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# Diagnosis of Upper-Quadrant Lymphedema Secondary to Cancer: Clinical Practice Guideline From the Oncology Section of APTA

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**Introduction:** The Oncology Section of APTA developed a clinical practice guideline to aid the clinician in diagnosing secondary upper-quadrant cancer-related lymphedema. **Methods:** Following a systematic review of published studies and a structured appraisal process, recommendations were written to guide the physical therapist and other health care clinicians in their diagnostic process. Overall, clinical practice recommendations were formulated on the basis of the evidence for each diagnostic method and were assigned a grade based on the strength of the evidence for different patient presentations and clinical utility. **Recommendations:** In an effort to make these clinically applicable, recommendations were based on the characteristics as to the location and stage of a patient's upper-quadrant lymphedema. (Rehab Oncol 2017;35:E1–E18) **Key words:** assessment, evidence-based practice

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## INTRODUCTION

Secondary lymphedema is a relatively underestimated and poorly understood sequela of cancer treatment that can adversely impact quality of life.<sup>1</sup> Cancer treatments, such as radiation therapy and resection of lymph nodes, can result in decreased lymph resorption and transport, leading to lymphatic insufficiency. When extracellular fluid is not resorbed by the impaired lymphatic system and reaches a measurable level of lymphatic insufficiency (which has been defined in a variety of ways), a patient receives a diagnosis of lymphedema.

The presence of secondary upper-quadrant lymphedema (SUQL) can lead to significant morbidity, activity and participation restrictions, reduced quality of life, and economic hardship.<sup>2-6</sup> In 2016 alone, it was estimated that 1.6 million people in the United States had a diagnosis of cancer,<sup>7</sup> many involving the upper quadrant, and thus a large number of cancer survivors are at risk of developing SUQL. Incidence rates of SUQL vary widely and are estimated at 6% to 70% in patients with breast cancer,<sup>8,9</sup> 5% in patients with upper-extremity melanoma,<sup>10</sup> and 73.5% in patients with head and neck cancer.<sup>11</sup> Reasons for the wide variations in incidence rates of SUQL following cancer treatment include heterogeneity in patient and clinical characteristics and the type and extent of medical interventions. In addition, variability across the populations studied, length of follow-up, diagnostic criteria and methods, and definitions of lymphedema contribute to inconsistencies in incidence and prevalence statistics.

Prior to establishing a plan of care, clinicians obtain a history and perform body function and structure tests and measures to establish a diagnosis, assess the stage and/or severity of the condition, and then determine the effect on activity and participation. At present, lymphedema is most often diagnosed by a clinical history, physical examination of tissue quality, symptomatology, and/or the presence of increased limb volume. On the basis of the medical history, clinicians inquire about risk factors and medical treatments known to impact lymphatic transport. As a part of differential diagnosis, clinicians also determine whether other pathologies known to cause edema such as blood clot or cancer recurrence are likely. If other causes of swelling are ruled out, clinicians then determine whether disruptions of the lymphatic system have impaired lymphatic transport capacity sufficiently to diagnose lymphedema. If lymphedema—either clinically apparent or subclinical—is suspected, further assessment is warranted.

Current objective measures of SUQL include bioimpedance analysis (BIA), circumferential measurement, water displacement, and perometry and imaging, which may incorporate differences between limbs or from baseline. Clinicians may also classify the severity of the lymphatic system impairment. The International Society of Lymphology (ISL) consensus document<sup>12</sup> classifies the severity of lymphedema by stage as follows:

*Stage 0:* Subclinical state where the peripheral swelling is not visible, but lymphatic transport is

impaired. Symptoms and subtle tissue changes may be noted.

*Stage I:* Early onset of swelling that is visible and subsides with elevation. Pitting may be present.

*Stage II:* Consistent volume change with pitting present. Elevation rarely reduces the swelling, and progressive tissue fibrosis occurs.

*Stage III:* Skin changes such as thickening, hyperpigmentation, increased skinfolds, fat deposits, and warty overgrowths occur. Tissue is very fibrotic, and pitting is absent.

Early detection of lymphatic insufficiency, coupled with appropriate intervention, may be important to prevent progression of the condition and may provide a cost-effective approach.<sup>13,14</sup> Diagnostic definitions of lymphedema that require a consistent volume increase, and thus being at ISL stage II or above, have the potential to hamper efforts to intervene at the early stages. Providing timely and appropriate care to patients with SUQL requires that physical therapists and other health care professionals have access to guidelines that assist in directing their assessment and management. By implementing this evidence-based practice guideline, health care professionals will be better able to detect lymphedema of the upper quadrant, at both the subclinical and clinically apparent stages, allowing this population to maintain maximum function and quality of life.

## NEED FOR CLINICAL PRACTICE GUIDELINE FOR DIAGNOSIS OF SECONDARY UPPER-QUADRANT LYMPHEDEMA

A review of the Agency for Healthcare Research and Quality's (AHRQ's) National Guideline Clearinghouse (CPGs) and PubMed yielded few clinical practice guidelines (CPGs) or systematic reviews focusing on the assessment of patients with secondary lymphedema. In 2008, Poage et al<sup>15</sup> provided guidelines for the nursing profession regarding cancer-related lymphedema interventions. Harris et al<sup>16,17</sup> presented recommendations about modalities and interventions used by clinicians in the treatment of breast cancer and lymphedema—but did not include diagnosis and assessment.

In 2010, the AHRQ conducted a technology assessment of diagnostic tests and nonpharmacologic treatments of secondary lymphedema.<sup>18</sup> The AHRQ summary stated that further research is needed in these areas. In 2013, Armer et al<sup>19</sup> published an expert opinion guideline on assessment, risk reduction, management, and surveillance but not for the diagnosis of post-breast cancer lymphedema. Currently, few guidelines exist to help the clinician determine the most appropriate methods for diagnosing SUQL.

The Oncology Section of APTA commissioned the writing of an evidence-based guideline for secondary lymphedema. The goals of the Guideline Development Group were to:

1. Describe evidence-based diagnostic methods and criteria for cancer-related SUQL.
2. Identify gaps in the research for the diagnosis of cancer-related SUQL.
3. Create reference publications for use by physical therapy professionals regardless of subspecialty and setting, as well as for other health care practitioners and students, identifying best practice related to the diagnosis of SUQL.

This document reflects the work of this group in developing recommendations for the detection and diagnosis of SUQL.

## METHODS

### Literature Search

With the assistance of academic reference librarians from Saint Louis University and University of Southern California, search strategies were developed and executed in the following databases: PubMed, CINAHL Plus with full text, Cochrane, AHRQ National Guideline Clearinghouse, SCOPUS, SPORTDiscus with full text, Physiotherapy Evidence Database (PEDro), and Occupational Systematic Evaluation of Evidence (OTseeker). The final search terms included the following: *Lymphedema*, *Elephantiasis*, and truncated text words *lymphedema\**, *lymphoedema\**, *elephantiasis*. Articles including the terms *filariasis*, *parasites*, *congenital*, *hereditary*, as well as *editorial*, *letter*, and *comment*, were excluded.

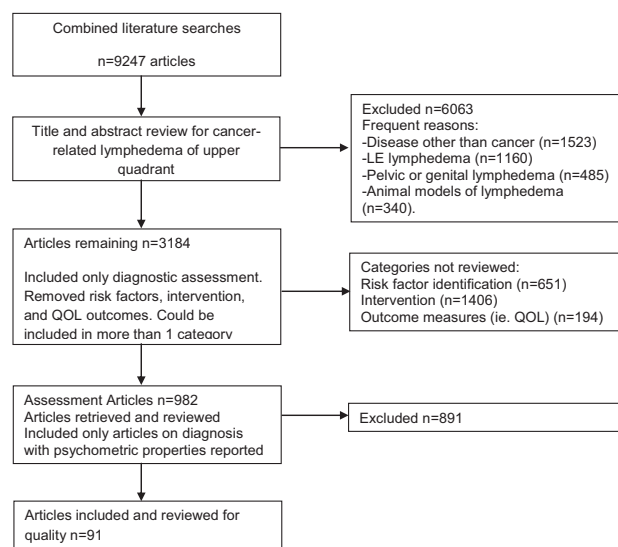
Literature published from January 1, 2000, through July 5, 2015, was searched and reviewed for inclusion (Figure 1). The search was run in 2 phases during CPG development: the initial search included studies from January 1, 2000, through June 30, 2013, and a second search included studies from July 1, 2013, through July 5, 2015. Titles and abstracts were reviewed by one Guideline

Development Group member for meeting the following eligibility criteria: investigated some aspect of cancer-related lymphedema of the upper quadrant, included relevant psychometrics, and the articles were written in the English language. Case studies and animal studies were excluded. On the basis of title and abstract reviews, articles were placed into the following categories: diagnosis and assessment, incidence and prevalence, risk factor identification, and intervention. Articles could be classified into more than 1 category. For this phase of the CPG development, only articles pertaining to assessment and diagnosis were retrieved and reviewed for inclusion by a Guideline Development Group member.

### Article Quality Appraisal Process

As the articles were diagnostic in nature, the Quality Appraisal of Diagnostic Reliability (QAREL) checklist was used to rate the quality of reliability studies and the Quality Assessment of Diagnostic Accuracy Studies–2 (QUADAS-2) tool was used to rate validity and diagnostic accuracy studies.<sup>20–23</sup> The 11-item QAREL checklist evaluates participant and examiner properties, blinding, order effects, time interval and test implementation and interpretation, and appropriateness of the statistical tests used.<sup>20,21</sup> The QUADAS-2 evaluates appropriateness of patients (*selection*), choice and application of reference standard with which to compare the results of the index test, blinding of testers to results of other tests, sources of potential bias, and clinical applicability.<sup>22,23</sup>

The Guideline Development Group completed critical appraisals on 5 test articles to establish interrater reliability before initiating the article review process. Each Guideline Development Group member completed a critical appraisal for all test articles, and, when a 100% agreement was achieved, appraisers were paired to review the remaining diagnostic articles. Two appraisers from the Guideline Development Group were assigned to review each article independently and then compare results. If these 2 appraisers could not come to consensus, a third member of the Guideline Development Group was recruited to appraise the article and consensus was achieved. A quality rating for each individual article was assigned according to criteria established by the Centre for Evidence-Based Medicine (<http://www.cebm.net/index.aspx?o=1025>) for diagnostic studies and used in other CPGs (Table 1).<sup>24,25</sup> If 2 Guideline Development Group members did not agree on the quality rating for a particular article, a third Guideline Development Group member was used to determine the rating.



**Fig. 1.** Literature search flowchart. QOL indicates quality of life; LE, lower extremity.

**TABLE 1**  
Quality Rating Scale for Individual Articles<sup>a</sup>

Level	Criteria
I	Evidence obtained from high-quality diagnostic studies, prognostic or prospective studies, cohort studies or randomized controlled trials, meta-analyses, or systematic reviews; critical appraisal score >50%
II	Evidence obtained from lesser-quality diagnostic studies, prognostic or prospective studies, cohort studies or randomized controlled trials, meta-analyses, or systematic reviews (eg, weaker diagnostic criteria and reference standards, improper randomization, no blinding, <80% follow-up); critical appraisal score ≤50%
III	Case-controlled studies, retrospective studies, or studies of only healthy control subjects

<sup>a</sup>Adapted from Phillips et al<sup>24</sup> and Delitto et al.<sup>25</sup>

to receive a higher evidence grade, the body of the evidence must have contained reliability, validity, and diagnostic accuracy studies. If an examination method did not have a diagnostic accuracy study, an evidence grade for that tool as an assessment of lymphedema—but not as a diagnostic measure—was assigned. Thus, the group distinguished between (1) tests and measures that could be used to support a diagnosis of lymphedema, and (2) assessment tools that provide important information about the condition at the body structure and function level but do not have evidence for their use as a diagnostic measure.

### Grades of Recommendations

Evidence grades were assigned on the basis of an overall appraisal by the Guideline Development Group for all aspects of psychometric properties for each diagnostic and assessment method. Clinical utility and cost were factored into the process by expert opinion and general availability of equipment. The criteria for these evidence grades were based on previous work of APTA Academy of Pediatrics

and Orthopaedic Section Guideline Development Groups (Table 3).<sup>25,26</sup> See Appendix A (Supplemental Digital Content 1, available at: <http://links.lww.com/REHABONC/A2>) for the quality rating for each article appraised.

### Recommendation Statements

Overall clinical practice recommendations (Table 4) were formulated on the basis of the evidence for each diagnostic method and were assigned a grade based on the strength of the evidence for different patient presentations and clinical utility as determined by the Guideline Development Group. In an effort to make these clinically applicable, recommendations were based on the characteristics of the location and stage of a patient's lymphedema within the upper quadrant. The categories and subcategories for practice recommendations were written for the following:

- All patients at risk for SUQL
- Secondary upper-extremity lymphedema
  - At risk, early
  - Moderate/established
  - Late
- Lymphedema primarily in the hand
- Trunk/breast lymphedema
- Head and neck lymphedema

An expert in guideline writing—as well as expert oncology clinicians (physical therapist, occupational therapist, physical medicine and rehabilitation physician, and breast surgeon) and researchers published in the field of lymphedema detection and diagnosis—completed a review of this article prior to its submission for review and publication. The CPG was also posted in the APTA Oncology Section Web site for public comment from practicing clinicians. Feedback on content from the expert panel of reviewers and the comments on clarity and clinical utility of the practice recommendations from the additional public commentary period were then used to revise the CPG.

**TABLE 2**  
Number of Studies at Each Evidence Level Across Diagnostic Methods

Diagnostic Method	Reliability			Validity			Diagnostic Accuracy			Total Number of Studies
	I	II	III	I	II	III	I	II	III	
Clinical examination	0	2	0	0	0	0	0	0	0	2
Questionnaires	0	2	0	0	3	3	0	4	2	11
Bioelectric impedance analysis	0	4	3	1	5	8	0	6	1	21
Circumferential measures	8	12	3	1	6	7	0	5	1	30
Water displacement	6	8	4	1	1	1	0	1	0	18
Perometry	2	4	0	0	1	5	0	0	0	10
3-Dimensional scanning	0	0	3	0	1	3	0	0	0	5
Tissue dielectric constant	1	2	0	0	2	4	0	0	0	7
Ultrasonography	0	0	2	0	3	2	1	0	0	7
Dual-energy x-ray absorptiometry	1	1	0	1	1	1	0	0	0	4
Magnetic resonance imaging	0	0	0	0	0	1	0	0	1	2
Computed tomography	0	0	0	0	1	0	0	0	1	2
Lymphoscintigraphy	0	2	0	0	0	0	0	0	1	3
Lymphography	0	0	0	0	0	0	0	1	1	2
Tonometry	1	2	0	0	0	0	0	0	0	3

TABLE 3

Evidence Grades Modified From Delitto et al<sup>25</sup> and Kaplan et al<sup>26</sup>

Grade	Recommendation	Criteria
A	Strong	A preponderance of level I studies, but at least 1 level I study directly on the topic supports the recommendation
B	Moderate	A preponderance of level II studies, but at least 1 level II study directly on the topic supports the recommendation
C	Weak	A single level II study at <25% critical appraisal score or a preponderance of level III and IV studies, including consensus statements by content experts, support the recommendation
D	Theoretical/foundational	A preponderance of evidence from animal or cadaver studies, from conceptual/theoretical models/principles, or from basic science/bench research or published expert opinion in peer-reviewed journals supports the recommendation
EO	Expert opinion	Recommended practice based on current clinical practice norms, exceptional situations where validating studies have not or cannot be performed, and there is clear benefit, harm, or cost and/or the clinical experience of the Guideline Development Group

## Recommendations and Summary of Evidence for Individual Diagnostic Methods

On the basis of the evidence, a recommendation was made for each diagnostic method. These recommendations were then used to formulate the overall clinical practice recommendations presented in Table 4. Results are reported for clinical examination and patient-reported symptom assessment, BIA, volume measures, and other diagnostic measures.

## CLINICAL EXAMINATION AND PATIENT-REPORTED SYMPTOM ASSESSMENTS

### Clinical Examination Recommendation

- The clinician may palpate the upper quadrant for fibrosis, pitting, and overall tissue quality. Results from the palpation of the upper limb and trunk have not been investigated for diagnostic utility or accuracy. (Evidence Quality: Level II validity, no reliability or diagnostic accuracy; Recommendation Strength: Expert Opinion)
- Clinical examination, using the Modified Head and Neck External Lymphedema and Fibrosis (HN-ELAF) assessment criteria for patients with head and neck lymphedema, may be incorporated into clinical practice and used in conjunction with circumferential measurement for diagnostic purposes. (Evidence Quality: Level II reliability and validity, no diagnostic accuracy; Recommendation Strength: Expert Opinion)

**Summary of Evidence.** Although stages of secondary lymphedema and tissue fibrosis are often assessed and documented by a clinician, there is no evidence to support a tool to use for clinical examination to diagnose SUQL. One level II study compared clinical staging with lymphoscintigraphy in patients with chronic lymphedema,<sup>27</sup> but the authors did not provide psychometric properties.

In the head and neck region, the HN-ELAF is used to assess and grade the severity of lymphedema, with outcomes ranging from grade 1 (no visible edema) to grade 5 (severe fibrosis). Reliability of the assessment criteria was

83% agreement for lymphedema and severity of fibrosis and 100% agreement within one grade. Deng et al<sup>28</sup> concluded that the HN-ELAF demonstrated significant agreement between testers ( $k = 0.75$ ; concordance correlation coefficient = 0.91). There were no studies to support diagnostic accuracy.

### Patient-Reported Symptom Assessment Recommendation

- Clinically, self-reported signs of swelling, heaviness, and numbness should be investigated to facilitate early diagnosis and should signal clinicians to use other SUQL measures. (Evidence Quality: Level II reliability and validity, Level II diagnostic accuracy; Recommendation Strength: Grade B)
- The following questionnaires should be considered to assist in the diagnosis of SUQL:
  - Norman Questionnaire. (Evidence Quality: Level II reliability and diagnostic accuracy, no validity; Recommendation Strength: Grade B)
  - Morbidity Screening Tool (MST). (Evidence Quality: Level II validity and diagnostic accuracy, no reliability; Recommendation Strength: Grade B)

**Summary of Evidence.** Assessment tools were included in this review only if they were used as a diagnostic method. There are several such assessment tools to guide the clinician in making a diagnosis and accurately staging lymphedema. The assessment tools reviewed require a yes/no response, self-report of symptoms, and/or marking a visual analog scale (VAS).

Hayes et al<sup>29,30</sup> describe a self-report questionnaire measuring a response of “yes or no” to the question: “Since the diagnosis of your breast cancer, have you experienced arm swelling?” A “yes” response may indicate the presence of lymphedema.<sup>29,30</sup> No reliability or validity studies were found. Self-report demonstrated sensitivity (65.1%) and specificity (76.9%).<sup>29</sup> In 2008, Hayes et al<sup>30</sup> reported a sensitivity of 61.3% and a specificity 58.6% when self-report was compared with BIA for early detection.

Asim et al<sup>31</sup> developed a 10-item questionnaire for patients to rate the severity of their symptoms (arm swelling,

heaviness, or tightness). The participants responded by circling on a 4-point scale (1 = no problem; 2 = a little; 3 = quite a bit; and 4 = very much).<sup>31</sup> There was a high sensitivity (97%) and a moderate specificity (55%) for this assessment tool to rate the severity of symptoms, but no reliability or validity studies are available.<sup>31</sup>

Norman et al<sup>32</sup> developed a telephone questionnaire to determine the presence or absence of lymphedema with yes/no responses. For example, “During the past 3 months, did your right and left (hands/lower arm/upper arms) seem to you to be different size from each other?” Although this study reported good interobserver reliability (weighted  $\kappa$  values of 0.83–0.84), no studies of the validity of this tool were identified.<sup>32</sup> It demonstrated a high sensitivity (93%–96%) and a moderate specificity (69%–75%).<sup>32</sup> In 2011, Smoot et al<sup>33</sup> also reported a high sensitivity (87%) and specificity (89%), with an area under the curve (AUC) of 0.88.

Another self-report measure of swelling, the VAS (0–10 cm line) demonstrates good intrarater reliability (interclass correlation coefficient [ICC] = 0.70).<sup>34</sup> The VAS moderately correlates with circumferential measurement using truncated cone ( $r = 0.66$ ), perometry of the affected arm ( $r = 0.65$ ), and BIA interlimb ratio ( $r = 0.71$ ).<sup>34</sup> There were no diagnostic accuracy studies.

The Lymphedema Symptom Intensity and Distress Survey–Arm (LSIDS-A) is a 36-item instrument that assesses arm lymphedema and related symptoms.<sup>35</sup> There is excellent reliability for overall intensity and distress scores of the LSIDS-A (Cronbach  $\alpha$  values = 0.93 and 0.94, respectively), as well as sexuality and mood (Cronbach  $\alpha = 0.90$ ). There was moderate test-retest reliability for function intensity (ICC = 0.69) and distress scores (ICC = 0.75). Of the 36 items, 9 symptoms occurred in more than 50% of the participants with stage 2 lymphedema. Those symptoms were swelling (90.2%), fatigue (75.7%), heavy arm (74.0%), tight arm (66.8%), appearance concerns (59.6%), decrease in physical activity (56.0%), and pain in the arm (51.9%). Convergent validity of the LSIDS-A was acceptable with the following questionnaires: Functional Assessment of Cancer Therapy (FACT)+4 (intensity  $r_s = 0.41$ ,  $r_s = 0.50$ ), Upper Limb-27 physical scores (intensity  $r_s = 0.52$ ; distress  $r_s = 0.45$ ), and Functional Assessment Screening Questionnaire (distress  $r_s = 0.40$ ). No diagnostic accuracy studies were found.

The Lymphedema and Breast Cancer Questionnaire (LBCQ) is a 19-item tool used to screen and assess lymphedema indicators, symptom frequency, and symptom management.<sup>36</sup> Test-retest reliability ( $r = 0.98$ ) of the LBCQ was established in healthy women. Of the 19 items, 3 symptoms were valid with a diagnosis of breast cancer–related lymphedema. They were “heaviness in the past year” (odds ratio = 8.0), “swelling now” (odds ratio = 97.0), and “numbness in the past year” (odds ratio = 1.0). No evidence was found for diagnostic accuracy.

The MST consists of 4 short forms that assess fatigue, upper-limb function, lymphedema, and pain. There was no evidence found for reliability. Validity studies concluded

that the MST poorly agreed with results from perometry ( $k = 0.14$ ) and moderately agreed with results from the LBCQ ( $k = 0.53$ ).<sup>37</sup> In 2014, Bulley et al<sup>38</sup> reported that the MST poorly correlated with results from the FACT-B ( $\rho = 0.27$ ) and moderately correlated with LBCQ ( $\rho = 0.48$ ). The MST demonstrated a low sensitivity (37%) and a moderate specificity (78.1%).<sup>37</sup>

## BIOIMPEDANCE ANALYSIS

### Bioimpedance Analysis Recommendation

- Bioimpedance analysis should be used to detect lymphatic transport impairments and diagnose sub-clinical and early-stage lymphedema in patients at risk for breast cancer–related lymphedema (stages 0 and 1). (Evidence Quality: Level II reliability, validity and diagnostic accuracy; Recommendation Strength: Grade B)
  - L-Dex score of more than 7.1 should be used as a diagnostic criterion for breast cancer–related lymphedema when no preoperative assessment is available. (Evidence Quality: Level II diagnostic accuracy; Recommendation Strength: Grade B)
  - L-Dex score of more than 10 above preoperative baseline measures should be used as a diagnostic criterion. (Evidence Quality: Level II diagnostic accuracy; Recommendation Strength: Grade B)
- In moderate- to late-stage breast cancer–related lymphedema, as fibrosis and tissue changes occur, BIA may be used as a diagnostic tool; however, clinicians must be aware of the potential for decreasing extracellular fluid even with increased tissue volume. (Evidence Quality: Level II diagnostic accuracy; Recommendation Strength: Grade B)

**Summary of Evidence.** Bioimpedance analysis has been used in research in the form of single and multifrequency devices to detect and measure fluid in a limb. When set at a very low frequency, BIA has the ability to measure extracellular fluid. The Imp XCA (ImpediMed Ltd, Brisbane, Queensland, Australia) single-frequency model was approved by the US Food and Drug Administration (FDA) in 2007 for clinical use.<sup>39</sup> In 2008, a multifrequency BIA device, ImpediMed L-Dex U400 BIS (bioimpedance spectroscopy) (ImpediMed Ltd), commonly used in research, was approved by the FDA for clinical use.<sup>40</sup> Additional BIA devices are available, such as the ImpediMed SFB7 (similar to U400), but are used primarily in research settings.

The measurement obtained from the clinical model (ImpediMed L-Dex U400) is expressed as an L-Dex score. The L-Dex score is derived from the ratio of extracellular fluid differences between the affected and unaffected limbs. These measures are compared with previously established baseline measures or normative standards for quantifying lymphedema. Normal L-Dex scores lie between  $-10$  and  $+10$ , which is equivalent to an impedance ratio range of 0.935 to 1.139 for at-risk dominant arms and 0.862 to 1.006 for at-risk nondominant arms, calculated as

3 standard deviations from the mean normative data.<sup>41</sup> Scores outside this range are indicative of lymphedema. According to Fu et al,<sup>41</sup> if no preoperative assessment scores are available, an L-Dex score of more than 7.1 can be considered diagnostic of lymphedema.

The literature includes reports on both research and clinical models of BIA. Bioimpedance analysis demonstrates excellent interrater and intrarater reliability (0.95 and 0.99, respectively) and highly reproducible measures (covariance = 0.2%-0.268%) in research models.<sup>42-44</sup> Newman et al<sup>45</sup> found that BIA has the precision capable of detecting (1.65%-1.86%) the onset of extracellular fluid accumulation indicative of early development of lymphedema. Test-retest reliability using the Imp XCA analyzer, a clinical BIA device, demonstrates strong agreement in the healthy and at-risk groups (ICC = 0.99) but only fair agreement in the group with known breast cancer–related lymphedema (ICC = 0.69).<sup>41</sup> Concurrent validity has been studied using a variety of assessment methods involving both clinical and research models of BIA devices. Moderate to strong correlations have been reported between BIA data and both self-report ( $r = 0.71$ , research model<sup>46</sup>) and perometry results ( $r = 0.71$ - $0.93$ , research model<sup>34,42,43,47</sup>;  $r = 0.40$ - $0.60$ , clinical model<sup>48</sup>). Correlation with circumferential measurement ranged from low (clinical model)<sup>49</sup> to moderate (0.31-0.52, research model,<sup>50</sup> clinical model<sup>41</sup>).

Bioimpedance analysis demonstrates a moderate to high sensitivity and specificity ranging from 0.66 to 1.00 and 0.84 to 0.98, respectively (research models,<sup>33,51-53</sup> clinical models<sup>41,48</sup>). According to a study by Smoot et al,<sup>33</sup> of the physical measures assessed (BIA, circumferential measurement, volume from circumferential measurement), BIA (research model) yielded the highest accuracy with an AUC of 0.88 for women whose dominant arm was the affected arm. Using a clinical model, Fu et al<sup>41</sup> provided evidence that an L-Dex score with a diagnostic cutoff of more than 7.1 provides the best properties for discriminating between at-risk breast cancer survivors and survivors with breast cancer–related lymphedema with a sensitivity of 0.80, a specificity of 0.90, and an AUC of 0.86. Variances in study results were attributed to differences in the BIA device used and stages of lymphedema examined. Bioimpedance analysis may not capture tissue changes such as fibrosis or adipose infiltration that are seen in later-stage lymphedema.<sup>41</sup> Adequate evidence exists to support the use of both research and clinical BIA models; thus, it is recommended that multifrequency or spectroscopy BIA be used in early-stage and at-risk breast cancer survivors. When considering the use of BIA for diagnostic or assessment purposes, the cost of electrodes and equipment should be considered.

## VOLUME MEASURES

There are a number of different options for clinicians conducting a volume assessment—including circumferential measures, water displacement, and perometry—some

of which have established diagnostic criteria. One of the considerations when using volume assessment as a diagnostic criterion is that body size can influence the effect of an absolute volume change (see the “Perometry Recommendation” section).<sup>54</sup> A few authors have also considered limb asymmetry due to arm dominance when classifying volume changes. These types of considerations have been used sparingly to influence diagnostic decisions and have not been tested sufficiently in regard to the diagnosis of upper-extremity lymphedema. It is also important to note that different volume measurement techniques are not equivalent and thus are not interchangeable; therefore, clinicians should use the same method for all assessments of an individual.<sup>55-58</sup>

## Circumferential Measurement Recommendation

- Circumferential measurement should be used to diagnose upper-extremity lymphedema (with or without hand involvement) at stage I or greater. (Evidence Quality: Level I reliability, validity and Level II diagnostic accuracy; Recommendation Strength: Grade B)
  - A volume ratio of 1.04 may be indicative of upper-extremity lymphedema. (Evidence Quality: Level II diagnostic accuracy; Recommendation Strength: Grade B)
  - Calculated volume differential between sides ( $\geq 200$  mL) will help rule in lymphedema, but values below 200 mL cannot be used to rule out. (Evidence Quality: Level II diagnostic accuracy; Recommendation Strength: Grade B)
  - If preoperative measures are available, a 5% or greater volume change from baseline above and below the elbow is diagnostic of upper-extremity lymphedema. (Evidence Quality: Level II diagnostic accuracy; Recommendation Strength: Grade B)
  - Circumferential measurement taken at any single site along the upper extremity, and specifically a difference of 2 cm or more, should not be used as a diagnostic criterion for upper-extremity lymphedema due to poor accuracy. (Evidence Quality: Level II diagnostic accuracy; Recommendation Strength: Grade B)
- For hand lymphedema, “figure-of-eight” method of circumferential measurement may be used as an assessment tool for determining hand volume; however, this method has not been studied as a diagnostic test. (Evidence Quality: Level I reliability and validity no diagnostic accuracy; Recommendation Strength: Expert Opinion)
- For head and neck lymphedema, circumferential measurement taken at a single point of the upper neck (under the jawline) may be useful for assessment but has not been studied as a diagnostic test. (Evidence Quality: Level I reliability, Level II validity; no diagnostic accuracy; Recommendation Strength: Expert Opinion)

**Summary of Evidence.** Circumferential measurement using a standard tape measure is a simple and easy method for obtaining the girth of a limb, which is then used to calculate limb volume.

Reliability for limb volumes calculated from circumferential measurement demonstrates excellent interrater and intrarater reliability (ICC = 0.93-0.99) for the arm with and without the hand measurements.<sup>55,59-64</sup> Furthermore, utilization of the single or summed frustum cone for calculating arm volumes demonstrates excellent intrarater (ICC = 0.96-0.99) and interrater reliability (ICC = 0.94-0.99).<sup>55</sup> The more widely accepted truncated frustum cone formula assumes that the arm resembles a cone shape, rather than a cylinder, which may be a truer representation of a lymphedematous limb.<sup>63,65</sup> Using either method can result in an overestimation of the actual limb volume. The literature suggests that the cylindrical formula may overestimate the limb volume up to 5% and the single or summed truncated cone formula by at least 100 mL.<sup>65-67</sup> There is level I evidence of good intertester (ICC = 0.84) and excellent intratester reliability (ICC = 0.89-0.92) using the “figure-of-eight” circumferential measurement for hand swelling due to breast cancer-related lymphedema.<sup>68</sup> There is level I evidence regarding the reliability of circumferential measurement in patients with head and neck cancer-related lymphedema, specifically where excellent interrater reliability was demonstrated at 3 points: ear to ear (ICC = 0.94); upper neck (ICC = 0.97); and lower neck (ICC = 0.98).<sup>69</sup>

Volumes calculated from circumferential measurement have been found to be highly correlated with water displacement of the arm ( $r = 0.93-0.98$ ), suggesting validity for this method of determining limb volume.<sup>56-58,66</sup> Although narrow (8 mm) and wide (15 mm) tape measures were highly correlated with water displacement (Pearson’s correlation coefficient = 0.92 and 0.88, respectively), Tewari et al<sup>70</sup> suggested that the use of a narrow tape measure yields more accurate estimations of volume. Furthermore, circumferential measurement at either 4 specific points or every 10 cm along the arm is highly correlated with water displacement ( $r = 0.88-0.95$ ).<sup>71</sup> Use of 4 specific points, as is commonly used for garment measuring, may save the clinician time during the examination. Circumferential measurements taken by physical therapists are highly correlated with patient measurements ( $r = 0.70-0.81$ ).<sup>64</sup>

A strong correlation ( $r = 0.70-0.75$ ) exists between “figure-of-eight” for hand lymphedema and water displacement.<sup>68</sup> There is level III evidence to support using circumferential measurement at the upper neck point (under the jaw line) to detect lymphedema in patients with head and neck cancer when compared with healthy controls ( $t = 2.22, P = .39$ ).<sup>69</sup> In addition, 3 of the tape measurements for patients with head and neck (ear to ear; circumferential measurement of upper neck and lower neck) correlated with MoistureMeterD (MMD) readings of extracellular fluid ( $r_s = 0.37-0.38$ ).<sup>69</sup>

Historically, a diagnosis of lymphedema has been established with circumferential measurement using a variety of cut points, including an absolute volume difference of between 75 and 200 mL or interlimb volume differences of between 3% and 10%. Smoot et al<sup>33</sup> reported that a diagnostic cutoff for a difference of 200 mL or more between the affected and unaffected limbs demonstrated a high specificity (1.00) but a low sensitivity (0.39), with an AUC of 0.69. In addition, Smoot et al<sup>33</sup> found that the volume ratio of 1.04 had the highest accuracy (sensitivity = 0.67, specificity = 0.89, AUC = 0.78) for identifying existing cases of upper-extremity lymphedema in a sample of 144 women with and without lymphedema after breast cancer treatment. The ratio was calculated from the circumference volume of affected/unaffected upper extremity. For example, a volume of 2000 mL in the affected upper extremity compared with 1915 mL in the unaffected upper extremity would be a ratio of 1.044.<sup>33</sup> A recent systematic review of upper- and lower-extremity lymphedema assessment pooled data from multiple studies and found a standard error of measurement (SEM) for circumferential measurement of 2.8% and a smallest detectable change (SDC) of 6.6%.<sup>72</sup> Thus, the 1.04 ratio, indicating a 4% difference between limbs, is above the SEM but is below the SDC and yet is within the calculated variance. A high AUC (0.76) using the 75-mL interlimb volume difference suggested good accuracy for detecting lymphedema (sensitivity = 0.67, specificity = 0.85); however, because this value is still below the SEM, use of this threshold may misdiagnose a number of individuals.<sup>33</sup>

In 2003, Bland et al<sup>73</sup> concluded that preoperative baseline measures above and below the elbow may provide better diagnostic accuracy if using a 5% volume change from the preoperative measurement (sensitivity = 0.80, specificity = 0.71). In 2005 and 2008, Hayes et al<sup>29,30</sup> investigated using the sum of area of circumference as a diagnostic criterion for upper-extremity lymphedema and determined that this method is inferior to other diagnostic criteria. Thus, the debate over the most appropriate cut point for diagnosis continues. Currently, the best sensitivity and specificity, while being above the SEM, come from using either the volume difference of 200 mL or more or the 1.04 ratio of affected:unaffected limb.

If used to calculate limb volumes or at the upper neck point in patients following treatment of head and neck cancer, circumferential measurements can be useful diagnostic aids for patients with known lymphatic insults related to cancer and its treatment. Clinicians must take the time to calculate volumes from limb measurements and should understand that using a criterion of more than 200 mL volume differential between limbs may incorrectly classify milder cases of lymphedema (eg, 150-mL interlimb difference) as not having lymphedema. Likewise, some of the criteria that are more sensitive, such as the 1.04 ratio or the 5% volume increase, may still misclassify some individuals when used as a sole diagnostic criterion. A 5% volume change in a limb may better detect lymphedema



and is closer to the SDC of the measure, but it requires preoperative measurement for comparison purposes.

### Water Displacement Recommendation

Water displacement may be used to diagnose lymphedema with volumetry of more than 200 mL when compared with the contralateral arm and with volumes of more than 10% interlimb difference. This technique is limited by clinical utility. (Evidence Quality: Level I reliability and validity; Level II diagnostic accuracy; Recommendation Strength: Grade B)

**Summary of the Evidence.** There are numerous methods for performing water displacement as an indirect measure for lymph volume. Although there are variations in methodology among multiple articles with a high level of evidence, water displacement demonstrates excellent interrater and intrarater reliability (ICC = 0.97-0.99).<sup>55-59,61,63,64,74-81</sup>

Because of its excellent reliability, water displacement is considered the reference standard in much of the validity and diagnostic accuracy research.<sup>56-58,63,71,79,82</sup> Water displacement is highly correlated ( $r = 0.81-0.91$ ) with circumferential measurement for the hand and the upper limb.<sup>78,80</sup> When compared with magnetic resonance imaging (MRI) and computed tomographic (CT) scans, simplified water displacement demonstrated good construct ( $k$  coefficient = 0.78) and concurrent validity ( $R = 0.87-0.90$ ).<sup>83</sup>

There is little evidence on the diagnostic accuracy of water displacement. Godoy et al<sup>84</sup> combined water displacement with circumferential measurement for diagnosing lymphedema. The authors reported the highest accuracy (77.8%) and sensitivity (90.0%) and the greatest negative predictive value (93.5%) with measurements of volumetry at more than 200 mL when compared with the contralateral arm. The highest specificity (78.3%) was reflected with volumes of more than 10% interlimb difference. Chen et al<sup>61</sup> reported a minimally detectable change as more than 150 mL when using water displacement clinically.

Many authors reported concerns with the use of water displacement due to time constraints and the costs involved with setup and administration of the methods.<sup>58,59,82</sup> Because of concerns for cross-contamination in individuals with skin breakdown and open wounds, water displacement is contraindicated in this patient population.<sup>70</sup> Although water displacement includes measurement of the hand, it does not allow for complete immersion of the upper arm. It is important for clinicians to standardize the distance of the limb when placing it in the volumeter. Despite water displacement's excellent reliability and validity, it should not be used interchangeably with other clinical measure methods.<sup>55-58</sup>

### Perometry Recommendation

Perometry may be used for assessment of volume but not as a diagnostic tool for upper-extremity lymphedema.

This technique is limited in clinical utility. (Evidence Quality: Level I reliability, Level II validity, no diagnostic accuracy; Recommendation Strength: Expert Opinion)

**Summary of the Evidence.** A perometer is an optical-electrical imaging device for measuring indirect limb volume. The arm volume is then calculated, summing the volumes of elliptical segments every centimeter for 40 cm using computer software. Ancukiewicz et al<sup>85</sup> reported that obtaining 2 measurements of each arm at each time point would reduce error in the volume ratios. There is excellent interrater and intrarater reliability with the static (ICC = 0.99)<sup>55</sup> or mobile perometer (ICC = 0.98-0.99).<sup>86</sup>

Perometry demonstrated a strong correlation with hand water volumetry ( $r_c = 0.88$ ),<sup>82</sup> circumferential measurement, lymphometry, and BIA measures ( $r > 0.70$ ).<sup>87</sup> In addition, when used on healthy women, perometry strongly correlated with circumferential measurement using truncated cone ( $r = 0.86-0.98$ ) and cylinder ( $r = 0.85-0.98$ ) formulas.<sup>88</sup> Lee et al<sup>82</sup> reported that the use of perometry resulted in overestimated volume if participants did not hold their fingers together during testing.

There are no specific diagnostic accuracy studies, but several discrepancies in the literature exist when attempting to use perometry as a diagnostic method. Breast cancer-related lymphedema is defined as an absolute volume change that may vary with body size and shape.<sup>89</sup> In 2010, using perometry, Czerniec et al<sup>46</sup> defined breast cancer-related lymphedema as a 200-mL or 10% limb volume difference. Ancukiewicz et al<sup>85</sup> reported that a relative volume change between the affected and unaffected arms expressed as a percentage is more reliable in quantifying lymphedema. In 2012, Ancukiewicz et al<sup>54</sup> reported that an absolute change in arm volume (200 mL) correlated to a relative arm volume change that varied between 2.9% and 15.7% on the basis of body size. Dylke et al<sup>88</sup> determined that, in women older than 40 years, an interlimb difference of more than 380 mL is required for the diagnosis of lymphedema if the dominant arm is affected. If the clinical cutoff of 200 mL was used as previously described in the literature, 8% of their study subjects would be incorrectly diagnosed as having lymphedema. This highlights the need to consider underlying dominant versus nondominant arm asymmetry and thus reinforces the importance of baseline measurements. Stout et al<sup>13</sup> defined breast cancer-related lymphedema as an increase of more than 3% limb volume as compared with a preoperative volume measurement (coefficient of determination  $r^2 = 0.95$ ).<sup>90</sup>

Clinical utility issues include equipment expense, bulkiness, and current lack of availability of the perometer through US distributors. Perometers can be used to measure volume in an efficient manner, but their diagnostic properties do not outperform other forms of volume measurement.

### Three-Dimensional Camera Imaging Recommendation

Although 3-dimensional (3D) camera imaging may not be used as a diagnostic tool, it can be used to calculate

volume measurements, as it has not been studied for diagnostic purposes. (Evidence Quality: Level III reliability, Level II validity and no diagnostic accuracy; Recommendation Strength: Expert Opinion)

**Summary of Evidence.** A new imaging technique, using 3D imaging cameras, calculates volume measurements using different methods (6 digital single-lens reflex cameras,<sup>81</sup> positional laser and 3 cameras,<sup>91</sup> and Microsoft Kinect infrared sensor) to develop a 3D model.<sup>92</sup>

There is excellent interrater and intrarater reliability (ICC = 0.99).<sup>81</sup> Correlations have been established for 3D imaging with water displacement ( $r = 0.98$ ).<sup>81</sup> Validity was established using water displacement as well as laser ( $r^2 = 0.04$ ); however, 3D imaging tends to overestimate volume.<sup>91</sup> The Kinetic system is highly correlated with water displacement ( $r = 0.98$ ), but there was only 1 individual with lymphedema in the sample population.<sup>93</sup> The Kinetic system could potentially be an inexpensive method for self-monitoring the upper limb, but further testing is needed in people without an established diagnosis of lymphedema, as there were no diagnostic accuracy studies.

## OTHER DIAGNOSTIC MEASURES

### Tissue Dielectric Constant Recommendation

Tissue dielectric constant (TDC) may not be used as a diagnostic tool for SUQL but can be used for assessment. This technique is limited in clinical utility. (Evidence Quality: no diagnostic accuracy studies; Recommendation Strength: Expert Opinion)

- Breast cancer. (Evidence Quality: Level III reliability, Level II validity)
- Head and neck cancer. (Evidence Quality: Level I reliability, Level III validity)

**Summary of Evidence.** Tissue dielectric constant assesses changes in tissue water and skin thickness in patients at risk for moderate stages of lymphedema.<sup>94,95</sup> In research, an MMD (Delfin Ltd, Kuopio, Finland) uses an ultrahigh-frequency electromagnetic wave to measure the water content in the tissue.<sup>69</sup> Higher values indicate increased levels of swelling.<sup>69</sup> Mayrovitz et al<sup>95</sup> found TDC normative values at the forearm for men to be  $33.2 \pm 4.0$  and women to be  $29.4 \pm 2.7$ .

A study reported that bilateral TDC forearm measurement at 2.5-mm depth had excellent intrarater reliability (ICC >0.99).<sup>94</sup> In a population of patients with head and neck cancer, Purcell et al<sup>69</sup> reported excellent interrater and intrarater reliability (ICC = 0.97). Validity was established in patients with head and neck cancer using the 2.5-cm probe of the MMD on the skin 8 cm below the edge of the lower lip, and there was moderate correlation with the MD Anderson Head and Neck Lymphedema Rating Scale<sup>96</sup> ( $r_s = 0.59$ ).<sup>69</sup> Strong correlations were found between arm TDC ratios and arm volume ( $r = 0.69$ ) as well as segmental volume measures ( $r = 0.77$ ). Mayrovitz et al<sup>94</sup> demonstrated a significant relationship between interarm TDC ratios and the number of nodes removed ( $r = 0.55$ ),

as well as patients who reported more than 1 symptom of swelling ( $r = 0.57$ ). Using the TDC, a greater number of patients with breast cancer were detected to have interarm increases exceeding 10% that were not detected using BIA ratios, which may indicate a greater sensitivity to localized tissue water changes.<sup>94</sup> There is no evidence on diagnostic accuracy at this time.

Measurement takes approximately 10 seconds at multiple sites and measures locally, so clinically this is an efficient technique; however, currently, it has limited availability.<sup>69</sup> The multiprobe MMD has FDA approval, but the integrated-probe MMD Compact is only being sold under the status of experimental use.

### Ultrasound Recommendation

Ultrasound should be used to detect SUQL and to identify tissue changes. (Evidence Quality: Level III reliability [healthy subjects], Level II validity, Level I diagnostic accuracy; Recommendation Strength: Grade B)

**Summary of Evidence.** High-frequency ultrasound (HFUS) uses a noninvasive probe to scan the dermis and subcutis composition to evaluate edema and tissue quality.<sup>97-102</sup> Cutaneous epifascial and subfascial tissue thickness, as well as fibrosis and fluid collection, can be examined in real time. Normal breast skin thickness measurements using HFUS are between 1- and 2-mm thick (mean = 1.7 mm).<sup>103</sup> Impaired lymphatic drainage affects the echogenicity of tissue as demonstrated by the change in ultrasound images. A benefit of ultrasound is the ability to measure changes in both the extremity and the chest wall in patients following breast cancer treatment. Use of a 7.5-MHz probe demonstrated excellent intrarater and interrater reliability for the forearm (ICC = 0.82 and 0.81, respectively) and the upper arm (ICC = 0.90 and 0.72, respectively).<sup>97,99</sup> Hwang et al<sup>98</sup> reported excellent intrarater ( $r = 0.98$ ) and interrater reliability ( $r = 0.96$ ). Ultrasonography reliability has been completed only in healthy participants and not yet in the population of interest.

Validity studies of ultrasound elastography on breast tissue after radiation therapy demonstrated an increase in subcutis thickness as expected.<sup>101</sup> An early study by Mellor et al<sup>100</sup> found high correlations between ultrasound-measured skin thickness and arm circumference ( $r = 0.95$ ). Another study found high correlations between ultrasound and perometry ( $r = 0.76-0.79$ ) as well as arm circumference ( $r = 0.68-0.80$ ).<sup>98</sup> Choi et al<sup>97</sup> found mixed results when comparing ultrasound-measured skin thickness with arm circumferential measurement (forearm:  $r = 0.756$ ,  $P = .001$ ; upper arm:  $r = 0.54$ ,  $P = .003$ ) and BIA impedance ratios (forearm:  $r = 0.56$ ,  $P = .002$ ; upper arm:  $r = 0.50$ ,  $P = .006$ ). Measures taken at the forearm yielded the highest associations.<sup>97</sup> Although the classification criterion was vague, Balzarini et al<sup>104</sup> compared ultrasonography with clinical signs of edema and found that in patients with palpable soft edema, 68.4% had fluid accumulation, 64.2% had both fibrosis and medium

fluid accumulation, and 76.9% had firm edema with diffuse fibrosclerosis without fluid accumulation. Another study found no significant correlations between ultrasound elastography, HFUS, and patient report.<sup>101</sup> Thus, validity of ultrasound is mixed, potentially due to study design and the use of participants with and without SUQL.

Diagnostic accuracy of ultrasound, when compared with circumferential measurement, had a moderate sensitivity at the triceps (67%) but a low sensitivity at the wrist and lower forearm (40% and 33%, respectively). The specificity at these locations ranged from moderate to high (67%, 93%, and 93%, respectively).<sup>105</sup>

Ultrasonography allows the clinician to assess the soft tissue in real time, with the potential ability to measure different body regions, but the evidence base for the chest wall and other areas is extremely limited. Cost of the unit is less than that of many other diagnostic imaging modalities, but the gel and gel pad need to be factored into the unit's use. In addition, physical therapists require training in use of ultrasound imaging for diagnostic purposes, as this is not a standard component for most physical therapist professional education programs.

### Dual-Energy X-Ray Absorptiometry Recommendation

Dual-energy x-ray absorptiometry (DXA) may not be used as a diagnostic tool for SUQL but can be used for assessment to calculate arm volumes. (Evidence Quality: Level I reliability, Level II validity; no diagnostic accuracy; Recommendation Strength: Expert Opinion)

**Summary of Evidence.** Volumes are calculated using DXA from 2 different sources. Newman et al<sup>45</sup> measured the affected and nonaffected arms of patients with breast cancer-related lymphedema and noted a significant difference in fat and lean mass (increase in both by 15%,  $P < .0001$ ) but only a 0.6% change in bone mass. The interrater reliability of DXA to measure arm volumes was excellent (ICC = 0.99).<sup>63</sup> There are strong correlations both to perometry ( $r_p = 0.99$ ) in a healthy population<sup>106</sup> and to water displacement ( $r = 0.996$ ) in participants with breast cancer-related lymphedema.<sup>107</sup> There were no diagnostic accuracy studies.

Dual-energy x-ray absorptiometry is easy and quick to perform, even in patients who are medically compromised, are elderly, or have skin disorders, but it does require referral for conduction of the test and interpretation.<sup>63</sup> Several disadvantages of DXA include exposure to radiation, cost of the DXA lunar prodigy (research grade) scanner, and lack of portability.

### Magnetic Resonance Imaging Recommendation

Magnetic resonance imaging may be used as a diagnostic tool of SUQL. (Evidence Quality: no reliability, Level III validity and diagnostic accuracy; Recommendation Strength: Grade C)

**Summary of Evidence.** With imaging, the presence of edema is determined if partial or complete fluid retention

is observed in subcutaneous tissue. No reliability studies were found for MRI. Validity was demonstrated for a chemical exchange saturation transfer MRI using amide proton transfer (APT). Patients with breast cancer-related lymphedema demonstrated an increase in APT contrast in the affected arms when compared with healthy controls ( $P = .025$ ; Cohen  $d = 0.24$ ).<sup>108</sup> Mihara et al<sup>109</sup> reported a high sensitivity and specificity (100%) using T2-weighted or short-time inversion recovery sequence MRI in participants with ISL stage I lymphedema. Disadvantages of using MRI include the high associated cost, need for referral for conduct of the test, and the extended time before diagnosis can be achieved, as images need to be read by a radiologist.<sup>110</sup> Current literature shows the use of different forms of MRI, and all forms require more study before a recommendation can be made for use. Magnetic resonance imaging uses a strong magnet; therefore, there are some strong precautions for MRI use in patients with pacemakers or cochlear implants; patients with metal implants are unable to be imaged.

### Computed Tomography Recommendation

Computed tomography may be used as a diagnostic tool for SUQL. (Evidence Quality: no reliability, Level II validity, Level III diagnostic accuracy; Recommendation Strength: Grade C)

**Summary of Evidence.** Computed tomography uses special x-ray equipment to create a series of detailed body images. Each image demonstrates a thin "slice" (0.5 mm) of tissue. A fibrous component in the subcutaneous fat layer is diagnostic for lymphedema.<sup>109</sup> Secondary changes are observed on CT in the subcutaneous tissue, skin, and overgrowth of fibrous tissue as lymphedema progresses.<sup>109</sup> Evidence for reliability and validity of CT for lymphedema diagnosis is lacking. Brorson et al<sup>111</sup> reported that CT-computed arm volume was highly correlated with water displacement ( $r = 0.996$ ), but this was in a small sample of subjects about to undergo liposuction surgery after failed conservative management. Diagnostic accuracy of CT scans demonstrates a low sensitivity (33%) and a high specificity (100%).<sup>109</sup> The high cost of equipment and need for referral for conduct of the test and radiologist interpretation make this a more expensive diagnostic option. In addition, CT exposes the patient to radiation.

### Lymphoscintigraphy Recommendation

Lymphoscintigraphy may be used to detect lymphatic system impairment. (Evidence Quality: Level II reliability, no validity, Level III diagnostic accuracy; Recommendation Strength: Grade C)

**Summary of Evidence.** Lymphoscintigraphy uses a low-energy, high-resolution, dual-head collimator-equipped GE Millennium VG (scinticamera) (GE Medical Systems-Americas, Milwaukee, Wisconsin) to produce images of lymphatic flow to observe anatomic and transport capacity abnormalities. As such, it has the potential to determine lymphatic system impairment. A radioisotope

is injected between the second and third digits before taking images of the upper extremity. Dermal backflow of the radioisotope is observed and graded to diagnose lymphedema.<sup>109,112</sup> Reliability of lymphoscintigraphy image readings, using a previous method to determine dermal backflow, demonstrated adequate interobserver agreement (Fleiss  $k = 0.42$ ) and poor (Cohen  $k = 0.06$ ) to excellent intraobserver reliability (Cohen  $k = 1.0$ ).<sup>112</sup> Reproducibility was excellent (ICC = 0.75-0.85) for change of axillary uptake and change of extraction from hands.<sup>105</sup> No validity studies were found in this patient population. The diagnostic accuracy of lymphoscintigraphy has a moderate sensitivity (0.62) and a high specificity (1.0) when compared with the unaffected limb.<sup>109</sup> Clinical utility challenges include associated costs, need for referral to another medical specialist, current low resolution, invasive nature of testing, and radiation exposure.

### Lymphography Recommendation

Lymphography may be used to detect lymphatic system impairment. (Evidence Quality: no reliability or validity, Level II diagnostic accuracy; Recommendation Strength: Grade C)

**Summary of Evidence.** Lymphography is a real-time imaging technique where indocyanine green (ICG) dye is injected in the interdigit web space, illuminating the superficial lymphatic flow, and is considered to be safer than the isotope used in lymphoscintigraphy because it is water soluble and attaches to albumin. Currently, ICG is used to detect sentinel lymph nodes in breast cancer. The light emitted by the injected dye traveling in the lymphatic vessels is imaged using a specialized camera system. Normal lymphatic flow is linear, and abnormalities in lymphatic flow result in a splash, stardust, or diffuse pattern.<sup>113</sup>

There are no reliability or validity studies in an at-risk population. Diagnostic accuracy in patients with known lymphedema demonstrated a sensitivity of 1.0 and a specificity of 1.0 when compared with CT and MRI.<sup>109</sup> In 2013, Akita et al<sup>113</sup> reported a high sensitivity (0.97), a moderate specificity (0.55), a positive likelihood ratio of 2.15 and a negative likelihood ratio 0.05, and an accuracy of 0.82 when comparing lymphography with lymphoscintigraphy. This measure needs further testing using subjects without an established diagnosis of lymphedema. Compared with lymphoscintigraphy, ICG lymphography has the advantages of reduced costs and a less invasive nature,<sup>113</sup> but it requires additional time and referral for specialized testing.

### Tonometry Recommendation

Tonometry is not recommended to diagnose SUQL. (Evidence Quality: Level I reliability, no validity or diagnostic accuracy; Recommendation Strength: Expert Opinion)

**Summary of the Evidence.** Tonometry measures the presence of fibrosis with an increased volume of interstitial fluid. Clinicians consider the amount of tissue fibrosis as influencing choice of interventions and a prognostic indi-

cator for a potential number of visits. Presently, clinicians rely on palpation for tissue resistance to determine the degree of fibrosis. The tonometer measures fibrotic changes in tissue when placed perpendicular to the skin.

The inter/intrarater reliability was fair to good (ICC = 0.66-0.87) with an SEM of 4.3% to 17.8%.<sup>61</sup> When measuring breast tissue resistance, a low covariance (1.29%-3.25%) was determined, suggesting consistency and good reproducibility between subjects.<sup>114</sup> In another study, significant differences between testers were found.<sup>115</sup> Therefore, to reduce measurement error, it is recommended that the same tester conduct baseline and follow-up assessments and that 3 measurements be taken at each time point. There were no validity and diagnostic accuracy studies.

### SUMMARY OF RECOMMENDATIONS

At present, SUQL is most often diagnosed by clinical history, physical examination of tissue quality, and a measurement of increased limb volume. Subclinical or early-stage lymphedema may not display a sufficient or persistent volume change to meet this diagnostic criterion. Research indicates the importance of early detection of SUQL to minimize body function and structure impairments that may progress to functional limitations and activity and participation restrictions.<sup>13,14</sup> For patients at risk for SUQL, symptoms of swelling, heaviness, and numbness should be identified during the history, as it may assist in identifying those with subclinical or early-stage lymphedema. The Norman Questionnaire and the MST should be considered to determine the presence or absence of lymphedema in conjunction with volume measures. For all patients, the physical examination should consist of observation, palpation, and other measurements. For subclinical/early-stage lymphedema, BIA should be used to assist in the diagnosis of SUQL. A volume measure should also be taken but may not be consistently increased at this point. In the moderate and late stages, circumferential measurement should be used, and water displacement may be used in some cases, for the diagnosis of upper-extremity lymphedema (see practice recommendations in Table 4 for cut points). Perometry may be used for upper-extremity volume assessment in the early, moderate, and late stages; however, diagnostic criteria have not been fully evaluated. In late stage, ultrasonography should be used to detect underlying tissue changes, which may be helpful for clinicians to determine appropriate management. *Clinicians need to be aware that none of the diagnostic criteria are perfect in their diagnostic accuracy, and especially patients whose measurement values fall just under or over a cut point have the potential to be misclassified. Thus, we encourage clinicians to cluster findings from their examination to draw a conclusion on diagnosis.*

There are emerging diagnostic methods that detect tissue quality, visualize edema, or evaluate structural lymphatic transport capacity. These methods include 3D camera, TDC, DXA, MRI, CT, lymphoscintigraphy,

**TABLE 4**

Practice Recommendations Based on Patient Presentation

Patient Presentation	Practice Recommendations
All patients at risk for secondary upper-quadrant lymphedema	<p>Self-reported symptoms of swelling, heaviness, and numbness should be investigated for early diagnosis. (Grade B)</p> <p>Palpation for fibrosis, pitting, and overall tissue quality may be clinically helpful for staging; however, it has not been investigated for diagnostic purposes. (Expert Opinion)</p> <p>If a questionnaire is used to assist with diagnosis, the Norman Questionnaire or Morbidity Screening Tool should be considered. (Grade B)</p>
At-risk/early-stage upper-extremity lymphedema (ILS stages 0-1)	<p><i>Bioimpedance analysis:</i></p> <p>BIA should be used to detect subclinical/early-stage lymphedema. (Grade B)</p> <p>Cut point of &gt;7.1 L-Dex score should be used for the diagnosis of breast cancer–related lymphedema when preoperative baseline measures are not available. (Grade B)</p> <p>Cut point of &gt;10 L-Dex score above preoperative baseline should be used for the diagnosis of breast cancer–related lymphedema. (Grade B)</p> <p>Preoperative assessment using BIA may enhance the ability to detect changes in tissue fluid earlier indicating lymphedema. (Grade B)</p> <p><i>Volume measures:</i></p> <p>Volume determined from circumferential measurements should be used to diagnose lymphedema (Grade B) but may not capture subclinical and early-stage lymphatic transport impairment. (Expert Opinion)</p> <p>When using circumferential measurements, volume should be calculated. (Grade B)</p> <p>Calculated volume differential between sides <math>\geq 200</math> mL, or a volume ratio of &gt;1.04 (affected:unaffected), will help rule in lymphedema, but values &lt;200 mL cannot be used to rule out. (Grade B)</p> <p>Water displacement may be used in diagnosing lymphedema but is limited by clinical utility. (Grade B)</p> <p>Volume can also be assessed by perometry, but diagnostic criteria need to be evaluated for this method. (Expert Opinion)</p> <p>Methods of volume measurement are not interchangeable; use the same method at each time point. (Grade A)</p>
Moderate- or established upper-extremity lymphedema (ILS stage II)	<p><i>Bioimpedance analysis:</i></p> <p>BIA is less useful in diagnosing lymphedema at this stage, and self-reported symptoms or volume measures should be used. (Grade B)</p> <p>Accuracy with BIA in diagnosing moderate- to late-stage lymphedema may decline due to tissue changes/fibrosis. (Expert Opinion)</p> <p><i>Volume measures:</i></p> <p>Volume measurements should be taken and used in the diagnosis of lymphedema. (Grade B)</p> <p>When using circumferential measurements, volume should be calculated. (Grade B)</p> <p>Calculated volume differential between sides of <math>\geq 200</math> mL, or a volume ratio of &gt;1.04 (affected:unaffected), will help rule in lymphedema, but values &lt;200 mL cannot be used to rule out. (Grade B)</p> <p>Water displacement may be used in diagnosing lymphedema but is limited by clinical utility. (Grade B)</p> <p>Volume can also be assessed by perometry, but diagnostic criteria need to be evaluated for this method. (Expert Opinion)</p> <p>Methods of volume measurement are not interchangeable; use the same method at each time point. (Grade A)</p>
Late-stage upper-extremity lymphedema (ILS stage III)	<p>As tissue changes progress, excess fluid may decrease, but excess volume may remain because of fibrosis, increased fat deposition, and other skin changes. (Grade B)</p> <p><i>Volume measures:</i></p> <p>Volume measurements should be taken and used in the diagnosis of lymphedema. (Grade B)</p> <p>When using circumferential measurements, volume should be calculated. (Grade B)</p> <p>Calculated volume differential between sides of <math>\geq 200</math> mL, or a volume ratio of &gt;1.04 (affected:unaffected), will help rule in lymphedema, but values &lt;200 mL cannot be used to rule out. (Grade B)</p> <p>Water displacement may be used in diagnosing lymphedema but has limited clinical utility. (Grade B)</p> <p>Volume can also be assessed by perometry, but diagnostic criteria need to be evaluated for this method. (Expert Opinion)</p> <p>Methods of volume measurement are not interchangeable; use the same method at each time point. (Grade A)</p> <p><i>Ultrasonography:</i></p> <p>Ultrasonography should be used to detect underlying tissue changes. (Grade B)</p>

(continues)

TABLE 4

Practice Recommendations Based on Patient Presentation (*Continued*)

Patient Presentation	Practice Recommendations
Hand lymphedema	Little research is available to guide the diagnosis of hand lymphedema. Water displacement and “figure-of-eight” method of circumferential measurement may be used for assessment but have not been studied as diagnostic tests. (Expert Opinion)
Trunk or breast lymphedema	Little research is available to guide the diagnosis of truncal or breast lymphedema. Ultrasonography has the potential to determine tissue changes consistent with different stages of lymphedema. (Expert Opinion) Tissue dielectric constant is an emerging diagnostic tool that may be useful in assisting with assessment of lymphedema. (Grade C)
Head and neck lymphedema	Modified Head and Neck External Lymphedema and Fibrosis assessment criteria when combined with circumferential measurements may be useful for diagnostic purposes. (Expert Opinion) Circumferential measurements at the upper neck point may be used in assessment. (Expert Opinion) Tissue dielectric constant is an emerging diagnostic tool that may be useful in assessing lymphedema. (Expert Opinion) Recommend a combined approach involving both the Modified Head and Neck External Lymphedema and Fibrosis assessment and either circumferential measures or tissue dielectric constant. (Expert Opinion)

Abbreviations: BIA, bioimpedance analysis; ILS, International Society of Lymphology.

lymphography, and tonometry. Because of lack of evidence, high costs, or the invasive nature for some of these tests, these methods are not recommended to be incorporated into general clinical practice for diagnosing SUQL at this time. Lymphatic system imaging, including lymphoscintigraphy and lymphography, can be useful in determining the full extent of lymphatic system impairment, and the results may assist the clinician when traditional interventions are not successful. Another emerging area is the diagnosis and assessment of lymphedema in patients treated for head and neck cancer. A combined approach of HN-ELAF, circumferential measurement at the upper neck point, and TDC may be useful for diagnostic purposes. Little research is currently available to guide the diagnosis of hand, trunk, and breast lymphedema.

Overall, on the basis of the evidence in this CPG, there is no one diagnostic tool that can be used definitively to diagnose SUQL, but using these recommendations can facilitate early identification and should lead to an examination of activity and participation restrictions and appropriate interventions. A number of measures of activity and participation restriction and quality of life have been developed but are beyond the scope of this review. Davies et al<sup>116</sup> provide a review of such measurement tools.

Measures of the effect of lymphedema add important information and should be included in overall patient assessment. To further support clinical practice in this area, The Oncology Section of APTA plans to create guidelines on risk factor identification and appropriate intervention for SUQL in the near future.

## LIMITATIONS

There were several limitations in the development of this CPG. The literature was searched from January 1, 2000, through July 5, 2015; therefore, evidence from inception and newer articles may have been missed. For example, a recent systematic review of lymphedema measures<sup>72</sup> was not included because of this limitation. Thus, it is

important that clinicians also keep abreast of more recent additions to the literature. The Oncology Section plans to update this CPG every 5 years, adding the most recent literature to the development of our recommendations. In addition, articles not in the English language were excluded from this study. Of the articles retrieved from this growing body of literature, there was a lack of high-quality evidence.

It is also important to note that more research may have been published on certain diagnostic methods than on others, not because the well-published methods are superior to other measures but because they have been used over a long period of time.

There is no single quality rating tool for all psychometric properties of diagnostic measures; therefore, multiple tools were used to review the quality of the evidence. The lack of standardization and the variations in diagnostic criteria, as well as the limited study of certain measures in a variety of cancer populations representing all stages of SUQL, may confound the findings.

Finally, this CPG was created by physical therapists, was not piloted in clinical practice, and did not include perspectives from patients or other medical and rehabilitation professionals in its inception and conduct. The authors addressed this limitation by inviting feedback from a wider audience of other physical therapists, physicians, nurses, and occupational therapists.

## IMPLEMENTATION

As part of the dissemination and implementation of the CPG, the Guideline Development Group shared the preliminary findings at the Combined Section Meeting of APTA in 2016. We also solicited feedback on the CPG from multiple stakeholders, which in itself acts as a form of dissemination. In addition, the group is committed to the following:

- Ensure open access to the CPG and reference material upon publication.

- Develop a guide to implementation of the CPG in clinical practice, made available through the Oncology Section of APTA.
- Present the CPG at national conferences for health care professionals, allowing dissemination to other disciplines.
- Create a podcast or similar electronic media that can be used in physical therapy and other health care professional education.

## FUTURE RESEARCH

There are several important directions for future research:

- Further psychometric testing needs to be completed on the tools currently being used to assess and diagnose SUQL. This includes the emerging methods that lack diagnostic accuracy studies.
- Much of the evidence focuses on one diagnostic method, although current practice dictates using a combination of history, symptoms, and other measurements for diagnosis. Further research is needed to determine which combination of signs, symptoms, and measures is most accurate for diagnosing SUQL.
- There is a need for high-quality studies on at-risk populations, as well as on the population in various stages of lymphedema.
- The bulk of the evidence includes patients with upper-extremity lymphedema due to breast cancer treatments. Further research is needed for diagnosing lymphedema both in the trunk and in the head and neck region.
- Early diagnosis is crucial to maintain quality of life and minimize upper-quadrant morbidity for patients at risk for SUQL; therefore, there is a need for research to determine appropriate preoperative measurements and prospective monitoring protocols.

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