Prior Authorization Review Panel
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
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Plan: Keystone First Community HealthChoices	**Submission Date**: 10/27/2023
Policy Number: ccp.1430	**Effective Date:** 12/2019 **Revision Date:** October 1, 2023
Policy Name: MarginProbe®	

Type of Submission – Check all that apply:

x New Policy
Revised Policy*
Annual Review – No Revisions
Statewide PDL

***All revisions to the policy must be highlighted using track changes throughout the document.**

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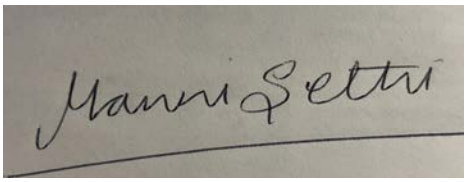
New submission

Name of Authorized Individual (Please type or print): Manni Sethi, MD, MBA, CHCQM	**Signature of Authorized Individual:** 

Keystone First
Community HealthChoices

MarginProbe®

Clinical Policy ID: CCP.1430

Recent review date: 10/2023

Next review date: 2/2025

Policy contains: Breast cancer, lumpectomy, MarginProbe; radiofrequency spectroscopy; tumor margin.

Keystone First Community HealthChoices has developed clinical policies to assist with making coverage determinations. Keystone First Community HealthChoices' clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by Keystone First Community HealthChoices when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Keystone First Community HealthChoices' clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Keystone First Community HealthChoices' clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First Community HealthChoices will update its clinical policies as necessary. Keystone First Community HealthChoices' clinical policies are not guarantees of payment.

Coverage policy

MarginProbe® (Dune Medical Devices Inc., Framingham, Massachusetts, now distributed by Dilon Technologies, Inc., Newport News, Virginia) is investigational/not clinically proven and, therefore, not medically necessary for increasing the efficacy of a breast cancer lumpectomy procedure.

Limitations

No limitations were identified during the writing of this policy.

Alternative covered services

Standard tissue histopathology assessment.

Background

Early-stage breast cancer is defined as having a tumor size of 4 cm or less, with three or fewer positive nodes. In women with early breast cancer, 70% elect lumpectomy, a type of breast-conserving surgery (Agarwal, 2014). Lumpectomy, combined with subsequent radiation, is as effective or more effective in the treatment of early-stage breast cancer as mastectomy alone or mastectomy with radiation and is associated with reduced mortality compared with these other procedures (Agarwal, 2014; Kurian, 2014).

The efficacy of lumpectomy is achieved by attaining tumor-free margins around the surgical resection site. When tumor-free margins are not obtained, additional surgery to re-excise breast tissue is often necessary. Histologic examination of excised tissues after completion of surgery is the sole method of ascertaining whether clear margins were achieved. The evaluation of surgical margins during surgery through methods such as specimen imaging, frozen section pathology, or touch print cytology is either not sufficiently accurate or not feasible due to

unavailability or the length of time needed for testing. Thus, intraoperatively determining whether surgical margins are clear would enhance the efficacy of the primary lumpectomy procedure.

The MarginProbe System is a handheld radiofrequency spectroscopy diagnostic device designed to intraoperatively identify cancerous tissue at the margins of excision specimens, along with standard methods (such as intraoperative imaging and palpation), in patients undergoing breast lumpectomy for previously diagnosed breast cancer. It is not intended to replace standard tissue histopathology assessment (Dilon Technologies, 2022).

MarginProbe uses radiofrequency spectroscopy to measure the dielectric properties of tissue with which it comes in contact. The handheld probe is applied to a small area of the excised lumpectomy specimen within 20 minutes of removal. It analyzes whether the margins are likely malignant or benign based on the different signals produced by cancer cells as compared to normal breast tissues. 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. MarginProbe was granted expedited review status as the first device of its kind, and received premarket approval from the U.S. Food and Drug Administration in 2012 (U.S. Food and Drug Administration, 2022).

Findings

The National Comprehensive Cancer Network's (2023) guideline for the evaluation of margin status does not include use of an intraoperative device for assessing tissue specimens. For invasive breast cancer (with or without ductal carcinoma in situ) undergoing lumpectomy with whole breast radiation, "no ink on tumor" is the applied definition of negative margin, whereas for ductal carcinoma in situ with or without microinvasion treated with lumpectomy and radiation, margins should be at least 2 millimeters.

Likewise, a consensus guideline from the Society of Surgical Oncology, American Society for Radiation Oncology, and the American Society of Clinical Oncology recommends the 2 millimeters margin as the standard for an adequate margin in patients with ductal carcinoma in situ treated with whole body radiation therapy. Margins of at least 2 millimeters are associated with a reduced risk of ipsilateral breast tumor recurrence compared with positive margins defined as ink on ductal carcinoma in situ. Clinical judgment should be used in determining the need for further surgery in patients with negative margins less than 2 millimeters. The guideline discusses limitations in intraoperative margin assessment but does not mention MarginProbe as an alternative (Morrow, 2016). In 2015, the American Society of Breast Surgeons Consensus Conference produced recommendations to reduce the variability of reoperation rates and improve cosmetic outcomes in patients undergoing breast conserving surgery for cancer. While a randomized trial (Schnabel, 2014) found MarginProbe was associated with fewer reoperations, the majority voted to omit these devices from consideration until further investigation (Landercasper, 2015).

Systematic reviews that examined MarginProbe include:

- Various techniques for margin assessment, including MarginProbe, require more large studies before conclusions can be made (Butler-Henderson, 2014).
- Of 35 studies, only one included MarginProbe, which had sensitivity and specificity rates of 71.4% and 67.7% (St. John, 2017).

- MarginProbe had a specificity rate of 70%, leading authors to note that the relatively high false positive rate results in greater volume of tissue removal (Gray, 2018).

A randomized, open-label study (Schnabel, 2014; ClinicalTrials.gov, 2014) of MarginProbe is based on the largest sample to date. The investigators enrolled 596 women with non-palpable breast malignancies to receive either (1) the standard of care lumpectomy procedure (n = 298), or (2) standard of care plus use of the MarginProbe device (n = 298). Randomization took place after specimens were removed and inspected. In the device arm, researchers used MarginProbe to examine the collected specimens to determine whether additional excision was needed. Using the device, surgeons examined all six surfaces of the main specimens, taking five to eight measurements per face. A margin was positive based on a single positive reading, in which case surgeons were required to excise additional tissue from the corresponding cavity face. The primary endpoint was reached two weeks after surgery. Pathologists who read the specimens were blinded to the study arms.

- The results showed that standard assessment was more than twice as likely to miss tumor cells, and that MarginProbe was about three times more likely to indicate tumor cells where there were none remaining. In the device and control arms, false-negative rates were 24.8% and 66.1%, and false-positive rates were 53.6% and 16.6%, respectively.
- Among the patients with remaining positive cells, a higher proportion (almost three times as many) of those whose specimens were tested with MarginProbe had further tissue removal than with standard assessment. Positive margins on positive main specimens were resected in 62% (101 of 163) in the device arm, versus 22% (33 of 147) in the control arm (P < .001).
- About a quarter more patients in the standard assessment arm had to return for a second procedure to remove more tissue. In the device arm, 19.8% (59 of 298) of participants underwent a re-excision procedure compared with 25.8% (77 of 298) in the control arm.

The difference in tissue volume removed was not significant. The authors concluded that the use of MarginProbe improved surgeons' ability to identify and resect positive lumpectomy margins in the absence of intraoperative pathology assessment, thereby reducing the number of patients needing re-excision, and that MarginProbe "may aid performance of breast-conserving surgery by reducing the burden of re-excision procedures for patients and the health care system." While this outcome is encouraging, the false-negative and false-positive rates are concerning, and there was no long-term follow-up and thus no data comparing recurrence in the two groups.

More recent reports with at least 150 patients are:

- Sebastian (2015) reported that the use of MarginProbe in 165 women resulted in a re-excision surgery rate of 9.9%, compared to 25.8% in historic controls.
- Blohmer (2016) reported that in a prospective clinical study of 150 patients, there was an overall reduction in re-excision rates of 14.6% compared to historical controls (from 61.7% to 23.1% in those with intraductal carcinoma, and from 37.0% to 19.0% among those people with invasive lobular carcinomas).
- Coble (2017) compared the re-excision rates among 137 women in whom MarginProbe was used to 199 women who had full cavity shave procedures. With use of MarginProbe, the re-excision rate decreased from 15.1% to 6.6% (*P* = .026). The overall tissue volume removed was reduced by 32%, from 115 cc^3 to 78 cc^3 (*P* = .0023).
- Kupstas (2018) reported on a single center retrospective chart review that evaluated re-excision rates in 120 consecutive patients before and after the institution of the device (240 in all), and compared intraoperative feedback with postoperative pathology reports. The findings showed a 10-point decrease in the re-lumpectomy rate in the device group (5.8% compared to 15.8%, *P* = .039) without increasing the total volume of tissue resected. The authors concluded that MarginProbe's use resulted in a reduction

of positive margins after lumpectomy and in the number of re-excisions, thereby significantly improving outcomes.

As of this writing, the most recent study of MarginProbe included 60 breast cancer cases. Based on 360 measurement sites, MarginProbe (as an adjunct to standard operating procedure) had a sensitivity of 67% and specificity of 60%, similar to standard operating procedure alone. Re-excision rates were 6.6% and 8.6% for MarginProbe and for standard treatment (LeeVan, 2020).

The device only showed moderate sensitivity and poor specificity characteristics; therefore, it will miss some cancers and provide frequent false-positive results. Although several historical control studies have shown lower re-excision rates among patients in whom MarginProbe was used, the studies lacked adequate rigor to demonstrate whether the outcomes are attributable to MarginProbe.

The studies also did not report recurrence outcomes, which is indicated for assessing the adequacy of resection. A randomized trial that assesses recurrence rates is needed to evaluate whether the net health outcome improves with handheld radiofrequency spectroscopy compared with standard intraoperative surgical margin evaluation, including histologic techniques. The evidence is insufficient to determine the effects of the technology on health outcomes (U.S. Food and Drug Administration, 2022).

The Agency for Healthcare Research and Quality issued a horizon-scanning cost analysis of potentially high-impact interventions that are not yet widely used includes MarginProbe among them. It is described as a novel device intended to reduce the rate of second lumpectomy surgeries. “The case of MarginProbe is very unusual among new medical technologies because it does not change the course of follow-up care beyond re-excision, nor life expectancy. This leaves a simple trade-off between cost and the probability of re-excision” (Cuevas, 2015).

Based on the data reviewed, MarginProbe does appear to consistently reduce the need for re-excision. However, the false negative rate of 24.8% found by Schnabel (2014) and the relatively low sensitivity and specificity rates found by others diminish its utility.

In 2022, we added three new single institution studies. A retrospective analysis of 214 participants who had neoadjuvant chemotherapy and breast conservation surgery found MarginProbe use was associated with a lower re-excision rate than gross assessment to assess lumpectomy margins (6% versus 31%, respectively) (Cen, 2021). Another retrospective study of 66 patients (86 lumpectomies) found MarginProbe and gross assessment reduced positive margins more than gross assessment alone during breast conserving surgery. Margins were considered positive using “no ink on tumor” guideline for invasive cancer, and 2 mm or greater margin for ductal carcinoma in-situ (Qafiti, 2022).

Hoffman (2022) prospectively analyzed MarginProbe in 48 patients with 51 tumors who underwent lumpectomy. Patients with breast tissue too dense for MarginProbe analysis were excluded. In the 12 patients who required re-excision, MarginProbe readings were compared to pathological evaluation of the lumpectomy margins. Twelve lumpectomies yielded 13 involved or close margins in need of additional shavings. Four of the 13 positive margins had pathological evidence of ink on tumor (2 invasive ductal carcinoma, 2 ductal carcinoma in situ) and nine (all ductal carcinoma in situ) had pathological close margins of 1 mm or less. The authors pointed out that out of the 12 patients in need of re-excision, MarginProbe would have prevented only two re-excisions. No policy changes are warranted.

In 2023, we added one guideline (Morrow, 2016) and a new meta-analysis of three randomized controlled studies and seven retrospective studies (n = 2,335 total participants) comparing MarginProbe to historical controls. The meta-analysis determined an overall relative reduction in re-excision rate of 0.49 (95% confidence interval 0.38 to 0.64, $P < .001$). However, local recurrence rates were not evaluated, and the small size and heterogeneity of surgical techniques, tumor types, and margin assessment protocols prevented firm conclusions regarding the

impact of MarginProbe on care management and patient outcomes (Wang, 2023). No policy changes are warranted.

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On August 15, 2023, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “breast cancer,” “lumpectomy,” “margin assessment,” “breast neoplasms (MeSH),” “MarginProbe,” and “radiofrequency spectroscopy.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

10/2019: initial review date and clinical policy effective date: 12/2019

11/2020: Policy references updated.

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