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NCCN Guidelines® Panel: Breast Cancer

On behalf of ImpediMed Limited, I respectfully request the NCCN Breast Cancer Guideline Panel to review the enclosed data to support the use of L-Dex as an objective tool for early detection of lymphedema.

Specific Change

Request to amend the language in BINV-E

From: 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).

To: 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. [Endeavor to obtain a pretreatment measurement of both arms as a baseline for patients with risk factors for lymphedema, and establish a program of regular follow up using an objective, reproducible tool such as L-Dex](#). See NCCN Guidelines for Survivorship: Lymphedema (SLYMPH-1).

FDA Clearance

The SOZO Body Fluid Analyzer has 510(k) clearance for the following use:
For adult human patients at risk of lymphedema:

A bioimpedance spectroscopy device for use on adult human patients, utilizing impedance ratios that are displayed as an L-Dex ratio that supports the measurement of extracellular volume differences between the limbs and is presented to the clinician on an L-Dex scale as an aid to their clinical assessment of lymphedema.

The use of the device to obtain an L-Dex score is only indicated for patients who will have or who have had lymph nodes, from the axillary and/or pelvic regions, either removed, damaged or irradiated.

Rationale

As noted from previous NCCN guidelines, lymphedema is a significant concern for patients and early detection is key. Tape measurement is being utilized to assess for lymphedema in an overwhelming majority of clinics and hospitals; however, studies have consistently demonstrated high rates intra and inter-observer variability with tape measurement.[1, 2] Additionally, tape measurement has been consistently shown to lack the sensitivity to detect early stage fluid accumulation or sub-clinical lymphedema.[3] Consistent with the NCCN's previous breast cancer and survivorship guidelines, data has shown that technologies including bioimpedance spectroscopy are able to detect sub-clinical lymphedema, allowing for earlier detection by measuring changes in fluid status rather than simply volume which may not be fluid related in all patients; this allows for treatment initiation

earlier and therefore higher success with BCRL management as noted in the NCCN survivorship guidelines.[4] To this point, several studies including single centers as well as multi-institutional studies of between 100 and 600 patients have demonstrated the ability for bioimpedance spectroscopy (BIS) using L-Dex to detect early stage lymphedema and a 50-75% reduction in rates of chronic BCRL as compared to historical rates, even in high-risk patients.[5-8] Koelmeyer et al demonstrated the utility of bioimpedance as compared to traditional models, with reductions in severe lymphedema as (24% vs. 4%) with bioimpedance surveillance.[9] Data from the Cleveland Clinic has also shown the utility of BIS to assess for BCRL in patients undergoing lymphaticovenous bypass.[10]

Growing data is now available comparing L-Dex and tape measurement. The interim analysis of the randomized PREVENT trial was published with more than 500 patients and demonstrated a 10% reduction in chronic BCRL with L-Dex as compared to tape measurement, resulting in a <5% incidence of chronic lymphedema in the L-Dex group.[11] Recently, 24 month data utilizing a trajectory analysis was published demonstrated that tape measure did not correlate with symptoms while L-Dex did.[12] Finally, a meta-analysis, yet to be published, comparing bioimpedance and tape measure, found that L-Dex absolute rates of chronic lymphedema were significantly reduced compared to tape measure with tape measurements not improving outcomes as compared to background studies.

Clinical Practice and Cost Savings

Koelmeyer et al, demonstrated that L-Dex can be implemented as a prospective surveillance model of care, in both public and private multidisciplinary breast cancer centers.[13] Additionally, L-Dex represents an evidence based BCRL surveillance approach that is cost-effective. Previous studies have highlighted the costs of chronic BCRL which include not only treatment but potential hospitalizations.[14] Previously, Stout et al demonstrated the value of prospective BCRL surveillance, while data from the PREVENT trial was used in a cost-effectiveness analysis and demonstrated the earlier detection of BCRL with L-Dex and subsequent intervention will result in significantly better patient outcomes and reduced costs of care.[15, 16]

The articles submitted in support of this change are listed on the next page.

Yours sincerely,



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SVP Medical Affairs
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2. Ridner, S.H., et al., *Bioelectrical Impedance for Detecting Upper Limb Lymphedema in Nonlaboratory Settings*. Lymphat Res Biol, 2009.
3. Hayes, S., B. Cornish, and B. Newman, *Comparison of methods to diagnose lymphoedema among breast cancer survivors: 6-month follow-up*. Breast Cancer Res Treat, 2005. **89**(3): p. 221-6.
4. Ward, L., *Is BIS ready for prime time as the gold standard measure?* Journal of Lymphoedema, 2009. **4**(2): p. 52-56.
5. Kaufman, D.I., et al., *Utilization of bioimpedance spectroscopy in the prevention of chronic breast cancer-related lymphedema*. Breast Cancer Res Treat, 2017. **166**(3): p. 809-815.
6. Whitworth, P.W., et al., *Preventing Breast Cancer-Related Lymphedema in High-Risk Patients: The Impact of a Structured Surveillance Protocol Using Bioimpedance Spectroscopy*. Front Oncol, 2018. **8**: p. 197.
7. Kilgore, L.J., 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.
8. 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.
9. Koelmeyer, L.A., et al., *Early surveillance is associated with less incidence and severity of breast cancer-related lymphedema compared with a traditional referral model of care*. Cancer, 2018. **125**(6): p. 854-862.
10. Schwarz, G.S., et al., *Axillary reverse mapping and lymphaticovenous bypass: Lymphedema prevention through enhanced lymphatic visualization and restoration of flow*. J Surg Oncol, 2019. **120**(2): p. 160-167.
11. Ridner, S.H., 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.
12. Ridner, S.H., et al., *L-Dex, arm volume, and symptom trajectories 24 months after breast cancer surgery*. Cancer Medicine, 2020. **n/a**(n/a).
13. Koelmeyer, L., et al., *Implementing a prospective surveillance and early intervention model of care for breast cancer-related lymphedema into clinical practice: application of the RE-AIM framework*. Supportive Care in Cancer, 2020.
14. Basta, M.N., et al., *Complicated breast cancer-related lymphedema: evaluating health care resource utilization and associated costs of management*. Am J Surg, 2016. **211**(1): p. 133-41.
15. Stout, N.L., et al., *Breast cancer-related lymphedema: comparing direct costs of a prospective surveillance model and a traditional model of care*. Phys Ther, 2012. **92**(1): p. 152-63.
16. Shah, C., *Bioimpedance spectroscopy in the detection of breast cancer-related lymphedema: An ounce of prevention*. Breast J, 2019. **25**(6): p. 1323-1325.