excision rates resulted in at least equivalent local recurrence rates. Without knowing if the recurrence rate is at least equivalent, a lower re-excision rate could reflect inadequate initial surgery.

The study also reports the diagnostic characteristics of MarginProbe. Out of 1,788 margins with final histopathology, MarginProbe® readings were valid or not missing in 1,750. Three hundred twenty seven margins were positive, and MarginProbe® was positive in 246 for a sensitivity of 75.2%. Out 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 study indicates that MarginProbe® was positive for at least one margin in almost every patient in the study, even though the prevalence of at least one positive margin was 52%.

Conclusions: The reviewed study showed a non-statistically significant difference in the re-excision rate in the two study arms. The declared principal outcome of the study, complete surgical resection, is not directly clinically relevant and is biased against the control arm of the study. The study does not follow patients long enough to assess the local recurrence rate, which would be important to assess when evaluating the adequacy of initial excision. The diagnostic characteristics of the device show only moderate sensitivity and poor specificity; thus the device will miss some cancers and have frequent false positive results.

Ongoing Clinical Trials

No ongoing studies on MarginProbe® for assessment of surgical margins during breast conservation surgery are currently listed at online site ClinicalTrials.gov.

Summary

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. Handheld radiofrequency spectroscopy for intraoperative assessment of surgical margins (i.e., 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. The one clinical trial of MarginProbe® does not provide sufficient evidence that it improves the adequacy of initial surgical treatment of localized breast cancer. This device has not been assessed in comparison to other techniques of
intraoperative margin assessment. Lacking evidence for improved net health outcomes, the use of handheld radiofrequency spectroscopy for intraoperative assessment of surgical margins during breast conservation surgery is considered investigational.

**Practice Guidelines and Position Statements**

There are no clinical practice guidelines or position statements related to this device.

**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:**

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*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

**The following ICD-10 diagnosis codes will be effective October 1, 2014:**

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IX. REFERENCES

1. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Handheld Radiofrequency Spectroscopy for Intraoperative Margin Assessment During Breast-Conserving Surgery. TEC Assessments 2013, Volume 28, Tab TBD.


X. POLICY HISTORY