Policy Number	**SUR701.024**
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Surgery for Lipedema and Lymphedema

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Related Policies (if applicable)
SUR716.001: Cosmetic and Reconstructive Procedures
SUR716.011: Reconstructive Breast Surgery
SUR716.012: Reduction Mammaplasty

Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For Illinois only: Illinois Public Act 103-0123 (IL HB 1384) Coverage for Reconstructive Services requires the following policies amended, delivered, issued, or renewed on or after January 1, 2025 (Individual and family PPO/HMO/POS; Student; Group [Small Group; Mid-Market; Large Group Fully Insured PPO/HMO/POS] or Medicaid), to provide coverage for medically necessary services that are intended to restore physical appearance on structures of the body damaged by trauma.

EXCEPTION: For HCSC members residing in the state of Arkansas, § 23-99-405 related to coverage of mastectomy and reconstruction services, should an enrollee elect reconstruction after a mastectomy, requires coverage for surgery and reconstruction of the breast on which the mastectomy has been performed, surgery and reconstruction of the other breast to produce a symmetrical appearance, and protheses and coverage for physical complications at all stages of a mastectomy, including lymphedema. This applies to the following: Fully Insured Group, Student, Small Group, Mid-Market, Large Group, HMO, EPO, PPO, POS. Unless indicated by the group, this mandate or coverage will not apply to ASO groups.

Coverage

Lipedema

Suction assisted protein lipectomy (also known as suction lipectomy and liposuction) for the treatment of lipedema, including any subsequent revisions, **may be considered medically necessary** when **ALL** the following criteria are met:

1. There is documentation of significant physical functional impairment (e.g., difficulty ambulating or difficulty performing activities of daily living) or medical complication, such as recurrent cellulitis; and
2. The individual has not responded to at least 3 consecutive months of optimal medical management (such as conservative treatment with compression garments and manual lymph drainage); and
3. The plan of care postoperatively is to continue to wear compression garments as instructed to maintain the benefits of treatment; and
4. For the diagnosis of lipedema, the individual has ALL the following clinical exam findings:
   a. Bilateral symmetric adiposity in the extremities;
   b. Non-pitting edema;
   c. Tissue in affected areas is soft to palpation;
   d. Tissue in affected areas is tender to palpation; and
5. Submission of photographs document the affected extremities requested for treatment.

Lymphedema

Suction assisted protein lipectomy (also known as suction lipectomy and liposuction) **is considered experimental, investigational and/or unproven** for lymphedema, including but not limited to lymphedema resulting from the treatment for melanoma.

Surgery for prevention or treatment of lymphedema (e.g., microsurgical lymphovenous anastomoses or vascularized lymph node transfer) **is considered experimental, investigational and/or unproven**.

Reverse lymphatic mapping **is considered experimental, investigational and/or unproven**.

Policy Guidelines

NOTE 1: See SUR716.001 Cosmetic and Reconstructive Procedures for CoolSculpting (may also be known as cryolipolysis or fat freezing).

NOTE 2: For suction assisted lipectomy in reconstructive and contralateral mammaplasty see medical policy SUR716.011.

NOTE 3: For the use of liposuction in reduction mammoplasty see medical policy SUR716.012.

NOTE 4: This policy does not address abdominal procedures, refer to SUR716.001 Cosmetic and Reconstructive Procedures for specific language on abdominal procedures, including but not limited to, panniculectomy and suction assisted lipectomy.

NOTE 5: For removal of excess skin, refer to medical policy SUR716.001 on cosmetic and reconstructive procedures.

Description

Lipedema

Lipedema, also known as lipoedema, is a rare disorder characterized by a large amount of subcutaneous fat in the extremities. The cause is unknown but is most frequently seen in women with a family history. The exact prevalence is uncertain as it does not have a diagnosis in the International Classification of Diseases (ICD-10). Lipedema is often misdiagnosed as obesity or lymphedema.

Lipedema is typically observed in the legs and thighs without affecting the feet, and the adipose tissue is painful. The arms may also be affected without edema of the hands. Symptoms include heaviness, pain (particularly with pressure), loss of strength, easy bruising, and a reduction in daily activity levels that affects the health and quality of life of the individual. The excessive fat deposits are typically unresponsive to traditional weight loss interventions and there is no cure.

Table 1. Diagnostic Criteria of Lipedema (2)

Almost exclusive occurrence in women	Arms are affected 30% of the time*
Bilateral and symmetrical manifestation with minimal involvement of the feet	Hypothermia of the skin*
Minimal pitting edema	
Negative Kaposi-Stemmer sign	Swelling worsens with orthostasis in summer*
Easy bruising	Unaffected by caloric restriction*
Persistent enlargement after elevation of the extremities or weight loss	Telangiectasias*

The diagnostic criteria for lipedema was first described in 1951 by Wold et al. and have been modified in recent years by Herbst. * Added by Herbst.

Untreated lipedema may result in secondary problems including osteoarthritis and reduced mobility. Over time, the weight of the excessive fat build-up can impair the ability to walk. Initially, the lymphatic system can cope with the increased amount of interstitial fluid, but in the later stages, secondary lymphedema (lipolymphoedema) can occur if the fatty deposits compromise the lymphatic system.

<u>Management and Treatment</u>

Lipedema management aims to minimize symptoms, prevent progression, and improve physical and psychological function. Conservative treatment includes manual lymph drainage,

compression therapy, and physical mobilization therapy. Other conservative treatment options to reduce symptoms include physical activity, diet, and nutrition. However, diet and exercise often fail to reduce fat buildup caused by lipedema. When conservative treatment and medical procedures do not work, liposuction and excision surgery are recommended. (1)

Generally performed by a board-certified plastic surgeon, liposuction is a surgical procedure used to remove fat to treat lipedema. The four types of liposuction are: tumescent, ultrasound-assisted, laser-assisted, and power-assisted. Tumescent liposuction is the most common method and involves injection of a sterile, saline solution and aspiration of fat and fluid using a cannula. Ultrasound-assisted liposuction involves use of a metal rod intended to emit ultrasonic energy, break fat, and facilitate fat removal. Laser-assisted liposuction uses high-intensity lasers to break down and emulsify fat. Power assisted liposuction involves a vibrating cannula intended to facilitate fat removal and increase precision. (1)

Lymphedema

Lymphedema is an abnormal accumulation of interstitial fluid and fibroadipose tissue in subcutaneous tissues or body cavities. In the extremities, capillaries in the superficial lymphatic system drain the lymph in the skin and subcutaneous tissue, which then flows into the deep system and then the lymph nodes, finally draining into the venous circulation. Accumulation of interstitial lymph fluid occurs when the accumulation of lymph exceeds the capacity of the system to drain. The excessive fluid may cause the accumulation and hypertrophy of fat cells.

Primary lymphedema may occur due to congenital anomalies or an inherited condition. Secondary lymphedema has a variety of causes that reduce lymph drainage including surgical removal of lymph nodes, post-radiation fibrosis, scarring of lymphatic channels, obesity, and chronic lymphatic overload. Cancer-associated lymphedema can occur due to obstruction, infiltration, removal of lymph nodes, irradiation, or medications. Nearly all cases of lymphedema in the U.S. are secondary to cancer or cancer treatment.

The most common cancer-associated lymphedema occurs in women who have undergone axillary surgery and/or axillary radiation therapy for breast cancer. The risk of developing arm lymphedema is associated with the extent of axillary lymph node dissection, and there is a greater risk of lymphedema in breast cancer patients who undergo dissection compared to those who undergo biopsy.

<u>Diagnosis and Staging</u>

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.

The International Society of Lymphology categorizes lymphedema stage and severity as outlined in Table 2. (3)

Table 2. Recommendations for Staging Lymphedema

Stage	Severity
0: A subclinical, usually asymptomatic condition with impaired lymph transport	---
1: Edema that resolves with limb elevation, usually within 24 hours	Mild: <20% increase in extremity volume
2: Pitting edema that is unresolved with limb elevation	Moderate: 20% to 40% increase in extremity volume
3: Changes in skin character and thickness, with excess fat deposits and fibrosis	Severe: >40% increase in extremity volume

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.

Table 3. Comparison of Findings in Lipedema, Lymphedema, and Lifestyle-induced Obesity (2)

	Lipedema	Lymphedema	Lifestyle-induced Obesity
Sex	Women	Women and men	Women and men
Adiposity	Bilateral extremities Symmetric	Unilateral or bilateral extremities Asymmetric	Whole body, proportionate Symmetric
Edema	Nonpitting Minimal change with elevation Minimal change with compression	Pitting Reduced by elevation Reduced with compression	None No change with elevation No change with compression
Tissue Turgor	Soft	Firm	Soft
Pain	Tender to palpation	Usually nontender	None

Infection	Rare	Common	Rare

Regulatory Status
Liposuction is a surgical procedure and, as such, is not subject to regulation by the U.S. Food and Drug Administration (FDA).

The FDA regulates the sale of medical devices and drugs that physicians use to perform liposuction. This includes equipment such as cannulas, pumps, collecting containers, and ultrasound probes, as well as anesthetics used during the procedure.

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

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

Rationale

This medical policy was originally developed in July 2009 and has been updated periodically using the PubMed database. The most recent literature review was performed through October 2023.

Medical policies 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 (QOL), 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 one or more intended clinical uses 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.

LIPEDEMA

Liposuction

There is no cure for lipedema. The goal of therapy is to reduce symptoms, disability, and functional limitations, and prevent disease progression. Conservative treatment includes manual lymphatic drainage, compression stockings, intermittent pneumatic compression, skin care, and exercise. Individuals with lipedema may have obesity as a comorbidity, and diet is frequently prescribed. Conservative care may alleviate symptoms, but treatments are short-lived and may require repeat treatment within days. For individuals who do not respond to conservative treatment, liposuction may be recommended.

The purpose of liposuction in individuals who have lipedema is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with lipedema/lipoedema or lipolymphedema who have failed to respond to conservative therapy.

In stage I lipedema the skin is smooth and the subcutaneous layer is thickened, soft, and with an even structure. In stage II lipedema the skin becomes uneven and subcutaneous nodules develop. In stage III lipedema there are bulging protrusions of fat along with tender subcutaneous tissue. In an advanced stage, sometimes referred to as stage IV lipedema, the excess fat can impair lymphatic vessel function leading to secondary lymphedema (lipolymphedema).

Interventions

The therapy being considered is liposuction.

Liposuction reduces the amount of fatty tissue but does not eliminate it, and multiple sessions may be needed.

Comparators

Conservative treatment (decongestive therapy) consists of manual lymphatic drainage, compression garments, intermittent pneumatic compression, skin care, and exercise. Diet is also used to prevent or treat obesity associated with lipedema.

Outcomes

The general outcomes of interest are symptoms, change in disease status, functional outcomes, and quality of life.

Reported outcomes for lipedema are reduction in size of extremities, circumferential measurement, restriction of movement, spontaneous pain or discomfort, sensitivity to pressure, edema/swelling, bruising, trophic skin changes, and 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 long-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.

Systematic Reviews

The Canadian Agency for Drugs and Technologies in Health (2019) conducted a qualitative systematic review of liposuction for the treatment of lipedema. (4) The authors identified 5 uncontrolled before-and-after studies in the English language that suggested that liposuction may be effective in reducing the size of the extremities, symptoms, and functional limitations of lipedema.

The case series with over 100 patients are described in greater detail below (Tables 4 and 5).

Observational Studies

Schmeller et al. (2012) reported a case series of patients with lipedema who were treated between 2003 and 2009. (5) Over multiple procedures that averaged 2 hours each, a mean of 9846 mL of fatty tissue was removed, resulting in a reduction in thigh circumference of 8 cm. Out of 165 patients who had at least 6 months of follow-up and received standardized questionnaires, 112 patients (68%) returned the questionnaires, and the data could be analyzed. The patients who returned the questionnaires reported significant improvements in spontaneous pain and pain with pressure, movement, and quality of life. The need for decongestive therapy was reduced or eliminated in a majority of these patients. The authors concluded that tumescent liposuction was a highly effective treatment for lipedema with good morphological and functional long-term results.

Follow-up out to 12 years from this series was reported by Baumgartner et al. (2021). (6) Sixty patients (36%) had returned questionnaires at 4, 8, and 12 years. All of the patients who were included in the follow-up had stage I or stage II lipedema. In those who returned questionnaires, improvements were maintained over the 12 years of follow-up.

Wollina and Heinig (2019) reported a consecutive series of 111 patients with advanced lipedema with pain and/or leg volume who had been treated with liposuction. (7) They reported that 7 patients had stage I lipedema, 50 patients had stage II, and 48 patients had stage III lipedema (n=105). All of the patients had either not responded to decongestive therapy for at least 6 months or had progressed. The mean reduction in fatty tissue with liposuction was 4700 mL (range, 950 to 14,250 mL), with an improvement in thigh circumference of 6 cm. Serious adverse events from treatment were noted in 1.2% of patients. At a median follow-up

of 2 years, patients reported a significant reduction in pain and improvement in mobility; 16% of patients no longer needed decongestive therapy.

A prospective cohort of water-assisted liposuction (WAL) for liposuction was reported by Witte et al. (2020), consultants for the producer of the WAL device. (8) The 130 patients enrolled in the study had stage I or II lipedema diagnosed by 2 specialists. No patients with advanced lipedema were included. Patients underwent weight loss, exercise, and treatment of varicose veins in addition to WAL. Manual lymphatic drainage and compression garments were worn for 8 weeks after the procedure. At a mean of 22 months after the procedure all symptoms decreased in severity, and use of conservative therapy (compression garments or manual lymphatic drainage) was reduced in these patients from 100% pre-treatment to 44% after liposuction.

Kruppa et al. (2022) completed a 10-year retrospective before-and-after study of 106 patients who underwent a total of 298 liposuctions for treatment of lipedema. (9) The authors reported that 11 patients had stage I lipedema, 61 patients had stage II, and 34 had stage III disease. A total of 65 (61.3%) patients had upper extremity involvement and the majority of patients (58.5%) had onset of lipedema symptoms occurring during puberty. Preoperative body mass index was higher in stage III patients compared to stage I and II patients. Liposuction was shown to reduce symptom severity and the need for conservative treatment, especially among patients with a body mass index <35 kg/m^2 at an early stage of disease. Thirty-seven patients did not need to wear compression garments and 27 patients did not require any conservative treatment postoperatively.

The publication by Wollina and Heinig (2019) notes a German language study by Munch (2017) that reported an improvement of pain, bruising, mobility, and quality of life using WAL in 141 patients. (10) An English language abstract of the study indicates that out of 141 patients treated between 2010 and 2016, 71 were re-evaluated after a mean of 35.9 months. The 50% of patients who had follow-up reported improvement in the 10 complaints from 6.1 to 3.1 on a visual analog scale (VAS) and in 38.3% of cases conservative therapy was reduced or found to be more effective.

Table 4. Summary of Key Case Series Characteristics

Study	Country	Years	Participants	Treatment Delivery	Follow-Up
Schmeller et al. (2012), Baumgartner et al. (2021) (5, 6)	Germany	2003-2009	Patients had undergone conservative therapy for a period of years. 165 patients received standardized questionnaires.	Liposuction under tumescent local anesthesia with a vibrating microcannula. The average time of surgery was 2 hours. The number of treatments ranged from 1 to 7 times spaced from 1 month to 1 year.	3, 4, 8, and 12 years 5 step Likert scale

			112 patients returned the questionnaires and could be analyzed.		
Wollina and Heinig (2019) (7)	Germany	2007-2018	111 patients with advanced lipedema with pain and/or leg volume not responding to decongestive therapy for at least 6 months	Inpatient liposuction under tumescent local anesthesia or laser-assisted liposuction, followed by compression garments for at least 6 months.	Median of 2.0 (2.1 SD) years. Pain was measured on a 10 point VAS. Improvement in mobility and bruising was assessed with a 3 point scale.
Witte et al. (2020) (8)	Germany	2016-2019	130 patients with stage I or II lipedema diagnosed by 2 specialists were enrolled, 63 patients had follow-up	One to 3 treatments with WAL under tumescent anesthesia following weight loss, exercise, and treatment of varicose veins when appropriate. Decongestive therapy was performed for 8 weeks after liposuction.	Median of 22 months with a standardized questionnaire with 11 items scored with a VAS.
Kruppa et al. (2022) (9)	Germany	2009-2019	106 patients with lipedema who had received preoperative complex decongestive therapy for at least 6 months	Power-assisted liposuction or WAL was utilized; the surgical goal of fat removal equivalent to approximately 6% of the patient's body weight often required megaliposuction (defined as large volume liposuction with a minimum of 4 L of pure fat or 5 L of total aspirate; 69.1% of all liposuctions met the definition of megaliposuction)	Minimum of 6 months since last liposuction (median 20 months; range, 6 to 115 months); assessed with a nonvalidated disease-related questionnaire to evaluate pre- and postoperative lipedema-associated complaints

SD: standard deviation; VAS: visual analog scale; WAL: water-assisted liposuction.

Table 5A. Summary of Key Case Series Results

Study	Mean Reduction in Fatty Tissue	Mean Reduction in Limb	Spontaneous Pain (SD)	Pain with Pressure (SD)

		Circumference (SD)		
Schmeller et al. (2012) (5)	9846 mL	8 cm in thighs	Before: 1.88 (1.33) After: 0.37 (0.60) Effect size: 1.36 p<.001	Before: 2.91 (1.33) After: 0.91 (0.92) Effect size: 2.01 p<.001
Wollina and Heinig (2019) (7)	4700 mL (range, 950 to 14,250 mL)	6 (1.6) cm	Before: 7.8 (2.1) median After: 2.2 (1.3) p<.03	
Witte et al. (2020) (8)	12,922 mL (2922 mL SD)		Before: 6.47±2.05 After: 1.39±1.66 p<.001	Before: 7.14±1.9 After: 1.55±1.79 p<.001
Kruppa et al. (2022) (9)			Before (median, IQR): 80.0; 70 to 90 After: 30; 10 to 50* p<.0001	Before (median, IQR): 80; 70 to 90 After: 30; 20 to 55* p<.0001

IQR: interquartile range; SD: standard deviation.
*Visual analog scale of symptom severity ranging from 0 to 100 in increments of 5, with 100 indicating the greatest severity.

Table 5B. Summary of Key Case Series Results

Study	Restriction of Movement (SD)	Quality of Life (SD)	Use of Physical Decongestive Therapy	Adverse Events	General Impairment
Schmeller et al. (2012) (5)	Before: 2.03 (1.06) After: 0.91 (0.60) Effect size: 1.58 p<.001	Before: 1.88 (1.33) After: 0.37 (0.60) Effect size: 2.95 p<.001	Before: 67 patients After: 13 of 67 had no improvement	Wound infection rate of 1.4%	
Wollina and Heinig (2019) (7)	All patients reported an improvement in mobility		16.4% no longer needed decongestive therapy	1.2% serious adverse events	
Witte et al. (2020) (8)	Before: 5.28±3.04 After: 0.6±1.1 p<.001		Before: 84% After: 39.7% p<.001	NR	
Kruppa et al. (2022) (9)		Before (median,	Reduction in the complex		Before (median, IQR): 90; 80 to 100

		IQR): 75; 40 to 82.5 After: 30; 10 to 50* p<.0001 (impairment of sexual quality of life specifically)	decongestive therapy score with a median of 37.5% (IQR, 0% to 88.8%) seen for all stages of lipedema p<.001		After: 60; 30 to 82.5* p<.0001

IQR: interquartile range; NR: not reported; SD: standard deviation.
*Visual analog scale of symptom severity ranging from 0 to 100 in increments of 5, with 100 indicating the greatest severity.

Section Summary: Lipedema

No controlled trials were identified evaluating liposuction for the treatment of lipedema. The available evidence includes case series and several before- and after-treatment studies that suggest that liposuction may reduce pain and improve QOL at up to 12-year follow-up in patients with lipedema.

LYMPHEDEMA

Liposuction

Clinical Context and Therapy Purpose

Lymphedema is a chronic condition that is managed with lifelong care. Care is aimed at improving comfort, reducing limb volume, and slowing the rate of progression. For the relatively few individuals who fail conservative treatment, surgical options may be recommended. Surgical approaches include lymphatic surgery and soft tissue reduction.

The purpose of liposuction in individuals who have lymphedema is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with who have failed to respond to conservative therapy or present with more advanced lymphedema with fat deposition and tissue fibrosis.

Interventions

The therapy being considered is liposuction.

Liposuction reduces the amount of fatty tissue but does not eliminate it, and multiple sessions may be needed.

Comparators
Conservative treatment consists of skin care, exercise and weight reduction, compression garments, manual lymphatic drainage, and in more severe cases intermittent pneumatic compression. Decongestive therapy involves intensive treatment by a health care professional for 5 days a week.

Outcomes
The general outcomes of interest are symptoms, change in disease status, functional outcomes, and quality of life.

Reported outcomes for lymphedema are reduction in size of extremities, direct circumferential measurement, restriction of movement, spontaneous pain or discomfort, edema/swelling, trophic skin changes, and quality of life. Assessment of the fat layer with magnetic resonance imaging, bioimpedence spectroscopy, and perometry have also been reported.

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.

Systematic Reviews
Literature on the use of liposuction to treat lymphedema is limited.

A 2021 meta-analysis sponsored by the American Association of Plastic Surgeons evaluated the evidence on surgical treatment of lymphedema. (11) Pooled analysis of 2 studies (n=48) showed a 63.95% greater reduction in volume and pooled analysis of 2 studies (n=69) showed a greater reduction in volume by 895 mL for liposuction compared to compression therapy alone. Durability of the procedure was not addressed.

A qualitative systematic review of liposuction for lymphedema of the lower limb was published by Forte et al. (2019). (12) The authors identified 8 articles with 191 patients (4 were case reports) that met the inclusion criteria of the review. The mean duration of lymphedema ranged from 10 to 20 years. Volume reduction of greater than 50% was reported following liposuction and compression therapy, with a greater volume reduction for secondary lymphedema compared to primary lymphedema. One study reported improvement in function, quality of life, and rate of infection. No comparative studies were identified.

Randomized Controlled Trials

Alamoudi et al. (2018) reported a non-blinded RCT on submental liposuction for cervical lymphedema following head and neck cancer treatment. (13) Twenty patients with cervical lymphedema were randomized into treatment with liposuction or to no treatment control. Patients filled out 2 surveys after consenting for the trial and at 6 months. Compared to the no-treatment group, patients in the liposuction group showed statistically significant improvement in patient's self-perception and subjective scoring of appearance. Limitations of the study include the lack of description of randomization and allocation concealment, lack of blinding combined with subjective outcome measures, lack of a physiotherapy control, small sample size, and short duration of follow-up to assess the durability of the procedure.

Observational Studies

Hoffner et al. (2018) reported on a series of 105 consecutive patients with secondary non-pitting lymphedema who had been treated with liposuction and compression garments at their institution between 1993 and 2012. (14) Lymphedema began at a mean of 2.9 (5.0) years after the breast cancer operation and persisted for a mean of 10 (7.4) years at the time of treatment. Criteria for liposuction included excess volume measured by plethysmography with concomitant subjective discomfort, failure of conservative treatment, no or minimal pitting as a sign of adipose tissue hypertrophy, and customized to the use of compression garments preoperatively. Standardized forms were used to collect pre-, peri-, and postoperative data and measurements were conducted by the same physiotherapist and occupational therapist. The surgical procedure and post-operative management with gradual alterations in the sizing and changing of compression garments was reported in detail. Patients were followed at 0.5, 1, 2, 6, 9, and 12 months after surgery, and then annually. The preoperative excess volume was 1573 mL (range, 570 to 33,520 mL) with a ratio between the affected arm and the healthy arm of 1.5 (range, 1.2 to 2.1). The mean aspirate volume was 1831 mL (range, 650 to 3780 mL) and contained 94% fat (range, 58 to 100), resulting in a reduction in excess volume at 6 months of 107% (range, 73 to 179). The reduction in excess volume was maintained for 5 years, with a mean reduction in excess volume of 117% (range, 25 to 191) and a ratio of 0.9 (range, 0.8 to 1.4) compared to the healthy arm. The compression protocol was standardized and carefully reported, but there was no comparison to treatment with the compression protocol alone and patient-reported outcomes were not assessed.

In a cohort study, Hoffner et al. (2017) assessed liposuction plus controlled compression therapy in patients with lymphedema of an arm secondary to breast cancer treatment. (15) The aim of the study is to test the hypothesis that liposuction improves health-related quality of life (HRQoL). Sixty female patients with arm lymphedema were followed for a one-year period after surgery. The 36-item short-form health survey (SF-36) was used to assess HRQoL. Patients completed the SF-36 questionnaire before liposuction, and after one, three, six, and 12 months. They reported a mean difference between affected and unaffected limbs of 1365 mL (standard error of the mean [SEM] 73) at baseline, which declined to 75 mL (SEM 35) at one month, –26 mL (SEM 40) at three months, –133 mL (SEM 40) at six months, and –213 mL (SEM 35) at one year, indicating > 100% reduction in excess volume on average. They reported that 82% (49 of 60) patients had complete resolution of their lymphedema. The adipose tissue volume removed at surgery was 1373 – 56 mL. One month after liposuction, better scores were found in mental

health. After three months, an increase in physical functioning, bodily pain, and vitality was detected. After one year, an increase was also seen for social functioning. The physical component score was higher at three months and thereafter, while the mental component score was improved at three and 12 months. Limitations of this study include: a lack of control or comparator group; observational study; and insufficient length of follow-up to determine long-term outcomes.

In a cohort study, Lamprou et al. (2017) reported the long-term results of circumferential suction-assisted lipectomy (CSAL) in end-stage primary and secondary lymphedema of the leg. (16) Patients were treated with CSAL for unilateral chronic irreversible lymphedema of the leg (n=88). Compression therapy was resumed after surgery. Leg volumes were measured before surgery, and at one, six, 12 and 24 months after the procedure. A total of 47 patients with primary lymphedema had a median preoperative volume difference between affected and unaffected legs of 3686 (interquartile range [IQR]), 2851 to 5121) mL. Two years after surgery, this volume difference was reduced to 761 ml, a 79% reduction. In the 41 patients treated for secondary lymphedema, the median preoperative volume difference was 3320 (IQR 2533-4783) ml, decreasing after two years to -38 ml indicating a 100% reduction in excess volume on average. The preoperative volume difference and the sex of the patient significantly influenced the final outcome after two years. The outcome was not related to body mass index (BMI) or other patient characteristics. Subsequent continuous compression, weight control, physical exercise, and lifestyle alterations are still needed to achieve the maximum effect.

Section Summary: Liposuction for Lymphedema

Lymphedema can be associated with hypertrophy of fat cells due to the excessive fluid buildup with non-pitting of the skin. The evidence identified on liposuction for lymphedema includes case reports and case series, a few small, controlled trials, and uncontrolled observational studies, including one with 5-year follow-up. A systematic review of the controlled trials for arm lymphedema suggests a greater reduction in volume compared to compression alone, but durability of the procedure was not assessed. No comparative studies were identified for lymphedema of the lower limb. One RCT with numerous limitations was identified on liposuction for cervical lymphedema following head and neck cancer treatment. Limitations included the lack of blinding combined with subjective outcome measures, lack of a physiotherapy control, small sample size, and short duration of follow-up. In the observational study, the criteria for the procedure included subjective discomfort, failure of conservative treatment, and no or minimal pitting. The compression protocol was standardized and carefully reported, but there was no comparison to treatment with the complex compression protocol alone. Patients who had lymphedema for a mean of 10 years at the time of treatment experienced a complete reduction of excess volume with aspirate that contained an average of 94% fat. Patients were required to maintain compression after liposuction. Follow-up at 5 years indicated that the gains in arm volume achieved at 6 months after liposuction persisted for 5 years with continued compression. Further study is needed to evaluate the impact of liposuction on health outcomes when compared to a rigorous decongestive therapy protocol.

Physiologic Microsurgery to Treat Lymphedema

Clinical Context and Therapy Purpose

The purpose of physiologic microsurgery treatments for lymphedema in individuals 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 following PICO was used to select literature to inform this policy.

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 policy 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 2).

Interventions

This policy focuses on physiologic microsurgical interventions. 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 6 includes a brief description of the surgeries.

Table 6. 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	Healthy lymph nodes are transferred to the affected limb	• Inpatient procedure; requires

	and vascularized lymph node transfer		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 medical policy MED201.036 (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. (17) 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. (18)

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 QOL.

<u>Study Selection Criteria</u>
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.

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. (19) 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

Three systematic reviews specifically evaluating microsurgical procedures using the venous system (lymphaticovenular anastomosis [LVA], lymphovenous bypass) have been reported. (20, 21, 18) Three broader systematic reviews of treatments for lymphedema including several microsurgical procedures have also been reported. (19, 22, 23) Cornelissen 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 30. Forty publications on LVA and lymphovenous bypass were included across the 5 systematic reviews. Characteristics of the reviews are shown in Table 7.

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. (23) 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 8.

Coriddi et al. (2020) reported on a systematic review of PROs following surgical treatment of lymphedema, including lymphovenous bypass and VLNT. (18) 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 8.

Cornelissen et al. (2018) reported on a systematic review assessing the effect of LVA in breast cancer-related lymphedema. (20) 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. (21) 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 7. Characteristics of Systematic Reviews Assessing Lymphedema Surgeries Using the Venous System

Study	Dates	Studies	Participants	N (Range)	Design	Duration (Range)
Chang et al. (2021) (23)	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 cohort and case-control studies	LVA: 6 to 68 months
Coriddi et al. (2020) (18)	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 months (range, 4.2-43.1 months)

Cornelissen et al. (2018) (20)	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 months (2 months - 8 years)
Scaglioni et al. (2017) (21)	Up to 2016	18	With lymphedema of any cause except filariasis-related	939 (5 to 154) (number with breast cancer-related lymphedema NR)	• Prospective cohort, uncontrolled: 8 • Retrospective cohort, uncontrolled: 10	24 months (5-55 months)
Carl et al. (2017) (22)	2000-2016	Overall:69 LVA: 27 [a]	With extremity lymphedema of any cause	NR	• Observational, retrospective and prospective controlled and uncontrolled	LVA: 6-120 months
Leung et al. (2015) (19)	2000-2014	Overall:13 LVA: 6	With breast cancer- related lymphedema	146 (6 to 89)	• Observational [b], uncontrolled	LVA: 17 months - 8 years

LVA: lymphaticovenular anastomosis; NR: not reported; PRO: patient-reported outcome; 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 8. 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 8. 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) (23)				
Total N	134 (10 studies)	NR	37 (3 studies)	NR
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 versus after surgery (mean difference, 2.57; 95% CI, 1.75 to 3.38)	
I^2 (p)	NR (<.00001)		NR	
Coriddi et al. (2020) (18)				
Total N	NR	596	NR	NR
Narrative		• All studies showed an improvement in QOL (range, 50% - 100%) • Validated instruments: QOL improvement, 50% (1 study) • Non-validated instruments: QOL improvement, 57% - 100% (11 studies)		
Cornelissen et al. (2018) (20)				
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		• 1 study reported 2 complications (skin irritation on the contrast injection site)

		varied from 50% to 100%		• 10 studies reported no complications • 4 studies did not report whether complications occurred
Scaglioni et al. (2017) (21)				
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 number of cellulitis episodes present in all cases	
	• Excess Circumference Reduction (%)			
Carl et al. (2017) (22)				
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) (19)				
Total N	146	NR	NR	109
Narrative	• Mean percent reduction in volume at 1 year was 2%, 35%, and 42% in 3 studies • Mean absolute circumference reduction was 4.1			• No complications in 2 studies • Remaining studies did not report on complications

	cm and 0.85 cm in 2 studies			

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

Nonrandomized or Observational Studies

Additional single-arm studies have been published since the systematic reviews. (24) 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 versus 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 30. Characteristics of systematic reviews of surgeries for lymphedema are shown in Table 7. Ozturk et al. (2016) reported on a systematic review of VLNT for treatment of lymphedema. (25) 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. (19, 22, 25, 26) 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 10. (23, 18) Forte et al. (2019) reported results from a systematic review specifically of treatment with vascularized omental lymph node transfer. (26) Li et al. (2021) reported results from a systematic review specifically evaluating intra-abdominal VLNT. (27)

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. (28)

Table 9. Characteristics of Systematic Reviews Assessing Lymphedema Surgeries Using Lymph Tissue Transfer

Study	Dates	Studies	Participants	N (Range)	Design	Duration
Li et al. (2021) (27)	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 months
Chang et al. (2021) (23)	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 months)
Coriddi et al. (2020) (18)	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 months (range, 4.2 to 43.1 months)
Forte et al. (2019) (26)	Up to 2019	6	With lymphedema treated with VOLNT	137 (7 to 42)	Observational, uncontrolled	Mean, 9.6 months to 4 years
Demiri et al. (2018) (28)	NR	11	With breast cancer-related lymphedema	189 (8 to 42)	RCT: 1 Case series: 11	Mean, 38 months

			treated with VLNT			(range, 6 to 132 months)
Carl et al. (2017) (22)	2000-2016	Overall:69 VLNT:17[a]	With extremity lymphedema of any cause	NR	Observational or single-arm	NR
Ozturk et al. (2016) (25)	1980-2015	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 months
Leung et al. (2015) (19)	2000-2014	Overall:13 LNT: 6	With breast cancer-related lymphedema	80 (3 to 24)	Observational[b], uncontrolled	LNT: 6 months to 8 years

NR: not reported; RCT: randomized controlled trial; VLNT: vascularized lymph node transfer; LNT: lymph node transfer; LVB: lymphovenous bypass; QOL: quality of life; 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 10. In Ozturk (2016), Carl (2017), Forte (2019), Coriddi (2020), and Chang 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 and narrative summaries were provided by Ozturk (2016), Demiri (2018), and Leung (2015). 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 10. 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) (27)				

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) (23)				
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 versus after surgery (mean difference, 2.34; 95% CI, 1.82 to 2.85)	
I^2 (p)	NR (<.0001)		NR (<.00001)	
Coriddi et al. (2020) (18)				
Total N	NR	121	NR	NR
Narrative		• Validated instruments: range of QOL improvement, 84%-100% (3 studies) • Non-validated instruments: range of QOL improvement, 83%-100% (3 studies)		
Forte et al. (2019) (26)				
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)

				• 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) (28)				
Total N	NR	NR	NR	189
Narrative				Donor limb lymphedema: • 3 (1.6%) cases • 8 studies reported donor-site complications: ○ Seroma (n=8) ○ Lymphocele (n=3) ○ Lymphorrhea (n=2) ○ Wound infection (n=2) ○ Delayed wound healing (n=3) ○ Donor-site pain, numbness, or discomfort (n=9) ○ Transient edema of donor site (n=1) ○ Lymphedema of lower limb (n=3)
	Excess Circumference Reduction (%)			
Carl et al. (2017) (22)				
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	• Quantitative summaries not given

			• Improved function, appearance, and mood • Decreased pain	• 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) (25)				
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) (19)				
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; QOL: quality of life.

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. (29) Trial characteristics are shown in Table 11.

Table 11. Characteristics of RCTs of Lymphedema Surgeries Using Lymph Tissue Transfer

Study	Countries	Sites	Dates	Participants	Interventions	
					Surgery	Control
Dionyssiou et al. (2016) (29)	Greece	1	2011-2014	Women with stage II, unilateral, upper-limb lymphedema related to breast cancer treatment and 1+ infections during last year	18 received VLNT followed by physical therapy[a] for 6 months	18 received physical therapy[a] for 6 months

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.

RCT results reported in Dionyssiou (2016) are shown in Table 12. 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 versus 1.16; treatment effect not reported, p=.001). The trial had several limitations described in Tables 13 and 14. 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 12. 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) (29)		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 13. 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) (29)				4. Did not use validated measures of quality of life	

The study limitations stated in this table are those notable in the current literature 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 14. Study Design and Conduct Limitations of RCTs of Lymphedema Surgeries Using Lymph Tissue Transfer

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Follow-Up[d]	Power[e]	Statistical[f]
Dionyssiou et al. (2016) (29)	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 literature 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. (30-33) 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. (34)

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 following PICO was used to select literature to inform this policy.

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

Interventions
This policy 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. (35, 36) 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. (36)

<u>Study Selection Criteria</u>
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.

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. (37, 38) Systematic review characteristics are shown in Table 15. 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 30.

Table 15. Characteristics of Systematic Reviews of LYMPHA to Prevent Lymphedema

Study	Dates	Studies	Participants	N(Range)	Design	Duration, months
Ciudad et al. (2022) (38)	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) (37)	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; RCT: randomized controlled trial.

Results of the systematic review are shown in Table 16. 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 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 16. Results of Systematic Reviews of LYMPHA to Prevent Lymphedema

Study	Incidence of Lymphedema	Lymphedema Symptoms	Quality of Life	Complications
Ciudad et al. (2022) (38)				
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) (37)				
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 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.

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). (39) 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 17.

Table 17. Characteristics of RCTs of LYMPHA to Prevent Lymphedema

Study	Countries	Sites	Dates	Participants	Diagnosis of Lymphedema	Interventions	
						Active	**Comparator**
Boccardo et al. (2011) (39)	Italy	1	2008-2009	Women referred for complete axillary dissection for breast cancer treatment	Difference in excess volume of ≥100 mL versus 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 18. 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 19 and 20. 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 18. 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) (39)					
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 19. 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) (39)	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 years would be needed to assess incidence and durability

The study limitations stated in this table are those notable in the current literature 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 20. Study Design and Conduct Limitations of RCTs of LYMPHA to Prevent Lymphedema

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Boccardo et al. (2011) (39)	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 literature 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. (40) 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).

In addition to the literature identified above, other studies were reviewed. (41-52) These studies were limited by its small sample size (N=13 to N=106) and lacked controlled randomization. Several techniques were used (SAPL, LVA, VLNT, autologous lymph node transplantation [ALNT], or a combination of techniques) in these studies and the etiology of the lymphedema varied (cancer treatment, congenital causes, traumatic injury, postoperative complications). One study reported on the results from using vascularized lymph node transfer with hilar perforators in 21 patients (45) and another performed simultaneous breast and lymphatic reconstruction in 87 patients. (43)

AXILLARY REVERSE MAPPING IN SENTINEL LYMPH NODE BIOPSY (SLNB)

Clinical Context and Therapy Purpose

The purpose of axillary reverse mapping (ARM) simultaneous to breast cancer surgery is to prevent lymphedema in individuals who are being treated for breast cancer. The National Lymphedema Network has issued a set of lymphedema risk reduction practices. (53) Pre-treatment, these include patient education and arm and weight measurements. Post-treatment prevention measures include appropriate skin care; monitoring of activity/exercise level; avoiding limb constriction; use of well-fitting compression clothing, particularly during strenuous activity and air travel; and avoiding extreme temperatures. However, most recommendations are based on clinical opinion and direct evidence on lymphedema prevention is limited. A 2011 systematic review of preventive measures for lymphedema 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. (54) A subsequent 2016 review of the evidence for lifestyle-related breast cancer lymphedema risk factors that included air travel, ipsilateral arm blood pressure measurements, skin puncture, extreme temperatures, and skin infections found mostly low-level or inconclusive evidence of association. (55)

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals undergoing ARM at the time of SLNB for treatment of breast cancer.

Interventions

The therapy being considered is ARM.

During ARM, blue dye, fluorescence, or radioisotope is injected into the upper inner ipsilateral arm. This allows for differentiation of the lymphatic drainages of the breast from those of the arm.

Comparators
The comparator of interest is 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. Axillary reverse mapping could also be used in conjunction with standard care.

Outcomes
Outcomes of interest include diagnosis of lymphedema, lymphedema symptoms, quality of life, and treatment-related morbidity.

Diagnosis of lymphedema is based on history and physical examination, although imaging may also be used. Symptoms that may indicate lymphedema include chronic swelling, atrophic skin changes, and recurrent infections. 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 a separate policy.

The International Society of Lymphology (3) categorizes lymphedema stage and severity as outlined in Table 2.

As development of lymphedema can occur 3 or more years following breast cancer surgery, duration of follow-up of a year or more is needed to accurately assess lymphedema risk.

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. (17) 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. (18)

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 long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

A 2017 systematic review conducted by Parks et al. (2017) (56) designed to assess comparative, clinical trial evidence comparing SLNB + ARM versus SLNB alone failed to identify any studies meeting inclusion criteria. The review authors concluded that a large RCT specifically comparing SLNB + ARM to SLNB alone should be performed before ARM could be utilized in routine clinical practice.

Two systematic reviews conducted by Wijaya et al. (2020) (57) and Han et al. (2016) (58) assessed ARM in individuals undergoing SLNB or axillary lymph node dissection (ALND), and conducted subgroup analyses limited to those individuals who underwent SLNB. The reviews included a similar set of prospective, nonrandomized, single-arm studies (Table 21).

Table 21. Primary Studies Included in Systematic Reviews & Meta-Analyses of ARM in SLNB

	Systematic Reviews	
Primary Studies	**Wijaya et al. (2020) (57)**	**Han et al. (2016) (58)**
Boneti et al. (2009)* (59)		●
Boneti et al. (2012)* (60)		●
Casabona et al. (2009) (61)	●	●
Connor et al. (2013)* (62)	●	●
Deng et al. (2011) (63)	●	●
Han et al. (2012) (64)	●	●
Kuusk et al. (2014) (65)	●	●
Ma et al. (2019) (66)	●	
Noguchi et al. (2012) (67)	●	●

Ochoa et al. (2014)* (68)	●	●
Rubio et al. (2012) (69)	●	●
Sakurai et al. (2014) (70)	●	●
Tummel et al. (2017)* (71)	●	

ARM:axillary reverse mapping; SLNB:sentinel lymph node biopsy
*Study conducted in the United States

Table 22. Study Characteristics of Systematic Reviews & Meta-Analyses of ARM in SLNB

Study	Dates	Studies	Participants	N (Range)	Design	Duration
Wijaya et al. (2020) (57)	Through January 2020	11	Adults undergoing ARM and SLNB	1,889 (36-472)	Prospective, nonrandomized, single-arm studies	Mean duration not reported (range 9 to 45 months in 9 studies, duration not reported in 2 studies)
Han et al. (2016) (58)	Through September 2015	11	Adults undergoing ARM and SLNB	1,741 (36-372)	Prospective, nonrandomized, single-arm studies	Mean duration not reported (range 6 to 45 months in 10 studies, duration not reported in 1 study)

ARM: axillary reverse mapping; SLNB: sentinel lymph node biopsy

Table 23. Results of Systematic Reviews & Meta-Analyses of ARM in SLNB

Study	BCRL	ARM Lymph Node/Lymphatics Identification Rate	SLN-ARM Crossover Rate
Wijaya et al. (2020) (57)			
Total N	NR	N=1424	N=1817
Pooled rate (95% CI)	2% (1% to 3%)	37.0% (31.0% to 44.0%)	12.0% (6.0% to 19.0%)

I^2	26.1%	83.5%	93.7%
Han et al. (2016) (58)			
Total N	N=556	N=1539	N=1297
Pooled rate (95% CI)	2.7% (1.0% to 7.2%)	38.2% (32.9% to 43.8%)	19.6% (14.4% to 26.1%)
I^2	66.6%	70.5%	89.7%

ARM: axillary reverse mapping; BCRL: breast cancer-related lymphedema; CI: confidence interval; NR: not reported; SLN: sentinel lymph node; SLNB: sentinel lymph node biopsy

Nonrandomized Studies

The largest nonrandomized, single-arm study included in the reviews described above was conducted by Tummel et al. (2017). (71) The study was conducted in the United States and included 654 individuals enrolled from 2007 to 2013, of whom 492 underwent ARM + SLNB. ARM was accomplished through split mapping, that is, technetium injection was used to identify sentinel lymph nodes, and isosulfan blue dye was used to identify axillary lymph nodes and lymphatics. ARM identified axillary lymphatics in 138 individuals (29.2%), which were spared in 107 of these individuals (77.5%). After a mean 26 months follow-up, lymphedema rates ranged from 0.8% to 3.4%, depending on lymphedema definition. Specifically, among individuals who underwent ARM and SLNB, lymphedema rate was 0.8% (3/350) based on arm volumetric measure and 2.5% (9/350) based on subjective patient report, resulting in a total rate of 3.4%. Lymphedema rates were similar when stratified according to individuals in whom ARM successfully identified lymph nodes and lymphatics (1.2%; 1/79) and those who did not have ARM-identified lymph nodes and lymphatics (1.7%; 5/291). There were no instances of axillary recurrence in individuals with ARM-identified and preserved nodes. This study is primarily limited by its single-arm, uncontrolled design, and comparative evidence is needed to accurately determine the net health benefit of ARM in SLNB.

Section Summary: Axillary Reverse Mapping in Sentinel Lymph Node Biopsy

The evidence for ARM in individuals undergoing SLNB includes nonrandomized studies and systematic reviews of those studies. Evidence from 2 systematic reviews found ARM identified axillary lymphatics in about 38% of individuals undergoing SLNB, with lymphedema rates of 2% to 3% in individuals who underwent ARM during SLNB. Other outcomes such as quality of life were not reported. The systematic reviews had numerous limitations, including unclear mean duration of follow-up and inclusion of only single-arm, uncontrolled studies. Evidence from well-designed RCTs or controlled cohort studies is needed to determine the net health benefit of ARM in SLNB.

Axillary Reverse Mapping in Axillary Lymph Node Dissection

Clinical Context and Therapy Purpose

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals undergoing ARM at the time of ALND for treatment of breast cancer.

Interventions
The therapy being considered is ARM.

During ARM, blue dye, fluorescence, or a radioisotope is injected into the upper inner ipsilateral arm. This allows for differentiation of the lymphatic drainages of the breast from those of the arm.

Comparators
The comparator of interest is 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. Axillary reverse lymphatic mapping could also be used in conjunction with standard care.

Outcomes
Outcomes of interest include diagnosis of lymphedema, lymphedema symptoms, quality of life, and treatment-related morbidity.

Diagnosis of lymphedema is based on history and physical examination, although imaging may also be used. Symptoms that may indicate lymphedema include chronic swelling, atrophic skin changes, and recurrent infections. 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 a separate policy.

The International Society of Lymphology (3) categorizes lymphedema stage and severity as outlined in Table 2.

As development of lymphedema can occur 3 or more years following breast cancer surgery, duration of follow-up of a year or more is needed to accurately assess lymphedema risk.

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. (17) 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. (18)

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 long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

Two systematic reviews of ARM in individuals undergoing ALND have included RCTs and nonrandomized studies; study characteristics are summarized in Table 24. As the reviews reported different outcomes, study results are summarized narratively below.

A systematic review and meta-analysis conducted by Guo et al. (2021) included 5 RCTs of ARM in individuals undergoing ALND for treatment of breast cancer. (72) The review found individuals who had ARM had a lower risk of breast cancer-related lymphedema (BCRL) of the arm compared with no ARM (4.7% vs. 18.8%; OR, 0.20; 95% CI, 0.13 to 0.29), but there was some heterogeneity present in the analysis (I^2=38%). This finding was consistent in sensitivity analyses that stratified studies according to study setting (single center or multicenter), mapping agent (blue dye alone and in combination with fluorescence or a radioisotope), and measurement of arm lymphedema (volumetric measurement or arm circumference measurement). When stratified according to duration of follow-up, odds ratios for ARM versus no ARM and risk of BCRL were 0.70 (95% CI, 0.32 to 1.51) at 6 months, 0.18 (95% CI, 0.10 to 0.33) at 6 to 12 months, and 0.23 (95% CI, 0.15 to 0.36) at 20 months follow-up, based on 3 studies included in analyses at each time point. Oncological safety, based on rate of metastatic ARM nodes, was not significantly different between ARM and no ARM groups based on analysis of 2 studies (1% vs. 0%). Other outcome measures such as quality of life were not reported. The review's findings were heavily influenced by one study (73) conducted in China that accounted for 82% of the total review population (1354/1659). Risk of bias among the included studies was assessed using Cochrane Collaboration criteria, and all of the included studies were judged to have low or moderate risk of bias. The review is limited by the inclusion of a small number of RCTs with results dominated by 1 trial, and heterogeneity among the included studies in terms of outcome assessment and duration of follow-up.

A 2020 systematic review and meta-analysis conducted by Wijaya et al. (2020) included 29 studies, 4 of which were RCTs included in the Guo systematic review discussed above, and the remaining studies were prospective, nonrandomized studies. (57) Based on a pooled analysis of 27 studies, ARM was associated with an 82% (95% CI, 77% to 87%; I^2=88%) identification rate of axillary lymph nodes and lymphatics, and a crossover rate between ARM and sentinel lymph nodes of 12% (95% CI, 6% to 19%; I^2=94%) in pooled analysis of 11 studies. Subgroup analyses could not account for the heterogeneity of either of these findings. The prevalence of lymphedema was 14% (95% CI, 5% to 26%; I^2=93%) in a pooled analysis of 6 studies, and preservation of visualized ARM lymph nodes and lymphatics was associated with a lower risk of lymphedema when compared with resection of ARM nodes (OR, 0.27; 95% CI, 0.20 to 0.36; I^2=31%).

In terms of oncological safety, the review found the pooled rate of metastatic ARM nodes was 13% (95% CI, 10% to 17%; I^2=75%) in an analysis of 27 studies. When comparing metastatic rate according to breast cancer stage, the review found individuals with stages pN0-1 had a significantly lower risk of ARM metastasis than those with pN2-3 disease (OR, 0.11; 95% CI, 0.05 to 0.25; I^2=23.4%) based on analysis of 6 studies. Analysis of 5 studies did not find a significant association between preoperative neoadjuvant chemotherapy and rate of ARM node metastasis (OR, 1.20; 95% CI, 0.74 to 1.94; I^2=49.4%), suggesting that neoadjuvant chemotherapy may not reduce the risk of metastatic ARM nodes.

The studies included in the review had numerous limitations, including unclear and/or inadequate duration of follow-up, lack of adjustment for confounding variables, and varying methods of diagnosing lymphedema. The review is also limited by including a mix of randomized and nonrandomized studies with limited subgroup analysis according to study design, and pooled estimates generally demonstrating high heterogeneity that could not be accounted for in subgroup analyses.

Table 24. Study Characteristics of Systematic Reviews & Meta-Analyses of ARM in ALND

Study	Dates	Studies	Participants[1]	N (Range)	Design	Duration
Guo et al. (2021) (72)	Through December 2020	5	Adult females undergoing ALND and ARM or no ARM	1659 (48 to 1354)	RCT	Mean 24 months (range 6 to 37 months)
Wijaya et al. (2020) (57)	Through January 2020	29	Adults undergoing ARM and ALND	4954 (21 to 1354)	RCT (4) or prospective, nonrandomized studies (25)	Mean not reported (range 6 to 45 months in 17

						studies, duration not reported in 12 studies)

ALND: axillary lymph node dissection; ARM: axillary reverse mapping; RCT: randomized controlled trial; SLNB: sentinel lymph node biopsy
[1] Key eligibility criteria.

Randomized Controlled Trials

As noted above, the RCT reported by Yuan et al. (2019) (73) contributed data from 1,354 individuals included in both the Guo et al. (2021) (72) and Wijaya et al. (2020) (57) systematic reviews and is described below as it is the largest RCT of ARM for ANLD published to date.

Yuan et al. (2019) randomized 1,354 individuals undergoing ALND with ARM (n=689) or standard ALND without ARM (n=665). (73) Study characteristics are summarized in Table 25. Of the 689 individuals randomized to the ALND + ARM group, 131 were excluded from the analysis due to lack of visualization of either arm sentinel lymph nodes (n=116) or lymphatics (n=13), resulting in an axillary lymphatic system identification rate of 81% (558/689) with ARM. An additional 15 individuals in the ALND + ARM group and 17 individuals in the standard ALND group were lost to follow-up, resulting in 543 and 648 individuals available for analysis, respectively. Study results are summarized in Table 26. After a median 37 months follow-up, the rate of objective and subjective lymphedema was lower in the ALND + ARM group than the standard ALND group. Rates of local, regional, and distant cancer recurrence were generally similar in both groups. However, axillary recurrence was twice as likely in the ANLD + ARM group compared with the standard ANLD group (2.9% vs. 1.4%; p=.03), and the rate of ARM node metastasis in the ALND + ARM group was 7% (38/558).

Table 25. Study Characteristics of RCTs of ARM in ALND

Study; Trial	Countries	Sites	Dates	Participants[2]	Interventions[1]	
					Active	**Comparator**
Yuan et al. (2019) (73)	China	2 (1 surgeon)	2013-2017	Adults with clinically node-positive breast cancer or positive sentinel lymph node(s) and no neoadjuvant chemotherapy	n=689 ALND + ARM, with the intent of preserving axillary lymphatics	n=665 Standard ALND (no ARM)

ALND: axillary lymph node dissection; ARM: axillary reverse mapping; RCT: randomized controlled trial
[1] Number randomized; intervention; mode of delivery; dose (frequency/duration).
[2] Key eligibility criteria

Table 26. Study Results of RCTs of ARM in ALND

Study	BCRL (Arm, by volumetric measure)	BCRL (Arm, by subjective report)	Local Recurrence	Regional Recurrence	Axillary Recurrence	Distant Metastasis
Yuan et al. (2019) (73)	N=1,191	N=1,191	N=1,191	N=1,191	N=1,191	N=1,191
ARM n/N (%)	18/543 (3.3%)	33/543 (6.1%)	8/543 (1.5%)	10/543 (1.4%)	18/543 (2.9%)	27/543 (5.0%)
No ARM n (%)	99/648 (15.3%)	104/648 (16.0%)	9/648 (1.4%)	8/648 (1.2%)	9/648 (1.4%)	30/648 (4.6%)
p value	<.001	<.001	.90	.39	.03[1]	.78

ALND: axillary lymph node dissection; ARM: axillary reverse mapping; BCRL: breast cancer-related lymphedema; CI: confidence interval; HR: hazard ratio; NNT: number needed to treat; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk.
[1] p-value calculated by BCBSA

The purpose of the study limitations tables (Tables 27 and 28) is to display notable limitations identified in each study. In addition to the limitations delineated below, the study author's noted that ARM is not routinely used in clinical practice because of uncertain oncological safety, which remains unclear.

Table 27. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Yuan et al. (2019 (73)		5. Unclear if directly applicable to US-based practice due the use of a			

		staged tracing procedure			

The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.
[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 28. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Yuan et al. (2019) (73)	3. Allocation concealment is unclear	3, 5. Blinding of participants is unclear; unclear outcome assessors for lymphedema		5. Post-randomization exclusion of 131 individuals in the intervention group	4. Not adequately powered based on the power assumption of a 90% axillary lymphatics detection rate (actual detection rate was 81%)	

The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.
[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.

Section Summary: Axillary Reverse Mapping in Axillary Lymph Node Dissection

The evidence for ARM in individuals undergoing ALND includes RCTs, nonrandomized studies, and systematic reviews of those studies. Pooled evidence from a systematic review of 5 RCTs showed a lower risk of lymphedema with ARM compared with no ARM (OR, 0.20; 95% CI, 0.13 to 0.29), and another systematic review of RCTs and nonrandomized studies found a pooled lymphedema prevalence of 14% and lower risk of lymphedema with ARM and preserved axillary lymph nodes compared with resected lymph nodes (OR, 0.27; 95% CI 0.20 to 0.36). In the same review, ARM was associated with an 82% identification rate of axillary lymph nodes and lymphatics, and a crossover rate between ARM and sentinel lymph nodes of 12%. Other health outcomes, including quality of life, were not reported. The safety of ARM in ALND has not been established, and the rate of metastatic ARM nodes was 13% based on pooled analysis of 27 studies in one systematic review. ARM in ALND was also associated with a lower risk of lymphedema in the largest RCT conducted to date, which was also included in the systematic reviews, but oncological safety could not be determined, and the trial also had important study relevance and design limitations.

Summary of Evidence

Lipedema

For individuals with lipedema who receive liposuction, the evidence includes case series and several before- and after-treatment studies that suggest that liposuction may reduce pain and improve quality of life (QOL) at up to 12-year follow-up. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with lymphedema who receive liposuction, the evidence includes case reports and case series, a few small, controlled trials, and uncontrolled observational studies, including one with 5-year follow-up. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. The available studies suggest that arm volume can be reduced by the procedure, but follow-up is limited, and the trials have a number of other limitations that include lack of blinding, subjective outcome measures, lack of a physiotherapy control, and small sample size. The most rigorous evidence to date is a consecutive series of over 100 patients with detailed methodology. This series indicates that patients who have failed conservative therapy can have complete reversal of excess volume in the short term and that gains can persist through 5 years of follow-up when compression therapy is continued after surgery. However, no studies were identified that compared liposuction to a decongestive therapy protocol with continued compression. Further study is needed to evaluate the impact of liposuction when compared to a decongestive therapy protocol. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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 randomized controlled trial (RCT), observational studies, and systematic reviews. Relevant outcomes are symptoms, morbid events, functional outcomes, health status measures, QOL, resource utilization, and treatment-related morbidity. Several physiologic microsurgeries have been developed; examples include lymphaticovenular anastomosis and vascularized lymph node transfer. No RCTs of lymphaticovenular anastomosis 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 versus conservative treatment or decongestive therapy, or the comparative efficacy of different microsurgery techniques. RCTs 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, QOL, and treatment-related morbidity. Lymphatic Microsurgical Preventing Healing Approach (LYMPHA) 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 Lymphatic Microsurgical Preventing Healing Approach group and 30% in the control group by 18 months of follow-up. However, because the cumulative incidence of lymphedema of 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 2 controlled observational studies with inadequate description of control selection and uncontrolled studies. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with breast cancer undergoing sentinel lymph node biopsy (SLNB) who receive axillary reverse mapping (ARM), the evidence includes nonrandomized studies and systematic reviews of those studies. Relevant outcomes are symptoms, change in disease status, morbid events, quality of life, and treatment-related morbidity. Evidence from 2 systematic reviews found ARM identified axillary lymphatics in about 38% of individuals undergoing SLNB, with lymphedema rates of 2% to 3% in individuals who underwent ARM during SLNB. Other outcomes such as quality of life were not reported. The systematic reviews had numerous limitations, including unclear mean duration of follow-up and inclusion of only single-arm,

uncontrolled studies. Evidence from well-designed RCTs or controlled cohort studies is needed to determine the net health benefit of ARM in SLNB. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with breast cancer undergoing axillary lymph node dissection (ALND) who receive ARM, the evidence includes RCTs, nonrandomized studies, and systematic reviews of those studies. Relevant outcomes are symptoms, change in disease status, morbid events, quality of life, and treatment-related morbidity. Pooled evidence from a systematic review of 5 RCTs showed a lower risk of lymphedema with ARM compared with no ARM (odds ratio [OR], 0.20; 95% confidence interval [CI], 0.13 to 0.29), and another systematic review of RCTs and nonrandomized studies found a pooled lymphedema prevalence of 14% and lower risk of lymphedema with ARM and preserved axillary lymph nodes compared with resected lymph nodes (OR, 0.27; 95% CI, 0.20 to 0.36). In the same review, ARM was associated with an 82% identification rate of axillary lymph nodes and lymphatics, and a crossover rate between ARM and sentinel lymph nodes of 12%. Other health outcomes, including quality of life, were not reported. The safety of ARM in ALND has not been established, and the rate of metastatic ARM nodes was 13% based on pooled analysis of 27 studies in one systematic review. ARM in ALND was associated with a lower risk of lymphedema in the largest RCT conducted to date, which was also included in the systematic reviews, but oncological safety could not be determined, and the trial also had important study relevance and design limitations. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

German Society of Phlebology (DGP)

Revised guidelines were published on lipedema that were developed under the auspices of and funded by the DGP. The summary states that the combination of conservative and surgical therapies can achieve significant improvements in findings and alleviation of complaints. The initial treatment attempt should involve conservative measures. If complaints fail to improve, liposuction should be considered; in a considerable proportion of patients, liposuction can considerably reduce or even eliminate conservative therapy. (74)

Dutch Society of Dermatology and Venereology

In 2017, the First Dutch guidelines on lipedema using the international classification of functioning, disability and health noted the “Tumescent liposuction is the treatment of choice for patients with a suitable health profile and/or inadequate response to conservative and supportive measures.” (75)

Canadian Agency for Drugs and Technologies in Health (CADTH)

A 2019 Review of Clinical Effectiveness and Guidelines for Liposuction for the Treatment of Lipedema published by the CADTH stated the following: Liposuction is the main surgical interventions for lipedema. Commonly used liposuction methods for lipedema are tumescent anesthesia (TA) liposuction, and water assisted liposuction (WAL). In TA liposuction, tumescent is infused in the subcutaneous tissues to cause the fat cells to swell and vessels to constrict;

then blunt micro-cannulas are used to suction the fat. Water assisted liposuction uses a pressure spray of tumescent fluid to dislodge the fat from the connective tissue, rather than utilizing a cannula. Unlike traditional liposuction, both TA and WAL rely on the local anesthetics in the tumescent fluid and do not require general anesthesia. (4)

International Consensus Conference on Lipedema

A 2017 international consensus conference on lipedema identified studies from Germany that reported long-term benefits for up to 8 years following liposuction, concluding that lymph-sparing liposuction is the only effective treatment for lipedema. (76)

National Lymphedema Network

The National Lymphedema Network published a position paper on the diagnosis and treatment of lymphedema in 2011. (77) 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."

International Society of Lymphology

In 2020, the International Society of Lymphology published a consensus document on the diagnosis and treatment of peripheral lymphedema. (3) The consensus of the panel was that liposuction has been shown to completely reduce non-pitting lymphedema due to excess fat deposition, but long-term management requires strict patient adherence to compression garments.

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 (Lymphatic Microsurgical Preventing Healing Approach [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. (78) The

document stated that "the Panel agrees that LVA and VLNT may be effective for early secondary breast cancer-related lymphedema."

The 2022 American Society of Breast Surgeons consensus guideline on axillary management of patients with in-situ and invasive breast cancer indicates that axillary reverse mapping (ARM) is one of several promising techniques for prevention of lymphedema, but also states "well-designed prospective studies with uniform criteria for patient selection, procedure, and outcome assessment are needed." The guideline recommends considering ARM if it is readily available when axillary lymph node dissection (ALND) is required. (79)

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. (80) 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. (81)

American Association of Plastic Surgeons

A 2021 consensus document sponsored by the American Association of Plastic Surgeons evaluated the evidence on surgical treatment of lymphedema. (11) The conference recommended, based on grade 1C (very low quality) evidence, that there is a role for debulking procedures such as liposuction and for liposuction combined with physiologic procedures in reducing the nonfluid component in lymphedema.

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. (11) 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."

The 2021 publication of the consensus recommendations did not include any recommendations specific to the use of ARM, but the following general statement was included within the text of the publication: "mapping of the lymphatics is encouraged when harvesting lymph nodes adjacent to the limbs such as reverse lymphatic mapping to avoid lymphatics draining the limb and to minimize the risk of donor-site lymphedema."

National Institute for Health and Care Excellence (NICE)

The National Institute for Health and Care Excellence (NICE) issued clinical guidance addressing the use of liposuction for chronic lymphedema in 2022. (82) The guidance reviewed the evidence and concluded that current evidence on the safety and efficacy of liposuction for chronic lymphedema is adequate to support the use of this procedure provided that standard arrangements are in place for clinical governance, consent, and audit. The evidence on safety shows that the potential risks include venous thromboembolism, fat embolism, and fluid overload. Patient selection should only be done by a multidisciplinary team with expertise in managing lymphedema. The procedure should only be done in specialist centers by clinicians with training and expertise in liposuction for lymphedema following agreed perioperative protocols.

The NICE also issued guidance for liposuction in lipedema in 2022. (83) They recommend liposuction for lipedema should be used only in the research setting because the safety data for liposuction in lipedema is inadequate but concerning.

Ongoing and Unpublished Clinical Trials
Some currently ongoing and/or unpublished trials that might influence this policy are listed in Table 29.

Table 29. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
NCT04272827	Multicenter, Controlled, Randomized, Investigator-blinded Clinical Study on Efficacy and Safety of Surgical Therapy of Lipedema Compared to Complex Physical Decongestive Therapy Alone (LIPLEG)	450	Sep 2025
NCT03428581	Preventing Lymphedema in Patients Undergoing Axillary Lymph Node Dissection Via Axillary Reverse Mapping and Lympho-venous Bypass	264	Feb 2024
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
NCT05040685	Axillary Reverse Mapping (ARM): Validation of Surgical Technique in Breast Cancer Surgery	30	Dec 2023
NCT03428581	Preventing Lymphedema in Patients Undergoing Axillary Lymph Node Dissection Via Axillary Reverse Mapping and Lympho-venous Bypass	264	Feb 2026
NCT05094102	Intraoperative Evaluation of Axillary Lymphatics for Breast Cancer Patients Undergoing Axillary Surgery	9	Apr 2023
NCT03927027	ARM: Axillary Reverse Mapping - A Prospective Trial to Study Rates of Lymphedema and Regional Recurrence After Sentinel Lymph Node Biopsy and Sentinel Lymph Node Biopsy Followed by Axillary Lymph Node Dissection With and Without Axillary Reverse Mapping	534	Jan 2024
NCT04446494	Identification and Preservation of Arm Lymphatics (DEPART) in Axillary Dissection for Breast Cancer to Reduce Arm Lymphedema Events: A Multicenter Randomized Clinical Tria	1200	Sep 2025

NCT: national clinical trial.

APPENDIX

Appendix Table 30. Comparison of Studies Included in Systematic Reviews of Lymphedema Surgeries Using the Venous System

Study	Chang et al. (2021) (23)	Coriddi et al. (2020) (18)	Cornelissen et al. (2018) (20)	Scaglioni et al. (2017) (21)	Carl et al. (2017) (22)	Leung et al. (2015) (19)
O'Brien et al. (1977)				●		
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)				●		
Chen et al. (2015)			●	●	●	
Hara et al. (2015)				●		
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 31. Comparison of Studies Included in Systematic Reviews of Lymphedema Surgeries Using Lymph Tissue Transfer

Study	Li et al. (2021) (27)	Chang et al. (2021) (23)	Coriddi et al. (2020) (18)	Forte et al. (2019) (26)	Ozturk et al. (2016) (25)	Demiri et al. (2018) (28)	Carl et al. (2017) (22)	Leung et al. (2015) (19)
Abalmosov et al. (2003)					●			
Abbas Khan et al. (2011)								●
Agko et al. (2018)	●							
Akita et al. (2015)					●			
Asuncion et al. (2018)		●	●					
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)							●	
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. (2020)	●							
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 32. Comparison of Studies Included in Systematic Reviews of LYMPHA to Prevent Lymphedema

	Ciudad et al. (2022) (38)	Jorgensen et al. (2017) (37)
Orefice et al. (1988)	●	●
Takeishi et al. (2006)	●	●

Boccardo et al. (2009)	●	●
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

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	15758, 15830, 15832, 15833, 15834, 15835, 15836, 15837, 15838, 15839, 15876, 15877, 15878, 15879, 38308, 38999
HCPCS Codes	None

*Current Procedural Terminology (CPT®) ©2022 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <http://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
02/01/2024	Document updated with literature review. Coverage unchanged. Added/updated the following references: 2-4, 6, 8-10, 12, 13, 27, 38, 53-73, 80-82, and 84.
02/01/2023	Reviewed. No changes.
04/01/2022	Document updated with literature review. The following changes were made to Coverage: 1) Added "including any subsequent revisions" to the suction assisted protein lipectomy for the treatment of lipedema medically necessary statement; 2) Added an experimental, investigational and/or unproven statement for reverse lymphatic mapping; and 3) Added NOTE 4: This policy does not address abdominal procedures, refer to SUR716.001 Cosmetic and Reconstructive Procedures for specific language on abdominal procedures, including but not limited to, panniculectomy and suction assisted lipectomy. References 10, 15, 18, 24, 52 and 53 were added and others updated.
04/01/2021	Reviewed. No changes.
11/15/2020	Document updated with literature review. The following change was made to Coverage: Added conditional criteria for suction assisted protein lipectomy for the treatment of lipedema. Added references 1-2, 4-8, 42-47 and 49. Title changed from Surgery for Lymphedema.
02/15/2020	Document updated with literature review. The following changes were made to Coverage: 1) Prevention or treatment was added to the Surgery for Lymphedema experimental, investigational and/or unproven statement. 2) Suction assisted protein lipectomy (also known as suction lipectomy and liposuction) is considered experimental, investigational and/or unproven for lymphedema, including but not limited to as a result of treatment for melanoma was added. 3) NOTE 2: For suction assisted lipectomy in reconstructive and contralateral mammaplasty see medical policy SUR716.011 was added. 4) NOTE 3: For the use of liposuction in reduction mammoplasty see medical policy SUR716.012 was added. References 1-10, 12-21, and 27-37 were added and some references removed.
04/15/2017	Document updated with literature review. The following change was made to the Coverage Section: A NOTE was added that states "See SUR716.001 Cosmetic and Reconstructive Procedures for CoolSculpting (may also be known as cryolipolysis or fat freezing)."
04/15/2016	Document updated with literature review. Coverage unchanged.
10/01/2015	Reviewed. No changes.
12/01/2014	Document updated with literature review. The following example has been added to the coverage statement: vascularized lymph node transfer. CPT/HCPCS code(s) updated.
02/01/2012	Document updated with literature review. Coverage unchanged.

11/15/2010	Document updated with literature review. Coverage unchanged. CPT code added.
07/01/2009	New medical document