Clinical Evidence Summary
Lymphedema Prevention Program with BIS Technology

PREVENT Trial

Timing of Breast Cancer Related Lymphedema Development Over 3 Years: Observations from a Large, Prospective Randomized Screening Trial Comparing Bioimpedance Spectroscopy (BIS) Versus Tape Measure

Shah C, Boyages J, Koelmeyer LA, Chen SL and Vicini FA

Annals of Surgical Oncology, July 2024, DOI: https://doi.org/10.1245/s10434-024-15706-x

Secondary analysis of PREVENT study data to understand the timing of sBCRL and cBCRL following breast cancer treatment. The timing of sBCRL trigger for 209 patients and cBCRL trigger for 30 patients was reviewed at 3 months intervals.

- A total of 209 patients developed sBCRL druing the study with over half of the cases detected within 9 months post breast cancer treatment indicating a critical period for monitoring.
- Patients continued to trigger for sBCRL throughout the 3-year follow-up with consistent rates of detection the second and third years, highlighting the need for ongoing surveillance for at least 3 years.
- High risk patients may benefit from more frequent monitoring than the six month interval used in the study to improve outcomes.

Axillary Treatment and Chronic Breast Cancer Related Lymphedema: Implications for Prospective Surveillance and Intervention From a Randomized Controlled Trial

Boyages J, Vicini FA, Azimi Manavi B, Gaw RL, Koelmeyer LA, Ridner SH and Shah C.

JCO Oncology Practice, December 2023, DOI: https://doi.org/10.1200/OP.23.00060

This study findings represents secondary analysis of PREVENT Trial study data to identify risk factors on the basis of axillary treatment. The findings reinforce extent of axillary treatment is a significant risk factor for chronic breast cancer-related lymphedema (C-BCRL), in addition to other factors which increase risk.

- Increasing BMI, rurality, SCF radiation and taxane chemotherapy also increase risk for C-BCRL.
- Propose a risk-based screening program that increases in frequency as the risk of C-BCRL increases.
- Kaplan Meier actuarial risks for progression to C-BCRL were significantly lower (approximately 50%) in the BIS group across the entire monitoring period (1 year, BIS: 2.1% vs TM: 4.7%, p=0.04, 2 year, BIS: 3.6% vs TM: 8.3%, p=0.001, and 3 year, BIS: 6.4% vs TM: 10.3%, p=0.03).

A Comparison of Bioimpedance Spectroscopy or Tape Measure Triggered Compression Intervention in Chronic Breast Cancer Lymphedema Prevention

Ridner, S. H., Dietrich, M. S., Boyages, J., et al.

Lymphatic Research and Biology, January 2022, DOI: https://doi.org/10.1089/lrb.2021.0084

The findings from this study come from the PREVENT Trial's three-year primary endpoint analysis. Compared to tape measure (TM), bioimpedance spectroscopy (BIS) provided a more precise identification of patients likely to benefit from an early compression intervention. Furthermore, L-Dex® screening should be a standard approach for prospective breast cancer-related lymphedema surveillance.

- The PREVENT Trial is the largest randomized trial to assess lymphedema prevention.
- The primary endpoint result found a significantly lower progression to chronic lymphedema with early detection using L-Dex and intervention (7.9%) versus using tape measure (19.2%).
- The three-year primary endpoint analysis also found that L-Dex was more precise and reliable than tape measure for lymphedema detection, with only 20.1% of the L-Dex population triggering compared to tape measure at 27.2%.

Prospective Surveillance with Compression for Subclinical Lymphedema: Symptoms, Skin, and Quality-of-Life Outcomes Dietrich, M. S., Gaitatzis, K., Koelmeyer, L., et al.

Lymphatic Research and Biology, September 2022, DOI: https://doi.org/10.1089/lrb.2022.0020

This study's findings, which are secondary aims from the PREVENT Trial, demonstrate that prospective surveillance and compression intervention promote lower progression rates from subclinical breast cancer-related lymphedema (S-BCRL) to chronic breast cancer-related lymphedema (C-BCRL).

- Early detection and intervention of breast cancer-related lymphedema reduces the burden of chronic lymphedema on patients.
- L-Dex testing is more effective than tape measure at identifying the optimal time to intervene to stop lymphedema progression.

Risk Factors for Breast Cancer–Related Lymphedema in Patients Undergoing 3-Years of Prospective Surveillance with Intervention

Koelmeyer, L. A., Gaitatzis, K., Dietrich, M. S., et al.

Cancer, July 2022, DOI: https://doi.org/10.1002/cncr.3437

This study reinforces known breast cancer-related lymphedema (BCRL) risk factors including axillary lymph node dissection, taxane-based chemotherapy, regional nodal irradiation, and obesity.

- The Prospective Surveillance and Early Intervention (PSEI) model of care allows for successful management of subclinical BCRL and lymphedema prevention.
- The current analysis provides novel data on the increased risk of BCRL in patients living in a rural area as well as no increased risk from air travel.

The Risk of Subclinical Breast Cancer-Related Lymphedema by the Extent of Axillary Surgery and Regional Node Irradiation: A Randomized Controlled Trial

Boyages, J., Vicini,F., Shah. C., et al.

International Journal of Radiation Oncology, October 2020, DOI: https://doi.org/10.1016/j.ijrobp.2020.10.024

Bioimpedance spectroscopy (BIS) was associated with lower trigger rates and better discrimination of the risk of subclinical breast cancer-related lymphedema (S-BCRL) by receipt and type of regional nodal irradiation (RNI) compared with tape measure (TM).

- The risk of S-BCRL and triggering increased with more extensive axillary treatment
- Triggering by TM was greater than 25% for most subgroups and was inferior to BIS in discriminating the risk of S-BCRL by use of RNI or axillary surgery.
- The lower trigger rate for BIS compared with TM suggests that TM might be associated with a higher rate of false-positive results.

Implementing a Prospective Surveillance and Early Intervention Model of Care for Breast Cancer-Related Lymphedema into Clinical Practice: Application of the RE-AIM Framework

Koelmeyer, L., Gaitatzis, K., Ridner, S.H., et al.

Supportive Care in Cancer, June 2020, DOI: https://doi.org/10.1007/s00520-020-05597-5

Implementation of the prospective surveillance and early intervention model of care (PSM) used in the PREVENT Trial has assisted in changing clinical practices and improving the quality and effectiveness of the health care system. The PSM for breast cancer related lymphedema can be successfully implemented by applying the RE-AIM approach retrospectively, the RE-AIM approach stands for reach, effectiveness, adoption, implementation, and maintenance.

L-Dex, Arm Volume, and Symptom Trajectories 24 Months After Breast Cancer Surgery

Ridner, S. H., Shah, C., Boyages, J., et al.

Cancer Med, June 2020, DOI: https://doi.org/10.1002/cam4.3188

Interim data from the PREVENT Trial supports the need for long-term (24 months) prospective surveillance with regular assessments (every 3 months) at least 15 months after surgery.

- Statistically significant convergence of symptom cluster scores with L-Dex unit change supports bioimpedance spectroscopy (BIS) as beneficial in the early identification of subclinical lymphedema.

A Randomized Trial Evaluating Bioimpedance Spectroscopy Versus Tape Measurement for the Prevention of Lymphedema Following Treatment for Breast Cancer: Interim Analysis

Ridner, S.H., Dietrich, M.S., Cowher, M.S., et al.

Annals of Surgical Oncology, May 2019, DOI: https://doi.org/10.1245/s10434-019-07344-5

This study was performed as pre-specified interim analysis after at least 500 trial participants had 1 year of follow-up. The study showed that post-treatment surveillance with bioimpedance spectroscopy (BIS) reduced the absolute rates of progression of breast cancer-related lymphedema requiring complex decongestive physiotherapy (CDP) by approximately 10%, a clinically meaningful improvement. Additionally, compared with tape measure (TM), BIS had a lower rate of triggers in the arm, suggesting higher specificity and cost effectiveness.

Real World Studies

Comprehensive Strategies in Breast Cancer-Related Lymphedema Prevention: Insights from a Multifaceted Program

Bhimani F, McEvoy M, Chen Y, Gupta A, Pastoriza J, Cavalli A, Obaid L, Rachofsky C, Fruchter S, Feldman S
Frontiers in Oncology, July 2024, DOI: https://doi.org/10.3389/fonc.2024.1418610

The study highlights a multifaceted lymphedema prevention program that includes axillary reverse mapping (ARM) surgery, three to six monthly screening from baseline using BIS (SOZO) with early intervention and extensive patient education.

- Among 212 patients who underwent the comprehensive prevention program (83% of whom were ethnic minorities and had a higer BMI), only 1.41% developed persistent lymphedema demonstrating the effectiveness of the implemented strategies.
- This is significantly lower than the previously reported two- to three-fold increased risk in similar demographic populations.

Breast Cancer-Related Lymphedema (BCRL) and Bioimpedance Spectroscopy: Long-Term Follow-Up, Surveillance Recommendations, and Multidisciplinary Risk Factors

Jeffers EJ, Wagner JL, Korentager SS, Larson KE, Balanoff CR, Baker J, Chollet-Hinton L and Kilgore LJ
Annals of Surgical Oncology, October 2023, DOI: https://doi.org/10.1245/s10434-023-13956-9

High risk patients (ALND) followed up for a mean of 55 months can benefit from routine surveillance using L-Dex monitoring from baseline and early at home intervention to stop abnormal triggers (44% incidence) progressing to persistent BCRL (8% incidence). There was a statistically significant difference in resolution of breast cancer-related lymphedema depending on the presenting stage ($p<0.001$), where patients with stage 0 and 1 returned to normal BIS measures more often, confirming importance of close monitoring and early intervention.

Early Surveillance is Associated with Less Incidence and Severity of Breast Cancer–Related Lymphedema Compared with a Traditional Referral Model of Care

Koelmeyer, L. A., Borotkanics, R. J., Alcorso, J., et al.
Cancer, December 2018, DOI: https://doi.org/10.1002/cncr.31873

Women who underwent early surveillance received lymphedema care almost 2 years earlier than women in the traditional referral group and had a significantly lower incidence of clinical lymphedema. These findings support the adoption of an early prospective surveillance model of care using bioimpedance spectroscopy (BIS) for the early detection and management of breast cancer-related lymphedema (BCRL).

Reducing Breast Cancer-Related Lymphedema (BCRL) Through Prospective Surveillance Monitoring Using Bioimpedance Spectroscopy (BIS) and Patient Directed Self-Interventions

Kilgore, L.J., Korentager, S.S., Hangge, A.N., et al.
Annals of Surgical Oncology, July 2018, DOI: https://doi.org/10.1245/s10434-018-6601-8

Study results demonstrated that early conservative intervention for breast cancer patients who are high risk for breast cancer-related lymphedema (BCRL) resulted in significantly lower rates of BCRL if lymphedema was detected early using bioimpedance spectroscopy (BIS), rather than detected late. These findings reinforce the importance of early prospective screening and intervention for BCRL.

Reducing Chronic Breast Cancer-Related Lymphedema Utilizing a Program of Prospective Surveillance with Bioimpedance Spectroscopy

Whitworth, P. W & Cooper, A.
The Breast Journal, October 2017, DOI: https://doi.org/10.1111/tbj.12939

Analysis done in this study offers support for the concept that prospective surveillance using bioimpedance spectroscopy (BIS) and intervention can result in lower rates of chronic breast cancer-related lymphedema (BCRL), as only 3% of study participants had unresolved clinically significant BCRL requiring complete decongestive physiotherapy. These findings further support the cost-effective allocation of resources for prospective, BIS-assisted, BCRL surveillance for breast cancer survivorship programs.

Utilization of Bioimpedance Spectroscopy in the Prevention of Chronic Breast Cancer-Related Lymphedema

Kaufman, D.I., Shah, C., Vicini, F.A., et al.

Breast Cancer Research and Treatment, August 2017, DOI: https://doi.org/10.1007/s10549-017-4451-x

Intervention triggered by subclinical breast cancer-related lymphedema (S-BCRL) detection with an elevated L-Dex score was not associated with any cases progressing to chronic, clinically detectable BCRL, even in very high-risk patient

The Impact of L-Dex Measurements in Assessing Breast Cancer-Related Lymphedema as Part of Routine Clinical Practice

Laidley, A & Anglin, B.

Frontiers in Oncology, September 2016, DOI: https://doi.org/10.3389/fonc.2016.00192

This study demonstrates both the viability and clinical efficacy of implementing L-Dex measurements in routine breast cancer care as L-Dex was able to identify an improvement in breast cancer-related lymphedema (BCRL) following treatment.

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

Soran, A., Ozmen, T., McGuire, K. P., et al.

Lymphatic Research and Biology, September 2014, DOI: https://doi.org/10.1089/lrb.2014.0035

This study found that progression to clinical lymphedema occurred in only 4.4% of patients over an average of 20 months follow-up, compared to 36.4% in the control group. These findings therefore suggest that periodic monitoring of women at high risk for lymphedema (LE) with bioimpedance spectroscopy (BIS) allows early detection and timely intervention for LE, which reduces the incidence of clinical LE and holds implications for quality of life and health care costs.

Cost Analysis

Bioimpedance Spectroscopy in the Detection of Breast Cancer-Related Lymphedema: An Ounce of Prevention

Chirag Shah, MD

The Breast Journal, June 2019, DOI: https://doi.org/10.1111/tbj.13618

Findings support that bioimpedance spectroscopy (BIS) should be considered a value-oriented breast cancer-related lymphedema (BCRL) surveillance strategy, and payors should consider reimbursing for BIS prospectively to reduce downstream costs.

- BIS generated a cost savings of $356-$770 per patient at 1 year.
- Incorporating the costs of hospitalizations, a difference of more than $16,000 per patient was noted.

Complicated Breast Cancer-Related Lymphedema: Evaluating Health Care Resource Utilization and Associated Costs of Management

Basta, M. N., Fox, J. P., Kanchwala, S., et al.

American Journal of Surgery, August 2015, DOI: https://doi.org/10.1016/j.amjsurg.2015.06.015

Complicated lymphedema develops in a measurable number of patients, and their health care burden demands further investigation into targeted, anticipatory management strategies for breast cancer–related lymphedema (BCRL).

- Out of all the women included in this study, 2.3% had at least 1 hospital admission for complicated lymphedema within 2 years of surgery.
- Women with complicated lymphedema experienced 5 times more all-cause admissions compared with women without lymphedema.
- Women with complicated lymphedema compared to those without experienced substantially higher health care charges This resulted in substantially higher health care charges ($58,088 vs $31,819 per patient).

Breast Cancer-Related Lymphedema: Comparing Direct Costs of a Prospective Surveillance Model and a Traditional Model of Care

Stout, N. L., Pfalzer, L. A., Springer, B., et al.

Physical therapy, January 2012, DOI: https://doi.org/10.2522/ptj.20100167

A prospective surveillance program potentially decreases direct treatment costs associated with managing breast cancer-related lymphedema (BCRL) and enables early intervention when these common impairments are less severe.

- Prospective interval assessment involving patient education and home-based exercise is the most cost-effective method to facilitate optimal rehabilitation outcomes.
- Prospective surveillance demonstrates that more conservative treatment is clinically effective in early stages of lymphedema and does not require the components of an intense complete decongestive therapy (CDT) program.
- Detection of early-stage BCRL may counteract or greatly reduce the need for decongestive therapy and resource utilization by reducing the severity of the condition.

Incidence, Treatment Costs, and Complications of Lymphedema after Breast Cancer Among Women of Working Age: a 2-Year Follow-Up Study

Shih, Y. C. T., Cormier, J. N., Giordano, S., et al.

Journal of Clinical Oncology, March 2009, DOI: https://doi.org/10.1200/jco.2008.18.3517

The substantial costs documented in this study suggest that further efforts should be made to clarify reduction and prevention strategies for breast cancer-related lymphedema (BCRL).

- In 2 years, the unadjusted cost difference unrelated to cancer treatment was $ 14, 600 more for woman with breast cancer related lymphedema vs those who were not diagnosed.

Summary & Meta Analysis

Evidence-Based Recommendations Regarding Risk Reduction Practices for People at Risk of or with Breast Cancer-Related Lymphedema: Consensus from an Expert Panel

Brunelle CL, Jackson K, Shallwani SM, Hunley JH, Kennedy A, Fench S, Hill A, Paskett ED, Rush K, Thiadens SRJ, White J and Stewart P

Medical Oncology, October 2024, DOI: https://doi.org//10.1007/s12032-024-02510-6

Combining scientific evidence with the consensus opinion of the lymphedema experts assembled at the Americal Cancer Society/Lymphology Association of North America Summit in October 2023, updated evidence-based recommendations for reducing risk for individuals at risk of or with lymphedema are formulated.

- All people at risk of BCRL should have access to prospective surveillance (screening) for BCRL, including pre-operative baseline measurements (such as arm volume and/or bioimpedance spectroscopy measurements) and regular follow-up based on individual risk.
- Ideally, screening would continue for five years post-surgery as most people who develop BCRL do so within this timeframe.

Current Diagnostic and Quantitative Techniques in the Field of Lymphedema Management: A Critical Review

Vargo M, Aldrich M, Donahue P, Iker E, Koelmeyer L, Crescenzi R and Cheville A

Medical Oncology, September 2024, DOI: https://doi.org// 10.1007/s12032-024-02472-9

Critical expert review of current status of diagnostic and quantitative measures for lymphedema against a grid framework of lymphedema characteristics and clinical needs to assist stakeholders in selecting appropriate diagnostic and surveillance modalities.

- The use of a comprehensive multi-modal assessment is recommended with clinical evalution and symptom recording also important.
- BIS offers high sensitivity, standardized cut-off measurements, and excellent inter-observer variability for screening and monitoring fluid changes in limbs.
- No single device to-date can adequately measure all elements of therapeutic change given the heterogeneity of lymphedema. Furthermore, utility may break down in the absence of a reliable benchmark for comparison such as a baseline measurement or unaffected contralateral limb.

Multinational Association of Supportive Care in Cancer (MASCC) clinical practice guidance for the prevention of breast cancer-related arm lymphoedema (BCRAL): international Delphi concensus-based recommendations

Wong HCY, Wallen MP, Chan AW, Dick N, Bonomo P, Bareham M, Wolf JR, Van den Hurk C, Fitch M, Chow E and Chan RJ

EClinical Medicine, February 2024, DOI: https://doi.org/ 10.1016/j.eclinm.2024.102441

A two-round international Delphi consensus process was performed to compile practical recommendations of 55 experts involved in the care and research of breast cancer and lymphoedema on developing evidence based strategies to prevent BCRAL.

- The expert panel recommended detailed guidelines on how prospective surveillance programs should be implemented.
- Bioimpedance spectroscopy (BIS) was recommended as the preferred method of detection.
- L-Dex thresholds to trigger early interventions include an increase in L-Dex score ≥6.5 compared to pre-treatment values.
- When early lymphoedema is detected in a surveillance program, the panel recommended compression sleeves as the initial treatment for at least 4–6 weeks.
- When patients are found to have L-Dex >10 or volume measurements are ≥10% compared to pre-surgery values or persistent symptoms despite initial treatments, more intensive treatment (e.g., complete decongestive therapy) is indicated.
- The panel also made recommendations on the schedule and logistics of a prospective surveillance program. First, pre-surgical measurements should be performed to allow better comparisons after surgery. The program should start within 3 months after surgery, and assessments repeated every 3–4 months in the first year then every 6–12 months thereafter for at least 24 months from surgery where feasible and resources allow.

The Prevention and Treatment of Breast Cancer- Related Lymphedema: A Review

McEvoy, M. P., Gomberawalla, A., Smith, M., et al.

Frontiers in Oncology, December 2022, DOI: https://doi.org/10.3389/fonc.2022.1062472

This study was done as a comprehensive lymphedema literature review by the American Society of Breast Surgeons Lymphatic Surgery Working Group to develop breast cancer-related lymphedema (BCRL) guidelines and found that early detection, before clinically apparent, is crucial to prevent irreversible lymphedema.

- Bioimpedance spectroscopy (BIS) is the only technology reported by the ASBS working group findings to detect subclinical BCRL.
- Screening programs should use tools that are objective and reproducible.
- Initial pre-operative measurement should be obtained followed by regularly scheduled post-operative measurements.

Bioimpedance Spectroscopy for Breast Cancer-Related Lymphedema Assessment: Clinical Practice Guidelines

Shah, C., Whitworth, P., Valente, S., et al.

Breast Cancer Research and Treatment, December 2022, DOI: https://doi.org/10.1007/s10549-022-06850-7

The updated clinical practice guidelines suggest a standardized approach for a prospective model of care using bioimpedance spectroscopy (BIS) for breast cancer-related lymphedema (BCRL) assessment based on level I evidence.

- Current data supports the utilization of BIS as part of a prospective model of care in which patients are followed closely at routine intervals that can result in early identification of lymphedema and improved patient outcomes.
- The first visit for patients who display no clinical signs of lymphedema is often considered their baseline, allowing for BCRL surveillance for all at risk patients.
- When patients demonstrate an L-Dex increase of greater than 6.5, they should be prescribed compression intervention.

Reducing Rates of Chronic Breast Cancer–Related Lymphedema with Screening and Early Intervention: an Update of Recent Data

Whitworth, P., Vicini, F., Valente, S.A., et al.

Journal of Cancer Survivorship, August 2022, DOI: https://doi.org/10.1007/s11764-022-01242-8

This study carried out a systematic literature review of 12 studies in total (2,907 patients), including 4 randomized and 8 prospective studies. The study reported that breast cancer survivors should undergo prospective breast cancer-related lymphedema (BCRL) screening with bioimpedance spectroscopy (BIS).

- Level 1 data demonstrate that BIS is superior to conventional tape measure, and it should be included as the standard method for subclinical BCRL detection.
- The PREVENT Trial has demonstrated early detection with bioimpedance spectroscopy (BIS), coupled with early intervention and a compression garment applied for 12 hours a day over 4 weeks greatly reduced BCRL compared to tape measure.

The Impact of Monitoring Techniques on Progression to Chronic Breast Cancer-Related Lymphedema: a Meta-Analysis Comparing Bioimpedance Spectroscopy versus Circumferential Measurements

Shah, C., Zambelli-Weiner, A., Delgado, N., et al.

Breast Cancer Research & Treatment, November 2020, DOI: https://doi.org/10.1007/s10549-020-05988-6

The current study conducted a literature review that included 50 eligible peer-reviewed studies published during or after 2013 and represented over 67,000 women. The study found that monitoring with bioimpedance spectroscopy (BIS) allowed for early intervention and significantly reduced the relative risk of chronic BCRL with a 69% and 81% reduction compared to background and circumference, respectively.

- Early detection can be used to trigger interventions, such as compression garments and physical therapy, to prevent the development of chronic BCRL.
- Earlier diagnosis and intervention along with informing patients can help reduce BCRL and allow for the reversal of the increased fluid volume, which holds great clinical importance.