Bioimpedance Devices for Detection and Management of Lymphedema

Medical Policy #: 02.01.57
Original Effective Date: January 2017
Reviewed: January 2022
Revised: January 2019

NOTICE: This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations, or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This medical policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

This Medical Policy document describes the status of medical technology at the time the document was developed. Since that time, new technology may have emerged, or new medical literature may have been published. This Medical Policy will be reviewed regularly and be updated as scientific and medical literature becomes available; therefore, policies are subject to change without notice.

DESCRIPTION

Lymphedema is a chronic accumulation of fluid and fibrous tissue that results from the disruption of lymphatic drainage. Primary lymphedema is a disorder of the lymphatic system that occurs on its own, it is inherited and uncommon (congenital lymphedema due to lymphatic aplasia or hypoplasia; Milroy's disease, an autosomal dominant familial form of congenital lymphedema; lymphedema praecox; lymphedema tarda). Secondary lymphedema is a disorder of lymphatic flow that is caused by some other disease or condition, and it is most commonly caused by surgery (lymph node dissection, such as for breast cancer), radiation therapy (especially axillary or inguinal), trauma, and lymphatic obstruction by tumor. Secondary lymphedema may also result from compression of the lymphatic and venous channels resulting from leakage of fluid into interstitial tissues in patients with chronic venous insufficient.

Lymphedema is usually staged observing a patient's physical condition. The International Society of Lymphology uses the following 3-stage scale for classification of lymphedematous limb:

- Stage I: Early accumulation of fluid relatively high in protein content (e.g., in comparison with "venous" edema) that subsides with limb elevation. Pitting may occur.
- Stage II: Limb elevation alone rarely reduces tissue swelling and pitting may or may not occur as tissue fibrous develops.
- Stage III: Lymphostatic elephantiasis. Tissue is hard (fibrotic) and pitting is absent. Trophic skin changes such as thickening, hyperpigmentation, increased skin folds, fat deposits and warty overgrowths develop.

An increasing number of lymphologists recognize an earlier stage of lymphedema, termed Stage 0, which refers to latent or subclinical condition where swelling is not evidence despite impaired lymphatic transport. Stage 0 exists for months or years before the onset of overt lymphedema.

The detection of subclinical lymphedema i.e., the early detection of lymphedema before clinical symptoms become apparent, is another area of study. Detection of subclinical lymphedema referred to as stage 0 lymphedema is problematic. This approach generally involves comparison of preoperative (i.e., baseline) with postoperative measurements. The use of bioimpedance has been proposed as a diagnostic test for this condition. In usual care, lymphedema is recognized clinically or via limb measurements. However, management via bioelectrical impedance spectroscopy has been proposed as a way to implement early treatment of subclinical lymphedema to potentially reduce its severity.

Bioimpedance spectroscopy (BIS) is based on the theory that the level of opposition to the flow of electric current (impedance) through the body is inversely proportional to the volume of fluid in the tissue. In lymphedema with the accumulation of excess interstitial fluid tissue impedance decreases.

Clinical Context and Test Purpose
The purpose of using bioimpedance spectroscopy (BIS) in patients who have known, or suspected lymphedema is to inform a diagnosis of subclinical lymphedema to initiate treatment sooner than with other diagnostic methods.

Patients
The relevant population of interest is individuals with known or suspected lymphedema.

Interventions
The relevant intervention of interest is bioimpedance spectroscopy (BIS).

Comparators
The relevant comparators of interest are volume displacement and circumferential measurement.

Outcomes
The general outcomes of interest are test accuracy and validity, symptoms, and quality of life (QOL).

Timing
The time frame for outcomes varies from months to years after onset of lymphedema symptoms.

Setting
During a physical examination conducted by a physician in an inpatient or outpatient setting.

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).

(2020) Bundred et al a prospective cohort study was completed by compared multi-frequency bioimpedance spectroscopy with arm volume measurement to detect breast cancer related lymphedema. Primary outcome measure was to ascertain if bioimpedance spectroscopy had equal sensitivity and specificity as perometry in the detection of lymphedema. Secondary outcomes included effect of lymphedema on quality of life, cancer survival, and risk factors for lymphedema. The study included 1100 individuals who underwent axillary clearance surgery. There were 309 individuals who either withdrew from the study, were lost to follow-up or died. For this study, relative arm volume increase was defined as greater than or equal to 10% increase from baseline. Self-reported symptoms were obtained by using the Lymphedema and Breast Cancer Questionnaire and the Functional Assessment of Cancer Therapy Breast +4 questionnaires. Participants who developed lymphedema were prescribed a compression-sleeve garment. By 24 months following surgery, the incidence of lymphedema was 22.4% by relative arm volume increase and 45.2% using bioimpedance spectroscopy. Compression-sleeve garments were required by 24.5%. Median time to lymphedema development was 11.3 months. At 6 months, sensitivity for bioimpedance spectroscopy greater than 10 was 69%, specificity was 82% and positive predictive value (PPV) was 28%. For bioimpedance greater than 7.5 sensitivity was 80%, specificity was 77% and PPV was 24%. Diagnostic accuracy was 89.3%. At 24 months, sensitivity and specificity for bioimpedance spectroscopy was unchanged, but PPV was improved at 31%. Diagnostic accuracy was 85.7%. Swelling and heaviness were associated with larger increases in the exact relative arm increase but not exact bioimpedance spectroscopy. Arm swelling was reported by 65.8% of participants. For the 221 participants who wore the compression-sleeve, sensitivity and specificity were compared between relative arm volume increase and bioimpedance spectroscopy. The authors noted bioimpedance spectroscopy identified high false positives in the diagnosis of lymphedema. Negative predictive value (NPV) was similar for both types of measurements. Quality of life scores increased for those wearing compression-sleeve garments. Relative arm volume increase changes were associated with increased reporting of symptoms. Swelling and heaviness

in the ipsilateral limb before surgery was reported in up to 25% of participants. Changes in relative arm volume increase were associated with increased symptom reporting. The lack of standardized criteria for lymphedema makes it difficult to accurately diagnose the true incidence of lymphedema.

(2020) Cavezzi et al completed a prospective cohort study and reported on 41 participants with unilateral lymphedema of the lower limb who received complex decongestive treatment daily for 6 days. The primary outcome was to assess immediate and early outcomes of complex decongestive treatment using circumference-based limb volumetry and bioimpedance spectroscopy. Secondary outcome was to assess correlation between the two methods during treatment. Each treatment session consisted of manual lymphatic drainage, electro-sound lymphatic drainage, compression bandage, low-carb nutrition, anti-edema/anti-inflammation dietary supplements, and anti-stasis exercising. Participants underwent volumetry by tape measurements and bioimpedance spectroscopy immediately before the start of complex decongestive treatment. Three days after treatment, resistance and reactance of the total limb were recorded. Following the last treatment, volumetry and measurements by bioimpedance spectroscopy of the treated limb were repeated. Before treatment, mean total limb volume was 11,072.9, mean resistance was 200.4, mean reactance was 12.3, and mean total limb lymphatic index was 18.9. At day 3, mean resistance and reactance was 225.7 and 15.0 respectively. Following 6 days of treatment, mean total limb volume was 10,493.1, mean resistance was 237.5, mean reactance was 16.6, and mean lymphatic index was 14.9. Leg mean volume before treatment was 3150.8 and 2980.3 after treatment. Mean leg resistance before treatment was 117.5 and 150.0 following treatment. Leg mean reactance before treatment was 7.7 before treatment and 11.5 following treatment. Leg mean lymphatic index before and after treatment was 24.7 and 14.8 respectively. Treatment was noted to be effective with reduction of limb volume seen in the leg and total limb. Resistance and reactance showed an increase with a decrease in lymphatic index. There is noted correlation between the two methods of lymphedema measurement, however the outcomes do not show superiority of bioimpedance spectroscopy to volumetry.

(2020) Cho et al reported on a prospective cohort study to evaluate the use of bioimpedance analysis (BIA) as a tool to measure lymphedema before and after treatment. The study included 29 patients with cancer treatment related lymphedema (CTRL) who were admitted to a secondary university hospital for complex decongestive therapy (CDT) (12 upper- and 17 lower-extremity CTRL). Circumferential measure (CM) and BIA were used to evaluate lymphedema at admission (initial) and before discharge (follow-up, FU). Volume was calculated from the CM using the truncated cone formula. The inter-limb ratios (ILRs) of the circumference, volume, and impedance were calculated as the unaffected limb to affected limb. Each parameter before and after treatment and correlations between parameters also were analyzed. Absolute value and the ILRs of circumference, volume or impedance, and extracellular water/total body water (ECW/TBW) were significantly improved at FU ($p < 0.01$, $p < 0.05$). The initial and FU absolute values, ILRs, ECW/TBW correlated significantly with each other ($p < 0.01$, $p < 0.05$). The cutoff values of ECW/TBW for moderate and severe degree of

CTRL were 0.3855 and 0.3955, respectively. The changes of ILRs between initial and FU assessments were significantly different among three groups according to lymphedema severity ($p < 0.01$, $p < 0.05$). The authors concluded that BIA data correlates significantly with clinical measurement, and therefore can be a practical tool in monitoring outcome measure after lymphedema treatment. The study was limited by the small number of participants and lack of randomization.

(2019) Spitz et al completed a retrospective review to evaluate the accuracy of bioimpedance spectroscopy measurements in the diagnosis of breast cancer-related lymphedema. In this single center study, participants had preoperative and postoperative evaluation for possible lymphedema by bioimpedance spectroscopy and limb circumference measurements. The authors used the device manufacturer's criteria to diagnose lymphedema (which lie outside the normal range of -10 to +10 or a 10-point increase from prior measurements). At each visit, participants received an examination which included checking for pitting edema, Stemmer's sign, range of motion, participant report of symptoms, and sensory and motor function. All participants also had bioimpedance measurements taken during the same visit. Diagnosis of lymphedema was determined by a lymphedema physical therapist. The mean follow-up period was 10.2 months. There were 134 participants with lymphedema and 261 participants without lymphedema based on physical exam and limb circumference measurements. The average postoperative bioimpedance spectroscopy score for all participants was 2.1 ± 6.4. For participants with lymphedema, the average absolute bioimpedance spectroscopy score was 2.2 ± 8.8; 10 participants demonstrated an absolute bioimpedance >10, 124 participants had an absolute bioimpedance <10, 33 participants had a relative change in bioimpedance >10, and 101 participants had a relative change in bioimpedance <10. For the participants without lymphedema, the average absolute bioimpedance score was 2.1 ± 4.6; 4 participants had an absolute bioimpedance >10, 258 had an absolute bioimpedance <10; 21 had a relative change in bioimpedance >10, and 241 had a relative change in bioimpedance <10. When using the manufacturer's criteria of an absolute bioimpedance measurement of greater than 10 units to diagnose lymphedema compared to those with a clinical diagnosis by physical exam and tape measurements, the bioimpedance demonstrated a sensitivity of 7.5%, specificity of 98.5%, positive predictive value of 71.4%, and a negative predictive value of 67.5%. When using criteria of a relative change in bioimpedance of +10 between two separate measurements, the bioimpedance showed a sensitivity of 24.6%, specificity of 92.0%, positive predictive value of 61.1%, and negative predictive value of 70.5% when compared to diagnosis based on physical exam and tape measurements. This study has limitations which include a limited long-term follow-up, its retrospective and single center nature, no control for arm dominance, and lack of a gold standard for diagnosing lymphedema. Currently there are variables between studies to draw conclusions to the accuracy of bioimpedance spectroscopy in the diagnosis of lymphedema. Specific protocols should be in place before drawing firm conclusions.

(2019) Ridner et al conducted a randomized controlled trial (RCT) comparing lymphedema progression rates using volume measurements calculated from the

circumference using a tape measure (TM) or bioimpedance spectroscopy (BIS) in breast cancer. Patients were enrolled and randomized to either TM or BIS surveillance. Patients requiring early intervention were prescribed a compression sleeve and gauntlet for 4 weeks and then re-evaluated. The primary endpoint of the trial was the rate of progression to clinical lymphedema requiring complex decongestive physiotherapy (CDP), with progression defined as a TM volume change in the at-risk arm ≥ 10% above the presurgical baseline. This prespecified interim analysis was performed when at least 500 trial participants had ≥ 12 months of follow-up. A total of 508 patients were included in this analysis, with 109 (21.9%) patients triggering pre-threshold interventions. Compared with TM, BIS had a lower rate of trigger (15.8% vs. 28.5%, $p < 0.001$) and longer times to trigger (9.5 vs. 2.8 months, $p = 0.002$). Twelve triggering patients progressed to CDP (10 in the TM group [14.7%] and 2 in the BIS group [4.9%]), representing a 67% relative reduction and a 9.8% absolute reduction ($p = 0.130$). The authors concluded, these interim results demonstrated that post-treatment surveillance with BIS reduced the absolute rates of progression of breast cancer related lymphedema (BCRL) requiring CDP by approximately 10%, a clinically meaningful improvement. These results support the concept of post-treatment surveillance with BIS to detect subclinical BCRL and initiate early intervention.

(2015) Barrio et al performed a prospective validation study comparing bioimpedance (L-Dex) and volume displacement measurements in a cohort of breast cancer patients at risk for lymphedema. Between 2010 and 2014 a total of 223 breast cancer patients were enrolled. Thirty-seven patients were excluded, leaving a sample size of 186. Prior to surgery participants received baseline volumetric measurements with bioimpedance device (L-Dex) and volume displacement (VD, the reference standard). Patients then had regular follow-up volumetric measurements every 3 to 6 months for 3 years. At a median follow up of 18.2 months, 152 patients were normal, 25 had an abnormal L-Dex and 9 developed lymphedema without a prior L-Dex abnormality. Of the 25 abnormal L-Dex patients, 4 progressed to lymphedema, for a total of 13 patients with lymphedema. Evaluating all time points, 186 patients had 829 follow-up measurements. Sensitivity and specificity of L-Dex compared with VD were 75 and 93%. There was no correlation between change in VD and change in L-Dex at 3 months ($r = 0.31$) or 6 months ($r = 0.21$). The authors concluded that VD and bioimpedance demonstrated poor correlation with inconsistent overlap of measurements considered abnormal. Of patient with abnormal L-Dex few progressed to lymphedema, most patients with lymphedema did not have prior L-Dex abnormality. Further studies are needed to understand the clinical significance of bioimpedance.

(2015) Blaney et al completed another prospective study and examined the feasibility of a breast cancer related lymphedema (BCRL) screening program, investigating the efficacy of bioimpedance analysis (BIA) compared to circumferential measurements (CM) in detecting BCRL. This was a 12-month prospective feasibility study and participants were recruited from two diagnostic breast clinics. Pre-surgical assessments were conducted, and participants were followed up at quarterly intervals. BIA and CM measurements were conducted at all time points. An L-Dex score of > 10 or a 10-U increase from

baseline or a > 5% increase in proximal, distal, or total percentage volume difference (PVD) from baseline was indicative of BCRL. Information was collected on subjective symptoms, potential risk factors, demographics, and medical data. Feasibility was based on uptake and retention. One hundred twenty-six participants were recruited with an attrition rate of 16.2%. Participants mean age was 59 years with the majority having stage I (63.9%), infiltrating ductal carcinoma (87.4%). 31.6% were identified has having BCRL, 90.3% detected by CM and 35.5% by BIA (p = < 0.0001). The authors concluded no significant correlation between BIA and CM. Work needs to continue to establish the most effective screening tool and the natural behavior of BCRL within the first-year post surgery.

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.

The ideal study design is a randomized controlled trial (RCT) comparing health outcomes in patients who are managed with and without the use of bioimpedance devices.

(2020) A clinical evidence assessment completed by the Emergency Care Research Institute (ECRI) reviewed a single concordance study compared measurements taken using SOZO and the predicate device, L-Dex U400 for assessing BIS, and reported similar agreement between the two measurements. No studies provided data on SOZO's diagnostic accuracy with respect to clinical lymphedema assessment, and no studies reported on clinical outcomes of lymphedema treatment guided by BIS with the SOZO device. The search identified no ongoing trials.

The findings included the following information:

- One prospective study (Koelmeyer et al. 2020) reported good concordance between L-Dex U400 and SOZO measurements in groups of subjects with and without lymphedema (correlation coefficient [r] = 0.92). However, authors reported that the measured values were not interchangeable between the devices.
- Evidence: Search dates: January 1, 2015, to April 29, 2020. We reviewed full text of 1 study reporting on 100 patients.
    - A full-text publication available through open access. Excluded studies of the predicate device, L-Dex U400, because differences in device characteristics (i.e., fixed versus free electrodes) may translate into different concordance.
    - One concordance study (Koelmeyer et al. 2020, n = 47 healthy volunteers and 53 patients with breast cancer, including 39 with confirmed unilateral lymphedema) reported on agreement measures taken with L-Dex U400 and SOZO BIS.
    - Safety: No MAUDE reports or ECRI Healthcare Product Alerts identified.
    - Ongoing Trials: No trials of BIS with SOZO identified.

- Two randomized controlled trials (RCTs) of lymphedema management with L-Dex U400 are ongoing.

Evidence limitations included no diagnostic accuracy studies available. The available study provides only concordance data with the predicate device and no data on important clinical outcomes of interest (lymphedema diagnosis and evaluation using clinical criteria, follow-up). No data are available comparing SOZO to angiographic imaging methods (e.g., fluorescent lymphangiography, lymphoscintigraphy, magnetic resonance angiography). The study is also at high risk of bias from small size and single-center focus. The evidence is inconclusive due to not enough data.

(2020) A systematic review by Forte et al evaluated the literature regarding the use of bioimpedance spectroscopy in evaluating individuals with breast cancer-related lymphedema. There were 11 studies which included 4 were prospective, 4 were retrospective, and 3 were cross-sectional. Six of the studies evaluated the use of bioimpedance spectroscopy in assessing response to treatment for breast cancer-related lymphedema and all reported reduction in bioimpedance scores which correlated with improvement of lymphedema. One study evaluated the use of bioimpedance spectroscopy to assess L-Dex changes within 12 months after surgery. The authors reported that 17.1% of participants had a maximum L-Dex change of 7 units or more from baseline. The maximum change occurred at a median of 6 months after surgery. Another study assessed volume changes following breast cancer surgery. The authors reported that L-Dex scores changed according to lymph node action and those with four or more lymph nodes removed had higher L-Dex values. One study assessed changes in volume by using a special equation and reporting bioimpedance measurements into units of volume. The authors noted that the volumes measured with perometry strongly correlated with the fluid volumes predicted by bioimpendance spectroscopy however cautioned that further studies were necessary to determine accuracy of predicted fluid volumes. Another study correlated clinical staging with bioimpedance spectroscopy scores and reported that L-Dex ratios increased as the interlimb circumference differences increased. Another study compared two types of bioimpedance analysis: single-frequency bioimpedance analysis and multiple-frequency bioimpedance analysis. It was reported that both types of bioimpedance spectroscopy detected extracellular fluid in the affected lymphedematous limb. There was a lack of heterogeneity among the studies with different objectives, evaluations, and protocols. Further studies with similar purpose and evaluations are necessary.

(2018) Asklöf et al conducted a systematic review to summarize the current knowledge of non-invasive bioelectrical impedance analysis (BIA) used with gynecological surgical patients in regard to postoperative development of lymphedema and determination of perioperative fluid balance, and as a prognostic factor in cancer mortality and a predictor of postoperative complications. Two of the articles were retrospective; five had a cross-sectional, and nine were prospective. Three different methods of BIA were used: single frequency-BIA, multifrequency-BIA and bioimpedance spectroscopy. BIA was found to detect lymphedema with a sensitivity of 73% and a specificity of 84%. Studies indicated

that BIA was able to detect lower limb lymphedema at an early stage even before it became clinically detectable. The authors note that so far, all studies have set up cut-off limits within the study population, and reference values for a general population need to be defined and there are few studies on a gynecological study population. The authors note that there is a need for further studies within gynecological surgery focusing on early detection of lower limb lymphedema, perioperative fluid balance, and postoperative complications in order to establish the value of BIA in clinical praxis.

(2018) Kilgore et al conducted a prospective surveillance monitoring using bioimpedance spectroscopy (BIS) and patient directed self-interventions. Breast cancer patients with unilateral disease high-risk for breast cancer related lymphedema (BCRL) from a single institution were evaluated from November 2014 to December 2017. High risk was defined as axillary lymph node dissection (ALND) with radiation and/or taxane chemotherapy. Patients received preoperative baseline BIS measurements followed by postoperative measurements with at least two follow-ups. Patients with BIS results that were 2 standard deviations above baseline (10 + points) started home conservative interventions for 4-6 weeks. Postintervention measurements were taken to assess improvement. A total of 146 patients high-risk for BCRL were included. Forty-nine patients (34%) developed early BCRL and started self-directed treatment. Forty patients (82%) had elevated BIS measurements return to normal baseline range. Nine (6%) patients had persistent BCRL requiring referral for advanced therapy. Patients with persistent BCRL had significant nodal burden on surgical pathology; eight (89%) had N2/N3 disease. Six (76%) with BCRL refractory to conservative measures died of their breast cancer. The authors concluded; the results demonstrated that early conservative intervention for breast cancer patients' high risk for BCRL who were prospectively monitored by utilizing BIS significantly lowers rates of BCRL. These findings support early prospective screening and intervention for BCRL. Early detection with patient-directed interventions improves patient outcomes and decreases the risk of persistent BCRL.

(2016) Laidley et al evaluated the role of bioimpedance spectroscopy (BIS) in the early detection of breast cancer related lymphedema (BCRL), as well as assessment of response to BCRL treatment. A retrospective review of 1,133 patients treated between November 2008 and July 2013 at two surgical practices was performed. Eligible patients (n = 326) underwent preoperative and postoperative L-Dex measurements. Patients were identified as having subclinical lymphedema if they were asymptomatic and the L-Dex score increased >10 U above baseline and were monitored following treatment. Patients were stratified by lymph node dissection technique [sentinel lymph node biopsy (SLNB) versus axillary lymph node dissection (ALND)] and receipt of BCRL treatment. The average age of the cohort was 56.2 years old, and mean follow-up was 21.7 months. Of the 326 patients, 210 underwent SLNB and 116 underwent ALND. BCRL was identified by L-Dex in 40 patients (12.3%). The cumulative incidence rate of subclinical lymphedema was 4.3% for SLNB (n = 9) and 26.7% for ALND (n = 31). Of those diagnosed with BCRL, 50% resolved following treatment, 27.5% underwent treatment without resolution, and 22.5% had resolution without treatment. The prevalence of

persistent, clinical BCRL was 0.5% for SLNB and 8.6% for ALND. There are limitations to the current analysis. This was a retrospective review and therefore, subject to the limitations of such an analysis. While the initial cohort was large, due to the small number of events, further data are required to validate these findings. Additionally, they were unable to evaluate other factors associated with an increased risk of lymphedema (i.e., radiation therapy, BMI) due to limits on the data available. Finally, because intervention was based on clinician discretion, no cut point for beginning intervention could be determined at this time. However, this study represents one of the few studies available that demonstrate the ability to use L-Dex as part of routine clinical breast care to identify subclinical BCRL and allow early intervention to prevent long-term chronic BCRL. The authors concluded, this study demonstrates both the feasibility and clinical utility of implementing L-Dex measurements in routine breast cancer care. L-Dex identified patients with possible subclinical BCRL and allowed for assessment of response to therapy.

(2014) Soran et al did a controlled observational study comparing clinical lymphedema rates in patients managed with and without bioimpedance analysis. This study involved prospective detection of subclinical lymphedema in 186 patients diagnosed with breast cancer undergoing axillary lymph node dissection (ALND) who were managed with L-Dex or tape measurement of limb circumference (circumferential arm measurements). Baseline measurements were obtained at 3–6-month intervals for 5 years. Subclinical lymphedema was defined as L-Dex value outside the normal range or that increased at least 10 units from baseline. Patients diagnosed with subclinical lymphedema received short term physical therapy, compression garments, and education about exercise, elevation, infection precautions, BMI and hand usage. A total of 180 women were included in the analysis. Seventy-two women had both preoperative bioimpedance and tape measurements (preoperative group). Forty-four women had preoperative bioimpedance and tape measurements but only had tape measurements postoperatively (control group). The remaining sixty-four women and postoperative bioimpedance and tape measurements, but no preoperative measurements (no preoperative group). The authors compared demographic and clinical characteristics of the preoperative and control groups and of the preoperative and postoperative groups; they did not identify any statistically significant differences.

In the preoperative group, 28 of 72 women (36%) were diagnosed with subclinical lymphedema and referred for treatment; 2 women progressed to clinical lymphedema. In the control group, 16 women (36%) developed clinical lymphedema during follow up. A limitation of the study is that there was no alternative method for detecting subclinical lymphedema in the control group so they could receive treatment early. Moreover, the women were not randomized to a treatment group and complete information (pre- and post-operative measures of lymphedema) was available for only a subset of the total population.

This study had several limitations, including non-randomized design, lack of blinding, lack of complete information on a substantial number of patients in the study, and lack of

a systematic method for diagnosing lymphedema in the control group. The authors reported a significantly lower rate of clinical lymphedema in patients who were managed with bioimpedance analysis (BIA) and who received treatment for subclinical lymphedema. Additional studies to confirm these findings are needed, especially RCTs and trials that include an alternative method for early or subclinical lymphedema detection.

Summary of Evidence
The evidence for bioimpedance devices in individuals who have known, or suspected lymphedema includes several prospective studies, retrospective studies and one randomized controlled trial (RCT). There were no randomized controlled trials (RCTs) evaluating the clinical utility of bioimpedance devices in the management of patients with lymphedema or at high risk of developing lymphedema. While some of the studies show promise in patients managed with bioimpedance devices, the lack of randomized controlled trials (RCTs) provides limited data demonstrating the impact of this test (bioimpedance) on clinical outcomes (clinical utility). Based on the current scientific evidence and because the impact on net health outcome is unknown, use of this testing in the diagnosis or management or patients with known or suspected lymphedema, or to detect subclinical lymphedema is considered investigational. The evidence is insufficient to determine the effects of this technology on net health outcomes.

Practice Guidelines and Position Statements

National Cancer Institute

- Lymphedema (PDQ) – Health Professional Version (2019)
    - If the diagnosis is not evident on the basis of clinical assessment, imaging of the lymphatic system with lymphoscintigraphy (radionuclide imaging) may be necessary. Lymphangiography is generally no longer a favored diagnostic test and may be contraindicated in patients with malignancy because of concern that it may contribute to metastatic spread of tumor. Additional imaging techniques such as magnetic resonance imaging may complement information obtained via lymphoscintigraphy by providing anatomic and nodal detail.

    - The wide variety of methods described in the literature for evaluating limb volume and lack of standardization makes it difficult for the clinician to assess the at-risk limb. Options include water displacement, tape measurement, infrared scanning, and bioelectrical impedance measures.

    - The most widely used method to diagnose upper-extremity lymphedema is circumferential upper-extremity measurement using specific anatomical landmarks. Arm circumference measures are used to estimate volume differences between the affected and unaffected arms. Sequential measurements are taken at four points on both arms: the metacarpal-

phalangeal joints, the wrist, 10 cm distal to the lateral epicondyles, and 15 cm proximal to the lateral epicondyles. Differences of 2 cm or more at any point compared with the contralateral arm are considered by some experts to be clinically significant. However, measuring specific differences between arms may have limited clinical relevance because of implications, for example, of a 3-cm difference between the arm of an obese woman and the arm of a thin woman. In addition, there can be inherent anatomic variations in circumference between the dominant and nondominant limb related to differences in muscle mass and variations after breast cancer treatment that may occur with atrophy of the ipsilateral arm or hypertrophy of the contralateral arm. A small study comparing various methods of assessing upper-limb lymphedema did not show any superiority of any one method. Sequential measurements over time, including pretreatment measurements, may prove to be more clinically meaningful.

(*Accessed December 2021*)

National Comprehensive Cancer Network (NCCN)

- **Breast Cancer Version 1.2022**
  - Axillary Lymph Node Staging
    - Lymphedema is a potential side effect after the treatment of axillary lymph node surgery resulting from damage to the lymphatic system. Early detection/diagnosis of lymphedema is key for optimal management. Consider pretreatment measurement of both arms as a baseline for patients with risk factors for lymphedema. See NCCN Guidelines for Survivorship: Lymphedema (SLYMPH-1). (*Accessed December 2021*)

- **Survivorship Version 3.2021**
  - Definitions and Stages of Lymphedema
    - Definition: Lymphedema occurs when lymph fluid accumulates in the interstitial tissue, causing swelling of the limb or other areas such as the neck, trunk, or genitals. It is a common side effect of cancer treatment, occurring on the same side of the body as the cancer treatment, as a result of dysfunction of the lymphatic system.
    - Stage 0 (latent/subclinical): Lymphatic dysfunction without swelling; subtle symptoms, such as feeling of heaviness or fatigue in the limb, may be present.
    - Stage 1 (spontaneously reversible): Accumulation of fluid and protein causing swelling; pitting edema may be evident; increased girth, heaviness, and/or stiffness of affected area. For the limbs, swelling is relieved with elevation.
    - Stage 2 (irreversible): Spongy tissue consistency, with pitting edema that becomes less evident as swelling increases; tissue fibrosis causing

hardness and increase in size. For the limbs, swelling is not relieved with elevation.

- Stage 3 (lymphostatic elephantiasis): Severe dry, scaly, thickened skin; increased swelling and girth of affected area; can be debilitating. In the limbs, fluid leakage and blisters are common. Fungal infection and papilloma may occur. Putting can be absent due to progressive deposition of fat and fibrosis, which is the hallmark of later stage lymphedema.

(*Accessed December 2021*)

- **Principals of Lymphedema**
  - Lymphedema is a potential side effect after the treatment of cancer resulting from damage to the lymphatic system. Approximately 3 in 4 cases of lymphedema are diagnosed within 3 years of treatment; however, it can develop anytime in the life of the survivor. Depending on the stage of diagnosis, lymphedema can be an acute or chronic condition.
  - Swelling on the same side as the cancer treatment is a universal symptom of lymphedema. Additional initial symptoms may include sensation of heaviness, fatigue, fullness or tightness in the skin or pain. Symptoms including decreased range of motion or strength and thickening of the skin may occur in later stages.
  - Survivors who had surgery or radiation to the axillary, supraclavicular, cervical, or inguinal lymph node system are at risk for the development of lymphedema. Sentinel node biopsy also increases the risk of lymphedema, although it poses less risk than complete dissection.
  - Obesity (BMI >30 kg/m2), localized infection, increased number of nodes removed, and higher initial extent of disease raise risk of the lymphedema development.
  - Pretreatment limb measurement of both sides should be performed as a baseline for survivors with treatment-related or individual risk factors, preferably by a trained lymphedema specialist.
  - Early detection/diagnosis is key for optimal lymphedema management because stage 0 and 1 are reversible, whereas stages 2 and 3 are less responsive to treatment. Therefore, survivors should be told to inform their medical provider if subtle swelling or any other symptoms (e.g., fullness, tightness, heaviness, pain) on the treated side are noted.
  - Lymphedema may cause or exacerbate psychological distress.
  - Survivors at risk for lymphedema and those with lymphedema are at a higher risk of localized infection in the affected area. These infections can require hospitalization for IV antibiotics. Therefore, survivors with or at risk for lymphedema should be educated to inform their medical provider immediately for signs of infection in the affected area.

- Progressive weight training under supervision and physical activity are not associated with exacerbation or development of lymphedema.
- Observational studies have demonstrated that air travel, venipuncture, and blood pressure measurement (via arm cuff) are not associated with exacerbation or development of lymphedema, and precautionary measures are likely unnecessary. In the absence of high-level data, however, the panel recommends that medical procedures such as venipuncture and blood pressure measurements be done on the non-at-risk arm/limb if possible. If necessary, procedures may be done using the at-risk arm/limb. More research is needed to determine the effect of these procedures on the risk of lymphedema.

(*Accessed December 2021*)

- **Work-up if Lymphedema is Suspected**
  - Rule out recurrence of cancer
  - Refer to certified lymphedema therapist (if available) for assessments such as:
    - Subjective symptoms/signs
    - Limb volume measurement
    - Clinical examination, which may include, but is not limited to range of motion, muscle performance, circulation, sensation, hemodynamic monitoring, and functional mobility.
  - Assess distress

(*Accessed December 2021*)

These NCCN guidelines referenced above do not mention the use of bioimpedance in the diagnosis, surveillance or treatment of patients with lymphedema.

Regulatory Status

Device	FDA 510(k) Clearance Year	Description
ImpediMed L-Dex U400	2007	It is an aid in the clinical assessment of unilateral lymphedema in the arms in women It is a tool to assist in the clinical assessment of lymphedema by a medical provider. L-Dex values that lie outside the normal range may indicate early signs of lymphedema and values that have changed +10 L-Dex units from baseline may also indicate early lymphedema. It is not intended to diagnose or predict lymphedema. *The L-Dex U400 was discontinued November 1, 2018. ImpediMed will provide product service and support*

		for five years from the date of manufacture of the device.
MoistureMeterD	2015	It helps to aid informing a clinical judgement of unilateral lymphedema in women. It is not intended to diagnose or predict lymphedema. It is a tool to assist in the clinical assessment of lymphedema by a medical provider.
SOZO (ImpediMed)	2018	SOZO is a medical device that provides a detailed, individualized measurement of extracellular fluid, intracellular fluid, and total body water, to measure a patient's fluid status.

This is not an all-inclusive list.

PRIOR APPROVAL

Not applicable.

POLICY

See Related Medical Policy:

- 07.01.76 Surgical Treatment of Lymphedema

Devices using bioimpedance (bioelectrical impedance spectroscopy) are considered **investigational** for use in the diagnosis, surveillance, or treatment of patients with lymphedema, including use in subclinical secondary lymphedema because their effectiveness for these indications has not been established. The evidence is insufficient to determine the effects of the technology on net health outcomes.

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 93702 Bioimpedance spectroscopy (BIS), extracellular fluid analysis for lymphedema assessment(s)

SELECTED REFERENCES

- Czerniec SA, Ward LC, Refshauge KM, et. al. Assessment of breast cancer-related arm lymphedema comparison of physical measurement methods and self-report. Cancer Invest 2010;28(1):54-62. PMID 19916749
- Warren AG, Janz BA, Slavin SA, et. al. The use of bioimpedance analysis to evaluate lymphedema. Ann Plast Surg. 2007;58(5):541-543. PMID 17452840
- AHRQ Technology Assessment: Diagnosis and Treatment of Secondary Lymphedema.

- Cornish BH, Chapman M, Hirst C, et. al. Early diagnosis of lymphedema using multiple frequency bioimpedance. Lymphology 2001;34(1):2-11. PMID 11307661
- Hayes S, Janda M, Cornish B, et.al. Lymphedema secondary to breast cancer: how choice of measures influences diagnosis, prevalence, and identifiable risk factors. Lymphology 2008;41(1):18-28. PMID 18581955
- Barrio AV, Eaton A, Frazier TG. A prospective validation study of bioimpedance with volume displacement in early-stage breast cancer patients at risk for lymphedema. Ann Surg Oncol Dec 2015;22 Suppl 3:370-375. PMID 26085222
- Blaney JM, McCollum G, Lorimer J, et. al. Prospective surveillance of breast cancer related lymphedema in the first-year post surgery: feasibility and comparison of screening measures. Support Care Cancer. June 2015;23(6):1549-1559. PMID 25398360
- Soran A, Ozmen T, McGuire KP, et. al. The importance of detection of subclinical lymphedema for the prevention of breast cancer related clinical lymphedema after axillary lymph node dissection; a prospective observational study. Lymphat Res Biol 2014 Dec;12(4):289-94. PMID 25495384
- UpToDate. Clinical Features and Diagnosis of Peripheral Lymphedema. Emile R Mohler III, M.D. and Babak Mehrara M.D. Topic last updated April 22, 2016.
- UpToDate. Clinical Staging and Conservative Management of Peripheral Lymphedema. Emile R. Mohler III, M.D. and Babak Mehrara M.D., Topic last updated January 22, 2016.
- UpToDate. Breast Cancer Associated Lymphedema. Emile R Moher III, M.D., Babk Mehrara M.D., Topic last updated March 22, 2016.
- ECRI. Product Brief. L-Dex U400 Extracellular Fluid Analyzer (Impedimed, Ltd.) for Aiding Detection of Lymphedema.
- National Lymphedema Network. Position Statement of National Lymphedema Network, The Diagnosis and Treatment of Lymphedema. February 2011.
- Impedimed. L-Dex.
- Shah C, Arthur DW, Wazer D, et. al. The impact of early detection and intervention of breast cancer-related lymphedema: a systemic review. Cancer Med. June 2016;5(6): 1154-1162. PMID 26993371
- Dylke ES, Schembri GP, Bailey DL, et. al. Diagnosis of upper limb lymphedema: development of an evidence based approach. Acta Oncol. Dec 2016;55912): 1477-1483. PMID 27333213
- Laidley A, Anglin B. The impact of L-Dex® Measurements in assessing breast cancer-related lymphedema as part of routine clinical practice. Front Oncol. 2016;6:192 PMID 27656420
- ImpediMed. SOZO and L-Dex U400.
- Shaitelman SF, Cromwell KD, Rasmussen JC, et. al. Recent progress in the treatment and prevention of cancer-related lymphedema. CA Cancer J Clin 2015 Jan-Feb;65(1):55-81. PMID 25410402
- Executive Committee. The diagnosis and treatment of peripheral lymphedema: 2016 consensus document of the International Society of Lymphology. Lymphology 2016 Dec;49(4):170-84. PMID 29908550

- Ridner SH, Dietrich MS, Cowher MS, et. al. A randomized trial evaluating bioimpedance spectroscopy versus tape measurement for the prevention of lymphedema following treatment for breast cancer: interim analysis. Ann Surg Oncol 2019 Oct;26(10):3250-3259. PMID 31054038
- Brayton KM, Hirsch AT, O Brien PJ, et. al. Lymphedema prevalence and treatment benefits in cancer: impact of therapeutic intervention on health outcomes and costs. PLoS One 2014 Dec 3;9(12):e114597. PMID 25470383
- Kaufman DI, Shah C, Vicini FA, et. al. Utilization of bioimpedance spectroscopy in the prevention of chronic breast cancer-related lymphedema. Breast Cancer Res Treat 2017 Dec;166(3):809-815. PMID 28831622
- Koelmeyer LA, Borotkanics RJ, Alcorso J, et. al. Early surveillance is associated with less incidence and severity of breast cancer-related lymphedema compared with traditional referral model of care. Cancer 2019 Mar 15;125(6):854-862. PMID 30521080
- Whitworth PW, Cooper A. Reducing chronic breast cancer-related lymphedema utilizing a program of prospective surveillance with bioimpedance spectroscopy. Breast J 2018;24(1):62-65. PMID 29063664
- Kilgore LJ, Korentager SS, Hangge AN, et. al. Reducing breast cancer-related lymphedema (BCRL) through prospective surveillance monitoring using bioimpedance spectroscopy (BIS) and patient directed self-interventions. Ann Surg Oncol 2018 Oct 25(10):2948-2952. PMID 29987599
- National Comprehensive Cancer Network (NCCN) Breast Cancer Version 6.2020. Also available at https://www.nccn.org
- National Comprehensive Cancer Network (NCCN) Survivorship Version 2.2020. Also available at https://www.nccn.org
- Lim SM, Han Y, Kim S, et.al. Utilization of bioelectrical impedance analysis for detection of lymphedema in breast cancer survivors: a prospective cross-section study. BMC Cancer 2019 Jul 8;19(1):669 PMID 31286884
- Kaufmann D, Shah C, Vicini F, et. al. Utilization of bioimpedance spectroscopy in the prevention of chronic breast cancer-related lymphedema. Breast Cancer Res Trat 2017 Dec;166(3):809-815. PMID 28831632
- Whitworth P, Shah C, Vicini F, et. al. Preventing breast cancer-related lymphedema in high-risk patients: the impact of a structured surveillance protocol using bioimpedance spectroscopy. Front Oncol 2018 Jun 12;8:197. PMID 29946531
- Cho KH, Han EY, Lee SA, et. al. Feasibility of bioimpedance analysis to assess the outcome of complex decongestive therapy in cancer treatment-related lymphedema. Front Oncol 2020;10:111. PMID 32117760
- National Comprehensive Cancer Network (NCCN) Breast Cancer Version 1.2022. Also available at https://www.nccn.org
- National Comprehensive Cancer Network (NCCN) Survivorship Version 3.2021. Also available at https://www.nccn.org
- Spitz JA, Chao AH, Peterson DM, et al. Bioimpedance spectroscopy is not associated with a clinical diagnosis of breast cancer-related lymphedema. Lymphology. 2019; 52(3):134-142.

- Cavezzi A, Urso SU, Paccasassi S, et al. Bioimpedance spectroscopy and volumetry in the immediate/short-term monitoring of intensive complex decongestive treatment of lymphedema. Phlebology. 2020; 35(9):715-723.
- Bundred N, Foden P, Todd C, et al. Increases in arm volume predict lymphoedema and quality of life deficits after axillary surgery: a prospective cohort study. Br J Cancer. 2020; 123(1):17-25.
- Forte AJ, Huayllani MT, Boczar D, et al. Bioimpedance spectroscopy for assessment of breast cancer-related lymphedema: a systematic review. Plast Surg Nurs. 2020; 40(2):86-90.
- Cho KH, Han EY, Lee SA, et al. Feasibility of Bioimpedance Analysis to Assess the Outcome of Complex Decongestive Therapy in Cancer Treatment-Related Lymphedema. Front Oncol. 2020 Feb 11;10:111
- Asklöf M, Kjølhede P, Wodlin NB, et al. Bioelectrical impedance analysis; a new method to evaluate lymphoedema, fluid status, and tissue damage after gynaecological surgery - A systematic review. Eur J Obstet Gynecol Reprod Biol. 2018 Sep;228:111-119
- National Cancer Institute. Lymphedema (PDQ®)–Health Professional Version. 2019.https://www.cancer.gov/about-cancer/treatment/side-effects/lymphedema/lymphedema-hp-pdq

POLICY HISTORY		
Date	**Reason**	**Action**
January 2022	Annual Review	Policy Renewed
January 2021	Annual Review	Policy Renewed
January 2020	Annual Review	Policy Renewed
January 2019	Annual Review	Policy Revised
January 2018	Annual Review	Policy Renewed
January 2017		New Policy Created

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

*CPT® is a registered trademark of the American Medical Association.