7.01.162	Surgical Treatments for Breast Cancer-Related Lymphedema		
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Section:	7.0 Surgery	**Page:**	Page 1 of 31

Policy Statement

I. Lymphatic physiologic microsurgery to treat lymphedema in individuals who have been treated for breast cancer is considered **investigational** including, but not limited to, utilization of **any** of the following:
   A. Lymphatico-lymphatic bypass
   B. Lymphovenous bypass
   C. Lymphaticovenous anastomosis (LVA)
   D. Autologous lymph node transplantation
   E. Vascularized lymph node transfer (VLNT)
   F. Liposuction

II. Lymphatic physiologic microsurgery performed during nodal dissection or breast reconstruction to prevent lymphedema in individuals who are being treated for breast cancer is considered **investigational** including, but not limited to, utilization of the Lymphatic Microsurgical Preventing Healing Approach.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

This policy does not address non-surgical approaches to the treatment of lymphedema, including bioimpedance devices for the detection of lymphedema (see Blue Shield of California Medical Policy: Bioimpedance Devices for Detection and Management of Lymphedema) and pneumatic compression pumps for the treatment of lymphedema (see Blue Shield of California Medical Policy: Pneumatic Compression Pumps for Treatment of Lymphedema and Venous Ulcers).

California SB 255 (Health and Safety Code 1367.635, para a3) requires insurance plans to "cover all complications from a mastectomy, including lymphedema."[28] The health plan does provide medically necessary treatments for lymphedema caused by mastectomy, but these do not include the bypass, LVA, Autologous lymph node transplantation, VLNT, liposuction or Lymphatic Microsurgical Preventing Healing Approach procedures referenced in this policy.

Coding

There is no specific CPT code for lymphatic physiologic microsurgery to treat lymphedema, but the following code may be used:

- **38308**: Lymphangiotomy or other operations on lymphatic channels
- **38999**: Unlisted procedure, hemic or lymphatic system

Description

Surgery and radiotherapy for breast cancer can lead to lymphedema and are some of the most common causes of secondary lymphedema. There is no cure for lymphedema. However, physiologic microsurgical techniques such as lymphaticovenular anastomosis or vascularized lymph node transfer have been developed that may improve lymphatic circulation, thereby decreasing symptoms and risk of infection. This review focuses on physiologic microsurgical interventions and will not consider reductive (also known as excisional or ablative) surgical interventions such as liposuction.

Related Policies

- Bioimpedance Devices for Detection and Management of Lymphedema
- Pneumatic Compression Pumps for Treatment of Lymphedema and Venous Ulcers

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

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

Rationale

Background

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 other 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.[1,]

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 of lymphedema in patients with breast cancer.

In 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.[2,] 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. The incidence of breast cancer-related lymphedema was found by DiSipio et al as well as other authors to be up to 30% at 3 years after treatment.[2,3,4,]

Studies have also suggested that Black breast cancer survivors are nearly 2.2 times more likely to develop breast cancer-related lymphedema compared to White breast cancer survivors.[5,] These observations may be linked to racial disparities with regards to access to treatment and the types of treatments received. Black women are more likely than White women to undergo axillary lymph node dissection, which is associated with greater morbidity than the less invasive sentinel lymph node biopsy. While this may be explained in part by Black individuals having a higher likelihood of being diagnosed with more aggressive tumors, there is evidence that even when adjusting for stage and grade of tumors, Black women are more likely to undergo axillary lymph node dissection, putting Black women at greater risk of breast cancer-related lymphedema. Additionally, Black breast cancer survivors, on average, have higher body mass indexes than White breast cancer survivors, which could contribute to development of lymphedema in this setting as well.

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.

Literature Review

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.

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 1 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. Randomized controlled trials 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 are some 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 PICO was used to select literature to inform this review.

Populations

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) (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 • Scarring at donor site
	Lymphovenous bypass and lymphaticovenular anastomosis	Lymphatic vessels in an 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 to 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; this technology is reviewed in Blue Shield of California Medical Policy: Bioimpedance Devices for Detection and Management of Lymphedema.

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 found that most studies included generic PRO instruments or oncology PRO instruments.[6,] Lymphedema-specific instruments are occasionally used; specifically, the Upper Limb Lymphedema 27 was found to have strong psychometric properties. An additional systematic review of PROs by Coriddi et al (2020) identified the most commonly used validated scale across 32 studies was the lymph quality of life measure for limb lymphedema (LYMQOL); however, non-validated instruments were used in half of all studies.[7,]

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.

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

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

Review of Evidence
Surgeries That Reconstruct or Bypass Using Donor Lymph Vessels

Systematic Review
Leung et al (2015) reported on a systematic review of the surgical management of breast cancer-related lymphedema.[8,] 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 the donor leg.

Surgeries That Reconstruct or Bypass Using the Venous System

Systematic Reviews

Three systematic reviews specifically evaluating microsurgical procedures using the venous system (lymphaticovenular anastomosis [LVA], lymphovenous bypass) have been reported.[9,10,7,]Three broader systematic reviews of treatments for lymphedema including several microsurgical procedures have also been reported.[8,11,12,] 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. Forty publications on LVA and lymphovenous bypass were included across the 5 systematic reviews. Characteristics of the reviews are shown in Table 3.

Chang et al (2021) reported on a systematic review and meta-analysis of LVA, liposuction, and vascularized lymph node transfer (VLNT) for treatment of lymphedema.[12,] The results of liposuction will not be reviewed. Overall, 66 total studies were included, with 16 studies included on LVA. Follow-up ranged from approximately 6 to 68 months. The number of patients with breast cancer-related lymphedema was not described. In addition, studies evaluating use of these procedures for both upper and lower extremity lymphedema were included. The study reported findings for limb circumference and incidence of cellulitis. Results for patients treated with lymphovenous bypass are presented in Table 4.

Coriddi et al (2020) reported on a systematic review of PROs following surgical treatment of lymphedema, including lymphovenous bypass and VLNT.[7,] Overall, 32 studies were identified (details regarding study design were not reported) with follow-up ranging from approximately 4 months to 43 months. The number of patients with breast cancer-related lymphedema was not described. The study reported findings for both validated and non-validated instruments assessing quality of life; however, only 18 studies (n=717 patients) reported individual patient data to permit quantitative assessment of the proportion of patients experiencing quality of life improvements. Results for patients treated with lymphovenous bypass are presented in Table 4.

Cornelissen et al (2018) reported on a systematic review assessing the effect of LVA in breast cancer-related lymphedema.[9,] 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.[10,] 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)
Chang et al (2021)[12,]	Up to 2019	Overall: 66 LVA: 16	With secondary lymphedema undergoing lymphovenous bypass (n=16 studies), VLNT (n=17 studies), liposuction (n=43), or combination therapy (n=3)	NR (4 to 124)	• Randomized controlled trials, prospective and retrospective	LVA: 6 to 68 mo

Study	Dates	Studies	Participants	N (Range)	Design	Duration (Range)
					cohort and case-control studies	
Coriddi et al (2020)[7,]	Up to 2019	32	With lymphedema undergoing lymphovenous bypass (n=18 studies) or VLNT (n=14 studies)	954 (6 to 100)	• Studies reporting QOL outcomes after physiologic procedures[b]	Weighted average, 9.2 mo (range, 4.2 to 43.1 mo)
Cornelissen et al (2018)[9,]	1999-2017	15	With breast cancer-related lymphedema	268 (3 to 39)	• Prospective cohort, uncontrolled: 9 • Prospective cohort, controlled: 2 • Retrospective cohort, uncontrolled: 4	20 mo (2 mo to 8 y)
Scaglioni et al (2017)[10,]	Up to 2016	18	With lymphedema of any cause except filariasis-related	939 (5 to 154) (no. with breast cancer-related lymphedema NR)	• Prospective cohort, uncontrolled: 8 • Retrospective cohort, uncontrolled: 10	24 mo (5 to 55 mo)
Carl et al (2017)[11,]	2000-2016	Overall: 69 LVA: 27[a]	With extremity lymphedema of any cause	NR	• Observational, retrospective and prospective controlled and uncontrolled	LVA: 6 to 120 mo
Leung et al (2015)[8,]	2000-2014	Overall: 13 LVA: 6	With breast cancer-related lymphedema	146 (6 to 89)	• Observational[b], uncontrolled	LVA: 17 mo to 8 y

LVA: lymphaticovenular anastomosis; NR: not reported; QOL: quality of life; VLNT: vascularized lymph node transplant.
[a] Only 12 "high-quality" LVA studies were discussed.
[b] Further details of study design were not provided.

Results of the systematic reviews are shown in Table 4. In 4 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 Chang (2021) and Carl (2017) reviews, meta-analyses were performed for the outcome measure of percent excess circumference reduction, although only a limited 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
Chang et al (2021)[12,]				
Total N	134 (10 studies)	NR	37 (3 studies)	NR

Study	Reduction in Circumference or Volume of Affected Limb	Reduction in Symptoms	Infection Frequency	Postoperative Complications
PE (95% CI) or narrative	LVA plus compression reduced circumference by a mean of 3.8 cm (2.93 to 4.67 cm)		Reduction in number of cellulitis infections before vs. after surgery (mean difference, 2.57; 95% CI, 1.75 to 3.38)	
I^2 (p)	NR (<.00001)		NR	
Coriddi et al (2020)[7],				
Total N	NR	596	NR	NR
Narrative		• All studies showed an improvement in QOL (range, 50% to 100%) • Validated instruments: QOL improvement, 50% (1 study) • Non-validated instruments: QOL improvement, 57% to 100% (11 studies)		
Cornelissen et al (2018)[9],				
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)[10],				
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)[11],				
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)

Study	Reduction in Circumference or Volume of Affected Limb	Reduction in Symptoms	Infection Frequency	Postoperative Complications
I^2 (p)	0% (.17)			
Leung et al (2015)[8,]				
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.

Nonrandomized or Observational Studies

Additional single-arm studies have been published since the systematic reviews.[13,] 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. Randomized controlled trials of physiologic microsurgeries that bypass the obstructed lymphatic vessels using the venous system plus conservative therapy versus conservative therapy alone are needed.

Surgeries that Transfer Lymph Tissue

Review of Evidence

Systematic Reviews

Systematic reviews evaluating microsurgical procedures that transfer lymph tissue (autologous 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.[14,] 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. Four systematic reviews of various surgical methods previously described also included a review of lymph node transfer.[8,11,7,12,] Two of these, Chang et al (2021) and Corridi et al (2020), reported results stratified by procedure; results for patients treated with VLNT are presented in Table 5.[7,12,]Forte et al (2019) reported results from a systematic review specifically of treatment with vascularized omental lymph

node transfer.[15,] Li et al (2021) reported results from a systematic review specifically evaluating intra-abdominal VLNT.[16,]

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.[17,]

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

Study	Dates	Studies	Participants	N (Range)	Design	Duration
Li et al (2021)[16,]	Up to Feb 2021	21	With lymphedema treated with intra-abdominal VLN flaps	594 (NR)	Non-randomized controlled trial, prospective and retrospective cohorts	Up to 52 mo
Chang et al (2021)[12,]	Up to 2019	Overall: 66 VLNT: 17	With secondary lymphedema undergoing lymphovenous bypass (n=16 studies), VLNT (n=17 studies), liposuction (n=43 studies), or combination therapy (n=3 studies)	NR (5 to 180)	Randomized controlled trials, prospective and retrospective cohort and case-control studies	NR (6 to 56.3 mo)
Coriddi et al (2020)[7,]	Up to 2019	32	With lymphedema treated with LVB (n=18 studies) or VLNT (n=14 studies)	954 (6 to 100)	• Studies reporting QOL outcomes after physiologic procedures	Weighted average, 9.2 mo (range, 4.2 to 43.1 mo)
Forte et al (2019)[15,]	Up to 2019	6	With lymphedema treated with VOLNT	137 (7 to 42)	Observational, uncontrolled	Mean, 9.6 mo to 4 y
Demiri et al (2018)[17,]	NR	11	With breast cancer-related lymphedema treated with VLNT	189 (8 to 42)	RCT: 1 Case series: 11	Mean, 38 mo (range, 6 to 132 mo)
Carl et al (2017)[11,]	2000-2016	Overall: 69 VLNT: 17[a]	With extremity lymphedema of any cause	NR	Observational or single-arm	NR
Ozturk et al (2016)[14,]	1980 to 2015	18	With primary or secondary upper- or lower-limb lymphedema (63% breast cancer-related)	305 (6 to 52)	Retrospective cohort: 13 Prospective cohort: 3 Case series: 2	2 to 132 mo
Leung et al (2015)[8,]	2000-2014	Overall: 13 LNT: 6	With breast cancer-related lymphedema	80 (3 to 24)	Observational[b], uncontrolled	LNT: 6 mo to 8 y

LNT: lymph node transfer; LVB: lymphovenous bypass; NR: not reported; QOL: quality of life; RCT: randomized controlled trial; VLN: vascularized lymph node; VLNT: vascularized lymph node transfer; VOLNT: vascularized omental lymph node transfer.
[a] Only 10 "high-quality" VLNT studies were discussed.
[b] Further details of study design were not provided.

Results of the systematic reviews are shown in Table 6. In Ozturk (2016), Carl (2017), Forte (2019), Coriddi (2020), Chang et al (2021), and Li et al (2021), 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 for mostoutcomes and narrative summaries were provided by Ozturk (2016), Demiri (2018), Leung (2015), and Li et al (2021). Chang (2021) and 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 1 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
Li et al (2021)[16,]				
Total N	594 (21 studies)			
PE (95% CI) or narrative	Range, 0.38% to 70.8%			Donor-site complication rate, 1.4% (0 to 4.1) Recipient-site complication rate, 3.2% (1.4 to 5.5)
Chang et al (2021)[12,]				
Total N	72 (5 studies)	NR	248 (8 studies)	NR
PE or narrative	VLNT (plus compression and complex decongestive therapy) reduced circumference by a mean of 1.64 cm (0.87 to 2.42 cm)		Reduction in number of cellulitis infections before vs. after surgery (mean difference, 2.34; 95% CI, 1.82 to 2.85)	
I^2 (p)	NR (<.0001)		NR (<.00001)	
Coriddi et al (2020)[7,]				
Total N	NR	121	NR	NR
Narrative		• Validated instruments: range of QOL improvement, 84% to 100% (3 studies) • Non-validated instruments: range of QOL improvement, 83% to 100% (3 studies)		
Forte et al (2019)[15,]				
Total N	Range, 7 to 42 (4 studies)	NR	NR	Range, 7 to 42 (6 studies)
Narrative	Range, 39.5% to 74%			• Hematoma (n=5) • Increased volume (n=4)

Study	Reduction in Circumference or Volume	Reductions in Symptoms	Infection Frequency	Postoperative Complications
				• Pancreatitis, paresthesia, seroma (n=3) • Hematoma, seroma (n=2) • Flap loss, graft loss (n=1) • Hyperesthesia (n=1) • Ileus (n=1)
Demiri et al (2018)[17,]				
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)
o	Excess Circumference Reduction (%)			
Carl et al (2017)[11,]				
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% (.85)			
Ozturk et al (2016)[14,]				
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	• 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%

Study	Reduction in Circumference or Volume	Reductions in Symptoms	Infection Frequency	Postoperative Complications
	• 16/114 patients evaluated by volume showed no improvement			
Leung et al (2015)[8,]				
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; QOL: quality of life; PRO: patient-reported outcome; VLNT: vascularized lymph node transfer.
[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 a RCT that evaluated VLNT plus physical therapy versus physical therapy alone for lymphedema in 36 women with stage II breast cancer-related lymphedema.[18,] 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)[18,]	Greece	1	2011-2014	Women with stage II, unilateral, upper-limb lymphedema related to breast cancer treatment and 1+ infections during last year. The racial/ethnic backgrounds of included patients were not described.	18 received VLNT followed by physical therapy[a] for 6 mo	18 received physical therapy[a] for 6 mo

RCT: randomized controlled trial; VLNT: vascularized lymph node transfer.
[a] Physical therapy included manual lymphatic drainage for 1 month and pressure garments for 5 months.

Results reported in Dionyssiou et al (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<.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=.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)[18,]		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); <.001	NR (NR);.001	NR (NR);.001	

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

Table 9. Study Relevance Limitations 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)[18,]	5. Racial/ethnic backgrounds of enrolled patients were not described			4. Did not use validated measures of quality of life	

The study limitations 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. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 10. Study Design and Conduct Limitations 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)[18,]	3. No description of allocation concealment	1, 2. No blinding of patients, staff, or outcome assessors	1. Registration not described	Note: flow of participants not described; unclear if any patients lost or crossed over	1-3. Power calculation not described	3, 4. Comparative treatment effects and related CIs not provided

The study limitations 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; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.

[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[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); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[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; 5. Other.

Nonrandomized or Observational Studies

Additional single-arm studies using lymph tissue transfer have been published since the systematic reviews.[19,20,21,22,] 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 versus 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., the Lymphatic Microsurgical Preventing Healing Approach [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.[23,]

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 PICO was used to select literature to inform this review.

Populations

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.[24,25,] 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.[25,]

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.

Review of Evidence

Systematic Reviews

Ciudad et al (2022) and Jorgensen et al (2017) reported on systematic reviews of prophylactic LVA and shunts for preventing cancer-related lymphedema, not limited to breast cancer.[26,27,]Systematic review characteristics are shown in Table 11. Jorgensen et al (2017) included 12 articles in the qualitative analysis (5 specific to breast cancer) and 4 of those studies (2 specific to breast cancer) were included in a meta-analysis. Ciudad et al (2022) included 24 studies (15 specific to breast cancer). The overlap between the primary studies included in the systematic reviews is shown in Appendix Table 3.

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

Study	Dates	Studies	Participants	N (Range)	Design	Duration, mo
Ciudad et al (2022)[27,]	Through Dec 2020	24 (15 specific to breast cancer)	Underwent prophylactic LVA after oncological treatment	1547 (7 to 380)	RCT and observational	6 to 156
Jorgensen et al (2017)[26,]	1980-2016	12 (5 specific to breast cancer)	Underwent lymphadenectomy for cancer treatment and prophylactic LVA for prevention of extremity lymphedema	364 (8 to 74)	RCT and observational	6 to 69

LVA: lymphaticovenular anastomosis; LYMPHA: Lymphatic Microsurgical Preventing Healing Approach; NR: not reported; RCT: randomized controlled trial.

Results of the systematic reviews 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% confidence interval [CI], 0.19 to 0.56) favoring prophylactic LVA versus

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. Ciudad et al (2022) reported that the pooled cumulative rate of upper and lower extremity lymphedema after oncological surgical treatment and LVA was 5.15% (95% CI, 2.9 to 7.5) and 6.66% (95% CI, <1 to 13.4), respectively. When compared to no intervention, the LVA reduced the incidence of upper and lower limb lymphedema by -18.7% (95% CI, -29.5 to -7.9) and -30.3% (95% CI, -46.5% to -14%), respectively.

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

Study	Incidence of Lymphedema	Lymphedema Symptoms	Quality of Life	Complications
Ciudad et al (2022)[27,]				
N	1547			
TE (95% CI); p-value	Upper extremity: 5.15% (2.9 to 7.5); <.01 Lower extremity: 6.66% (<1 to 13.4); <.01			
Risk difference (95% CI); p-value	Upper extremity: -18.7% (-29.5 to -7.9); <.001 Lower extremity: 30.3% (-46.5 to -14); <.001			
Jorgensen et al(2017)[26,]				
Meta-analysis				
N	176	NR	NR	NR
RR (95% CI)	0.33 (0.19 to 0.56)			
I^2 (p)	0% (.74)			
Qualitative synthesis				
N range	8 to 74	NR	NR	Not clear
Range estimates	0% to 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; TE: treatment effect.

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.

Ciudad et al (2022) also performed a risk of bias assessment and noted that "all articles were highly biased, and the protocols of the included studies were not documented on international registries."

Randomized Controlled Trials

Boccardo et al (2011) reported on results of a 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).[28,] 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)[28,]	Italy	1	2008-2009	Women referred for complete axillary dissection for breast cancer treatment. The racial/ethnic backgrounds of included patients were not described.	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<.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)[28,]					
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);.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. Study Relevance Limitations of RCTs of LYMPHA to Prevent Lymphedema

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Boccardo et al (2011)[28],	5. Racial/ethnic backgrounds of enrolled patients were not described			• No patient reported outcomes • No reporting of harms • Used 100 mL volume displacement to diagnose lymphedema; 200 mL is more commonly used • No discussion of clinically important differences	• Follow-up of ≥3 y would be needed to assess incidence and durability

The study limitations 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. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 16. Study Design and Conduct Limitations 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)[28],	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 study limitations 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; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[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); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[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; 5. Other.

Nonrandomized or Observational Studies

Additional single-arm studies have been published since the systematic reviews.[29,] 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 blinding. Systematic reviews have indicated that most of the remaining available evidence for LYMPHA comes from uncontrolled studies, although 2 observational studies in women with breast cancer with control groups including patients without prophylactic LVA 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 a 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 lymphaticovenular anastomosis and VLNT. No RCTs of lymphaticovenular anastomosis or similar surgeries involving the venous system were identified. One RCT of VLNT 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 versus conservative treatment or decongestive therapy, or the comparative efficacy of different microsurgery techniques. Randomized controlled trials are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are undergoing lymphadenectomy for breast cancer who receive physiologic microsurgery to prevent lymphedema, the evidence includes a RCT, observational studies, and systematic reviews. Relevant outcomes are symptoms, change in disease status, morbid events, quality of life, and treatment-related morbidity. Lymphatic Microsurgical Preventing Healing Approach is a preventive lymphaticovenular anastomosis 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. However, because the cumulative incidence of lymphedema after breast cancer treatment approximates 30% at 3 years, longer follow-up is needed to assess the durability of the procedure. The trial methods of randomization and allocation concealment were not described and there was no blinding, potentially introducing bias. The remaining evidence consists of uncontrolled studies and systematic reviews of these studies. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Lymphedema Network

The National Lymphedema Network published a position paper on the diagnosis and treatment of lymphedema in 2011.[30,] The paper provided the following statements, although notably, the document has been retracted and the Network is currently in the process of drafting a new position statement:

> "Microsurgical and supramicrosurgical (much smaller vessels) techniques have been developed to move lymph vessels to congested areas to try to improve lymphatic drainage. Surgeries involve connecting lymph vessels and veins, lymph nodes and veins, or lymph vessels to lymph vessels. Reductions in limb volume have been reported and a number of preliminary studies have been done, but there are no long-term studies of the effectiveness of these techniques."

An update of this position paper is in development as of July 2022.

International Society of Lymphology

The International Society of Lymphology published an updated consensus document on the diagnosis and treatment of peripheral lymphedema in 2020. [31,]The document stated the following on lymphaticovenous (or lymphovenous) anastomoses (LVA):

> "LVA are currently in use at multiple centers around the world. These procedures have undergone confirmation of long-term patency (in some cases more than 25 years) and some demonstration of improved lymphatic transport (by objective physiologic measurements of long-term efficacy). Multiple lymphatic-venous anastomoses in a single surgical site, with both the superficial and deep lymphatics, allow the creation of a positive pressure gradient (lymphatic-venous) and evade the phenomenon of gravitational reflux without interrupting the distal peripheral superficial lymphatic pathways. Some centers particularly in areas of endemic filariasis also practice lymph nodal-venous shunts as a derivative method. Multiple centers are using LVA (LYMPHA) as a preventative measure in high risk patients."

American Society of Breast Surgeons

The American Society of Breast Surgeons published recommendations from an expert panel on preventive and therapeutic options for breast cancer-related lymphedema in 2017.[32,] The document stated that "the Panel agrees that LVA and VLNT may be effective for early secondary breast cancer-related lymphedema."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) published recommendations on management of lymphedema as part of its guideline on survivorship; however, it does not discuss physiologic microsurgical techniques.[33,] The guideline states that high-level evidence in support of treatments for lymphedema are lacking. In addition, the NCCN guideline on breast cancer does not give recommendations on use of physiological microsurgical techniques for preventing or treating lymphedema.[33,]

American Association of Plastic Surgeons

The American Association of Plastic Surgeons sponsored a conference to create consensus statements and recommendations for surgical treatment and prevention of upper and lower extremity lymphedema.[12,] The recommendations were based on the results of a systematic review and meta-analysis. The relevant recommendations include:

> "There is evidence to support that lymphovenous anastomosis can be effective in reducing severity of lymphedema (grade 1C). There is evidence to support that vascular lymph node transplantation can be effective in reducing severity of lymphedema (grade 1B). Currently, there is no consensus on which procedure (lymphovenous bypass versus vascular lymph node transplantation) is more effective (grade 2C). A few studies show that prophylactic lymphovenous bypass in patients undergoing extremity lymphadenectomy may reduce the incidence of lymphedema (grade 1B). More studies with longer follow-up are required to confirm this benefit."

U.S. Preventive Services Task Force Recommendations

No U.S. Preventive Services Task Force recommendations for lymphedema have been identified.

Medicare National Coverage

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.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 17.

Table 17. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02790021	Improving Quality of Survivorship for Breast Cancer-related Lymphedema by Lymphaticovenous Anastomosis: A Randomized Controlled Trial	60	Aug 2022
NCT03428581	Preventing Lymphedema in Patients Undergoing Axillary Lymph Node Dissection Via Axillary Reverse Mapping and Lympho-venous Bypass	264	Feb 2023
NCT04687956	Effect of Lymphatic Microsurgical Preventing Healing Approach (LYMPHA) for Primary Surgical Prevention of Breast Cancer-related Lymphedema	72	Dec 2027
NCT02790021	Improving the Quality of Life of Patients With Breast Cancer-related Lymphedema by Lymphaticovenous Anastomosis (LVA): A Randomized Controlled Trial	120	Aug 2022
NCT04579029	Prospective Randomized Evaluation of Lymphaticovenous Anastomosis Using Dynamic Imaging in Breast Cancer-related Lymphoedema	64	Apr 2024
NCT04328610	A Randomized Controlled Trial to Assess the Efficacy of the Lymphatic Microsurgical Preventive Healing Approach (LYMPHA) to Prevent Lymphedema After Axillary Dissection for Breast Cancer	34	Feb 2022

NCT: national clinical trial.

Appendix 1

Appendix Table 1. Comparison of Studies Included in Systematic Reviews of Lymphedema Surgeries Using the Venous System

Study	Chang et al (2021)[12,]	Coriddi et al (2020)[7,]	Cornelissen et al (2017)[9,]	Scaglioni et al (2017)[10,]	Carl et al (2017)[11,]	Leung et al (2015)[8,]
O'Brien et al (1977)				●		

Study	Chang et al (2021)[12,]	Coriddi et al (2020)[7,]	Cornelissen et al (2017)[9,]	Scaglioni et al (2017)[10,]	Carl et al (2017)[11,]	Leung et al (2015)[8,]
O'Brien et al (1979)	●					
Gong-Kang et al (1981)	●					
Huang et al (1985)	●					
Ipsen et al (1988)	●					
O'Brien et al (1990)		●		●		
Koshima et al (1996)	●					
Koshima et al (2000)			●	●		●
Koshima et al (2004)					●	
Matsubara et al (2006)	●				●	
Damstra et al (2009)		●	●	●	●	●
Demirtas et al (2009)		●			●	
Chang et al (2010)		●	●	●		●
Naurshima et al (2010)	●				●	
Furukawa et al (2011)						●
Auba et al (2012)	●	●	●	●	●	●
Maegawa et al (2012)					●	
Mihara et al (2012)		●	●			
Ayestaray et al (2013)	●	●	●		●	
Chang et al (2013)			●	●	●	●
Yamamoto et al (2013)[a]				●		
Yamamoto et al (2013)[b]				●		
Akita et al (2014)				●		
Ayestaray et al (2014)	●					
Boccardo et al (2014)	●					
Mihara et al (2014)				●		
Chang et al (2013)		●				
Chen et al (2015)			●	●	●	
Hara et al (2015)				●		

Study	Chang et al (2021)[12],	Coriddi et al (2020)[7],	Cornelissen et al (2017)[9],	Scaglioni et al (2017)[10],	Carl et al (2017)[11],	Leung et al (2015)[8],
Seki et al (2015)				●		
Shi et al (2015)	●					
Torrisi et al (2015)			●			
Weiss et al (2015)					●	
Chen et al (2016)	●			●		
Campisi et al (2016)					●	
Gennaro et al (2016)			●			
Ito et al (2016)	●			●		
Masia et al (2016)		●				
Mihara et al (2016)		●		●		
Cornelissen et al (2017)		●	●			
Engel et al (2017)			●			
Gentileschi et al (2017)	●	●				
Lee et al (2017)			●			
Poumellec et al (2017)		●	●			
Winters et al (2017)	●	●	●			
Salgarello et al (2018)		●				
Chung et al (2019)		●				
Winters et al (2019)		●				

Appendix Table 2. Comparison of Studies Included in Systematic Reviews of Lymphedema Surgeries Using Lymph Tissue Transfer

Study	Li et al (2021)[16],	Chang et al (2021)[12],	Coriddi et al (2020)[7],	Forte et al (2019)[15],	Ozturk et al (2016)[14],	Demiri et al (2018)[17],	Carl et al (2017)[11],	Leung et al (2015)[8],
Abalmosov et al (2003)					●			
Abbas Khan et al (2011)								●
Agko et al (2018)	●							
Akita et al (2015)					●			
Asuncion et al (2018)		●	●					

Study	Li et al (2021)[16],	Chang et al (2021)[12],	Coriddi et al (2020)[7],	Forte et al (2019)[15],	Ozturk et al (2016)[14],	Demiri et al (2018)[17],	Carl et al (2017)[11],	Leung et al (2015)[8],
Batista et al (2015)					●			
Batista et al (2017)							●	
Becker et al (2006)					●	●		
Becker et al (1991)					●			●
Belcaro et al (2008)							●	
Chen et al (2014)					●			●
Cheng et al (2012)		●			●		●	
Cheng et al (2013)		●						
Cheng et al (2018)			●					
Coriddi et al (2017)	●		●					
Ciudad et al (2015)	●						●	
Ciudad et al (2017a)	●		●	●				
Ciudad et al (2017b)	●	●		●				
Ciudad et al (2019)	●	●	●	●				
Ciudad et al (2020)	●							
Dancey et al (2013)							●	
De Brucker (2016)		●	●					
Di Taranto et al (2020)	●							
Di Taranto et al (2021)	●							
Dionyssious et al (2016)			●			●	●	
Feng et al (2003)					●			
Fret et al (2020)	●							
Gharb et al (2011)			●		●	●	●	●
Granzow et al (2014)					●	●		
Gratzon et al (2017)		●	●					
Gustafsson et al (2018)		●						
Ho et al (2019)		●						
Hou et al (2008)							●	

Study	Li et al (2021)[16],	Chang et al (2021)[12],	Coriddi et al (2020)[7],	Forte et al (2019)[15],	Ozturk et al (2016)[14],	Demiri et al (2018)[17],	Carl et al (2017)[11],	Leung et al (2015)[8],
Inbal et al (2017)			●					
Johnson et al (2019)	●							
Kaya et al (2020)	●							
Kenworthy et al (2018)	●			●				
Kraft et al (2019)	●							
Lee et al (2011)					●			
Lin et al (2009)		●			●	●	●	●
Manrique et al (2020)	●							
Manrique et al (2020a)	●							
Maruccia et al (2019)	●		●					
Montag et al (2019)	●	●						
Mousavi et al (2019)	●	●		●				
Nguyen et al (2015)					●			
Nguyen et al (2017)	●	●	●	●				
Nicoli et al (2015)		●						
Patel et al (2015)		●	●		●		●	
Patel et al (2014)					●			
Pons et al (2013)							●	
Saaristo et al (2012)		●			●			●
Travis et al (2015)							●	
Vignes et al (2013)						●	●	
Visconti et al (2019)			●					
Vitanen et al (2012)					●		●	
Viitanen et al (2013)		●						

Appendix Table 3. Comparison of Studies Included in Systematic Reviews of LYMPHA to Prevent Lymphedema

	Ciudad et al (2022)[27],	Jorgensen et al (2017)[26],
Orefice et al (1988)	●	●
Takeishi et al (2006)	●	●
Boccardo et al (2009)	●	●

	Ciudad et al (2022)[27],	Jorgensen et al (2017)[26],
Casabona et al (2009)	●	●
Boccardo et al (2011)	●	●
Boccardo et al (2013)	●	●
Morotti et al (2013)	●	●
Boccardo et al (2014)	●	●
Campisi et al (2014)	●	
Onoda et al (2014)		●
Feldman et al (2015)	●	●
Boccardo et al (2016)	●	●
Yamamoto et al (2016)		●
Agrawal et al (2018)	●	
Hahamoff et al (2018)	●	
Ozmen et al (2018)	●	
Cakmakoglu et al (2019)	●	
Nacchiero et al (2019)	●	
Johnson et al (2019)	●	
Schwarz et al (2019)	●	
Cook et al (2020)	●	
Shaffer et al (2020)	●	
Somashekhar et al (2020)	●	
Levy et al (2020)	●	
Scaglioni et al (2020)	●	
Ezawa et al (2021)	●	

LYMPHA: Lymphatic Microsurgical Preventing Healing Approach

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Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	38308	Lymphangiotomy or other operations on lymphatic channels
	38999	Unlisted procedure, hemic or lymphatic system
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
03/01/2018	Custom Policy
09/01/2018	BCBSA medical policy adoption Policy number change from BSC7.15 Policy title change from Surgical Treatments for Lymphedema Policy revision without position change
05/01/2019	Policy revision without position change
09/01/2019	Policy revision without position change
09/01/2020	Annual review. No change to policy statement.
11/01/2020	No change to policy statement. Literature review updated.
11/01/2021	Annual review. No change to policy statement. Literature review updated.

Effective Date	Action
11/01/2022	Annual review. No change to policy statement. Literature review updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Surgical Treatments for Breast Cancer-Related Lymphedema 7.01.162 **Policy Statement:** Lymphatic physiologic microsurgery to treat lymphedema in individuals who have been treated for breast cancer is considered **investigational** including, but not limited to, utilization of **any** of the following: I. Lymphatico-lymphatic bypass II. Lymphovenous bypass III. Lymphaticovenous anastomosis (LVA) IV. Autologous lymph node transplantation V. Vascularized lymph node transfer (VLNT) VI. Liposuction Lymphatic physiologic microsurgery performed during nodal dissection or breast reconstruction to prevent lymphedema in individuals who are being treated for breast cancer is considered **investigational** including, but not limited to, utilization of the Lymphatic Microsurgical Preventing Healing Approach.	**Surgical Treatments for Breast Cancer-Related Lymphedema 7.01.162** **Policy Statement:** I. Lymphatic physiologic microsurgery to treat lymphedema in individuals who have been treated for breast cancer is considered **investigational** including, but not limited to, utilization of **any** of the following: A. Lymphatico-lymphatic bypass B. Lymphovenous bypass C. Lymphaticovenous anastomosis (LVA) D. Autologous lymph node transplantation E. Vascularized lymph node transfer (VLNT) F. Liposuction II. Lymphatic physiologic microsurgery performed during nodal dissection or breast reconstruction to prevent lymphedema in individuals who are being treated for breast cancer is considered **investigational** including, but not limited to, utilization of the Lymphatic Microsurgical Preventing Healing Approach.