Surgical Treatments for Breast Cancer–Related Lymphedema

Policy # 00635
Original Effective Date: 10/17/2018
Current Effective Date: 10/17/2018

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Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers lymphatic physiologic microsurgery to treat lymphedema (including, but not limited to, lymphatico-lymphatic bypass, lymphovenous bypass, lymphaticovenous anastomosis, autologous lymph node transplantation, and vascularized lymph node transfer) in individuals who have been treated for breast cancer to be **investigational.***

Based on review of available data, the Company considers lymphatic physiologic microsurgery performed during nodal dissection or breast reconstruction to prevent lymphedema (including, but not limited to, the Lymphatic Microsurgical Preventing Healing Approach [LYMPHA]) in individuals who are being treated for breast cancer to be **investigational.***

Background/Overview

LYMPHEDEMA
Lymphedema is an accumulation of fluid due to disruption of lymphatic drainage. Lymphedema can be caused by congenital or inherited abnormalities in the lymphatic system (primary lymphedema) but is most often caused by acquired damage to the lymphatic system (secondary lymphedema).

Diagnosis and Staging
A diagnosis of secondary lymphedema is based on history (e.g., cancer treatment, trauma) and physical examination (localized, progressive edema and asymmetric limb measurements) when other causes of edema can be excluded. Imaging, such as magnetic resonance imaging, computed tomography, ultrasound, or lymphoscintigraphy, may be used to differentiate lymphedema from others causes of edema in diagnostically challenging cases.

Table 1 lists International Society of Lymphology guidance for staging lymphedema based on "softness" or "firmness" of the limb and the changes with an elevation of the limb.

Table 1. Recommendations for Staging Lymphedema

Stage	Description
Stage 0 (subclinical)	Swelling is not evident and most patients are asymptomatic despite impaired lymphatic transport
Stage I (mild)	Accumulation of fluid that subsides (usually within 24 hours) with limb elevation; soft edema that may pit, without evidence of dermal fibrosis
Stage II (moderate)	Does not resolve with limb elevation alone; limb may no longer pit on examination
Stage III (severe)	Lymphostatic elephantiasis; pitting can be absent; skin has trophic changes

Breast Cancer–Related Lymphedema
Breast cancer treatment is one of the most common causes of secondary lymphedema. Both the surgical removal of lymph nodes and radiotherapy are associated with development lymphedema in patients with breast cancer.

A systematic review of 72 studies (N=29,612 women), DiSipio et al (2013) reported that approximately 1 in 5 women who survive breast cancer will develop arm lymphedema. Reviewers reported that risk factors for development of lymphedema that had a strong level of evidence were extensive surgery (i.e., axillary-lymph-node dissection, greater number of lymph nodes dissected, mastectomy) and being overweight or obese.

Management and Treatment
Early and ongoing treatment of lymphedema is necessary. Conservative therapy may consist of several features depending on the severity of the lymphedema. Patients are educated on the importance of self-care including hygiene practices to prevent infection, maintaining ideal body weight through diet and exercise, and limb elevation. Compression therapy consists of repeatedly applying padding and bandages or compression garments. Manual lymphatic drainage is a light pressure massage performed by trained physical therapists or by patients designed to move fluid from obstructed areas into functioning lymph vessels and lymph nodes. Complete decongestive therapy is a multiphase treatment program involving all of the previously mentioned conservative treatment components at different intensities. Pneumatic compression pumps may also be considered as an adjunct to conservative therapy or as an alternative to self-manual lymphatic drainage in patients who have difficulty performing self-manual lymphatic drainage. In patients with more advanced lymphedema after fat deposition and tissue fibrosis has occurred, palliative surgery using reductive techniques such as liposuction may be performed.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Physiologic microsurgery for lymphedema is a surgical procedure and, as such, is not subject to regulation by the U.S. FDA.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

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To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

PHYSIOLOGIC MICROSURGERY TO TREAT LYMPHEDEMA

Clinical Context and Therapy Purpose

The purpose of physiologic microsurgery treatments for lymphedema in patients who have been treated for breast cancer is to provide a treatment option that is an improvement on existing therapies such as conservative therapy with compression garments or bandages, manual lymph drainage or pneumatic pumps, and decongestive therapy. Both surgical treatment and radiotherapy for breast cancer can lead to lymphedema and is one of the most common causes of secondary peripheral lymphedema.

The question addressed in this evidence review is: Does lymphatic physiologic microsurgery for the treatment of breast cancer–related lymphedema improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is individuals who have been treated for breast cancer, who have developed secondary lymphedema, and who have insufficient symptom reduction with conservative therapy, who have recurrent cellulitis or lymphangitis, or who are dissatisfied with conservative therapy. Lymphedema in its late chronic phase is irreversible. The surgical techniques of interest in this review are those performed in individuals who have not reached the irreversible stage, i.e., those who have functioning lymphatic channels (stage I, II or early stage III) (see Table 1).

Interventions

This review focuses on physiologic microsurgical interventions; it does not consider reductive (also known as excisional or ablative) surgical interventions (e.g., liposuction). Physiologic microsurgical interventions include several techniques and can be broadly grouped into procedures that (1) reconstruct or bypass the obstructed lymphatic vessels to improve lymphatic drainage and (2) transfer lymph tissue into an obstructed area to reestablish lymphatic flow. Table 2 includes a brief description of the surgeries.

Table 2. Physiologic Microsurgical Interventions for Lymphedema

Purpose	Surgery	Description	Key Features
Bypass or reconstruct obstructed lymph vessels to improve drainage	Lymphatic-lymphatic bypass	Connects functioning lymphatic vessels directly to affected lymphatic vessels; healthy vessels come from donor site	• Lymphedema can develop in donor extremity • Scaring at donor site
	Lymphovenous bypass and lymphaticovenular anastomosis	Lymphatic vessels in a affected limb are connected to the venous system	• Outpatient procedure or usually discharged within a day • Quick return to daily activities
Transfer lymph tissue to reestablish lymphatic flow	Autologous lymph node transplantation and vascularized lymph node transfer	Healthy lymph nodes are transferred to the affected limb	• Inpatient procedure; requires 2-3 days of hospitalization • Lymphedema can develop in donor extremity

Comparators

Physiological microsurgery may be used as an adjunct to conservative therapy. Conservative therapy is multimodal. It involves meticulous skin hygiene and care, exercise, compression therapy, and physical therapy (manual lymphatic drainage). Complete decongestive therapy and pneumatic compression pumps are also used as adjuncts to conservative therapy.

Outcomes

Objective outcomes of interest include a reduction in limb circumference and/or volume and reduction in the rates of infections (e.g., cellulitis, lymphangitis). Volume is measured using different methods; e.g., tape measurements with geometry formulas, perometry, and water displacement. Bioimpedance spectroscopy may be used to detect changes in tissue fluid accumulation.

Patient-reported outcomes (PROs) of interest include symptoms, quality of life, and functional measures. A systematic review of PRO instruments and outcomes used to assess quality of life in breast cancer patients with lymphedema, Pusic et al (2013) found that most studies included generic PRO instruments or oncology PRO instruments. Lymphedema-specific instruments are occasionally used; specifically, the Upper Limb Lymphedema 27 was found to have strong psychometric properties.

There does not appear to be a consensus on minimally clinically important change for either objective outcomes such as changes in arm volume or subjective measures such as changes to patient symptoms or quality of life.

Timing

The existing literature supporting conservative therapies for lymphedema has varying lengths of follow-up, ranging from a few weeks to 1 year. In systematic reviews of microsurgical treatments for lymphedema discussed in the following sections, studies suggest less than a year of follow-up is insufficient to observe outcomes. Therefore, at least 1 year of follow-up is considered necessary to demonstrate efficacy.

Setting
Microsurgery for lymphedema is performed by surgeons with advanced training in highly specialized microsurgery and lymphology and also requires specialized imaging tools.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
c. To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
d. Studies with duplicative or overlapping populations were excluded.

Because multiple systematic reviews of studies were available for both classes of microsurgery, the focus is on systematic reviews published in 2015 or later.

Surgeries That Reconstruct or Bypass Using Donor Lymph Vessels
Leung et al (2015) reported on a systematic review of the surgical management of breast cancer–related lymphedema. The search included studies reporting on the efficacy of surgical techniques used for the prevention or treatment of breast cancer–related lymphedema published between 2000 and 2014. Only 1 study on lymphatico-lymphatic bypass was identified and published since 2000. The study included 7 patients followed for 2.6 years. One patient had “complete recovery” as measured by the circumference of the affected limb and the remaining 6 patients had a “reasonable outcome”. Postsurgery complications were cellulitis, donor-site lymphorrhea, and transient edema of donor leg.

Surgeries That Reconstruct or Bypass Using the Venous System

Systematic Reviews
Two systematic reviews specifically evaluating microsurgical procedures using the venous system (lymphaticovenular anastomosis [LVA], lymphovenous bypass) have been reported. Two broader systematic reviews of treatments for lymphedema including several microsurgical procedures have also been reported. Corneilissen et al (2018) and Leung et al (2015) were limited to studies of breast cancer–related lymphedema but the remaining reviews were not. The overlap between the primary studies included in the systematic reviews is shown in Appendix Table 1. Thirty-four publications on LVA were included across the 4 systematic reviews. Characteristics of the reviews are shown in Table 3.

Cornelissen et al (2018) reported on a systematic review assessing the effect of LVA in breast cancer–related lymphedema. Fifteen observational studies were identified (11 prospective, 4 retrospective) with follow-up times ranging from 2 months to 8 years. Although LVA surgery was performed in the included

studies, the technical procedure differed among studies: 6 studies used only end-to-end anastomoses; 4 studies used both end-to-end and end-to-side anastomoses; 1 study used the ‘‘Octopus technique’’; and 4 studies did not report the LVA technique used. Only 2 studies included a control group (bandaging, decongestive therapy).

Scaglioni et al (2017) reported on a systematic review of LVA for the treatment of lymphedema. Reviewers noted significant variations in surgical techniques, numbers of anastomoses, and supplementary interventions (i.e., compressive therapy, additional debulking surgery). Nine studies included secondary lymphedema alone, while 8 studies included patients with both primary and secondary lymphedemas. The number of patients with breast cancer–related lymphedema was not described. As mentioned, the Carl (2017) and Leung (2015) reviews included multiple surgical techniques. Leung (2015) was limited to breast cancer–related lymphedema while Carl (2017) was not.

Table 3. Characteristics of Systematic Reviews Assessing Lymphedema Surgeries Using the Venous System

Study	Dates	Studies	Participants	N (Range)	Design	Duration (Range)
Cornelissen et al (2018)	1999-2017	15	With breast cancer– related lymphedema	268 (3-39)	• Observational or single-arm: 11 • Prospective: 4	20 mo (2 mo to 8 y)
Scaglioni et al (2017)	Up to 2016	18	With lymphedema of any cause except filariasis-related	939 (5-154) (no. with breast cancer–related lymphedema NR)	• Observational or single arm: 8 • Prospective: 10	24 mo (5-55 mo)
Carl et al (2017)	2000-2016	Overall: 69 LVA: 27[a]	With extremity lymphedema of any cause	NR	• Observational or single-arm	LVA: 6-120 mo
Leung et al (2015)	2000-2014	Overall: 13 LVA: 6	With breast cancer– related lymphedema	146 (6-89)	• Observational or single-arm	LVA: 17 mo to 8 y

LVA: lymphaticovenular anastomosis; NR: not reported.
[a] Only 12 “high-quality” LVA studies were discussed.

Results of the systematic reviews are shown in Table 4. In 3 of the reviews, given the variability in the procedures, metrics for measuring the outcomes, and the time periods of reporting, meta-analyses were not possible and only a narrative synthesis was provided. In the Carl (2017) review, meta-analyses were performed for the outcome measure of percent excess circumference reduction, although only a small subset of studies reported this outcome and could be combined. Risk of bias was assessed in the Cornelissen systematic review and summarized as follows:

- 9 of 15 studies did not describe whether consecutive patients were included, so selection bias is possible;
- 9 of 15 studies did not describe the surgery team;
- 5 of 15 studies did not have sufficient follow-up to evaluate the long-term effects of LVA (i.e., <1 year).

Table 4. Results of Systematic Reviews Assessing Lymphedema Surgeries Using the Venous System

Study	Reduction in Circumference or Volume of Affected Limb	Reduction in Symptoms	Infection Frequency	Postoperative Complications
Cornelissen et al (2018)				
n	255	NR	NR	205
Narrative	Overall reduction in either circumference or volume reported in 13/15 studies	• Reduction in symptoms reported in 12/15 studies • Percent patients with improvements varied from 50% to 100%		• 1 study reported 2 complications (skin irritation on the contrast injection site) • 10 studies reported no complications • 4 studies did not report whether complications occurred
Scaglioni et al (2017)				
Total N	939	NR	NR	NR
Narrative	All studies reported reductions in circumference measurements	Vast majority reported subjective symptom relief based on patient opinion and feeling	Reduction in no. of cellulitis episodes present in all cases	
	Excess Circumference Reduction (%)			
Carl et al (2017)				
n	474 (3 LVA studies)	NR (5 studies)	NR	NR (2 studies)
PE (95% CI) or narrative	16.1 (2.6 to 29.6)	• 1 study reported 92% symptom improvement • 2 studies reported average satisfaction rate of 94.5% • 2 studies reported improved QOL in 90% of patients and subjective improvement in 50%		• Partial skin ulceration (n=1) • Wound dehiscence (n=1)
I^2 (p)	0% (0.17)			
Leung et al (2015)				
Total N	146	NR	NR	109
Narrative	• Mean percent reduction in volume at 1 y was 2%, 35%, and 42% in 3 studies • Mean absolute circumference reduction was 4.1 cm and 0.85 cm in 2 studies			• No complications in 2 studies • Remaining studies did not report on complications

CI: confidence interval; LVA: lymphaticovenular anastomosis; NR: not reported; PE: pooled effect; QOL: quality of life.

Randomized Controlled Trials

No RCTs were identified.

Nonrandomized or Observational Studies
Additional single-arm studies have been published since the systematic reviews. However, these studies suffer from the same limitations as the studies included in the systematic reviews and do not capture longer periods of follow-up and/or larger populations than the existing studies. Therefore, they are not discussed further.

Subsection Summary: Surgeries That Reconstruct or Bypass Using the Venous System
No controlled trials were identified evaluating the physiologic microsurgeries using techniques such as lymphovenous bypass or LVA that reconstruct or bypass the obstructed lymphatic vessels using the venous system in patients with breast cancer–related lymphedema. Systematic reviews have indicated that most of the available evidence for these procedures comes from uncontrolled studies including fewer than 40 participants each, most of which lack adequate descriptions of how patients were selected for inclusion. Surgical technique, the severity of lymphedema, outcomes metrics, and follow-up times varied across studies making it difficult to synthesize the evidence. Surgical complications have been inconsistently reported but appear to be rare. RCTs of physiologic microsurgeries that bypass the obstructed lymphatic vessels using the venous system plus conservative therapy vs conservative therapy alone are needed.

Surgeries That Transfer Lymph Tissue

Systematic Reviews
Systematic reviews evaluating microsurgical procedures that transfer lymph tissue (autologous lymph node transfer, vascularized lymph node transfer [VLNT]) have been reported. The overlap between the primary studies included in the systematic reviews is shown in Appendix Table 2. Characteristics of systematic reviews of surgeries for lymphedema are shown in Table 5. Ozturk et al (2016) reported on a systematic review of VLNT for treatment of lymphedema. They included treatment for both primary and secondary lymphedema and as such comprised a heterogeneous population. However, 191 of 305 of the surgeries were for breast cancer–related lymphedema. Eighteen studies were identified (3 prospective, 15 retrospective). For breast cancer–related lymphedema, VLNT with a skin island or VLNT with an autologous flap was used. There was inconsistent reporting of the staging of lymphedema. Reviewers did not state whether any of the studies included a control group. Two systematic reviews of various surgical methods previously described also included a review of lymph node transfer.

In addition to the systematic reviews of efficacy, Demiri et al (2018) reported on a systematic review of donor-site complications following autologous lymph node transfer for breast cancer–related lymphedema.

Table 5. Characteristics of Systematic Reviews Assessing Lymphedema Surgeries Using Lymph Tissue Transfer

Study	Dates	Studies	Participants	N (Range)	Design	Duration
Demiri et al (2018)	NR	11	With breast cancer–related lymphedema treated with VLNT	189 (8-42)	RCT, observational, or single-arm	Mean, 38 mo (range, 6-132 mo)
Carl et al	2000-2016	Overall: 69	With extremity	NR	Observational or	NR

(2017)		VLNT: 17[a]	lymphedema of any cause		single-arm	
Ozturk et al (2016)	1980 to 2015	18	With primary or secondary upper- or lower-limb lymphedema (63% breast cancer–related)	305 (6-52)	Observational or single-arm: 3 Prospective: 15	2-132 mo
Leung et al (2015)	2000-2014	Overall: 13 LNT: 6	With breast cancer–related lymphedema	80 (3-24)	Observational or single-arm	LNT: 6 mo to 8 y

NR: not reported; RCT: randomized controlled trial; VLNT: vascularized lymph node transfer; LNT: lymph node transfer.
[a] Only 10 "high-quality" VLNT studies were discussed.

Results of the systematic reviews are shown in Table 6. In Ozturk (2016) and Carl (2017), results in the subgroup of breast cancer–related lymphedema were not presented so the table includes all available participants. Due to differences in outcomes metrics and timing of measurements, meta-analyses were not possible and narrative summaries were provided by Ozturk (2016), Demiri (2018), and Leung (2015). Carl (2017) performed meta-analyses for the excess volume-outcome but only a few studies could be pooled in the combined estimate. Risk of bias was assessed in Ozturk (2016) using a checklist from the American Society of Plastic Surgeons guidelines for therapeutic studies. A summary of the assessment follows:

- 12 of 18 studies did not report whether patients were selected consecutively and one did not include consecutive patients;
- 13 of 18 studies had insufficient information on the surgical team;
- 3 of 18 studies had an insufficient follow-up to observe outcomes (i.e., <1 year).

Table 6. Results of Systematic Reviews Assessing Lymphedema Surgeries Using Lymph Tissue Transfer

Study	Reduction in Circumference or Volume	Reductions in Symptoms	Infection Frequency	Postoperative Complications
Demiri et al (2018)				
Total N	NR	NR	NR	189
Narrative				Donor limb lymphedema: • 3 (1.6%) cases • 8 studies reported donor-site complications: o Seroma (n=8) o Lymphocele (n=3) o Lymphorrhea (n=2) o Wound infection (n=2) o Delayed wound healing (n=3) o Donor-site pain, numbness, or discomfort (n=9) o Transient edema of donor site (n=1) o Lymphedema of lower limb (n=3)
	Excess Circumference Reduction (%)			

Study	Reduction in Circumference or Volume	Reductions in Symptoms	Infection Frequency	Postoperative Complications
Carl et al (2017)				
Total N	NR (4 studies)[a]	NR	NR (4 studies)[a]	NR (7 studies)[a]
PE (95% CI) or narrative	39.5% (36 to 43)		• Quantitative summaries not given • Improved function, appearance, and mood • Decreased pain	• Quantitative summaries not given • Cellulitis, lymphocele, donor-site pain, seroma, lymphedema hematoma, wound dehiscence, wound infection, hydrocele, partial skin graft loss, venous congestion
I^2 (p)	0% (0.85)			
Ozturk et al (2016)				
Total N	305[a]	105[a]	106[a]	198[a]
Narrative	• Overall reduction in either circumference or volume reported in all studies • 17/182 patients evaluated by limb circumference showed no improvement • 16/114 patients evaluated by volume showed no improvement	• Various PROs reported in 7 studies • 98/105 reported high level of patient satisfaction	• Decrease reported in 7 publications using various metrics • Remaining publications did not quantify decrease	• Delayed wound healing: 4% • Seroma/hematoma: 3% • Infection: 2% • Abdominal bulge: 0.5% • Persistent donor lymphedema: 0%
Leung et al (2015)				
Total N	80	NR	NR	52
Narrative	• Mean percent reduction in circumference was 40% and 51% in 2 studies • "Reduction" in circumference reported in 10/21 (47%), 22/24 (92%), and 7/9 (78%) in 3 studies			• Donor-site edema (n=1) • Wound infection (n=1) • Venous congestion (n=1) • Seroma (n=3) • Delayed wound closure (n=2) • 2 studies did not report on complications

CI: confidence interval; NR: not reported; PE: pooled effect; PRO: patient-reported outcome.
[a] All etiologies included; results not provided for subgroup of patients with breast cancer–related lymphedema.

Randomized Controlled Trials

Dionyssiou et al (2016) reported on an RCT that evaluated VLNT plus physical therapy vs physical therapy alone for lymphedema in 36 women with stage II breast cancer–related lymphedema. Trial characteristics are shown in Table 7.

Table 7. Characteristics of RCTs of Lymphedema Surgeries Using Lymph Tissue Transfer

Study	Countries	Sites	Dates	Participants	Interventions	
					Surgery	Control
Dionyssiou et al (2016)	Greece	1	2011-2014	Women with stage II, unilateral, upper-limb lymphedema related to breast	18 received VLNT followed by physical	18 received physical therapy[a] for 6 mo

		cancer treatment and 1+ infections during last year	therapy[a] for 6 mo

RCT: randomized controlled trial.
[a] Physical therapy included manual lymphatic drainage for 1 month and pressure garments for 5 months.

RCT results reported in Dionyssiou (2016) are shown in Table 8. At 18 months, the reduction in the excess volume of the affected limb as a percentage of the intact limb was 57% in the VLNT group and 18% in the physical therapy group (treatment effect not reported, p<0.001). The mean number of lymphedema-related infections per patient per year was lower in the VLNT group (0.28 vs 1.16; treatment effect not reported, p=0.001). The trial had several limitations described in Tables 9 and 10. Notably, there was no description of allocation concealment and the trial was not blinded, possibly introducing both selection and ascertainment bias. The reporting did not describe the power calculations or justify a clinically important difference for the reported outcomes. The trial was not registered, so selective reporting cannot be ruled out.

Table 8. Results of RCTs of Lymphedema Surgeries Using Lymph Tissue Transfer

Study	Reduction in Circumference of Affected Limb	Reduction in Volume of Affected Limb	Infections	Function or Quality of Life	Postoperative Complications
Dionyssiou et al (2016)		**Reduction in Excess Volume of Affected Limb as Percent of Intact Limb at 18 Months**	**Mean Episodes per Patient per Year**	**VAS for Functional Impairment at 18 Months**	
N	NR	36	36	36	18
Surgery	NR	57%	0.28	1.22	4[a]
Control	NR	18%	1.16	4.61	NA
TE (95% CI); p	NR	NR (NR); <0.001	NR (NR); 0.001	NR (NR); 0.001	

CI: confidence interval; NA: not applicable; NR: not reported; RCT: randomized controlled trial; TE: treatment effect; VAS: visual analog scale.
[a] Two with mild discomfort at donor side lower limb; 2 with prolonged lymphorrhea at donor area.

Table 9. Relevance Gaps of RCTs of Lymphedema Surgeries Using Lymph Tissue Transfer

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Dionyssiou et al (2016)				4. Did not use validated measures of quality of life 5, 6. No discussion of clinically important differences	

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
RCT: randomized controlled trial.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 10. Study Design and Conduct Gaps of RCTs of Lymphedema Surgeries Using Lymph Tissue Transfer

Study	Allocation[a]	Blinding[b]	Selective Reporting[d]	Follow-Up[e]	Power[d]	Statistical[f]
Dionyssiou et al (2016)	3. No description of allocation concealment	1, 2. No blinding of patients, staff, or outcome assessors	1. Registra-tion not described	Note: flow of participants not described; unclear if any patients lost or crossed over	1-3. Power calculatio n not described	3, 4. Comparative treatment effects and related CIs not provided

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
CI: confidence interval; RCT: randomized controlled trial.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Follow-Up key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Intervention is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Intervention is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Nonrandomized or Observational Studies

Additional single-arm studies have been published since the systematic reviews. However, these studies suffer from the same limitations as the studies included in the systematic reviews and do not capture longer periods of follow-up and/or larger populations than the existing studies. Therefore, they are not discussed further.

Subsection Summary: Surgeries That Transfer Lymph Tissue

One RCT with 36 participants was identified evaluating VLNT that uses lymph tissue transfer in patients with breast cancer–related lymphedema. The trial reported reductions in the excess volume of the affected limb and rates of lymphedema-related infections for VLNT plus physical therapy compared with physical therapy alone. Systematic reviews have indicated that most of the remaining available evidence for these procedures comes from uncontrolled studies including fewer than 50 participants each, most of which lacked adequate descriptions of how patients were selected for inclusion. Surgical techniques, the severity of lymphedema, outcomes metrics, and follow-up times varied across studies. Although surgical complications were inconsistently reported, a systematic review of complications estimated that donor-site lymphedema occurs in approximately 2% of surgeries and seroma occurs in approximately 4%. Additional

RCTs of physiologic microsurgeries that use lymph tissue transfer with conservative therapy vs conservative therapy alone are needed.

PHYSIOLOGIC MICROSURGERY TO PREVENT LYMPHEDEMA

Clinical Context and Therapy Purpose
The purpose of lymphatic physiologic microsurgery simultaneous to lymphadenectomy for breast cancer (i.e., LYMPHA) is to prevent lymphedema in individuals who are being treated for breast cancer. While recommendations on preventive measures for lymphedema exist, such as avoiding needle sticks, limb constriction, and air travel, most recommendations are based on clinical opinion. A systematic review of preventive measures for lymphedema by Cemal et al (2011) found strong scientific evidence only for the recommendations to maintain a normal body weight or avoid weight gain and to participate in a supervised exercise regimen.

LYMPHA is a preventive LVA procedure performed during nodal dissection or reconstructive surgery that involves anastomosing arm lymphatics to a collateral branch of an axillary vein.

The question addressed in this evidence review is: Does lymphatic physiological microsurgery for the prevention of breast cancer–related lymphedema improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals who are undergoing a lymphadenectomy or breast reconstruction procedure for breast cancer.

Interventions
This review focuses on a physiologic microsurgical intervention called LYMPHA.

Comparators
LYMPHA could be used as an adjunct to standard care. Standard care may involve education regarding lymphedema and recommendations for hygiene, avoidance of blocking the flow of fluids in the body, maintaining a normal body weight and exercise, as well as surveillance for lymphedema during follow-up with referral as needed.

Outcomes
Outcomes of interest include diagnosis of lymphedema, lymphedema symptoms, quality of life, and operative and postoperative complications. As discussed, the diagnosis of lymphedema is based on history and physical examination (localized, progressive edema, asymmetric limb measurements). There is no universal agreement on measurement criteria for asymmetric limbs. It may be quantified by a 2 or more centimeters difference in limb girth, a 200 mL difference in limb volume, or a 10% limb volume change from

baseline. Patient reports of heaviness or swelling, either "now" or "in the past year" may also be used to suggest lymphedema. The estimated incidence of lymphedema varies by the measurement criteria used.

Timing
Although lymphedema can occur decades after treatment for breast cancer, approximately 80% of patients that eventually develop lymphedema experience onset within 3 years of treatment. The remaining patients develop edema at a rate of about 1% per year.

For the purposes of this review, studies with at least 3 years of follow-up to observe cases of lymphedema are of primary interest.
Setting
Microsurgery for lymphedema is performed by surgeons with advanced training in highly specialized microsurgery and lymphology and also requires specialized imaging tools.

Study Selection Criteria
Methodologically credible studies were selected as described in the previous section.

Systematic Reviews
Jorgensen et al (2017) reported on a systematic review of prophylactic LVA and shunts for preventing cancer–related lymphedema, not limited to breast cancer. Systematic review characteristics are shown in Table 11. Twelve articles were included in the qualitative analysis (5 specific to breast cancer) and four of those studies (2 specific to breast cancer) were included in a meta-analysis.

Table 11. Characteristics of Systematic Reviews of LYMPHA to Prevent Lymphedema

Study	Dates	Studies	Participants	N (Range)	Design	Duration, mo
Jorgensen et al (2017)	1980-2016	12 (5 specific to breast cancer)	Underwent lymphadenectomy for cancer treatment and prophylactic LVA for prevention of extremity lymphedema	364 (8-74)	RCT, observational, single-arm	6-69

LVA: lymphaticovenular anastomosis; LYMPHA: Lymphatic Microsurgical Preventing Healing Approach; RCT: randomized controlled trial.

Results of the systematic review are shown in Table 12. Jorgensen et al (2017) performed a meta-analysis of the incidence of lymphedema that included 4 studies (2 specific to breast cancer) with a control group consisting of patients without prophylactic LVA. The relative risk for incident lymphedema was 0.33 (95% CI, 0.19 to 0.56) favoring prophylactic LVA vs control; however, because the incidence of lymphedema varies over time and the follow-up times varied across studies, it is not clear whether it would be appropriate to pool the risk including all time points.

Table 12. Results of Systematic Reviews of LYMPHA to Prevent Lymphedema

Study	Incidence of Lymphedema	Lymphedema Symptoms	Quality of Life	Complications
Jorgensen et al (2017)				
Meta-analysis				
n	176	NR	NR	NR
RR (95% CI)	0.33 (0.19 to 0.56)			
I^2 (p)	0% (0.74)			
Qualitative synthesis				
N range	8-74	NR	NR	Not clear
Range estimates	0%-30% with varying follow-up times			• 1 study reported lymphorrhea in 1 patient • Unclear if other studies reported no events or did not report on complications

CI: confidence interval; LYMPHA: Lymphatic Microsurgical Preventing Healing Approach; NR: not reported; RR: relative risk.

Jorgensen (2017) also performed a risk of bias assessment of the included studies. They noted the following:

- None of the studies had allocation concealment or blinding;
- Only 1 study was randomized;
- None of the studies were registered;
- Only 4 studies had a control group. Selection of the control groups was unclear or a potential source of bias in all 4 controlled studies.

Randomized Controlled Trials

Boccardo et al (2011) reported on results of an RCT including 46 women referred for axillary dissection for breast cancer treatment between 2008 and 2009 who were randomized to LYMPHA or no preventive surgery (control). All LVA procedures were performed by the same surgeon, reported to be skilled in lymphatic microsurgery. The LVA surgeon was not the same surgeon who performed lymph node dissection. The same axillary dissection treatment was performed in the 2 treatment groups. Lymphedema was diagnosed as a difference in excess volume of at least 100 mL compared with preoperative volume measurements. Trial characteristics are shown in Table 13.

Table 13. Characteristics of RCTs of LYMPHA to Prevent Lymphedema

Study	Countries	Sites	Dates	Participants	Diagnosis of Lymphedema	Interventions	
						Active	Comparator
Boccardo et al (2011)	Italy	1	2008-2009	Women referred for complete axillary dissection for breast cancer treatment	Difference in excess volume of ≥100 mL vs preoperative volume	23 LYMPHA	23 no preventive surgery for lymphedema

LYMPHA: lymphatic microsurgical preventing healing approach; RCT: randomized controlled trial.

Results of the Boccardo (2011) RCT are shown in Table 14. Lymphedema was diagnosed in 1 (4%) woman in the LYMPHA group and 7 women (30 %) in the control group by 18 months of follow-up. The change in volume with respect to baseline was reportedly higher in the control group than in the LYMPHA group at 1,

3, 6, 12, and 18 months (all p<0.01). The trial had several limitations described in Tables 15 and 16. Notably, the follow-up duration was only 18 months. Methods of randomization and allocation concealment were not described and there was no justification of the sample size. The patients and investigators were not blinded (i.e., no sham procedure was performed) and there was no discussion of whether outcome assessors were blinded. There is no indication that the trial was registered.

Table 14. Results of RCTs of LYMPHA to Prevent Lymphedema

Study	Incidence of Lymphedema	Change in Volume of Associated Limb, mL	Symptoms of Lymphedema	Quality of Life	Complications
	Cumulative at 18 Months	At 18 Months			
Boccardo et al (2011)					
N	46	46	NR	NR	NR
LYMPHA	4%	10th percentile: ≈ -60 mL[a] 90th percentile: ≈ +40 mL[a]			
Control	30%	10th percentile: ≈ +50 mL[a] 90th percentile: ≈ +130 mL[a]			
TE (95% CI); p	NR (NR); 0.05	NR			

CI: confidence interval; LYMPHA: Lymphatic Microsurgical Preventing Healing Approach; NR: not reported; RCT: randomized controlled trial; TE: treatment effect.
[a] Estimated based visual inspection of figure.

Table 15. Relevance Gaps of RCTs of LYMPHA to Prevent Lymphedema

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Boccardo et al (2011)				1. No patient reported outcomes 3. No reporting of harms 4. Used 100 mL volume displacement to diagnose lymphedema; 200 mL is more commonly used 5, 6. No discussion of clinically important differences	1. Follow-up of ≥3 y would be needed to assess incidence and durability

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
LYMPHA: lymphatic microsurgical preventing healing approach; RCT: randomized controlled trial.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 16. Study Design and Conduct Gaps of RCTs of LYMPHA to Prevent Lymphedema

Study	Allocation[a]	Blinding[b]	Selective Reporting[d]	Data Completeness[e]	Power[d]	Statistical[f]
Boccardo et al (2011)	Note that method of randomization was not described 3. Allocation concealment not described	1, 2. No blinding	1. No discussion of registration		1-3. No power calculations discussed	3, 4. Treatment effects and corresponding CIs not reported

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
CI: confidence interval; LYMPHA: lymphatic microsurgical preventing healing approach; RCT: randomized controlled trial.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Nonrandomized or Observational Studies

Additional single-arm studies have been published since the systematic reviews. However, these studies suffer from the same limitations as the studies included in the systematic reviews and do not capture longer periods of follow up and/or larger populations than the existing studies. Therefore, they are not discussed further.

Section Summary: Physiologic Microsurgery to Prevent Lymphedema

One RCT was identified evaluating LYMPHA to prevent lymphedema in 49 patients referred for axillary dissection for breast cancer. The trial reported that lymphedema developed in 4% of women in the LYMPHA group and 30% in the control group by 18 months of follow-up. Longer follow-up is needed to observe incident lymphedema occurring after 18 months and assess the durability of the procedure. The trial had limitations that could have introduced bias: methods of randomization and allocation concealment were not described, and there was no sham procedure or blinding. Systematic reviews have indicated that most of the remaining available evidence for LYMPHA comes from uncontrolled studies, although two controlled observational studies in women with breast cancer have been performed. Selection of the control group was identified as a potential source of bias in both controlled studies. Outcomes metrics and follow-up times varied across studies. Additional RCTs of LYMPHA are needed and 1 such trial is underway (see NCT03428581).

SUMMARY OF EVIDENCE

For individuals who have breast cancer–related secondary lymphedema who receive physiologic microsurgery to treat lymphedema along with continued conservative therapy, the evidence includes an RCT) observational studies, and systematic reviews. Relevant outcomes are symptoms, morbid events, functional outcomes, health status measures, quality of life, resource utilization, and treatment-related morbidity. Several physiologic microsurgeries have been developed; examples include LVA and vascularized lymph node transfer. No RCTs of LVA or similar surgeries involving the venous system were identified. One RCT of vascularized lymph node transfer with 36 participants has been conducted. Systematic reviews have indicated that the preponderance of the available evidence comes from single-arm clinical series from individual institutions. Surgical technique, outcomes metrics, and follow-up time have varied across these studies. These types of studies might be used for preliminary estimates of the amount of volume reduction expected from surgery, the durability of the reduction in volume, and the rates of adverse events. However, these studies are not adequate for determining the comparative efficacy of physiologic microsurgery vs conservative treatment or decongestive therapy, or the comparative efficacy of different microsurgery techniques. RCTs are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are undergoing lymphadenectomy for breast cancer who receive physiologic microsurgery to prevent lymphedema, the evidence includes an RCT, observational studies, and systematic reviews. Relevant outcomes are symptoms, change in disease status, morbid events, quality of life, and treatment-related morbidity. LYMPHA is a preventive LVA performed during nodal dissection. One RCT including 46 patients has been conducted. The trial reported that lymphedema developed in 4% of women in the LYMPHA group and 30% in the control group by 18 months of follow-up. Longer follow-up is needed to observe incident lymphedema occurring after 18 months and assess the durability of the procedure. The trial methods of randomization and allocation concealment were not described and there was no sham procedure or blinding, potentially introducing bias. The remaining evidence consists of 2 controlled observational studies with inadequate description of control selection and uncontrolled studies. The evidence is insufficient to determine the effects of the technology on health outcomes.

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Policy History

Original Effective Date: 10/17/2018
Current Effective Date: 10/17/2018
10/04/2018 Medical Policy Committee review
10/17/2018 Medical Policy Implementation Committee approval. New policy.
Next Scheduled Review Date: 10/2019

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Surgical Treatments for Breast Cancer–Related Lymphedema

Policy # 00635
Original Effective Date: 10/17/2018
Current Effective Date: 10/17/2018

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