7.01.173	Axillary Reverse Mapping for Prevention of Breast Cancer-Related Lymphedema		
Original Policy Date:	February 1, 2023	**Effective Date:**	January 1, 2024
Section:	7.0 Surgery	**Page:**	Page 1 of 18

Policy Statement

I. Axillary reverse mapping/reverse lymphatic mapping performed during sentinel lymph node biopsy to prevent lymphedema in individuals who are being treated for breast cancer is considered **investigational**.

II. Axillary reverse mapping/reverse lymphatic mapping performed during axillary lymph node dissection to prevent lymphedema in individuals who are being treated for breast cancer is considered **investigational**.

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

Policy Guidelines

The following codes may be used for this treatment:

- **38792**: Injection procedure; radioactive tracer for identification of sentinel node
- **38900**: Intraoperative identification (e.g., mapping) of sentinel lymph node(s) includes injection of non-radioactive dye, when performed (List separately in addition to code for primary procedure)
- **C9756**: Intraoperative near-infrared fluorescence lymphatic mapping of lymph node(s) (sentinel or tumor draining) with administration of indocyanine green (ICG) (List separately in addition to code for primary procedure)

Description

Surgery and radiotherapy for breast cancer can lead to lymphedema and are some of the most common causes of secondary lymphedema. Lymphedema is associated with a significant impact on quality of life, and there is no cure for lymphedema. Axillary reverse mapping, also called reverse lymphatic mapping, has been developed with the intent of sparing axillary lymph nodes and lymphatics during breast cancer surgery, minimizing disruption and potentially reducing the risk of subsequent lymphedema development.

Related Policies

- Bioimpedance Devices for Detection and Management of Lymphedema
- Surgical Treatments for Breast Cancer-Related Lymphedema

Benefit Application

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

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these

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instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

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). Mapping agents used to visualize lymphatic pathways (e.g. isosulfan blue,[5,] indocyanine green[6,]) may be subject to FDA regulation.

Rationale

Background
Lymphedema
Lymphedema is an accumulation of fluid due to a disruption of lymphatic drainage. Lymphedema can be caused by congenital or inherited abnormalities in the lymphatic system (primary lymphedema) but is most often caused by acquired damage to the lymphatic system (secondary lymphedema). Breast cancer treatment is one of the most common causes of secondary lymphedema. Specific treatment-associated risk factors associated with lymphedema development include:

- Lymphadenectomy
- Dissection or disruption of axillary lymph nodes; increasing the number of dissected/disrupted lymph nodes increases lymphedema risk
- Radiation therapy

The risk of breast cancer-related lymphedema is also increased in overweight or obese individuals, and in those with postoperative infections. Studies have suggested that Black breast cancer survivors are nearly 2.2 times more likely to develop breast cancer-related lymphedema compared to White breast cancer survivors.[1,] These observations may be linked to racial disparities with regards to access to treatment and the types of treatments received. Black women are more likely than White women to undergo axillary lymph node dissection, which is associated with greater morbidity than the less invasive sentinel lymph node biopsy. While this may be explained in part by Black individuals having a higher likelihood of being diagnosed with more aggressive tumors, there is evidence that even when adjusting for stage and grade of tumors, Black women are more likely to undergo axillary lymph node dissection, putting Black women at greater risk of breast cancer-related lymphedema. Additionally, Black breast cancer survivors, on average, have higher body mass indexes than White breast cancer survivors, which could contribute to the development of lymphedema in this setting as well.

Development of lymphedema may take months or years following breast cancer treatment, and the true prevalence of breast cancer-related lymphedema is unclear.[2,] Systematic reviews have found lymphedema rates up to 13% in individuals undergoing sentinel lymph node biopsy (SNLB) and as high as 77% in those undergoing axillary lymph node dissection (ANLD).[3,] The addition of radiation therapy to SNLB or ANLD may also increase risk of lymphedema. A prospective study of 1,815 individuals published in 2020 found a 5-year cumulative incidence of breast cancer-related lymphedema of 9.5%, which ranged widely from 8% to 30% when stratified according to type of treatment. The lowest incidence of lymphedema was found among those undergoing SLNB only (8%), increasing to 11% for SNLB + regional lymph node radiation, 25% for ANLD only, and 30% for ANLD + RLNR.[4,] While SNLB was associated with a lower lymphedema risk, some risk remains, particularly for those with multiple positive axillary nodes for whom the standard for care is ANLD with or without radiation.

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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 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 have occurred, palliative surgery using reductive techniques such as liposuction may be performed.

Axillary Reverse Mapping

Axillary reverse mapping (ARM) involves subcutaneous administration of blue dye, fluorescence (i.e., indocyanine green), or radioisotopes to allow for visualization of the lymphatic drainage pathways of the arm and breast. This visualization is intended to distinguish and enable preservation of axillary lymph nodes and lymphatics in individuals undergoing SLNB and/or ANLD. It is believed that because the axilla and breast have mostly separate drainage pathways, the risk of lymphedema is reduced by avoiding the removal of lymph nodes and lymphatics that only drain the axilla identified through ARM. In the event that ARM reveals that the axillary nodes cannot be spared, for example due to crossover of sentinel and axillary nodes, lymphatic physiologic microsurgery has been explored as a method to preserve the axillary nodes, though evidence is limited

Literature Review

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

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

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

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Axillary Reverse Mapping in Sentinel Lymph Node Biopsy

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.[7] 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.[8] 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.[9]

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

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 policy 2.01.82 (bioimpedance devices for detection and management of lymphedema).

The International Society of Lymphology[10] categorizes lymphedema stage and severity as follows:

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

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Stage	Severity
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

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.[11,] 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.[12,]

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.

Review of Evidence

Systematic Reviews

A 2017 systematic review conducted by Parks et al (2017)[13,] 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)[14,] and Han et al (2016)[15,] 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 1).

Table 1. Primary Studies Included in Systematic Reviews & Meta-Analyses of ARM in SLNB

	Systematic Reviews	
Primary Studies	**Wijaya et al (2020)[14,]**	**Han et al (2016)[15,]**
Boneti et al (2009)*[16,]		●
Boneti et al (2012)*[16,]		●
Casabona et al (2009)[17,]	●	●
Connor et al (2013)*[18,]	●	●
Deng et al (2011)[19,]	●	●
Han et al (2012)[20,]	●	●
Kuusk et al (2014)[21,]	●	●
Ma et al (2019)[22,]	●	

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	Systematic Reviews	
Noguchi et al (2012)[23,]	●	●
Ochoa et al (2014)*[24,]	●	●
Rubio et al (2012)[25,]	●	●
Sakurai et al (2014)[26,]	●	●
Tummel et al (2017)*[27,]	●	

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

Study characteristics of the systematic reviews are described in Table 2, and study results are summarized in Table 3. The reviews found similar lymphedema rates (2% and 3%) among individuals who underwent ARM during SLNB. Pooled sentinel lymph node identification rates were also similar and relatively low (37% and 38%), potentially because ARM-visualized lymphatics draining the upper extremity may be located deeper than the sentinel lymph nodes.[15,] In comparison, the sentinel lymph node identification rate in individuals undergoing ARM and ALND was 82% in the Wijaya review[14,] and 83% in the Han review.[15,] The crossover rate between sentinel and ARM nodes was slightly higher in the Han review (19.6%)[15,] than the Wijaya et al (2020) review (12%).[14,] For identification and crossover of sentinel lymph nodes, heterogeneity was high in both reviews (Table 3). Identification and crossover rates were similar in subgroup analyses stratified according to mapping agent used or study geographic area, but heterogeneity remained high.

The evidence in these systematic reviews has numerous limitations. All included studies were uncontrolled, single-arm studies, so no conclusions can be drawn about the comparative effectiveness of ARM + SLNB versus SLNB without ARM. Study duration ranged widely from less than one year to nearly 4 years, and neither review reported the mean or median duration across studies. As noted above, duration of follow-up of over one year and potentially over 3 years may be needed to accurately identify lymphedema development, and as such, studies with shorter follow-up may underestimate the true prevalence of lymphedema. Finally, health outcomes such as quality of life were not reported.

Table 2. Study Characteristics of Systematic Reviews & Meta-Analyses of ARM in SLNB

Study	Dates	Studies	Participants	N (Range)	Design	Duration
Wijaya et al (2020)[14,]	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)[15,]	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 3. 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)[14,]			

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Study	BCRL	ARM Lymph Node/Lymphatics Identification Rate	SLN-ARM Crossover Rate
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)[15,]			
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).[27,] 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 review.

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,

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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 procedural complications.

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. 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 policy 2.01.82 (bioimpedance devices for detection and management of lymphedema). The International Society of Lymphology[10,] categorizes lymphedema stage and severity as follows:

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

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.[11,] 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.[12,]

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.

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- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

Two systematic reviews of ARM in individuals undergoing ALND have included RCTs and nonrandomized studies; study characteristics are summarized in Table 4. 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.[28,] 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[29,] 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.[14,] 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.

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Table 4. Study Characteristics of Systematic Reviews & Meta-Analyses of ARM in ALND

Study	Dates	Studies	Participants[1]	N (Range)	Design	Duration
Guo et al (2021)[28,]	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)[14,]	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)[29,] contributed data from 1,354 individuals included in both the Guo et al (2021)[28,] and Wijama et al (2020)[14,] 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).[29,] Study characteristics are summarized in Table 5. 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 6. 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 5. Study Characteristics of RCTs of ARM in ALND

Study; Trial	Countries	Sites	Dates	Participants[2]	Interventions[1]	
					Active	Comparator
Yuan et al (2019)[29,]	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 6. 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)[29,]	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%)

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Study	BCRL (Arm, by volumetric measure)	BCRL (Arm, by subjective report)	Local Recurrence	Regional Recurrence	Axillary Recurrence	Distant Metastasis
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 7 and 8) 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 7. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Yuan et al (2019)[29],		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 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 8. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Yuan et al (2019)[29],	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 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

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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.

Supplemental Information

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

Practice Guidelines and Position Statements

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

American Society of Breast Surgeons

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.[30,]

The American Society of Breast Surgeons also published recommendations from an expert panel in 2017 that included prevention of breast cancer-related lymphedema.[31,] The panel stated that "emerging data on preventive surgical strategies with ARM and LYMPHA are promising and should be explored further with appropriate patients." The evidence for LYMPHA is discussed in Policy 7.01.162.

American Association of Plastic Surgeons

In 2017, 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. 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."[32,]

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U.S. Preventive Services Task Force Recommendations

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

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 9.

Table 9. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
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 Trial	1200	Sep 2025

NCT: national clinical trial.

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Documentation for Clinical Review

- No records required

Coding

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

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

Type	Code	Description
CPT®	38792	Injection procedure; radioactive tracer for identification of sentinel node
	38900	Intraoperative identification (e.g., mapping) of sentinel lymph node(s) includes injection of non-radioactive dye, when performed (List separately in addition to code for primary procedure)
HCPCS	C9756	Intraoperative near-infrared fluorescence lymphatic mapping of lymph node(s) (sentinel or tumor draining) with administration of indocyanine green (ICG) (List separately in addition to code for primary procedure)

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Policy History

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

Effective Date	Action
02/01/2023	New policy
01/01/2024	Annual review. No change to policy statement. Literature review updated.

Definitions of Decision Determinations

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

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

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

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

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

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

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

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

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language,

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including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

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Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Axillary Reverse Mapping for Prevention of Breast Cancer-Related Lymphedema 7.01.173 **Policy Statement:** I. Axillary reverse mapping/reverse lymphatic mapping performed during sentinel lymph node biopsy to prevent lymphedema in individuals who are being treated for breast cancer is considered **investigational**. II. Axillary reverse mapping/reverse lymphatic mapping performed during axillary lymph node dissection to prevent lymphedema in individuals who are being treated for breast cancer is considered **investigational**.	**Axillary Reverse Mapping for Prevention of Breast Cancer-Related Lymphedema 7.01.173** **Policy Statement:** I. Axillary reverse mapping/reverse lymphatic mapping performed during sentinel lymph node biopsy to prevent lymphedema in individuals who are being treated for breast cancer is considered **investigational**. II. Axillary reverse mapping/reverse lymphatic mapping performed during axillary lymph node dissection to prevent lymphedema in individuals who are being treated for breast cancer is considered **investigational**.

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