

Published Pathophysiology: Lymphedema manifests itself initially as a build up of extracellular fluid (ECF) (interstitial edema). In the later, irreversible stages of lymphedema, extracellular fluid levels can begin to approach normal due to the impact of fibrosis and adipose deposition. As progression occurs to				
Title	Citation	Primary Author	Year	Summary of Findings
The pathophysiology of lymphedema	Mortimer, P.S., The pathophysiology of lymphedema. Cancer, 1998. 83(12 Suppl American): p. 2798-802	Mortimer	1998	Edema represents an increase in interstitial fluid volume sufficient to manifest with swelling. Any edema, whatever the underlying cause, is due to an imbalance between capillary filtration and lymph drainage.
Lymphedema: A primer on the identification and management of a chronic condition in oncologic treatment	Lawenda, B.D., T.E. Mondry, and P.A. Johnstone, Lymphedema: a primer on the identification and management of a chronic condition in oncologic treatment. CA Cancer J Clin, 2009. 59(1): p. 8-24	Lawenda	2009	When increases in the lymphatic load exceed the maximum transport capacity, the lymphatic system becomes overwhelmed, causing lymphatic insufficiency or failure, which leads to interstitial edema.
Current concepts and future directions in the diagnosis and management of lymphatic vascular disease	Rockson, S.G., Current concepts and future directions in the diagnosis and management of lymphatic vascular disease. Vascular Medicine, 2010. 15(3): p. 223-231	Rockson	2010	A review of lymphatic biology, pathology and evolving concepts about the diagnostic and therapeutic approaches based on the relevant fluid changes. Discusses the capacity of BIS for early disease detection as it measures only extracellular fluid.
Breast Cancer–Related Lymphedema	Morrell, R.M., et al., Breast cancer-related lymphedema. Mayo Clin Proc, 2005. 80(11): p. 1480-4	Morrell	2005	"Lymphedema is the accumulation of lymph fluid in the interstitial space and may be secondary to infection, trauma, or congenital abnormalities. Fluid accumulation in the limbs causes enlargement, often with a feeling of heaviness. Chronic inflammation leads to fibrosis of the lymphatics, which compounds the problem."
Does the Effect of Weight Lifting on Lymphedema Following Breast Cancer Differ by Diagnostic Method; Results of a Randomized Controlled Trial	Hayes, S.C., et al., Does the effect of weight lifting on lymphedema following breast cancer differ by diagnostic method: results from a randomized controlled trial. Breast Cancer Res Treat, 2011	Hayes	2011	"Lymphedema secondary to breast cancer is caused by the disruption of the lymphatic system that in the initial stages leads to the accumulation of fluid in the interstitial tissue space and eventually is clinically presented as swelling of the arm, shoulder, neck, or torso. Later stages of lymphedema are characterized by deposition of fibrotic and adipose tissue, making treatment with more conservative measures difficult."
Quantitative bioimpedance spectroscopy for the assessment of lymphoedema	Ward, L.C., S. Czerniec, and S.L. Kilbreath, Quantitative bioimpedance spectroscopy for the assessment of lymphoedema. Breast Cancer Res Treat, 2009. 117(3): p. 541-7	Ward	2009	"...data indicate that the fluid increase, as judged by BIS, is predominantly expansion of the ECW. The mean ratio of ECW to ICW was 1.5:1 compared to a value of between 0.85:1 and 1:1 seen in control participants. This observation concurs with the accepted course of progression of lymphoedema in which the earliest events include accumulation of lymph, an extracellular fluid. As lymphoedema progresses further, the fluid increases in protein content with cellular infiltration eventually developing a pseudo tissue-like fibrotic structure. Increases in fat content may occur and a mixed picture of lymphoedema and lipidema can ensue. A consequence of this is that overall volume, as measured by perometry, may continue to increase but fluid content decreases proportionately. The slopes of the regression lines observed for the strong association observed between BIS and perometric measurements of volume support this view. The inference can also be drawn that BIS is better suited for monitoring early stage lymphoedema, where changes are predominantly in fluid volume."
The Third Circulation: Radionuclide Lymphoscintigraphy in the Evaluation of Lymphedema	Szuba, A., et al., The third circulation: radionuclide lymphoscintigraphy in the evaluation of lymphedema. J Nucl Med, 2003. 44(1): p. 43-57	Szuba	2003	"Regardless of etiology, lymphedema usually presents as slowly progressive extremity edema. Initially, the edema is soft and pitting, but over the course of weeks to months the skin thickens and the swelling becomes hard and nonpitting.....If lymphedema is untreated it will progress to the point of chronic limb enlargement, with disfiguration of the limb associated with severe functional and psychologic impairment. Early diagnosis and therapy to reduce edema are required to minimize the loss of function."

BIS Technical Performance: Studies that compare BIS measurements with the gold standard for extracellular fluid levels (radioisotopes); BIS measurements of ECF compared to the defacto standard of the tape for total volume measures for lymphedema; and those that compare results taken with the same				
Title	Citation	Primary Author	Year	Summary of Findings
Segmental Bioimpedance for Measuring Amlodipine-Induced Pedal Edema: A Placebo-Controlled Study	Schoeller, D.A., et al., Segmental bioimpedance for measuring amlodipine-induced pedal edema: a placebo-controlled study. Clin Ther, 2012. 34(3): p. 580-92	Schoeller	2012	Multicenter, randomized, placebo controlled, double blinded study. Found that segmental bioimpedance was comparable to water displacement and ankle circumference and outperformed clinical assessment of pitting for the detection of ankle edema, supporting the use of segmental bioimpedance as a drug-development tool to objectively quantify amlodipine-induced pedal edema.
Use of Bioimpedance Spectroscopy to determine extracellular fluid, intracellular fluid, total body water, fat mass and fat-free mass	Van Loan, M.D., et al., Use of bioimpedance spectroscopy to determine extracellular fluid, intracellular fluid, total body water, and fat-free mass. Basic Life Sci, 1993. 60: p. 67-70	Van Loan	1993	Extracellular fluid was determined by NaBr dilution (the reference method). Tests against a known electronic circuit resulted in accuracy of +/-1%. Test-retest in human subjects showed no significance difference with the reference method (p>0.41). Correlation with NaBr r=0.893. <u>Concludes that BIS can be used successfully for the determination of body fluid compartments and is of potential use in a wide variety of clinical diseases.</u>
Monitoring changes in fat-free mass in HIV-positive men with hypotestosteronemia and AIDS wasting syndrome treated with gonadal hormone replacement therapy	Van Loan, M.D., et al., Monitoring changes in fat-free mass in HIV-positive men with hypotestosteronemia and AIDS wasting syndrome treated with gonadal hormone replacement therapy. Aids, 1999. 13(2): p. 241-8	Van Loan	1999	Double-blind, Randomized Control Trial, placebo-controlled. Concludes that the BIS method is less costly, more convenient to use, and had results that more closely matched those from nitrogen balance and retention methods. "The ability of BIS to distinguish ECF from TBW may be the underlying reason for the greater accuracy in monitoring changes in body composition."
Bioelectrical impedance for monitoring the efficacy of lymphoedema treatment programmes	Cornish, B.H., et al., Bioelectrical impedance for monitoring the efficacy of lymphoedema treatment programmes. Breast Cancer Res Treat, 1996. 38(2): p. 169-76	Cornish	1996	Multiple measures of female patients with lymphedema (n = 20), and healthy female controls without lymphedema (n = 20). Daily measurements of both circumference and impedance were recorded for 20 lymphedema patients over a 4 week treatment program. Controls also run daily. Study demonstrated excellent precision for BIS - a good test-retest precision for ECW ratio values (mean ratio 103.1%; s.d. 2.4%). <u>Volume based measures, completely normalized by day 28 of treatment; the measured impedance ratio remained detectably elevated.</u> This observation can be interpreted to reflect a greater sensitivity for impedance when compared with the indirect measure of volumetric techniques.
Assessment of Breast Cancer-Related Arm Lymphedema—Comparison of Physical Measurement Methods and Self-Report	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	Czerniec	2010	Lymphedema in each arm of women with (n = 33) and without (n = 18) unilateral arm lymphedema, secondary to breast cancer was measured by self-report, bioimpedance spectroscopy (BIS), perometer, and the truncated cone method. The lymphoedema assessment methods reviewed in this study showed excellent reliability with the exception of self report, which was only moderately reliable. Although there was very high agreement in the physical methods of measuring lymphoedema, they were not found to be interchangeable. <u>The high degree of reliability observed for the relatively new technique of BIS lends confidence for its use in lymphoedema assessment, particularly where a change in limb volume may be due to factors other than lymphoedema</u> per se. Intrarater reliability refers to the stability of measurements recorded by one assessor over two or more occasions. Interrater reliability refers to variation between two or more assessors who measure the same group of participants. The interrater reliability of the physical measures, i.e., truncated cone, perometer, and bioimpedance spectroscopy, was also determined with five participants, measured by three different assessors at one single measurement occasion.
Early detection of lymphoedema after axillary dissection: A preliminary study investigating the intra- and inter- observer reliability of three measurement methods	Box, R.C., H. Reul-Hirche, and J.E. Bullock-Saxton, Early detection on lymphoedema after axillary dissection: A preliminary study investigating the intra- and inter- observer reliability of three measurement methods. European Journal of Lymphology and Related Problems, 1999. 7(27): p. 74-79	Box	1999	The reliability of circumference, volume (water displacement) and BIS was assessed in 9 women who had no history of axillary dissection. The 2 BIS devices were used to make the measurements which were performed by 2 physiotherapists each taking duplicate measurements on 2 occasions, separated by 2 weeks. Measurements were taken for 3 arm segments – forearm (0 – 20 cm), upper arm (20 – 40 cm) and whole arm (0 – 40 cm). <u>Findings: BIS had lower intra-observer reliability for forearm and upper arm but found acceptable reliability for whole arm.</u> Changes identified by clinicians using circumference or volume can be further assessed using BIS. All 3 methods for measuring arm size and volume have acceptable reliability. BIS shows the best reliability over the whole arm.

Reliability of Multiple Frequency Bioelectrical Impedance Analysis: An Intermachine Comparison	Ward, L., et al., Reliability of multiple frequency bioelectrical impedance analysis an intermachine comparison. . Am. J. Hum. Biol., 1997. 9: p. 63-72	Ward	1997	The <u>technical reliability (i.e. interinstrument and interoperator reliability) of three BIS devices</u> was assessed for both errors of measurement and associated analysis. In addition, intraoperator and instrument variability was evaluated for repeat measure over a 4 hour period. The interinstrument/operator variation for whole body measurement were recorded on human volunteers (29 subjects) with biases of less than 1% for measured impedance values.
Segmental measurement of breast cancer-related arm lymphoedema using perometry and bioimpedance spectroscopy	Czerniec, S., et al., Segmental measurement of breast cancer-related arm lymphoedema using perometry and bioimpedance spectroscopy. Support Care Cancer, 2010	Czerniec	2010	Women without a history of lymphoedema or breast cancer (n= 11) as well as those with clinically diagnosed lymphoedema secondary to breast cancer (n = 29) were recruited. Supports the tenet that <u>BIS was able to detect localized changes with a higher degree of sensitivity than measures reliant on limb volumes.</u> BIS ratios for the total arm and each arm segment were significantly higher than perometry ratios in women with lymphoedema but not in women without lymphoedema. BIS measures were therefore not simply overestimating inter-limb differences. BIS is designed to differentiate extracellular fluid from the confounding “noise” of total limb volume, and is therefore able to detect localized lymphoedema more readily than perometry.
Bioelectrical Impedance Analysis: Proven Utility in Lymphedema Risk Assessment and Therapeutic Monitoring	Ward, L.C., Bioelectrical impedance analysis: proven utility in lymphedema risk assessment and therapeutic monitoring. Lymphat Res Biol, 2006. 4(1): p. 51-6	Ward	2006	Variation of repeated assessments (same day) (Average ± Std Dev) - Lymphometer (Bioimpedance ECW ratio): 0.60 ± 15.4%; Tape measure ratio: 2.1 ± 35%; Arm Volume (Tape) : 1.4 ± 31%; Bioelectric impedance measurements using the Lymphometer were: 1)Faster, 2) Better accepted by nursing personnel, 3) <u>More consistent than either serial tape measurements or water displacement methods.</u>
Comparison of Diagnostic Accuracy of Clinical Measure of Breast Cancer Related Lymphedema: Area Under the Curve	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	Smoot	2011	UCSF cross sectional design study comparing methods used in assessment of lymphedema using ROC curves. Findings support the use of <u>BIS as the most accurate method tested.</u>
Confirmation of the Reference Impedance Ratios Used for Assessment of Breast Cancer-Related Lymphedema by Bioelectrical Impedance Spectroscopy	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	Ward	2011	Further <u>confirmation of the reference range of the inter-arm impedance ratio cut-off value</u> established as a criterion for the detection of breast cancer related unilateral lymphedema of the arm validated in Cornish 2001.
Operational Equivalence of Bioimpedance Indices and Perometry for the Assessment of Unilateral Arm Lymphedema	Ward, L.C., S. Czerniec, and S.L. Kilbreath, Operational equivalence of bioimpedance indices and perometry for the assessment of unilateral arm lymphedema. Lymphat Res Biol, 2009. 7(2): p. 81-5	Ward	2009	Impedance was measured in the arms of 45 women with lymphedema and a separate control group (n=21). Arm volume was measured at the same time by perometry. In conclusion, both approaches are suitable for assessment of lymphedema. Each has their own advantages and disadvantages. Both are rapid to perform and involve minimal inconvenience to the subject. Both methods require little technical training for the operator. <u>"Finally, the impedance technique would appear to be most suited for the early detection of or monitoring of the early stage of lymphedema when the changes are predominantly in extracellular fluid volume."</u>
Reliability of Bioimpedance Spectroscopy and Tonometry after Breast Conserving Cancer Treatment	Moseley, A. and N. Piller, Reliability of bioimpedance spectroscopy and tonometry after breast conserving cancer treatment. Lymphat Res Biol, 2008. 6(2): p. 85-7	Moseley	2008	14 women who had undergone breast conserving surgery for breast cancer (12 months ago) were recruited to assess the between subject reproducibility of tonometry and bioimpedance spectroscopy (BIS). With the participant supine, two repeat measurements of the resistance of the tissues to compression (tonometry) and fluid levels (BIS) of the treated and normal breast were taken for each of the four quadrants of the breast. <u>The reliability of these two measurement techniques provides an opportunity for researchers and clinicians to easily quantify breast tissue and fluid changes</u> which in turn may lead to the earlier diagnosis and targeted treatment of breast edema and lymphedema.
Quantitative bioimpedance spectroscopy for the assessment of lymphoedema	Ward, L.C., S. Czerniec, and S.L. Kilbreath, Quantitative bioimpedance spectroscopy for the assessment of lymphoedema. Breast Cancer Res Treat, 2009. 117(3): p. 541-7	Ward	2009	BIS comparison to perometry. Cohort was 33 patients with unilateral lymphedema of the arm and 13 normal control patients. Generally, <u>there was good agreement between the different methods in classifying participants as having lymphoedema or not.</u> Two participants who were classed as having lymphoedema based on volume measurement but not by BIS had their non-dominant limb affected. This classification assumed a correction in volume difference for dominance. If no correction was applied, both participants would have been re-classified as not having lymphoedema using a 200 ml cut-off in agreement with the BIS indices. Alternatively, these women may have progressed to the lipedema stage of lymphoedema. Clearly, these participants may be viewed as at-risk of lymphoedema and, in a clinical setting, would be monitored carefully.

Correlation between Bioelectrical Spectroscopy and Perometry in Assessment of Upper Extremity Swelling	Jain, M.S., J.V. Danoff, and S.M. Paul, Correlation between bioelectrical spectroscopy and perometry in assessment of upper extremity swelling. <i>Lymphology</i> , 2010. 43 : p. 85-94.	Jain	2010	NIH run concordance study between perometry and BIS. Ten women previously treated for breast cancer, between 49 and 67 years old were recruited through a breast cancer support organization. Subjects had all been treated for breast cancer and several already displayed classic signs of lymphedema according to the authors. Found <u>BIS is able to produce highly reliable inter- and intra-rater measurements of upper extremity edema (r=0.987 and r=0.993, respectively) and that there is also concurrent validity between BIS and perometry.</u> Non-concurrence in some patients, despite a positive correlation in values between the devices, demonstrates that BIS values reflect fluid values and limbs may increase in volume due to changes in other compartments. "The use of BIS is likely to be more important in following changes in fluid over time from pre-surgical baseline to establish the onset of lymphedema (when the condition is a predominantly fluid-based problem)."
Bioimpedance in the assessment of unilateral lymphedema of a limb: the optimal frequency	Gaw, R., R. Box, and B. Cornish, Bioimpedance in the assessment of unilateral lymphedema of a limb: the optimal frequency. <i>Lymphat Res Biol</i> , 2011. 9 (2): p. 93-9	Gaw	2011	Limb impedance was measured at 256 frequencies between 3 kHz and 1000 kHz for a sample control population, arm lymphedema population, and leg lymphedema population. The contralateral limb impedance ratio for arms and legs was used to calculate a lymphedema index (L-Dex) at each measurement frequency. Founds good differentiation between the arm and leg L-Dex measured for lymphedema subjects and the arm and leg L-Dex measured for control subjects up to a frequency of about 30 kHz. Concludes that impedance measurements above a frequency of 30 kHz decrease sensitivity to extracellular fluid and are not reliable for early detection of lymphedema. (The FDA cleared BIS device calculates impedance ratios based on an optimal 0 kHz frequency.)
Physiotherapy after breast cancer surgery: results of a randomised controlled study to minimise lymphoedema	Box, R.C., et al., Physiotherapy after breast cancer surgery: results of a randomised controlled study to minimise lymphoedema. <i>Breast Cancer Res Treat</i> , 2002. 75 (1): p. 51-64	Box	2002	Randomized Control Trial, 65 women were randomly assigned to either the treatment (TG) or control group (CG) and assessments were made preoperatively, at day 5 and at 1, 3, 6, 12 and 24 months postoperatively. Clinically significant lymphoedema was confirmed by an increase of at least 200 ml from the preoperative difference. <u>Important Note: this study looked at BIS for early detection versus volumetric measure as their standard but an experimental, non-validated BIS reading procedure (0 to 40 cm on the arm), completely different to today's FDA cleared device (whole arm using contralateral wrist) was used. In addition, two non-validated cut off's for differentiating normal/early lymphedema with this procedure were being investigated.</u> Because the reading procedures/volumes measures were different, manufacturer software & validated cut offs were not valid and could not be used. While the lead investigator (Box 1999) did a small study suggesting a 5% cut off for this unique procedure, that cut off was not tested in this trial. The study proved that the investigational cut offs were not appropriate for this reading procedure. It demonstrated the cut offs used were too high and supported the findings from Box 1999 that a lower cut off should have been considered (Box 1999). See Box 1999 above.

Diagnostic Performance*: Sensitivity, specificity, and positive and/or negative predictive value in appropriate populations of patients. (Note: BIS is referred to as MFBIA in early studies.)				
Title	Citation	Primary Author	Year	Summary of Findings
Bioelectrical impedance for monitoring the efficacy of lymphoedema treatment programmes	Cornish, B.H., et al., Bioelectrical impedance for monitoring the efficacy of lymphoedema treatment programmes. <i>Breast Cancer Res Treat</i> , 1996. 38(2): p. 169-76	Cornish	1996	Total cohort (n=40). The results demonstrate that MFBIA is significantly more sensitive than circumferential measurement both in the early diagnosis of lymphedema and in monitoring change. MFBIA exhibiting a greater sensitivity in the detection of lymphoedema. <u>"ECW occupies approximately 25% of the total body. Thus, a 40% increase in ECW of a body segment would lead to only a 10% increase in its total volume."</u> It is not surprising, therefore, that a technique such as MFBIA, which measures actual ECW, will have greater sensitivity and precision in detecting changes than one which measures total segment volume."
Early diagnosis of lymphedema using MFBIA	Cornish, B.H., et al., <i>Early diagnosis of lymphedema using multiple frequency bioimpedance</i> . <i>Lymphology</i> , 2001. 34(1): p. 2-11.	Cornish	2001	A three year prospective study to evaluate the efficacy of MFBIA to predict the early onset of lymphedema in 120 patients following treatment for breast cancer. Performance was measured to the clinical end point of diagnosed unilateral lymphedema of the arm. BIS measurements and circumferential measurements (tape) of each upper limb were recorded in healthy control subjects (n = 60) to determine the normal range of the ratio (dominant/non-dominant) of extracellular and total limb volumes respectively. BIS and circumferential measurements were recorded pre-surgery, one month post-surgery and then at two month intervals for 24 months. 21 patients developed lymphedema in the 24 months follow up period of this study. <u>In each of 21 lymphedema cases, BIS predicted the onset of the condition up to 10 months (ave. 4 months) before the condition could be clinically diagnosed. Sensitivity and specificity were 100% and 98%, respectively.</u> The author concluded the results confirmed the suitability of BIS as a reliable early detection system for lymphedema. <u>Tape showed a 5% sensitivity for early detection.</u> (At the time of detection by MFBIA, only one patient had a positive circumferential measurement result.)
Lymphedema secondary to breast cancer: how choice of measure influences diagnosis, prevalence, and identifiable risk factors	Hayes, S., et al., Lymphedema secondary to breast cancer: how choice of measure influences diagnosis, prevalence, and identifiable risk factors. <i>Lymphology</i> , 2008. 41(1): p. 18-28	Hayes	2008	287 female breast cancer survivors (treatments: 26% mastectomy, 87% lymph node dissection, 70% radiation, 40% chemotherapy and/or hormone therapy) who underwent BIS, circumferential measurements, and self-assessment of lymphedema. All 3 techniques were used at 3-month intervals for 1 year, beginning 6 months after surgery. Based on Cornish 2001, they used BIS as the diagnostic criteria for these early stage patient. <u>Compared with BIS, circumferential measurements had 42% sensitivity and 88% specificity for detection of lymphedema. For self-assessment, the sensitivity was 61% and the specificity was 59%.</u> Based on Cornish 2001 and the validated performance of BIS to the early detection of lymphedema, BIS was used in this study as the reference standard.
Does the Effect of Weight Lifting on Lymphedema Following Breast Cancer Differ by Diagnostic Method; Results of a Randomized Controlled Trial	Hayes, S.C., et al., Does the effect of weight lifting on lymphedema following breast cancer differ by diagnostic method: results from a randomized controlled trial. <i>Breast Cancer Res Treat</i> , 2011	Hayes	2011	<u>Trial supports BIS as a valid and important method of assessment for early stage lymphedema.</u> 295 female breast cancer survivors, 141 of whom had stable lymphedema at baseline. The majority of women with lymphedema in the trial had persistent lymphedema, whereby they had lived with lymphedema for longer than 1 year (60% had lymphedema for more than 3 years, and more than 30% for between 1 and 3 years). Very few of the women had been diagnosed with lymphedema in the previous year. Consequently, these women were beyond the preclinical phases of lymphedema development; their lymphedema was visible. The study highlights how ECF levels are of clinical relevance is early stages and less in advanced stages. "Bioimpedance spectroscopy was included as an additional lymphedema diagnostic method because it provides a sensitive measure of detecting lymphedema development in the nonlymphedema group and is also an appropriate measure for those with pitting lymphedema." It also shows how the volume techniques are better targeted for chronic, irreversible lymphedema. For early treatment strategies looking to prevent progression to irreversible stages, ECF differences have an important role to play.

Comparison of Diagnostic Accuracy of Clinical Measure of Breast Cancer Related Lymphedema: Area Under the Curve	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	Smoot	2011	A study published in 2011 by Smoot and colleagues reported on diagnostic test characteristics including sensitivity, specificity, and area under the receiver-operating-characteristic (ROC) curve for a number of tests used in the diagnosis of breast cancer-related lymphedema. For this study, a total of 141 women were classified as having (n =70) or not having (n =71) breast cancer-related lymphedema (BCRL) based on past diagnosis by a health care provider. Areas under the curve for a number of bioimpedance measures and volume measures were in the 0.79 to 0.88 range, with overlap in confidence intervals. Findings support the use of <u>BIS as the most accurate method tested</u> . Please note this population had a number of patients with chronic lymphedema, not subclinical yet BIS still proved to be the most accurate test in this population.
Comparison of methods to diagnose lymphoedema among breast cancer survivors: 6-month follow-up.	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	Hayes	2005	Objective for the study was to determine the prevalence of lymphoedema 6-months following breast cancer treatment and to examine potential risk factors among a population-based sample of women (n=176). Women were defined as having lymphoedema if the difference between the sum of arm circumferences (SOAC) of the treated and untreated sides was >5 cm (prevalence=11.9%) or >10% (prevalence=0.6%), their multi-frequency bioelectrical impedance (MFBI) score was >=3 standard deviations above the reference impedance score (prevalence=11.4%), or they reported 'yes' when asked if arm swelling had been present in the previous 6 months (prevalence=27.8%). Of those with lymphoedema defined by MFBI, sensitivity of the SOAC method (difference > 5 cm) was 35% and 65% via the self report method. Specificities for SOAC (difference > 5 cm) and self-report were 88.5% and 76.9%, respectively. <u>"Our work raises questions about the use of circumferences as the choice of measurement for lymphoedema in both research and clinical settings, and assesses MFBI as a potential alternative."</u>
Bioelectrical Impedance for Detecting Upper Limb Lymphedema in Nonlaboratory Settings	Ridner, S.H., et al., Bioelectrical Impedance for Detecting Upper Limb Lymphedema in Nonlaboratory Settings. Lymphat Res Biol, 2009	Ridner	2009	Primary aim of this study was to compare impedance ratios among breast cancer survivors with and without lymphedema, with that of healthy normal women. Study looked at a low frequency device designed only for lymphedema assessment (ECW measurement only). The sample (n =233) consisted of females ages 30 through 94 years old. Within the sample there were 60 healthy controls. The procedure implemented in this cross-sectional study <u>resulted in bioelectrical impedance values that clearly distinguished between individuals with and without lymphedema</u> and LIR (limb impedance ratio) means similar to those found in previous studies. These findings suggest that in addition to the ease of use and rapidity of measurement, bioelectrical impedance can be used outside laboratory settings to evaluate arm lymphedema. Findings also suggest that LIRs can be used with confidence as markers for lymphedema.
The Use of Bioimpedance Analysis to Evaluate Lymphedema	Warren, A.G., et al., The use of bioimpedance analysis to evaluate lymphedema. Ann Plast Surg, 2007. 58 (5): p. 541-3	Warren	2007	A total of 15 patients (plus 7 controls), with upper-extremity or lower extremity <u>lymphedema as documented by lymphoscintigraphy</u> underwent bioimpedance spectroscopy analysis using an ImpediMed SFB7 device. Seven healthy medical students and surgical residents (mean age: 26.9 years) were selected to serve as normal controls. The multifrequency bioimpedance device documented impedance values for each limb, with lower values correlating with higher levels of accumulated protein rich edematous fluid. <u>"Bioimpedance spectroscopy can be used as a reliable and accurate tool for documenting the presence of lymphedema in patients with either upper- or lower-extremity swelling. Measurement with the device is quick and simple and results are reproducible among patients.</u> Given significant limitations with other methods of evaluating lymphedema, the use of bioimpedance analysis may aid in the diagnosis of lymphedema and allow for tracking patients over time."

A new detection technique for lymphedema with application in both unilateral and bilateral cases	Cornish, B.H., et al., A new technique for the quantification of peripheral edema with application in both unilateral and bilateral cases. <i>Angiology</i> , 2002. 53(1): p. 41-7	Cornish	2002	Twenty patients receiving surgical treatment for breast cancer were monitored prior to surgery and again after diagnosis with unilateral lymphedema. The data recorded were total limb volume, by circumferential measurements; and BIA measurements of both limbs. From these measurements total limb volumes and extracellular fluid volumes were calculated and expressed as ratios of the affected limb to that of the unaffected limb. An index of the ratio of the extracellular fluid volume to the intracellular fluid volume was determined. This ECW/ICW index was calculated for both the affected and unaffected limbs at both measurement times. <u>Results confirmed that the established techniques of total limb volume and extracellular fluid volume normalized to the unaffected contralateral limb were accurate in the detection of lymphedema</u> (p < 10(-6)).
Breast Cancer Related Arm Lymphedema: Incidence Rates, Diagnostic Techniques, Optimal Management and Risk Reduction Strategies	Shah, C. and F.A. Vicini, Breast cancer-related arm lymphedema: incidence rates, diagnostic techniques, optimal management and risk reduction strategies. <i>Int J Radiat Oncol Biol Phys</i> , 2011. 81(4): p. 907-14	Shah	2011	"Traditional measures use total arm volume as a surrogate for LE (lymphedema). However, this is not completely accurate because LE represents an increase in the extracellular fluid volume.newer modalities can directly measure the extracellular volume, potentially providing increased diagnostic accuracy." "Significant heterogeneity exists in the literature regarding incidence, diagnosis, and management of BCRL. Surgical, radiation, and chemotherapeutic decisions should be made with insight regarding the incidence of BCRL for each procedure and in combination. <u>Newer diagnosis techniques including DEXA and BIS represent significant improvements over traditional techniques by providing standardized cutoffs, limiting observer variability, increasing sensitivity with the potential of subclinical detection, and accurately measuring the extracellular fluid space.</u> "
Is BIS ready for prime time as the gold standard measurement?	Ward, L., Is BIS ready for prime time as the gold standard measure? <i>Journal of Lymphoedema</i> , 2009. 4(2): p. 52-56.	Ward	2009	<i>Journal of Lymphedema</i> set up a debate asking whether BIS should be considered the new clinical gold standard in lymphedema detection. Experts on both sides of the debate were asked to build their arguments. The pro position, written by Ward, <u>makes the case that BIS technology now warrants consideration as the new gold standard method for LE assessment based on specificity, accuracy, precision, repeatability both within and between centers, limits of detection, sensitivity and practicability and applicability under normal conditions of use.</u>
Outcome measures for lymphoedema	Piller, N., Outcome measures for lymphoedema. <i>Journal of Lymphoedema</i> , 2010. 5(1)	Piller	2010	For the counter argument the Editor of JOL had problems finding views of dissent. He then wrote an editorial to address the counter argument. "We had a paper in JOL about BIS (Ward, 2009) — but we had problems finding views of dissent." "Ward (2009) in his paper asked the question, 'Is bioimpedance spectroscopy ready for prime time as the gold standard measure?', and <u>discussed the serious issues we suffer through using inappropriate technologies (or making the incorrect interpretation from them), and strongly suggested that the evidence is out there for considering bioimpedance spectroscopy (BIS) as 'the reference method'</u> for measuring lymphoedema. For those using other current technologies, such as immersion plethysmography and perometry, it does not mean that their techniques are invalid. In fact, we already have much evidence to support strong correlations between BIS and perometry on a point comparison basis."

* Under this payer defined title, please note the device is indicated only for aiding a medical provider in the clinical assessment of lymphedema – it is not meant to diagnose or assess risk.

Improved Outcomes with Earlier Treatment: evidence related to improvement of clinical outcomes with earlier treatment - demonstration that the diagnostic information can be used to improve patient outcomes.

Title	Citation	Primary Author	Year	Summary of Findings
Lymphoedema secondary to breast cancer: Possibility of diagnostic and therapeutic prevention	Campisi, C., et al., [Lymphedema secondary to breast cancer treatment: possibility of diagnostic and therapeutic prevention]. Ann Ital Chir, 2002. 73(5): p. 493-8	Campisi	2002	Prospective randomized study on 50 breast cancer patients - divided into 2 groups of 25 each - monitored for 5 years after surgery. All patients underwent surgery and radiation for breast cancer treatment between the period of April 1992 to June 1994 and were monitored for 5 years after surgery. The control group was only clinically monitored. In the treatment group, upper limb lymphoscintigraphy was performed and intervention undertaken if abnormal. Time points for lymphoscintigraphy assessment were baseline, 1,3,6 months, 1, 2 and 3 years. Patients who presented with lymphoscintigraphy alterations (dermal backflow, diffused or delayed transit of the tracer), before edema appeared clinically, underwent physical and rehabilitative therapy. Therapy for lymphoscintigraphy group included – bandages, manual lymph drainage, mechanical lymph drainage and elastic garments. In the control group, 9 cases (or 36%) of patients developed lymphoedema after a period varying from 1 week to 2 years (average of 6 months). <u>In the treatment group receiving lymphoscintigraphy diagnosis and early intervention, only 2 cases (or 8%) progressed to a clinically evident lymphedema. Study showed that early detection/intervention significantly reduced the clinical appearance of lymphedema even after 5 years from surgery.</u>
Prospective Evaluation of a Prevention Protocol for Lymphedema following Surgery for Breast Cancer	Boccardo, F.M., et al., Prospective evaluation of a prevention protocol for lymphedema following surgery for breast cancer. Lymphology, 2009. 42(1): p. 1-9	Boccardo	2009	European Randomized Control Trial in which 55 women treated for breast cancer including axillary node dissection were evaluated for a preventive protocol for lymphedema. Both control and treatment (preventive) groups had arm volume measurements performed preoperatively and at 1, 3, 5, 12, and 24 months postoperatively. The preventative protocol included principles to minimize lymphedema risk, lymphoscintigraphy preoperatively and at 6 months postoperatively, and early management of the condition once identified. Clinically significant lymphedema was an increase of at least 200 mL from the preoperative difference between the two arms. Assessments at 2 years were completed for 89% of the 55 women who were randomly assigned to either preventive group or control. Of the 49 who were measured at 2 years, 10 (21%) were identified with secondary lymphedema with an incidence of 8% in the preventive group and 33% in controls. <u>Prophylactic strategies appear to reduce the development of secondary lymphedema and alter its progression.</u>
Effectiveness of early physiotherapy to prevent lymphoedema after surgery for breast cancer: randomised, single blinded, clinical trial	Torres LaComba, M., et al., Effectiveness of early physiotherapy to prevent lymphoedema after surgery for breast cancer: randomised, single blinded, clinical trial. BMJ, 2010. 340: p. b5396	Torres LaComba	2010	Randomized Control Trial comparing pre-emptive treatment and education versus education only. 120 women who had breast surgery involving dissection of axillary lymph nodes between May 2005 and June 2007. The early physiotherapy group was treated by a physiotherapist with a physiotherapy programme including manual lymph drainage, massage of scar tissue, and progressive active and action assisted shoulder exercises. This group also received an educational strategy. The control group received the educational strategy only. 116 women completed the one year follow-up. Of these, 18 developed secondary lymphoedema (16%): 14 in the control group (25%) and four in the intervention group (7%). The difference was significant (P=0.01); risk ratio 0.28 (95% confidence interval 0.10 to 0.79). A survival analysis showed a significant difference, with secondary lymphedema being diagnosed four times earlier in the control group than in the intervention group (intervention/control, hazard ratio 0.26, 95% confidence interval 0.09 to 0.79). <u>Early physiotherapy could be an effective intervention in the prevention of secondary lymphoedema in women for at least one year after surgery for breast cancer. Supports the importance and efficacy of early intervention.</u>

Preoperative Assessment Enables the Early Diagnosis and Successful Treatment of Lymphedema	Stout Gergich, N.L., et al., Preoperative assessment enables the early diagnosis and successful treatment of lymphedema. Cancer, 2008. 112(12): p. 2809-19	Stout	2008	NIH prospective study: LE was identified in 43 of 196 women who participated in a prospective BC morbidity trial. Limb volume was measured preoperatively, 1 month and at 3- month intervals after surgery for 18 months. If an increase >3% in upper limb (UL) volume developed compared with the preoperative volume, then a diagnosis of LE was made, and a compression garment intervention was prescribed for 4 weeks. <u>A short intervention with off the shelf compression sleeves was effective in bringing all patients with subclinical lymphedema back to a pre-surgical baseline.</u> "In conclusion, preoperative assessment in the context of a prospective surveillance model enables the early detection and management of subclinical LE. An early intervention protocol with 20- to 30-mm Hg compression garments, as outlined in this report, significantly reduces the affected limb volume to near baseline measures and prevents progression to a more advanced stage of LE for at least the first year postoperatively."
Five Year Preliminary Outcomes of a Prospective Surveillance Model to Reduce Upper Extremity Morbidity Related to Breast Cancer Treatment	Poster, 2011 San Antonio Breast Cancer Symposia	Stout	2011	Five year follow up date from the above prospective study looking whether the early treatment/prevention of progression outcome was a long term benefit. All newly diagnosed Stage I-III BC patients at risk of unilateral LE. Measurements taken pre-operatively and 1,3,6,9,12 and 60 months with a Perometer using a 3% cut off. N = 196 at 12 months and 86 at 60 months. Overall range of lymphedema: 7%-22% at 12 months and 11%-38% at 60 months. 12 month to 60 month comparison by stage: Stage 0: 22% vs 38%; Stage I/II: 7% vs 11%; Stage III: 0% vs 0%, respectively. Preliminary data demonstrates long term benefits for early subclinical treatment of patients. <u>Preoperative assessment, prospective surveillance, and early intervention enhance function and reduces morbidity. Early assessment and intervention should be the standard of care for patients receiving breast cancer treatment.</u>

Outcomes based on treating at 200ml, 10% volume differences - often associated with the presentation of visible swelling - reactive care.

Title	Citation	Primary Author	Year	Summary of Findings
Arm lymphoedema in a cohort of breast cancer survivors 10 years after diagnosis	Johansson, K. and E. Branje, Arm lymphoedema in a cohort of breast cancer survivors 10 years after diagnosis. Acta Oncologica, 2010. 49(2): p. 166-173	Johansson	2010	Interesting study to contrast with the findings of the Stout 2008 study. Supports the importance of early detection and intervention. Two hundred and ninety two (292) patients treated with axillary node dissection and radiotherapy were included in this retrospective study. 111 were diagnosed with BCRL (incidence 38.7%) based on a 5% or greater difference in arm volume. Of these women, 98 were followed for up to 10 years after BCRL diagnosis. Forty consecutive patients without BCRL were included in the control group. Follow-up was performed twice a year including assessment of lymphoedema relative volume (LRV) by water displacement method. Additional intensive treatment consisting of pneumatic compression, manual lymph drainage and bandaging was given if LRV increased by more than 5% since the previous visit or exceeded 20% in total. <u>Data also shows that using a traditional definition of lymphedema with water displacement patients could be treated for up to 10 years but still not be brought back to a pre-surgical baseline.</u>
Post-breast cancer lymphedema: incidence increases from 12 to 30 to 60 months	Armer, J.M. and B.R. Stewart, Post-breast cancer lymphedema: incidence increases from 12 to 30 to 60 months. Lymphology, 2010. 43(3): p. 118-27	Armer	2010	Interesting study to contrast with the findings of the Stout 2008/2011 data. Trends for LE occurrence over three points in time (12, 30, and 60 months) among breast cancer survivors (n=211) using four diagnostic criteria based on three measurement techniques. Baseline limb volume and symptom assessment data were obtained. Participants were followed every 3 months for 12 months, then every 6 months thereafter for a total of 60 months. Limb volume changes (LVC) in both limbs were measured using three techniques: objectively by (a) circumferences at 4 cm intervals and (b) perometry, and subjectively by (c) symptom experience via interview. Four diagnostic criteria for LE most often reported in the literature were used: (i) 2 cm circumferential change; (ii) 200 mL perometry LVC; (iii) 10% perometry LVC; and (iv) signs and symptoms (SS). At 12 months (n =118), 21% (average for all techniques) of patients had developed lymphedema; at 30 months (n =211), 41% (average for all techniques) of patients had developed lymphedema, by 60 months 55% (43-94%) had developed lymphedema. <u>Contrast with Stout 2008 and 2011 demonstrates the comparative effectiveness and long term benefits of subclinical detection/intervention when compared to Armer's incidence rates reflecting traditional reactive care.</u>
The role of pneumatic compression in the treatment of postmastectomy lymphedema. A randomized phase III study	Dini, D., et al., The role of pneumatic compression in the treatment of postmastectomy lymphedema. A randomized phase III study. Ann Oncol, 1998. 9(2): p. 187-90	Dini	1998	Interesting study to contrast with the findings of the Stout 2008 study where they treated subclinical lymphedema. Dini trial performed a randomized study comparing pneumatic compression versus no treatment in patients with postmastectomy lymphedema. Patients with unilateral postmastectomy lymphedema were randomized to receive two cycles of intermittent pneumatic compression (PC group), i.e., five two hour sessions per week for two weeks, to be repeated after a five-week interval, or to no treatment (control group). The patients in both groups were instructed as to the prophylactic hygienic care of the limb. Lymphedema was assessed by the sum of differences in circumference measurements between affected and normal limbs ('delta'). Only patients with a baseline delta (deltabas) value >10 cm were considered to have a clinically significant lymphedema, and admitted into the trial. Response was defined as a greater than 25% reduction in delta value; 80 patients entered the study. No statistically significant differences in response rates between the two groups were observed: 20% in the control group (95% CI: 9%-36%), 25% in the PC group (95% CI: 13%—41%, P = 0.59). The absolute mean decrease in delta value was 1.9 ± 3.7 cm in the PC group and 0.5 ± 3.3 cm in the control group. <u>Conclusion of the author: "We demonstrated that intermittent pneumatic compression has a limited clinical role in the treatment of postmastectomy lymphedema. Efforts to prevent this complication should be undertaken."</u>

Additional Review Articles: on the benefits of Bioimpedance Spectroscopy in aiding clinical assessment and the benefits of early treatment				
Title	Citation	Primary Author	Year	Summary of Findings
Cancer-Related Lymphedema Risk Factors, Diagnosis, Treatment, and Impact: A Review	Paskett, E.D., et al., Cancer-related lymphedema risk factors, diagnosis, treatment, and impact: a review. J Clin Oncol, 2012. 30(30): p. 3726-33	Paskett	2012	"Perometry and bioimpedance emerged as attractive diagnostic technologies, replacing the use of water displacement in clinical practice." and "Central to this <limb volume> assessment is the need for preoperative measurement to ascertain a true baseline. This measurement, however, rarely occurs as a part of clinical practice." and "Water displacement was once considered the gold standard for LE diagnosis because of its affordability and excellent reliability and validity. However, other technologies, such as lymphoscintigraphy, perometry and bioimpedance, although more costly, provide equally reliable and valid limb volume measurements with greater ease and patient comfort."
Bioimpedance Analysis in the Assessment of Lymphoedema Diagnosis and Management	Rockson, S.G., Bioimpedance analysis in the assessment of lymphoedema diagnosis and management. Journal of Lymphoedema, 2007. 2(1): p. 44-8	Rockson	2007	MFBI in analysis of lymphedema has been proven to be fast, accurate and well accepted by patients. Will provide good standard for lymphedema detection and tracking.
Addressing the Unmet Needs in Lymphedema Risk Management	Rockson, S.G., Addressing the unmet needs in lymphedema risk management. Lymphat Res Biol, 2006. 4(1): p. 42-6	Rockson	2006	"Thus, in using breast cancer-associated disease as a paradigm for acquired lymphedema, one can conclude that this chronic debilitating disease is frequently under-recognized or misdiagnosed; consequently, it can be said that it is usually treated too late and very likely will not be treated at all. Lymphedema is a disease that is prevalent, yet its prevalence is likely under-estimated. Thus, the availability of newer technology, that will facilitate the objective documentation of disease and permit the detection of early and subclinical involvement will undoubtedly ameliorate the clinical response to these patients and provide a much needed link to foster epidemiologic investigations."
Bioelectrical Impedance Analysis: Proven Utility in Lymphedema Risk Assessment and Therapeutic Monitoring	Ward, L.C., Bioelectrical impedance analysis: proven utility in lymphedema risk assessment and therapeutic monitoring. Lymphat Res Biol, 2006. 4(1): p. 51-6	Ward	2006	Assessment of lymphedema by BIS has been found to be faster, more consistent, and better accepted by clinicians, therapists, and patients than serial tape measurements or water displacement methods. The equipment is highly portable, relatively inexpensive, and is easy to use by nonspecialist personnel. It is still a novel technique that is only now finding a place in the armamentarium of clinical practice.
Measuring lymphedema in patients with breast cancer go with the flow?	Hunt, K.K., R. Askew, and J.N. Cormier, Measuring lymphedema in patients with breast cancer: go with the flow? Breast Cancer Res Treat, 2009	Hunt	2009	"Ward et al. have responded to the need for more reliable measurement tools and standardized diagnostic criteria that will facilitate the early detection of lymphedema given the increasing number of breast cancer survivors."
Lymphedema: A primer on the identification and management of a chronic condition in oncologic treatment	Lawenda, B.D., T.E. Mondry, and P.A. Johnstone, Lymphedema: a primer on the identification and management of a chronic condition in oncologic treatment. CA Cancer J Clin, 2009. 59(1): p. 8-24	Lawenda	2009	Lawenda states - "It is hoped that this review will convey the importance of the early identification and management of this incurable disorder because this is essential to minimizing its complications." This Primer on lymphedema supports the importance of pre-surgical assessment of monitoring of patients at risk of developing lymphedema. Early detection and treatment are critical. Supports BIS as being reliable and accurate. "Without intervention, lymphedema can lead to progressive swelling, fibrosis of the soft tissues, neurologic changes (eg, pain and / or paresthesias), and infection. Early identification of the signs and symptoms of lymphedema should be integral to the management of all patients who have received surgery and/or radiation, and are thus at high risk. When treated in the earliest stages, complications of this condition may be minimized"
Time Course of Mild Arm Lymphedema After Breast Conservation Treatment for Early Stage Breast Cancer	Bar Ad, V., et al., Time course of mild arm lymphedema after breast conservation treatment for early-stage breast cancer. Int J Radiat Oncol Biol Phys, 2010. 76(1): p. 85-90	Bar Ad	2010	Looks at time to progression of mild arm lymphedema to more severe stages. Stresses importance of ongoing, objective measurement. Once advanced, normal limb volume and lymphatic function cannot be restored. Reinforces NIH findings of preventing progression to even mild lymphedema. Cites BIS and perometry as objective assessment methods.
Chapter 104 - Lymphedema	Kuerer's Breast Surgical Oncology (textbook) Published by McGraw-Hill. ISBN 978-0-07-160178-8 Copyright 2010	Norton	2010	Chapter dedicated to lymphedema identification and treatment. Refers to BIS as an emerging, affordable, portable technology widely available in clinical settings to support lymphedema diagnosis. List BIS with optoelectronic volumetry as sensitive to subtle changes above baseline of 3-5% allowing earlier diagnosis.
The How and Why of Body Composition Assessment (Chapter 30).	Handbook of Nutrition and Food. Edited by Carolyn D . Berdanier CRC Press 2002. Print ISBN: 978-0-8493-2705-6. eBook ISBN: 978-1-4200-3839-2	Van Loan	2002	The BIS technique using Cole-Cole modeling and Hanai mixing theory, can accurately assess changes in TBW (total body water), ECF (extracellular fluid) and lean tissue accretion.
Edema Volume, Not Timing, is the Key to Success in Lymphedema Treatment	Ramos, S.M., L.S. O'Donnell, and G. Knight, Edema volume, not timing, is the key to success in lymphedema treatment. Am J Surg, 1999. 178(4): p. 311-5	Ramos	1999	Initial volume of fluid edema in the tissues was key to predicting the success of therapy. Patients having the lowest volume of initial edema have the best chance for a successful outcome.

Lymphedema: How Do We Diagnose and Reduce the Risk of This Dreaded Complication of Breast Cancer Treatment?	Bernas, M., et al., Lymphedema: How Do We Diagnose and Reduce the Risk of This Dreaded Complication of Breast Cancer Treatment? Current Breast Cancer Reports, 2010. 2(1): p. 53-58	Bernas	2010	Encourages healthcare providers involved with cancer patients to become more educated about lymphedema, aware of current risk-reduction practices, and familiar with methods of diagnosis and assessment, <u>so that patients with early swelling can be referred to lymphedema treatment specialists at a time when treatment is more effective.</u>
Causes and consequences of lymphatic disease	Rockson, S., Causes and consequences of lymphatic disease. Ann N Y Acad Sci, 2010. 1207 S1(Lymphatics in the Digestive System: Physiology, Health and Disease): p. E2-E6	Rockson	2010	"In the early stages of lymphedema, with the accumulation of excess interstitial fluid, the impedance to lower frequencies decreases proportionately."
Bioimpedance analysis: Scientific background	Cornish, B., Bioimpedance analysis: scientific background. Lymphat Res Biol, 2006. 4(1): p. 47-50	Cornish	2006	"The lymphatic fluid is part of the extracellular fluid compartment which normally comprises approximately one-quarter of the total volume of the limb.....Bioimpedance is one of the few techniques of body composition analysis which differentiates the extracellular fluid compartment from the total limb volume."

Guidelines, Standards and White Papers				
Title	Citation	Primary Author	Year	Summary of Findings
National Accreditation Program for Breast Centers	http://napbc-breast.org/standards/centers.html	NAPBC	2012	Establishes Standard 2.15 for lymphedema management and risk-reduction. Provides NLN Recommendation describing BIS and opto-electric volumetry as "Strongly Recommended" to aid in assessment of patients. (See "Lymphedema Screening and Treatment Guidelines")
Screening and Measurement for Early Detection of Breast Cancer Related Lymphedema	http://www.lymphnet.org/pdfDocs/nlnBCLC.pdf	National Lymphedema Network (NLN) Position Paper	2011	Bioelectrical spectroscopy (BIS) or infrared perometry are suggested as alternative or adjunct methods to circumferential measurement.
White Paper: Recent Advances in Breast Cancer Related Lymphedema	http://www.avonfoundation.org/assets/le-meeting/le-white-paper.pdf	Avon Foundation for Women	2011	Proceedings from April 2011 Expert Panel. Supports use of BIS or perometry in pre-emptive model.
Guidelines for the diagnosis, assessment and management of lymphoedema	Clinical Resource Efficacy Support Team (CREST), www.crestni.org.uk (public domain)		2008	BIS (referred to in 2008 as Multiple Frequency Bioimpedance) has advantages over limb circumference. High sensitivity and high specificity.
Monitoring for the early detection of breast cancer related lymphoedema	http://www.lymphoedema.org.au/	Australasian Lymphology Association	2012	Criteria for early diagnosis of breast cancer related lymphoedema: Bioimpedance spectroscopy: L-Dex® that are above the normal range of 10 units, or have changes +10 L-Dex® units from baseline, or are showing an upward trend over time.
Health-Economics of BCRL				
Title	Citation	Primary Author	Year	Summary of Findings
Incidence, Treatment Costs, and Complications of Lymphedema After Breast Cancer Among Women of Working Age: A 2-Year Follow-Up Study	Shih, Y.C., et al., Incidence, Treatment Costs, and Complications of Lymphedema After Breast Cancer Among Women of Working Age: A 2-Year Follow-Up Study. J Clin Oncol, 2009	Shih	2009	Based on actual claims data review, breast cancer patients with lymphedema incurred significantly higher medical costs (\$14,877 to \$23,167) than those without lymphedema. These patients were twice as likely to have lymphangitis or cellulitis. (Note: ImpediMed believes that effective management of early stage lymphedema using a pre-emptive model of care can minimize the expense of chronic care associated with pneumatic compression pumps, custom compression garments, additional office visits, intensive physical therapy and hospitalization for infections.)