

# Topic Brief: Effectiveness of Surveillance Measures for Early Detection and Interventions to Prevent Breast Cancer-Related Lymphedema

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**Nomination Number:** 862

**Purpose:** This document summarizes the information addressing a nomination submitted on June 6, 2019 through the Effective Health Care Website. This information was used to inform the Evidence-based Practice Center (EPC) Program decisions about whether to produce an evidence report on the topic, and if so, what type of evidence report would be most suitable.

**Issue:** Breast cancer survivors' rate recurrence of their cancer as their number one concern, but their second concern is developing chronic lymphedema. Breast cancer guidelines require clinicians to monitor for lymphedema, but there are no summaries of the evidence recognizing importance of early detection of breast cancer-related lymphedema (BCRL) and recommended diagnostic tools for the early detection of BCRL. Payers are not covering technologies such as bioimpedance and have questioned the importance of the early detection of BCRL. As a result, patients are not being surveilled to detect early BCRL causing delayed treatment. As lymphedema progresses treatment becomes less effective, more complex and costly.

## Program Decision:

Topic meets all criteria but was not selected for a systematic review because the literature base was very small and there are a number of ongoing studies. Based on that it seemed premature to systematically review the literature at this time. No further activity on this nomination will be undertaken by the Effective Health Care (EHC) Program.

## Key findings

- This nomination meets all selection criteria.
- We found one systematic review and estimate 57 primary studies about BCRL detection and intervention. We considered the one systematic review partially duplicative with a portion (i.e. invasive, surgical interventions) with key question #3. However, it did not address non-surgical interventions to prevent progression of BCRL.

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## Background

In 2016, 245,299 new cases of female breast cancer were reported, and 41,487 women died of Female Breast Cancer in the United States.<sup>1</sup> Clinical and pathological features influence prognosis and treatment.<sup>2</sup>

Standard treatment options for early, localized, or operable breast cancer may include the following:<sup>3</sup>

- Surgery: either breast-conserving (lumpectomy and sentinel lymph node (SLN) biopsy) or modified radical mastectomy, either with or without axillary lymph node dissection for positive SLNs.
- Postoperative radiation therapy: regional or whole-breast
- Postoperative systemic therapy including tamoxifen, aromatase inhibitor therapy, ovarian function suppression and chemotherapy

Breast cancer-related lymphedema (BCRL) is an adverse effect of breast cancer treatment that results from disruption to the lymphatic system with impairment of drainage of lymph fluid and accumulation in the extracellular space. This results in swelling in the breast, trunk or upper extremity after breast cancer treatment. Lymphedema in limbs in general is graded on a three-stage scale from I to III based on physical characteristics of the limb. Functional severity assessment is based on volume differences with minimal (>5-10 to <20% increase), moderate (20 to 40% increase) or severe (>40% increase).<sup>4</sup> It has been reported to occur within days and up to 30 years after treatment for breast cancer.[11] Eighty percent of patients experience onset within 3 years of surgery; the remainder develop edema at a rate of 1% per year.[12] The overall incidence of arm lymphedema can range from 8% to 56% at 2 years post-surgery.[10]

Single-modality treatment of the axilla (surgery or radiation) is associated with a low incidence of BCRL. Women at higher risk of BCRL are those who receive both axillary node dissection and radiation therapy; partial and total mastectomy with axillary node sampling/dissection. Other risk factors for BCRL include lack of breast reconstruction surgery, high body mass index and greater number of positive lymph nodes.<sup>5</sup>

Lymphedema remains a major quality-of-life concern for breast cancer patients. Breast cancer survivors with arm lymphedema have been found to be more disabled, experience a poorer quality of life, and have more psychological distress than do survivors without lymphedema.<sup>6,7</sup> In addition, women reporting swelling have reported significantly lower quality of life with multiple functional assessments.<sup>8</sup> Lymphedema was shown to be the strongest risk factor for chronic pain in breast cancer survivors.<sup>9</sup>

It is important to diagnose and treat BCRL when it is mild because it can lead to preventable severe, debilitating lymphedema. Women with mild BCRL are more than three times as likely to develop severe BCRL than are women with no BCRL.<sup>10</sup> However, it is uncertain whether diagnosis of early lymphedema and subsequent treatment improves outcomes.

The wide variety of methods described in the literature for evaluating limb volume for BCR, and lack of standardization makes it difficult for the clinician to assess the at-risk limb. Options include water displacement, tape measurement, infrared scanning, and bioelectrical impedance spectroscopy (BIS).<sup>11</sup> Each test has unique diagnostic properties as well as variation in expense of equipment, administration time, training and space requirements. In 2016 the International Society of Lymphology issued general guidance on the detection and treatment of peripheral lymphedema, but does not make recommendations on preferred detection methods or surveillance and early detection of BCRL.<sup>4</sup> No U.S. medical specialty society has guidance on BCRL surveillance including when and how often to screen, the mode of measurement and interventions for prevention of progression. As a result, major variations in practice exist notably between academic centers as well as professions.

Practice variation also exists in the initiation and chosen modality of treatment of BCRL. Non-invasive approaches include compression therapy, manual lymphatic drainage and complex decongestive therapy. Invasive approaches include liposuction, lymphatic bypass and lymph node transfer. In general, evidence suggests non-invasive approaches for earlier stage LE and invasive approaches for later stage. Again, no U.S. medical specialty society has issued guidance on the timing and preferred treatment modality for BCRL.

## **Nomination Summary**

The nomination was submitted by ImpediMed, a manufacturer of a bioimpedance spectroscopy (BIS) device (L-Dex™ U400). It focused on the diagnostic accuracy of various methods to detect subclinical LE in breast cancer survivors, and the importance of detection and intervention at the subclinical phase to prevent clinical LE and its sequelae.

The author developed three draft key questions and PICOTS based on the nomination and discussions with the nominator. These were refined with input from two radiation oncologists from the NCI and Massachusetts General Hospital. We expanded the focus on diagnostic methods to include perometry, circumferential measurements and volume displacement compared to each other or other methods. The term subclinical lymphedema was rarely found in the literature and no consensus definition was identified. We revised the focus of the topic to the surveillance and early detection, and interventions to prevent progression of BCRL.

A systematic review would be highly impactful and valuable: the American Society of Breast Surgeons is planning to develop guidance to address known practice variation through either a future guideline or practice statement.

## **Scope**

1. What is the diagnostic accuracy of bioimpedance spectroscopy (BIS) and perometry compared to other techniques for the surveillance and detection of breast cancer related lymphedema (BCRL) in women after treatment for invasive breast cancer?
  - a. Does the effectiveness vary by clinical factors such as stage of cancer; tumor pathology; or type of surgical, chemotherapy, oral adjuvant therapy and radiation treatment received?
  - b. Does the effectiveness vary by patient characteristics such as age, race/ethnicity, other associated co-morbidities, (e.g. venous insufficiency) and body mass index?
2. Does the surveillance and early detection of BCRL in women with breast cancer prevent progression to advanced (moderate or severe) BCRL and improve patient-centered outcomes?
  - a. Does the effectiveness vary by factors such as stage of cancer; tumor pathology; or type of surgical, chemotherapy, oral adjuvant therapy and radiation treatment received?
  - b. Does the effectiveness vary by patient characteristics such as age, race/ethnicity, and body mass index?

3. What is the effectiveness of interventions to prevent the occurrence or progression of BCRL?
  - a. Does the effectiveness vary by factors such as stage of cancer; tumor pathology; or type of surgical, chemotherapy, oral adjuvant therapy and radiation treatment received?
  - b. Does the effectiveness vary by patient characteristics such as age, race/ethnicity, and body mass index?

**Table 1.** Questions and PICOTS (population, intervention, comparator, outcome, timing and setting)

|                      |   |   |  |
|----------------------|---|---|--|
| <b>Questions</b>     | 1. Diagnostic accuracy bioimpedance spectroscopy (BIS) and perometry  | 2. Surveillance and early detection of BCRL to prevent progression to advanced lymphedema   | 3. Interventions to prevent the occurrence or progression of mild to advanced BCRL   |
| <b>Population</b>    | Women with invasive breast cancer after cancer treatment<br>(a) Subgroups: cancer stage, tumor pathology, type of treatment (surgical, chemotherapy, radiation treatment)<br>(b) Subgroups age, race/ethnicity, BMI | Women with invasive breast cancer after cancer treatment<br>(a) Subgroups: cancer stage, tumor pathology, type of treatment (surgical, chemotherapy, radiation treatment)<br>(b) Subgroups age, race/ethnicity, BMI | Women with invasive breast cancer and mild BCRL<br>(a) Subgroups: cancer stage, tumor pathology, type of treatment (surgical, chemotherapy, radiation treatment)<br>(b) Subgroups age, race/ethnicity, BMI |
| <b>Interventions</b> | Bioimpedance spectroscopy (BIS), perometry  | Early detection of BCRL   | Compression sleeves<br>Complex decongestive physiotherapy<br>Other treatments to prevent progression   |
| <b>Comparators</b>   | Other techniques including circumferential measurement, and volume displacement   | Usual care  | Usual care<br>Other active treatment   |
| <b>Outcomes</b>      | breast cancer related lymphedema (sensitivity, specificity, etc)  | BCRL<br>Symptoms of lymphedema - arm pain/heaviness<br>Upper extremity function<br>Quality of life<br>Harms of treatment  | Severe BCRL<br>Symptoms of lymphedema - arm pain/heaviness<br>Upper extremity function<br>Quality of life<br>Harms of treatment  |
| <b>Timing</b>        | No exclusions   | No exclusions   | No exclusions  |
| <b>Setting</b>       | No exclusions   | No exclusions   | No exclusions  |
|                      |   |   |  |

Abbreviations: BCRL=breast cancer-related lymphedema; BMI=body mass index

## Assessment Methods

See Appendix A.

## Summary of Literature Findings

We found one systematic review and estimate 57 primary studies about BCRL 42 on detection, 8 on prevention and 7 on intervention. We considered the one systematic review partially duplicative with a portion (i.e. invasive, surgical interventions) with key question #3. However, it did not address non-surgical interventions to prevent progression of BCRL. The studies assessed different interventions for the diagnosis, detection and intervention of BCRL.

**Table 2.** Literature identified for each Question

| Question  | Systematic reviews (9/2015-9/2018)  | Primary studies (9/2014-8/2019)  |
|---|---|--|
| Question 1:<br>Diagnostic accuracy bioimpedance spectroscopy (BIS) and perometry                      | Total: 0  | Total: 42<br><ul style="list-style-type: none"> <li>• RCT: 1<sup>12</sup></li> <li>• Controlled, pre-post: 41<sup>13-52</sup></li> </ul> Clinicaltrials.gov: 0   |
| Question 2:<br>Surveillance and early detection of BCRL to prevent progression to advanced lymphedema | Total: 0  | Total: 8<br><ul style="list-style-type: none"> <li>• RCT: 1<sup>12</sup></li> <li>• Controlled, pre-post: 7<sup>5, 25, 53-57</sup></li> </ul> Clinicaltrials.gov: 9<br><ul style="list-style-type: none"> <li>• Recruiting: 5</li> <li>• Complete: 2</li> <li>• Active: 2</li> </ul> |
| Question 3:<br>Interventions to prevent occurrence or progression of BCRL                             | Total: 1<br><ul style="list-style-type: none"> <li>• Cochrane: 1<sup>58</sup></li> <li>• AHRQ: 0</li> </ul> | Total: 6<br><ul style="list-style-type: none"> <li>• RCT: 4<sup>59-62</sup></li> </ul> Controlled, pre-post: 2 <sup>63, 64</sup><br>Clinicaltrials.gov: 24<br><ul style="list-style-type: none"> <li>• Recruiting: 15</li> <li>• Complete: 4</li> <li>• Active: 5</li> </ul>         |

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; BCRL=breast-cancer related RCT=randomized controlled trial

See Appendix B for detailed assessments of all EPC selection criteria.

### Summary of Selection Criteria Assessment

This nomination meets all selection criteria. We found one systematic review and estimate 57 primary studies about BCRL 43 on detection, 8 on prevention and 6 on intervention. We considered the one systematic review partially duplicative with a portion (i.e. invasive, surgical interventions) with key question #3. However, it did not address non-surgical interventions to prevent progression of BCRL.

A new systematic review that synthesizes the evidence base could potentially address the practice variations in this field and provide clinicians updated findings that could address clinical uncertainty and better inform decision-making. A systematic review would be highly impactful and valuable: the American Society of Breast Surgeons is planning to develop guidance to address known practice variation through either a future guideline or practice statement.

Please see Appendix B for detailed assessments of individual EPC Program selection criteria.

### Related Resources

We identified additional information in the course of our assessment that might be useful.

We identified two out of date systematic reviews that relate to the key questions. Sierla et al published a systematic review in 2018 on how changes in upper body LE are assessed that was relevant to KQ #1 and 2.<sup>65</sup> The review included 55 studies from a literature search period from 2000 to March 2016. Shah et al published a systematic review in 2016 on the impact of early detection and intervention of BCRL that was relevant to KQ#3.<sup>66</sup> The review included 13 studies from a literature search period from 1992 to March 2015. We replicated the literature search strategies from each review beginning in 2016.

## References

1. U.S. Cancer Statistics Working Group USD, Centers for Disease Control and Prevention and National Cancer Institute. U.S. Cancer Statistics Data Visualizations Tool, based on November 2018 submission data (1999-2016). 2019. [www.cdc.gov/cancer/dataviz](http://www.cdc.gov/cancer/dataviz). Accessed on Sept 18 2019.
2. Simpson JF, Gray R, Dressler LG, et al. Prognostic value of histologic grade and proliferative activity in axillary node-positive breast cancer: results from the Eastern Cooperative Oncology Group Companion Study, EST 4189. *J Clin Oncol*. 2000 May;18(10):2059-69. doi: 10.1200/JCO.2000.18.10.2059. PMID: 10811671. <https://www.ncbi.nlm.nih.gov/pubmed/10811671>
3. Institute NIOHNC. Breast Cancer Treatment (PDQ®)–Health Professional Version. 2019. [https://www.cancer.gov/types/breast/hp/breast-treatment-pdq#\\_1](https://www.cancer.gov/types/breast/hp/breast-treatment-pdq#_1). Accessed on Sept 18 2019.
4. International Society of L. The diagnosis and treatment of peripheral lymphedema: 2013 Consensus Document of the International Society of Lymphology. *Lymphology*. 2013 Mar;46(1):1-11. PMID: 23930436. <https://www.ncbi.nlm.nih.gov/pubmed/23930436>
5. Zou L, Liu FH, Shen PP, et al. The incidence and risk factors of related lymphedema for breast cancer survivors post-operation: a 2-year follow-up prospective cohort study. *Breast Cancer*. 2018 May;25(3):309-14. doi: 10.1007/s12282-018-0830-3. PMID: 29397555. <https://www.ncbi.nlm.nih.gov/pubmed/29397555>
6. Deng J, Ridner SH, Dietrich MS, et al. Prevalence of secondary lymphedema in patients with head and neck cancer. *J Pain Symptom Manage*. 2012 Feb;43(2):244-52. doi: 10.1016/j.jpainsymman.2011.03.019. PMID: 21802897. <https://www.ncbi.nlm.nih.gov/pubmed/21802897>
7. Pyszel A, Malyszczak K, Pyszel K, et al. Disability, psychological distress and quality of life in breast cancer survivors with arm lymphedema. *Lymphology*. 2006 Dec;39(4):185-92. PMID: 17319631. <https://www.ncbi.nlm.nih.gov/pubmed/17319631>
8. Ridner SH. Quality of life and a symptom cluster associated with breast cancer treatment-related lymphedema. *Support Care Cancer*. 2005 Nov;13(11):904-11. doi: 10.1007/s00520-005-0810-y. PMID: 15812652. <https://www.ncbi.nlm.nih.gov/pubmed/15812652>
9. Leysen L, Beckwee D, Nijs J, et al. Risk factors of pain in breast cancer survivors: a systematic review and meta-analysis. *Support Care Cancer*. 2017 Dec;25(12):3607-43. doi: 10.1007/s00520-017-3824-3. PMID: 28799015. <https://www.ncbi.nlm.nih.gov/pubmed/28799015>
10. Norman SA, Localio AR, Potashnik SL, et al. Lymphedema in breast cancer survivors: incidence, degree, time course, treatment, and symptoms. *J Clin Oncol*. 2009 Jan 20;27(3):390-7. doi: 10.1200/JCO.2008.17.9291. PMID: 19064976. <https://www.ncbi.nlm.nih.gov/pubmed/19064976>
11. Ridner SH, Montgomery LD, Hepworth JT, et al. Comparison of upper limb volume measurement techniques and arm symptoms between healthy volunteers and individuals with

known lymphedema. *Lymphology*. 2007 Mar;40(1):35-46. PMID: 17539463.

<https://www.ncbi.nlm.nih.gov/pubmed/17539463>

12. Ridner SH, Dietrich MS, Spotanski K, et al. A Prospective Study of L-Dex Values in Breast Cancer Patients Pretreatment and Through 12 Months Postoperatively. *Lymphat Res Biol*. 2018 Oct;16(5):435-41. doi: 10.1089/lrb.2017.0070. PMID: 30130147.

<https://www.ncbi.nlm.nih.gov/pubmed/30130147>

13. Bakar Y, Tugral A, Uyeturk U. Measurement of Local Tissue Water in Patients with Breast Cancer-Related Lymphedema. *Lymphat Res Biol*. 2018 Apr;16(2):160-4. doi:

10.1089/lrb.2016.0054. PMID: 28749723. <https://www.ncbi.nlm.nih.gov/pubmed/28749723>

14. Batista BN, Baiocchi JMT, Campanholi LL, et al. Agreement between Perometry and Sequential Arm Circumference Measurements in Objective Determination of Arm Volume. *J Reconstr Microsurg*. 2018 Jan;34(1):29-34. doi: 10.1055/s-0037-1606267. PMID: 28841735.

<https://www.ncbi.nlm.nih.gov/pubmed/28841735>

15. Borri M, Gordon KD, Hughes JC, et al. Magnetic Resonance Imaging-Based Assessment of Breast Cancer-Related Lymphoedema Tissue Composition. *Invest Radiol*. 2017 Sep;52(9):554-61. doi: 10.1097/RLI.0000000000000386. PMID: 28538023.

<https://www.ncbi.nlm.nih.gov/pubmed/28538023>

16. Buendia R, Essex T, Kilbreath SL, et al. Estimation of Arm Adipose Tissue Quotient Using Segmental Bioimpedance Spectroscopy. *Lymphat Res Biol*. 2018 Aug;16(4):377-84. doi:

10.1089/lrb.2017.0050. PMID: 29252107. <https://www.ncbi.nlm.nih.gov/pubmed/29252107>

17. Bundred N, Todd C, Morris J, et al. Programme Grants for Applied Research.

Individualising breast cancer treatment to improve survival and minimise complications in older women: a research programme including the PLACE RCT. Southampton (UK): NIHR Journals Library

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18. Cau N, Galli M, Cimolin V, et al. Quantitative comparison between the laser scanner three-dimensional method and the circumferential method for evaluation of arm volume in patients with lymphedema. *J Vasc Surg Venous Lymphat Disord*. 2018 Jan;6(1):96-103. doi:

10.1016/j.jvsv.2017.08.014. PMID: 29248110. <https://www.ncbi.nlm.nih.gov/pubmed/29248110>

19. Chan WH, Huang YL, Lin C, et al. Acoustic Radiation Force Impulse Elastography: Tissue Stiffness Measurement in Limb Lymphedema. *Radiology*. 2018 Dec;289(3):759-65. doi:

10.1148/radiol.2018172869. PMID: 30106341. <https://www.ncbi.nlm.nih.gov/pubmed/30106341>

20. Coroneos CJ, Wong FC, DeSnyder SM, et al. Correlation of L-Dex Bioimpedance Spectroscopy with Limb Volume and Lymphatic Function in Lymphedema. *Lymphat Res Biol*. 2019 Jun;17(3):301-7. doi: 10.1089/lrb.2018.0028. PMID: 30388062.

<https://www.ncbi.nlm.nih.gov/pubmed/30388062>

21. de Carvalho RM, Miranda F, Jr. Communicating vessels volumeter to measure upper extremity in lymphedema after breast cancer: reliability and criterion validity compared to the gold standard. *Braz J Phys Ther*. 2018 Nov 12. doi: 10.1016/j.bjpt.2018.10.015. PMID: 30448062. <https://www.ncbi.nlm.nih.gov/pubmed/30448062>

22. De Vrieze T, Gebruers N, Nevelsteen I, et al. Reliability of the MoistureMeterD Compact Device and the Pitting Test to Evaluate Local Tissue Water in Subjects with Breast Cancer-

- Related Lymphedema. *Lymphat Res Biol.* 2019 Jul 19. doi: 10.1089/lrb.2019.0013. PMID: 31329510. <https://www.ncbi.nlm.nih.gov/pubmed/31329510>
23. De Vrieze T, Gebruers N, Tjalma WA, et al. What is the best method to determine excessive arm volume in patients with breast cancer-related lymphoedema in clinical practice? Reliability, time efficiency and clinical feasibility of five different methods. *Clin Rehabil.* 2019 Jul;33(7):1221-32. doi: 10.1177/0269215519835907. PMID: 30880473. <https://www.ncbi.nlm.nih.gov/pubmed/30880473>
24. DeSnyder SM, Kheirkhah P, Travis ML, et al. Optimizing Patient Positioning to Reduce Variation in the Measurement of Breast Cancer-Related Lymphedema. *Lymphat Res Biol.* 2019 Aug;17(4):440-6. doi: 10.1089/lrb.2018.0018. PMID: 30562149. <https://www.ncbi.nlm.nih.gov/pubmed/30562149>
25. Dylke ES, Schembri GP, Bailey DL, et al. Diagnosis of upper limb lymphedema: development of an evidence-based approach. *Acta Oncol.* 2016 Dec;55(12):1477-83. doi: 10.1080/0284186X.2016.1191668. PMID: 27333213. <https://www.ncbi.nlm.nih.gov/pubmed/27333213>
26. Engin O, Akalin E, Saribay E, et al. Easy Volumeter in Detection of Breast Cancer-Related Lymphedema: A Validity Study. *Lymphat Res Biol.* 2019 Feb 8. doi: 10.1089/lrb.2018.0040. PMID: 30735097. <https://www.ncbi.nlm.nih.gov/pubmed/30735097>
27. Ferro AP, Ferreira VTK, Rezende MS, et al. Intra- and Inter-Rater Reliability of Bioimpedance in the Evaluation of Lymphedema Secondary to Treatment of Breast Cancer. *Lymphat Res Biol.* 2018 Jun;16(3):282-6. doi: 10.1089/lrb.2017.0036. PMID: 29252100. <https://www.ncbi.nlm.nih.gov/pubmed/29252100>
28. Giray E, Yagci I. Diagnostic accuracy of interlimb differences of ultrasonographic subcutaneous tissue thickness measurements in breast cancer-related arm lymphedema. *Lymphology.* 2019;52(1):1-10. PMID: 31119909. <https://www.ncbi.nlm.nih.gov/pubmed/31119909>
29. Hameeteman M, Verhulst AC, Vreeken RD, et al. 3D stereophotogrammetry in upper-extremity lymphedema: An accurate diagnostic method. *J Plast Reconstr Aesthet Surg.* 2016 Feb;69(2):241-7. doi: 10.1016/j.bjps.2015.10.011. PMID: 26590631. <https://www.ncbi.nlm.nih.gov/pubmed/26590631>
30. Hashemi HS, Fallone S, Boily M, et al. Assessment of Mechanical Properties of Tissue in Breast Cancer-Related Lymphedema Using Ultrasound Elastography. *IEEE Trans Ultrason Ferroelectr Freq Control.* 2019 Mar;66(3):541-50. doi: 10.1109/TUFFC.2018.2876056. PMID: 30334756. <https://www.ncbi.nlm.nih.gov/pubmed/30334756>
31. Johnson KC, DeSarno M, Ashikaga T, et al. Ultrasound and Clinical Measures for Lymphedema. *Lymphat Res Biol.* 2016 Mar;14(1):8-17. doi: 10.1089/lrb.2015.0001. PMID: 26574872. <https://www.ncbi.nlm.nih.gov/pubmed/26574872>
32. Jung M, Jeon JY, Yun GJ, et al. Reference values of bioelectrical impedance analysis for detecting breast cancer-related lymphedema. *Medicine (Baltimore).* 2018 Nov;97(44):e12945. doi: 10.1097/MD.00000000000012945. PMID: 30383644. <https://www.ncbi.nlm.nih.gov/pubmed/30383644>
33. Landau MJ, Kim JS, Gould DJ, et al. Vectra 3D Imaging for Quantitative Volumetric Analysis of the Upper Limb: A Feasibility Study for Tracking Outcomes of Lymphedema Treatment. *Plast Reconstr Surg.* 2018 Jan;141(1):80e-4e. doi: 10.1097/PRS.00000000000003912. PMID: 28922322. <https://www.ncbi.nlm.nih.gov/pubmed/28922322>
34. Lim SM, Han Y, Kim SI, et al. Utilization of bioelectrical impedance analysis for detection of lymphedema in breast Cancer survivors: a prospective cross sectional study. *BMC Cancer.* 2019 Jul 8;19(1):669. doi: 10.1186/s12885-019-5840-9. PMID: 31286884. <https://www.ncbi.nlm.nih.gov/pubmed/31286884>



35. Lu IM, Dixon JB. Assessment of Upper Extremity Swelling Among Breast Cancer Survivors with a Commercial Infrared Sensor. *Lymphat Res Biol*. 2019 Aug;17(4):424-33. doi: 10.1089/lrb.2018.0010. PMID: 30694729. <https://www.ncbi.nlm.nih.gov/pubmed/30694729>
36. Mayrovitz HN. Assessing Upper and Lower Extremities Via Tissue Dielectric Constant: Suitability of Single Versus Multiple Measurements Averaged. *Lymphat Res Biol*. 2019 Jun;17(3):316-21. doi: 10.1089/lrb.2018.0016. PMID: 30339476. <https://www.ncbi.nlm.nih.gov/pubmed/30339476>
37. Mayrovitz HN, Mikulka A, Woody D. Minimum Detectable Changes Associated with Tissue Dielectric Constant Measurements as Applicable to Assessing Lymphedema Status. *Lymphat Res Biol*. 2019 Jun;17(3):322-8. doi: 10.1089/lrb.2018.0052. PMID: 30526306. <https://www.ncbi.nlm.nih.gov/pubmed/30526306>
38. Mazor M, Smoot BJ, Mastick J, et al. Assessment of local tissue water in the arms and trunk of breast cancer survivors with and without upper extremity lymphoedema. *Clin Physiol Funct Imaging*. 2019 Jan;39(1):57-64. doi: 10.1111/cpf.12541. PMID: 30207039. <https://www.ncbi.nlm.nih.gov/pubmed/30207039>
39. Preuss M, Killaars R, Piatkowski de Grzymala A, et al. Validity and Reliability of Three-Dimensional Imaging for Measuring Breast Cancer-Related Lymphedema in the Upper Limb: A Cross-Sectional Study. *Lymphat Res Biol*. 2018 Oct 3. doi: 10.1089/lrb.2017.0076. PMID: 30281382. <https://www.ncbi.nlm.nih.gov/pubmed/30281382>
40. Qin ES, Bowen MJ, Chen WF. Diagnostic accuracy of bioimpedance spectroscopy in patients with lymphedema: A retrospective cohort analysis. *J Plast Reconstr Aesthet Surg*. 2018 Jul;71(7):1041-50. doi: 10.1016/j.bjps.2018.02.012. PMID: 29650264. <https://www.ncbi.nlm.nih.gov/pubmed/29650264>
41. Rafn BS, McNeely ML, Camp PG, et al. Self-Measured Arm Circumference in Women With Breast Cancer Is Reliable and Valid. *Phys Ther*. 2019 Feb 1;99(2):240-53. doi: 10.1093/ptj/pzy117. PMID: 30289500. <https://www.ncbi.nlm.nih.gov/pubmed/30289500>
42. Rezende MS, Marsengo AL, Apolinario A, et al. Correlation Between Upper Limb Volume and Arterial and Venous Blood Flow Velocity in Lymphedema Secondary to Breast Cancer Treatment. *J Manipulative Physiol Ther*. 2017 May;40(4):241-5. doi: 10.1016/j.jmpt.2017.02.008. PMID: 28410763. <https://www.ncbi.nlm.nih.gov/pubmed/28410763>
43. Sen Y, Qian Y, Koelmeyer L, et al. Breast Cancer-Related Lymphedema: Differentiating Fat from Fluid Using Magnetic Resonance Imaging Segmentation. *Lymphat Res Biol*. 2018 Feb;16(1):20-7. doi: 10.1089/lrb.2016.0047. PMID: 28346854. <https://www.ncbi.nlm.nih.gov/pubmed/28346854>
44. Sharkey AR, King SW, Kuo RY, et al. Measuring Limb Volume: Accuracy and Reliability of Tape Measurement Versus Perometer Measurement. *Lymphat Res Biol*. 2018 Apr;16(2):182-6. doi: 10.1089/lrb.2017.0039. PMID: 28956715. <https://www.ncbi.nlm.nih.gov/pubmed/28956715>
45. Suehiro K, Yamamoto S, Honda S, et al. Perioperative variations in indices derived from noninvasive assessments to detect postmastectomy lymphedema. *J Vasc Surg Venous Lymphat Disord*. 2019 Jul;7(4):562-9. doi: 10.1016/j.jvsv.2019.02.012. PMID: 31203860. <https://www.ncbi.nlm.nih.gov/pubmed/31203860>
46. Sun F, Hall A, Tighe MP, et al. Perometry versus simulated circumferential tape measurement for the detection of breast cancer-related lymphedema. *Breast Cancer Res Treat*. 2018 Nov;172(1):83-91. doi: 10.1007/s10549-018-4902-z. PMID: 30062571. <https://www.ncbi.nlm.nih.gov/pubmed/30062571>
47. Sun F, Skolny MN, Swaroop MN, et al. The need for preoperative baseline arm measurement to accurately quantify breast cancer-related lymphedema. *Breast Cancer Res Treat*. 2016 Jun;157(2):229-40. doi: 10.1007/s10549-016-3821-0. PMID: 27154787. <https://www.ncbi.nlm.nih.gov/pubmed/27154787>

48. Timmer CY, Bosman J, Geertzen JHB, et al. Variation in Measurement Results Using Bioimpedance Spectroscopy to Determine Extracellular Fluid of Upper Extremity. *Lymphat Res Biol*. 2019 Aug 20. doi: 10.1089/lrb.2018.0020. PMID: 31429626.  
<https://www.ncbi.nlm.nih.gov/pubmed/31429626>
49. Wang L, Li HP, Liu AN, et al. A Scoring System to Predict Arm Lymphedema Risk for Individual Chinese Breast Cancer Patients. *Breast Care (Basel)*. 2016 Feb;11(1):52-6. doi: 10.1159/000443491. PMID: 27051397. <https://www.ncbi.nlm.nih.gov/pubmed/27051397>
50. Wolfs J, Bijkerk E, Schols RM, et al. Evaluation of a Novel Water-Based Volumetric Device for Measuring Upper Limb Lymphedema: First Experience with Healthy Volunteers. *Lymphat Res Biol*. 2019 Aug;17(4):434-9. doi: 10.1089/lrb.2018.0037. PMID: 30653398.  
<https://www.ncbi.nlm.nih.gov/pubmed/30653398>
51. Yang EJ, Kim SY, Lee WH, et al. Diagnostic Accuracy of Clinical Measures Considering Segmental Tissue Composition and Volume Changes of Breast Cancer-Related Lymphedema. *Lymphat Res Biol*. 2018 Aug;16(4):368-76. doi: 10.1089/lrb.2017.0047. PMID: 29338541.  
<https://www.ncbi.nlm.nih.gov/pubmed/29338541>
52. Yoo JN, Cheong YS, Min YS, et al. Validity of Quantitative Lymphoscintigraphy as a Lymphedema Assessment Tool for Patients With Breast Cancer. *Ann Rehabil Med*. 2015 Dec;39(6):931-40. doi: 10.5535/arm.2015.39.6.931. PMID: 26798607.  
<https://www.ncbi.nlm.nih.gov/pubmed/26798607>
53. Barrio AV, Eaton A, Frazier TG. A Prospective Validation Study of Bioimpedance with Volume Displacement in Early-Stage Breast Cancer Patients at Risk for Lymphedema. *Ann Surg Oncol*. 2015 Dec;22 Suppl 3:S370-5. doi: 10.1245/s10434-015-4683-0. PMID: 26085222.  
<https://www.ncbi.nlm.nih.gov/pubmed/26085222>
54. Iyigun ZE, Duymaz T, Ilgun AS, et al. Preoperative Lymphedema-Related Risk Factors in Early-Stage Breast Cancer. *Lymphat Res Biol*. 2018 Feb;16(1):28-35. doi: 10.1089/lrb.2016.0045. PMID: 28346852. <https://www.ncbi.nlm.nih.gov/pubmed/28346852>
55. Kim P, Lee JK, Lim OK, et al. Quantitative Lymphoscintigraphy to Predict the Possibility of Lymphedema Development After Breast Cancer Surgery: Retrospective Clinical Study. *Ann Rehabil Med*. 2017 Dec;41(6):1065-75. doi: 10.5535/arm.2017.41.6.1065. PMID: 29354584.  
<https://www.ncbi.nlm.nih.gov/pubmed/29354584>
56. Warren LE, Miller CL, Horick N, et al. The impact of radiation therapy on the risk of lymphedema after treatment for breast cancer: a prospective cohort study. *Int J Radiat Oncol Biol Phys*. 2014 Mar 1;88(3):565-71. doi: 10.1016/j.ijrobp.2013.11.232. PMID: 24411624.  
<https://www.ncbi.nlm.nih.gov/pubmed/24411624>
57. Whitworth PW, Cooper A. Reducing chronic breast cancer-related lymphedema utilizing a program of prospective surveillance with bioimpedance spectroscopy. *Breast J*. 2018 Jan;24(1):62-5. doi: 10.1111/tbj.12939. PMID: 29063664.  
<https://www.ncbi.nlm.nih.gov/pubmed/29063664>
58. Markkula SP, Leung N, Allen VB, et al. Surgical interventions for the prevention or treatment of lymphoedema after breast cancer treatment. *Cochrane Database Syst Rev*. 2019 Feb 19;2:CD011433. doi: 10.1002/14651858.CD011433.pub2. PMID: 30779124.  
<https://www.ncbi.nlm.nih.gov/pubmed/30779124>
59. Bloomquist K, Oturai P, Steele ML, et al. Heavy-Load Lifting: Acute Response in Breast Cancer Survivors at Risk for Lymphedema. *Med Sci Sports Exerc*. 2018 Feb;50(2):187-95. doi: 10.1249/mss.0000000000001443. PMID: 28991039
60. Buchan J, Janda M, Box R, et al. A Randomized Trial on the Effect of Exercise Mode on Breast Cancer-Related Lymphedema. *Med Sci Sports Exerc*. 2016 Oct;48(10):1866-74. doi: 10.1249/MSS.0000000000000988. PMID: 27187092.  
<https://www.ncbi.nlm.nih.gov/pubmed/27187092>

61. Ochalek K, Partsch H, Gradalski T, et al. Do Compression Sleeves Reduce the Incidence of Arm Lymphedema and Improve Quality of Life? Two-Year Results from a Prospective Randomized Trial in Breast Cancer Survivors. *Lymphat Res Biol*. 2019 Feb;17(1):70-7. doi: 10.1089/lrb.2018.0006. PMID: 30339481. <https://www.ncbi.nlm.nih.gov/pubmed/30339481>
62. Temur K, Kapucu S. The effectiveness of lymphedema self-management in the prevention of breast cancer-related lymphedema and quality of life: A randomized controlled trial. *Eur J Oncol Nurs*. 2019 Jun;40:22-35. doi: 10.1016/j.ejon.2019.02.006. PMID: 31229204. <https://www.ncbi.nlm.nih.gov/pubmed/31229204>
63. Miller CL, Colwell AS, Horick N, et al. Immediate Implant Reconstruction Is Associated With a Reduced Risk of Lymphedema Compared to Mastectomy Alone: A Prospective Cohort Study. *Ann Surg*. 2016 Feb;263(2):399-405. doi: 10.1097/sla.0000000000001128. PMID: 25607768
64. Soran A, Menekse E, Girgis M, et al. Breast cancer-related lymphedema after axillary lymph node dissection: does early postoperative prediction model work? *Support Care Cancer*. 2016 Mar;24(3):1413-9. doi: 10.1007/s00520-015-2933-0. PMID: 26349574. <https://www.ncbi.nlm.nih.gov/pubmed/26349574>
65. Sierla R, Dylke ES, Kilbreath S. A Systematic Review of the Outcomes Used to Assess Upper Body Lymphedema. *Cancer Invest*. 2018;36(8):458-73. doi: 10.1080/07357907.2018.1517362. PMID: 30289283. <https://www.ncbi.nlm.nih.gov/pubmed/30289283>
66. Shah C, Arthur DW, Wazer D, et al. The impact of early detection and intervention of breast cancer-related lymphedema: a systematic review. *Cancer Med*. 2016 Jun;5(6):1154-62. doi: 10.1002/cam4.691. PMID: 26993371
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## Appendix A: Methods

We assessed nomination for priority for a systematic review or other AHRQ Effective Health Care report with a hierarchical process using established selection criteria. Assessment of each criteria determined the need to evaluate the next one. See Appendix B for detailed description of the criteria.

### Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

### Desirability of New Review/Absence of Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last three years prior to August 7, 2019 on the questions of the nomination from these sources:

- AHRQ: Evidence reports and technology assessments
  - AHRQ Evidence Reports <https://www.ahrq.gov/research/findings/evidence-based-reports/index.html>
  - EHC Program <https://effectivehealthcare.ahrq.gov/>
  - AHRQ Technology Assessment Program <https://www.ahrq.gov/research/findings/ta/index.html>
- US Department of Veterans Affairs Products publications
  - Evidence Synthesis Program <https://www.hsrd.research.va.gov/publications/esp/>
  - VA/Department of Defense Evidence-Based Clinical Practice Guideline Program <https://www.healthquality.va.gov/>
- Cochrane Systematic Reviews <https://www.cochranelibrary.com/>
- PROSPERO Database (international prospective register of systematic reviews and protocols) <http://www.crd.york.ac.uk/prospero/>
- PubMed <https://www.ncbi.nlm.nih.gov/pubmed/>
- Epistemonikos <https://www.epistemonikos.org/>
- Health System Evidence <https://www.healthsystemevidence.org/>
- PDQ Evidence <https://www.pdq-evidence.org/>

### Impact of a New Evidence Review

The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

### Feasibility of New Evidence Review

We conducted a limited literature search in PubMed for the last five years on August 6, 2019. We conducted two additional limited literature searches in PubMed starting in 2016 that replicated relevant but search strategies that ended in 2015 and were published in two prior systematic reviews. We reviewed all studies identified titles and abstracts for inclusion. We classified identified studies by question and study design to estimate the size and scope of a potential evidence review.



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### III. Feasibility Key Questions #2 and 3

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AND

(Breast Cancer Lymphedema[Mesh] OR Lymphedema[Mesh:NoExp] OR lymphedema[tiab] OR  
lymphoedema[tiab])

AND

(Early Diagnosis[Mesh] OR "early management"[tiab] OR “early diagnosis”[tiab] OR “early  
detection”[tiab] OR “early screening” OR prospective[tiab] OR subclinical[tiab])

AND

("Systematic Review" [Publication Type] OR "Controlled Clinical Trial" [Publication Type] OR  
“Randomized Controlled Trial”[Publication Type] OR "Comparative Study" [Publication Type]  
OR "Observational Study" [Publication Type])

### IV. ClinicalTrials.gov Searched Sept 5, 2019

[https://clinicaltrials.gov/ct2/results?cond=Breast+Cancer+Lymphedema&term=&type=&rslt=&rcrs=b&rcrs=a&rcrs=f&rcrs=d&rcrs=e&age\\_v=&age=1&age=2&gndr=&intr=&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&strd\\_s=08%2F08%2F2016&strd\\_e=01%2F01%2F3000&pred\\_s=&pred\\_e=&sfpd\\_s=&sfpd\\_e=&lupd\\_s=&lupd\\_e=&sort=](https://clinicaltrials.gov/ct2/results?cond=Breast+Cancer+Lymphedema&term=&type=&rslt=&rcrs=b&rcrs=a&rcrs=f&rcrs=d&rcrs=e&age_v=&age=1&age=2&gndr=&intr=&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&strd_s=08%2F08%2F2016&strd_e=01%2F01%2F3000&pred_s=&pred_e=&sfpd_s=&sfpd_e=&lupd_s=&lupd_e=&sort=)

### Value

We assessed the nomination for value. We considered whether or not the clinical, consumer, or policymaking context had the potential to respond with evidence-based change; and if a partner organization would use this evidence review to influence practice.

## Appendix B. Selection Criteria Assessment

| Selection Criteria   | Assessment   |
|--|--|
| <b>1. Appropriateness</b>  |  |
| 1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?   | Yes. ImpediMed L-Dex™ U400 was cleared for marketing by the FDA in 2007 as an aid in the clinical assessment of unilateral lymphedema of the arms in women.  |
| 1b. Is the nomination a request for an evidence report?  | Yes.   |
| 1c. Is the focus on effectiveness or comparative effectiveness?  | Yes, comparative effectiveness of BIS and perometry compared to circumferential measurement or volume displacement.  |
| 1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?                        | Yes  |
| <b>2. Importance</b>   |  |
| 2a. Represents a significant disease burden; large proportion of the population  | Yes. Breast cancer is a prevalent condition in women and a high cause of death. BCRL is a common sequelae of breast cancer treatment and has an adverse effect on survivors quality of life.                               |
| 2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population       | Early detection and treatment of BCRL affects health care decision-making, outcomes and treatment costs in a significant proportion of breast cancer survivors.  |
| 2c. Incorporates issues around both clinical benefits and potential clinical harms   | Yes. Detection of early BCRL may lead to over diagnosis and unnecessary treatment given that an estimated 20% of patients developed BCRL   |
| 2d. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers                   | Yes. Evidence exists that surveillance for BCRL and early intervention is cost saving compared to later intervention.  |
| <b>3. Desirability of a New Evidence Review/Absence of Duplication</b>   |  |
| 3. A recent high-quality systematic review or other evidence review is not available on this topic   | Yes. One SR partially addressed KQ #3, other treatments to prevent BCRL progression, specifically surgical. Low certainty evidence was found for prevention of BCRL. Non-invasive treatments were not addressed in the SR. |
| <b>4. Impact of a New Evidence Review</b>  |  |
| 4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)? | Guidelines for the detection, surveillance and intervention for BCRL are not available.  |

|   |  |
|---|--|
| <p>4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?</p>   | <p>Standards of care do not exist for screening and intervention modalities for BCRL.</p>  |
| <p>5. Primary Research</p>  |  |
| <p>5. Effectively utilizes existing research and knowledge by considering:</p> <ul style="list-style-type: none"> <li>- Adequacy (type and volume) of research for conducting a systematic review</li> <li>- Newly available evidence (particularly for updates or new technologies)</li> </ul> | <p>Size/scope of review: total of 56 studies, 42 studies for KQ#1, 8 studies for KQ#2 and 6 studies for KQ#3, estimated size of review is small to medium.</p> <p>ClinicalTrials.gov: 0 KQ#1, 9 KQ#2, 24 KQ#3</p> <p>KQ#1</p> <ul style="list-style-type: none"> <li>• Interventions (not mutually exclusive): Perometry (9), Ultrasound (7), BIS (6), BIA (5), Lymphoscintigraphy (3), 3D imaging (3) and Lymphography (2)</li> </ul> <p>KQ#2</p> <ul style="list-style-type: none"> <li>• Population ranged from 201 to 1476 women with breast cancer</li> <li>• Interventions and comparisons included BIS (5), perometry (1), volume displacement (1), lymphoscintigraphy (1) and circumferential measurement (4)</li> <li>• Outcome was BCRL for all, although one study was limited to pre-operative baseline only</li> <li>• Follow up ranged from zero days to 3 years</li> </ul> <p>KQ#3</p> <ul style="list-style-type: none"> <li>• Population ranged from 21 to 616 women with breast cancer, one study population had BCRL at enrollment</li> <li>• Interventions included exercise (resistance versus aerobic, low versus heavy resistance), compression sleeves (3), LE self-management and immediate reconstruction versus none</li> <li>• Outcomes included acute (72 hour) BCRL, occurrence (4) and progression of BCRL (1). BCRL measurement was with circumferential measurement (4), BIS (1) and perometry (1)</li> </ul> |

|   |   |
|---|---|
|   | <ul style="list-style-type: none"> <li>Follow up (excluding the 72 hour acute BCRL) ranged from 12 weeks to 2 years</li> </ul>                                  |
| 6. Value  |   |
| 6a. The proposed topic exists within a clinical, consumer, or policy-making context that is amenable to evidence-based change | Yes. This topic is amenable to evidence-based change in the early detection and intervention of BCRL.   |
| 6b. Identified partner who will use the systematic review to influence practice (such as a guideline or recommendation)       | Yes, the American Society of Breast Surgeons intends to use the SR as a means to influence on practice through either a future guideline or practice statement. |

*Abbreviations:* AHRQ=Agency for Healthcare Research and Quality; BCRL=breast cancer related lymphedema; FDA=Food and Drug Administration; KQ=key question; SR=systematic review