Submitted by:

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Joan McClure, MS
Senior Vice President, Clinical Information & Publications
National Comprehensive Cancer Network (NCCN)
275 Commerce Dr, Suite 300
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Dear Ms McClure

NCCN Guidelines Panel: Breast Cancer

On behalf of ImpediMed, Inc., we respectfully request the NCCN Breast Cancer Guideline Panel to review the enclosed data for inclusion of the L-Dex® U400 for the early detection and management of breast cancer related lymphedema.

Specific Changes:

Request to include a section on early detection and management of breast cancer related lymphedema (BCRL).

Guidelines to achieve early detection of BCRL:

All persons diagnosed with breast cancer should have pre-treatment measurements recorded and should have similar measurements repeated at quarterly intervals for the first 2 years post treatment and then semi-annual visits for the subsequent 3 years.

Criteria for early diagnosis of BCRL:

Bioimpedance Spectroscopy (BIS): L-Dex values that are above the normal range of 10 units, or have changed +10 L-Dex units from baseline, or are showing an upward trend over time.

FDA Status:

L-Dex U400 is FDA-cleared for the measurement of extracellular fluid volume differences between the limbs as an aid to the clinical assessment of unilateral lymphedema of the arm and leg in women and the leg in men.

Rationale:

Lymphedema is a common sequela of breast cancer treatment. Incidence rates for lymphedema have been reported as high as 49%.[1] Breast Cancer Related Lymphedema (BCRL) begins as a subclinical process due to an impairment of the lymphatic drainage system; this impairment causes an increase in the extracellular fluid which then leads to clinically detectable lymphedema. Once BCRL is clinically detectable, patients can develop chronic, irreversible conditions which may include skin changes, infection (cellulitis, lymphangitis), pain and functional impairment of the affected limb (numbness and heaviness). [2]

Currently identification is often made late in the disease progression. The later lymphedema is diagnosed, the more costly and difficult it is to treat. The key to successful intervention is early identification. The literature has demonstrated that identification of subclinical lymphedema and subsequent treatment with a light-grade compression garment can prevent progression of the disorder.

The L-Dex U400 is a bioimpedance spectroscopy (BIS) device which specifically detects extracellular fluid accumulation. BIS has been shown to have 100% sensitivity and 98% specificity in detecting patients with lymphedema when compared to clinical diagnosis.[3] In a comparison of diagnostic accuracy of measures of breast cancer-related lymphedema (BIS and tape measure), BIS demonstrated the highest accuracy, and 2 cm cutoff using tape measure the lowest.[4] The reliability between physical methods (BIS, tape measure, perometry) and self-reported swelling has been reported by Czerniec et al. In this study, they found that BIS detected a difference in the extracellular fluid in limbs which was not reflected in a corresponding difference in limb volume. This finding suggests that BIS may be particularly useful in the early detection of lymphedema, before there is any volume change.[5] A recent retrospective data analysis from 4 clinical practices in the US followed patients from a pre-surgical baseline for changes in L-Dex score related to breast cancer treatment. The findings were that BIS can detect changes in fluid within 6 months of surgery, well before clinical changes develop in patients. This change in L-Dex score is associated with an increased amount of extracellular fluid, a finding seen with subclinical lymphedema, suggesting that L-Dex values do change following treatment in conjunction with increasing arm volumes. These findings are consistent with previously reported series.[2] The impedance ratio reference range used in the L-Dex U400 has been validated across 2 continents: Ward et al., Australia[6] and Ridner et al., Vanderbilt University[7].

In addition to the peer-reviewed literature there are a number of lymphedema guidelines which emphasize the need for early detection and the use of L-Dex as an objective, validated, reliable tool.

National Lymphedema Network (NLN) position statement:

Breast cancer treatment places individuals at life-long risk for the development of lymphedema. Early detection of lymphedema allows for early intervention that can prevent or slow progression of lymphedema to a chronic, harder-to-treat stage. Patient education regarding the signs and symptoms of developing lymphedema and objective measurement of arms is needed to promote early detection and improve patient outcomes.
Objective measurement: A pre-operative baseline measurement of arms or at least a post-operative should be a standard component of breast cancer care, which can be used to compare all subsequent measures throughout recovery and survivorship.

Australasian Lymphology Association (ALA) position statement:

The ALA endorses the need to monitor for the early detection of lymphedema following breast cancer treatment. The early detection and management of sub-clinical lymphedema may reduce the long term physical, functional and psychological effects caused by a later diagnosis and delayed management of the condition.
The ALA endorses the use of bioimpedance spectroscopy (BIS) as a validated and reliable tool to enable early detection of breast cancer related lymphedema (BCRL) of the arm.

The National Accreditation Program for Breast Centers recommends the NLN guidelines in its Standard for Support and Rehabilitation under the topic lymphedema management and risk reduction practices.

The following articles are submitted in support of this proposed change. Please contact me should you have any questions regarding this application and the supporting documentation.

Sincerely,

Catherine Kingsford

**Bibliography**


1. Warren, A.G., et al., *Lymphedema: A Comprehensive Review.* Ann Plast Surg, 2007. **59**(4): p. 464-472.
2. Vicini, F.A., et al., *Multi-institutional analysis of bioimpedance spectroscopy in the early detection of breast cancer related lymphedema.* Journal of Cancer Research & Therapy, 2013. **1**(1): p. 1-7.
3. Cornish, B.H., et al., *Early diagnosis of lymphedema using multiple frequency bioimpedance.* Lymphology, 2001. **34**(1): p. 2-11.
4. Smoot, B.J., J.F. Wong, and M.J. Dodd, *Comparison of diagnostic accuracy of clinical measures of breast cancer-related lymphedema: area under the curve.* Arch Phys Med Rehabil, 2011. **92**(4): p. 603-10.
5. Czerniec, S.A., et al., *Assessment of breast cancer-related arm lymphedema--comparison of physical measurement methods and self-report.* Cancer Invest, 2010. **28**(1): p. 54-62.
6. Ward, L., et al., *Confirmation of the reference impedance ratios used for assessment of breast cancer-related lymphedema by bioelectrical impedance spectroscopy.* Lymphatic Research and Biology, 2011. **9**(1): p. 47-51.
7. Ridner, S.H., et al., *Bioelectrical Impedance for Detecting Upper Limb Lymphedema in Nonlaboratory Settings.* Lymphat Res Biol, 2009.


**Position Statements**


A. National Lymphedema Network (NLN)
Screening and Measurement for Early Detection of Breast Cancer Related Lymphedema
By: NLN Medical Advisory Committee; Updated December 2013

B. Australasian Lymphology Association (ALA)
Monitoring for the Early Detection of Breast Cancer Related Lymphoedema
Approved by: ALA National Council; October 2012