



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
Fort Washington, PA 19034

Dear Ms. McClure:

NCCN Guidelines® Panel: Survivorship

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

Specific Changes:

Request to include an algorithm (see attached) to describe the early detection and management of cancer related lymphedema (CRL) using bioimpedance spectroscopy (L-Dex®).

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:

The 2015 NCCN Guidelines® for Breast Cancer recognized lymphedema as a common complication after treatment for breast cancer. The panel recommendation was to: “educate, monitor, and refer for lymphedema management.” We request that the panel develop guidelines for lymphedema management.

In the United States, secondary lymphedema is most commonly associated with malignancy and its treatment. Incidence rates for lymphedema following mastectomy have been reported as high as 49% [1]. Lymphedema of the lower limb is also a significant potential complication following surgery for melanoma, genitourinary cancers and sarcomas [2]. Incidence rates reported as high as 78.7% in patients undergoing radical surgery with adjuvant radiotherapy for International Federation of Gynecology and Obstetrics (FIGO) stage I to stage IIA cervical cancer [3].

Cancer Related Lymphedema (CRL) begins as a subclinical process due to an impairment of the lymphatic drainage system; this impairment causes an increase in extracellular fluid which then leads to clinically detectable lymphedema. At this stage 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) [4].

Currently, identification is often delayed until the disease has progressed to being clinically symptomatic, impairing function and quality of life. Further, 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 detection of subclinical lymphedema and subsequent treatment with a light-grade compression garment can prevent progression of the disorder [5, 6].

The L-Dex U400 is a bioimpedance spectroscopy (BIS) device which specifically detects extracellular fluid accumulation. BIS has been shown to have high sensitivity and specificity along with high inter and intra-rater reliability [7-9]. The impedance ratio reference range (upper and lower limb) used in the L-Dex U400 has been validated across 2 continents: Ward et al., Australia [10, 11] and Ridner et al., Vanderbilt University [12].

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

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.

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.”

National Accreditation Program for Breast Centers (NAPBC) standard 2014:

The NAPBC recommends the NLN guidelines in its Standard for Support and Rehabilitation (2.15) under the topic “lymphedema management and risk reduction practices.” Standard 2.20 Breast Cancer Survivorship Care recommends individualized survivorship care plans that include guidelines for monitoring.

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,

A handwritten signature in black ink, appearing to read "Frank Vicini".

Frank Vicini, MD, FACR
Chief Medical Officer, ImpediMed

Bibliography

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2. Shaitelman, S.F., et al., *Recent progress in the treatment and prevention of cancer-related lymphedema*. CA Cancer J Clin, 2014.
3. Kim, J.H., et al., *Incidence and risk factors of lower-extremity lymphedema after radical surgery with or without adjuvant radiotherapy in patients with FIGO stage I to stage IIA cervical cancer*. Int J Gynecol Cancer, 2012. **22**(4): p. 686-91.
4. 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.
5. Stout Gergich, N.L., et al., *Preoperative assessment enables the early diagnosis and successful treatment of lymphedema*. Cancer, 2008. **112**(12): p. 2809-19.
6. Soran, A., 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. **12**(4): p. 289-94.
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8. 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.
9. Czerniec, S.A., L.C. Ward, and S.L. Kilbreath, *Assessment of breast cancer-related lymphedema: a comparison of moisture meter and spot bioimpedance measurement*. Lymphat Res Biol, 2015. **13**(1): p. 10-9.
10. 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.
11. Ward, L., et al., *Reference ranges for assessment of unilateral lymphedema in legs by bioelectrical impedance spectroscopy*. Lymphatic Research and Biology, 2011. **9**(1): p. 43-46.
12. Ridner, S.H., et al., *Bioelectrical Impedance for Detecting Upper Limb Lymphedema in Nonlaboratory Settings*. Lymphat Res Biol, 2009.

Position Statements

- A. Australasian Lymphology Association (ALA)
Monitoring for the Early Detection of Breast Cancer Related Lymphoedema
Approved by: ALA National Council; October 2012
- B. National Lymphedema Network (NLN)
Screening and Measurement for Early Detection of Breast Cancer Related Lymphedema
By: NLN Medical Advisory Committee; Updated December 2013
- C. National Accreditation Program for Breast Centers (NAPBC)
Standards Manual 2014 Edition
Standard 2.15 and Standard 2.20

ASSESSMENT OF CANCER RELATED LYMPHEDEMA

Cancer Diagnosis

Pre-intervention (including neo-adjuvant chemotherapy)

- Patient education regarding symptoms of heaviness, tightness, swelling or redness
- Objective assessment of the at-risk area

Post-intervention follow up

- History and physical exam 1-4 times a year as clinically appropriate for 5 years and then annually
- Ongoing patient education and support
- Physical impairment, functional status, and subjective self-report of symptoms
- Objective assessment of the at-risk area

Measurements

- Volumetric measures such as tape measure/circumference measure/perometer:
 - Criteria for referral must be based on peer reviewed literature and defined by the institution
 - Measurements should be performed by a specialty-trained health care provider with monthly inter-rater reliability testing and documentation
- Bioimpedance Spectroscopy (BIS):
 - An L-Dex® score >10 from a pre-operative baseline requires further evaluation by a professional trained in lymphedema assessment and management
 - L-Dex measurements must be taken by trained operators

Lymphedema Treatment

- Referral for treatment must be documented
- Treatment must be carried out by either:
 - A certified Lymphedema Therapist who has met the minimum of 135 hours of lymphedema certification training as outlined by the Lymphology Association of North America (LANA®),
 - A Physician, Advanced Practice Nurse, or physician -assistant with knowledgeable about lymphedema and lymphedema management.