Bioimpedance Devices for Detection and Management of Lymphedema

**Description**

Secondary lymphedema may develop following surgery for breast cancer. Bioimpedance, which uses resistance to electrical current in comparing the composition of fluid compartments, could potentially be used as a tool to diagnose lymphedema.

**Background**

Secondary lymphedema of the upper extremity may develop following surgical treatment for breast cancer. It has been reported in approximately 25% to 50% of women following mastectomy. This can be a chronic, disfiguring condition. It results from lymphatic dysfunction or disruption and can be difficult to accurately diagnose and manage. One challenge is identifying the presence of clinically significant limb swelling through simple noninvasive methods. Many techniques have been used for documenting lymphedema including measuring differences in limb volume (volume displacement) and limb circumference. A number of newer techniques are being evaluated, including bioimpedance with use of bioimpedance spectroscopy (BIS) analysis, which uses resistance to electrical current in comparing the composition of fluid compartments. BIS is based on the theory that the amount of opposition to 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.

The detection of subclinical lymphedema, that is, 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. Subclinical disease may exist for months or years before overt edema is noted. This approach generally involves comparison of preoperative with postoperative measurements, since existing differences between upper extremities (like the effects of a dominant extremity) may obscure early, subtle differences resulting from the initial accumulation of fluid. Bioimpedance has been proposed as one diagnostic test for this condition. Those who support the approach to diagnose subclinical disease believe that early treatment of subclinical lymphedema should result in less severe chronic disease.
Regulatory Status

One of the devices is the ImpediMed L-Dex™ U400 cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process in 2007. According to FDA documents, the device is an aid in the clinical assessment of unilateral lymphedema of the arm in women. It is not intended to diagnose or predict lymphedema. FDA product code: OBH

Related Policies

1.01.18 Pneumatic Compression Pumps for Treatment of Lymphedema and Venous Ulcers
2.02.17 End-Diastolic Pneumatic Compression Boot as a Treatment of Peripheral Vascular Disease or Lymphedema

Policy

*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Devices using bioimpedance (bioelectrical impedance spectroscopy) are considered not medically necessary for use in the diagnosis, surveillance, or treatment of patients with lymphedema, including use in subclinical secondary lymphedema.

Benefit Application

The BCBS FEP contract stipulates that FDA-approved biologics, drugs and certain devices may not be considered investigational when used for their intended purpose and thus these products may only be assessed based on medical necessity.

Rationale

Assessment of a diagnostic technology typically focuses on 3 parameters: 1) technical performance; 2) diagnostic performance (sensitivity, specificity, and positive and negative predictive value) in appropriate populations of patients; and 3) demonstration that the diagnostic information can be used to improve patient outcomes (clinical utility). While in some cases, tests can be adequately evaluated using technical and diagnostic performance, when a test identifies a new or different group of patients with a disease, randomized controlled trials (RCTs) are needed to demonstrate impact of the test on the net health outcome.

Technical Performance

Technical performance of a device is typically assessed with 2 types of studies, those that compare test measurements with a criterion standard and those that compare results taken with the same device on different occasions (test-retest). While there is no absolute criterion standard for diagnosis of lymphedema, the de facto criterion standards are limb volume and/or limb circumference. Studies that address technical performance of bioimpedance devices are described next.
A 2010 publication by Czerniec et al reported on measurement of lymphedema in a small group of patients, 33 with lymphedema and 18 without. (1) This study was to determine the relationship between physical methods of measuring lymphedema and self-reported swelling. Measurement techniques included self-report, bioimpedance spectroscopy (BIS), perometer, and the truncated cone method. The authors noted that the physical measurement tools were highly reliable with high concordance (0.89 to 0.99, respectively). In this study, self-report correlated moderately with physical measurements (0.65 to 0.71, respectively) and was moderately reliable. The authors concluded that lymphedema assessment methods are concordant and reliable but not interchangeable.

In a U.S.-based study published in 2007, Warren et al evaluated 15 patients with upper- or lower-extremity secondary lymphedema documented by lymphoscintigraphy, along with 7 healthy controls using BIS analysis. (2) In addition, both the affected and unaffected limbs in lymphedema patients were evaluated so patients also served as their own controls. According to BIS in the lymphedema patients, the average ratio of current flow of the affected limb to the unaffected limb (the impedance ratio) was 0.9 (range: 0.67 to 1.01). In the control group, the average impedance ratio was 0.99 (range: 0.95 to 1.02). Lower impedance ratio values correlated with higher levels of accumulated fluid.

Diagnostic Performance

A technology assessment on the diagnosis and treatment of secondary lymphedema, performed under contract from Agency for Healthcare Research and Quality (AHRQ) by the McMaster University Evidence-based Practice Center, was released in May 2010. (3) As of October 2014, this assessment has not been updated. The AHRQ assessment identified 8 studies that reported the sensitivity and specificity of tests to diagnose secondary lymphedema. The investigators noted that there is no true “gold standard” to grade severity of lymphedema and that limb volume and circumference are used as a de facto “gold standards.” Two of the 8 studies on diagnostic performance of devices to detect secondary lymphedema evaluated bioimpedance devices. (4, 5) Overall, the investigators concluded that, due largely to heterogeneity among studies; the evidence does not permit conclusions on the optimal diagnostic test for detection of secondary lymphedema. The 2 studies on bioimpedance devices briefly described next.

Subsequent to the AHRQ review, several studies were published on the diagnostic performance of bioimpedance devices for detecting lymphedema. Prospective studies that compared bioelectrical impedance analysis to a reference standard are described next.

A 2015 study by Barrio et al enrolled 223 women with newly diagnosed breast cancer and a plan for unilateral axillary surgery. (6) Thirty-seven patients were excluded due to ineligibility or withdrawal, leaving a sample size of 186. Prior to surgery, participants received baseline volumetric measurements with a 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 the last follow-up (median, 18.2 months), 152 patients (82%) were normal, 21 (11%) had an abnormal L-Dex and no lymphedema by VD, 4 (2%) had an abnormal L-Dex and lymphedema by VD, and 9 (5%) had lymphedema without prior L-Dex abnormality. In an analysis including only patients with at least 6 months of follow-up, L-Dex had a sensitivity of 31% (4/13) and a specificity of 88% (129/147) for predicting subsequent lymphedema development. In addition, the correlation between
changes in VD and changes in L-Dex results were in the low-to-moderate range at 3 months (r=0.31) and 6 months (r=0.21). However, at the time of lymphedema diagnosis, the L-Dex ratio was abnormal in 12 of 13 patients (diagnostic sensitivity, 92%).

Another 2015 prospective study (by Blaney et al) included 126 women newly diagnosed with stages I-III unilateral breast cancer. (7) A total of 115 women underwent baseline assessment with a bioimpedance device (L-Dex) and circumferential measurement (CM). CM was used as the reference standard, although the authors noted the test is an imperfect criterion standard. Postsurgical follow-up assessments were planned every 3 months for a year. The number of women completing these assessments was 109 (95%) at 3 months, 89 (77%) at 6 months, 79 (69%) at 9 months, and 71 (62%) at 12 months. During the 12-month study, 31 participants were identified as having lymphedema by at least 1 of the assessment methods. Twenty-eight of 31 (90%) were identified by CM and 11 (35%) by bioimpedance analysis. There was no statistically significant correlation between bioimpedance analysis and CM.

Section Summary: Diagnostic Performance
An AHRQ technology assessment published in 2010 identified few studies on bioimpedance analysis for diagnosing lymphedema. A few prospective studies were published subsequent to the AHRQ review, and they tended to find suboptimal correlation between bioimpedance analysis and the reference standard. In the 1 study that reported measures of diagnostic accuracy, bioimpedance analysis had a low sensitivity and specificity for predicting lymphedema development.

Clinical Utility
The ideal study design is an RCT comparing health outcomes in patients who were managed with and without the use of bioimpedance devices. No RCTs were identified. However, there was 1 controlled observational study comparing clinical lymphedema rates in patients managed with and without bioimpedance analysis. This 2014 study, by Soran et al, involved prospective detection of subclinical lymphedema in 186 women with breast cancer who were managed with L-Dex or tape measurement of limb circumference. (8) Measurements were obtained at baseline and at 3- to 6-month intervals for 5 years. Subclinical lymphedema was defined as an L-Dex value outside the normal range or that increased at least 10 units from baseline. Patients diagnosed with subclinical lymphedema were treated with, eg, short-term physical therapy, compression garments, and received education on exercise and limb elevation. A total of 180 women were included in the analysis. Seventy-two women had both preoperative and postoperative 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 64 women had 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 women in the control group so that they could receive treatment early. Moreover, the women were not randomized to a treatment group and complete information (pre- and postoperative measures of lymphedema) was available for only a subset of the total population.

Section Summary: Clinical Utility
One prospective comparative study was identified that compared rates of clinical lymphedema in women managed with and without bioimpedance analysis. This study had several limitations, including nonrandomized 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 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.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in December 2015 did not identify any ongoing or unpublished trials that would likely influence this review.

Practice Guidelines and Position Statements
No relevant guidelines or statements were identified.

U.S. Preventive Services Task Force Recommendations
The U.S. Preventive Services Task Force has not addressed bioimpedance measurement devices.

Summary of Evidence
The evidence for bioimpedance devices in individuals who have known or suspected lymphedema includes several prospective studies on diagnostic accuracy and a controlled observational study evaluating clinical utility. Relevant outcomes are test accuracy and validity, symptoms, and quality of life. Recent diagnostic accuracy studies found a poor correlation between bioimpedance analysis and the reference standard (volume displacement or circumferential measurement). There are no randomized controlled trials evaluating the clinical utility of bioimpedance devices in the management of patients with lymphedema or at high risk of developing lymphedema. The single prospective comparative study found a significantly lower rate of clinical lymphedema in patients managed with bioimpedance devices. Limitations of this study include the retrospective design, lack of randomized or blinding, and lack of a systematic method of detecting early or subclinical lymphedema in the control group. The evidence is insufficient to determine the effects of the technology on health outcomes.

Medicare National Coverage
There is no national coverage determination on bioimpedance devices.
References

Policy History

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<tr>
<td>March 2013</td>
<td>Update Policy</td>
<td>Rationale rewritten. Reference 10 added; other references renumbered or removed.</td>
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**Keywords**

- Bioelectrical impedance testing
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- Lymphedema, bioimpedance testing
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- Plethysmography

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on June 24, 2016 and is effective July 15, 2016.

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