7.01.177	Peripheral Nerve Injury Repair Using Synthetic Conduits or Processed Nerve Allografts		
Original Policy Date:	May 1, 2025	**Effective Date:**	May 1, 2025
Section:	7.0 Surgery	**Page:**	Page 1 of 47

Policy Statement

I. The use of processed nerve allografts for the repair and closure of peripheral nerve gaps up to 70 mm may be considered **medically necessary** when direct primary repair is not feasible.

II. The use of synthetic nerve conduits for the repair and closure of peripheral nerve gaps may be considered **medically necessary** in **all** of the following scenarios (see Policy Guidelines):
   A. In the context of conduit-assisted repair as a technique for tension-relief at the peripheral nerve repair site or major nerve with a gap not exceeding 6 mm
   B. Repair of digital nerve injuries with gaps less than 15 mm
   C. Repair of digital nerve injuries with gaps 15-25 mm, where allograft nerve is not available
   D. Repair of major nerves with small gaps not exceeding 6 mm, where allograft nerve is not available

III. All other uses of processed nerve allografts and synthetic nerve conduits for individuals with peripheral nerve gaps are considered **investigational**.

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

Policy Guidelines

Feasibility of direct repair may be limited in individuals with large nerve gaps, segmental nerve loss, or chronic and complex injuries. While there are mixed data regarding comparability of autograft versus allograft repair, allograft repair offers the benefit of avoiding donor site morbidity. This is of particular importance where the primary consideration is the management or prevention of neuropathic pain. For larger sensory, motor, or mixed nerves, autograft repair should be considered the standard intervention except if there is insufficient donor material for autografting. The maximum available allograft length is 70 mm, and there is no data to support the technique of connecting allografts end-to-end.

For digital nerve injuries with gaps 15-25 mm, conduit repair yields acceptable sensory outcomes but is inferior to allograft repair. Therefore, conduit repair should only be used in such scenarios when allograft nerve is not immediately available (e.g. in the context of urgent traumatic injuries).

Nerve wraps are bioresorbable surgical implants designed to protect and support peripheral nerve healing following end-to-end repair with no gap. These devices provide a physical barrier that purports to reduce scar formation, reduce mechanical irritation, and promote a favorable environment for nerve regeneration. These materials are addressed in Blue Shield of California Medical Policy: Bioengineered Skin and Soft Tissue Substitutes (see Related Policies).

Contraindications

Both allograft and conduit repair are contraindicated in a surgical field with active infection. Synthetic conduits are contraindicated for individuals with a history of an allergic reaction or sensitivity to any component of the synthetic conduit (e.g., bovine, porcine, or chondroitin materials).

Coding

See the Codes table for details.

Description

Peripheral nerve injuries are common traumatic events for which the conventional treatment is the microsurgical repair for gaps <5 mm in length. Autologous grafting is used for repairing nerve gaps of greater length. Because autologous grafts must be harvested from the patient, there is a risk of donor site complications, and the overall success rate of autografting may be limited. Therapies such as processed nerve allografts and synthetic nerve conduits are being investigated to provide improved treatment alternatives.

Summary of Evidence

For individuals with peripheral nerve injury requiring repair and closure of the nerve gap who receive processed nerve allografts, the evidence includes 2 meta-analyses, 2 randomized controlled trials (RCTs) comparing allograft to collagen conduit repair with NeuraGen, 1 comparative case series, 1 retrospective cohort study, 1 case series, and 1 registry study. All studies, with the exception of 1 non-randomized controlled trial, used Avance allografts. The evidence base consisted primarily of peripheral nerve injuries to the fingers or upper extremities. Relevant outcomes were sensory and motor function changes, quality of life, and treatment-related morbidity. In 1 RCT that compared allograft to NeuraGen synthetic conduit, allograft patients had a greater return of protective sensation rate on the static 2-point discrimination (S2PD) score but did not differ on overall S2PD score or other outcome measures. The second RCT comparing allograft to Neuragen found that S2PD favored the Avance allograft group at 1-year follow-up, but no differences were noted in moving 2-point discrimination (M2PD), Semmes Weinstein Monofilament (SWMF) test, or the Disability of the Arm and Shoulder (DASH) questionnaire. Limitations in the RCT evidence base included a lack of intention to treat (ITT) analysis, high loss to follow-up, lack of reporting power calculations, and insufficient follow-up duration. Three non-randomized comparative studies found no difference between NeuraGen (n=2) and direct surgical repair (n=2) in sensory or functional outcomes and complications compared to allograft. One meta-analysis found comparable pooled rates of S2PD and M2PD across assessed interventions, including allograft, autograft, artificial conduits, and direct surgical repair, but all estimates had extreme heterogeneity. Another meta-analysis found that meaningful recovery (≥S3 on the British Medical Research Council [BMRC] recovery grading system) was significantly higher in allograft and autografting than for synthetic conduits. Data from the ongoing Avance registry study suggested durability of outcomes and safety at more than 2 years of follow-up. There is an absence of comparison of Avance to autografting in the included literature, which is a significant limitation as this is the current standard of care for repairing peripheral nerve gap discontinuities larger than 5 mm. Additionally, substantial interventional, comparator, and outcome heterogeneity across the evidence base make it challenging to compare outcomes across studies reliably. Randomized comparisons of allograft to autograft with sufficient follow-up using validated outcome measures are needed to evaluate the relative risk-benefit of allografting. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with peripheral nerve injury requiring repair and closure of the nerve gap who receive synthetic nerve conduits, the evidence includes 3 meta-analyses, 8 RCTs (2 comparing NeuraGen to allograft, 1 comparing Neurotube to autologous vein grafting, and 4 comparing conduit [1 Neurolac, 1 Polyhydroxybutyrate {PHB}, 1 polyglycolic acid {PGA}, and 1 silicone tube] to direct surgical repair), 1 non-randomized clinical trial, 1 comparative retrospective cohort study, 1 comparative case series, and 1 non-comparative case series. The evidence base consisted primarily of peripheral nerve injuries to the fingers or upper extremities. NeuraGen was evaluated in 3 studies, and all other synthetic conduits were represented by a single study (Neuromatrix, Neuroflex, Neurotube, Neurolac, PHB conduit, PGA conduit, and collagen-filled conduit). In 1 RCT that compared Avance allograft to NeuraGen, allograft patients had a greater return of protective sensation rate on static 2-point discrimination (S2PD) but did not differ on overall S2PD score or other outcome measures. The second RCT comparing Avance allograft to Neuragen found that S2PD favored the allograft group

at 1-year follow-up, but no differences were noted in moving 2-point discrimination (M2PD), Semmes Weinstein Monofilament (SWMF) test, or the Disability of the Arm and Shoulder (DASH) questionnaire. One RCT compared Neurotube conduit to an autologous vein conduit and found similar outcomes at a 2-year follow-up, but at 1-year analysis, the motor domain of the Rosen Model Instrument (RMI) favored the autologous treatment arm. Five other trials compared different types of conduits to direct surgical repair with generally equivalent outcomes; one RCT observed a significant difference in cold intolerance, which favored the synthetic conduit group, and another found that at short (<4 mm) and long nerve gaps (> 8 mm) M2PD was better in the PGA conduit group than in direct surgical repair or autograft. Major limitations identified in the trial evidence base included an absence of participant blinding, lack of intention to treat analysis, high loss to follow-up, absence of power calculations, and short duration of follow-up. Three non-randomized comparative studies found no difference between synthetic conduits and Avance (n=2), direct surgical repair (n=1), or autograft (n=1) in sensory or functional outcomes as well as complications. A Cochrane review found that there is no clear benefit to patients treated with artificial nerve conduits or nerve wraps over direct surgical repair, and that complications may be greater for participants treated with synthetic nerve conduits or wraps. The overall evidence base was considered very uncertain, with few outcomes having more than 1 included study. One other meta-analysis found comparable pooled rates of S2PD and M2PD across assessed interventions, but all estimates had extreme heterogeneity. The third meta-analysis found that meaningful recovery (≥S3 on the British Medical Research Council [BMRC] recovery grading system) was significantly higher in allograft and autografting than for synthetic conduits. No guideline evidence was identified for synthetic nerve conduits for the treatment of peripheral nerve injuries. Many of the included trials have significant limitations, and the substantial heterogeneity in patient and intervention characteristics makes it challenging to compare outcomes reliably across studies. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Additional Information

2025 Input

Clinical input was sought to help determine whether the use of processed nerve allograft or synthetic nerve conduit in individuals with peripheral nerve injuries requiring repair and closure of a nerve gap would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input was received from 3 respondents, including 1 specialty society-level response.

For individuals with peripheral nerve injuries requiring repair and closure of a nerve gap who receive processed nerve allograft or synthetic nerve conduit, clinical input supports this use provides a clinically meaningful improvement in net health outcomes and indicates this use is consistent with generally accepted medical practice.

Further details from clinical input are included in the Appendix.

Related Policies

- Bioengineered Skin and Soft Tissue Substitutes
- Microwave Tumor Ablation
- Nerve Graft with Radical Prostatectomy

Benefit Application

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

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

Regulatory Status

The U.S. Food and Drug Administration (FDA) regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation, title 21, parts 1270 and 1271. Avance Nerve Grafts subject to these regulations.

A number of processed nerve allografts and synthetic conduits have been approved through the FDA 510k process for individuals undergoing peripheral nerve repair (Table 1). This list includes products for which this reference medical policy did not find any published, peer-reviewed research that satisfied the PICO (Population, Intervention, Comparison, Outcome) criteria.

Table 1. FDA 510K Approved Processed Nerve Allografts and Synthetic Conduits for Peripheral Nerve Repair

Product (manufacturer)	Year	510(k)	Product Code
NeuraGen nerve guide (Integra LifeSciences, Corp)	2001	K011168	JXI
Neuroflex collagen conduit (Stryker Orthopedics)	2014	K131541	JXI
Neurolac nerve guide (Polyganics BV)	2003	K103081	JXI
Neuromatrix (Stryker Orthopedics)	2001	K012814	JXI
Reaxon Plus Nerve Guide (Medovent, GmbH)	2018	K180222	JXI
Rebuilder nerve guidance conduit (CelestRay Biotech Company, LLC.)	2024	K230794	JXI

Rationale

Background

Peripheral Nerve Injury

Injuries to the peripheral nerves are common and occur in approximately 2.5% of trauma patients in the United States, with an average incidence of over 550,000 annually.[1,] Based on hospital ICD-9 coding, the most commonly injured peripheral nerves reported by hospitals were the upper extremity digital nerves, ulnar nerve, radial nerve, and the brachial plexus. [2,] Functional regeneration of injured nerves requires peripheral nerve surgery to allow axon regrowth and remyelination.[3,]

Conventional Treatment

Direct surgical repair (e.g. end-to-end coaptation or neurorrhaphy) is the standard of care for transected nerves when the gap distance permits tensionless suturing. However, when the size of the peripheral nerve gap precludes tensionless direct surgical repair, the standard of care is nerve autograft.[4,] Alternatives to autografting are being investigated to bridge nerve discontinuities to avoid complications from harvesting (e.g., pain or numbness) at the donor site as well as issues such as nerve fascicle mismatch and damage to the autograft from tissue handling.[3,]

Alternative Treatments

Allogenic nerve grafts are derived from human donors and are generally used to bridge gaps resulting from peripheral nerve injuries that are >5mm.[4,] Allogenic grafts are preferred for their potential to minimize donor site morbidity, as they eliminate the need for autografts. Allogenic grafts also address the challenge of obtaining a sufficient graft length as they are available in multiple lengths and diameters; this is particularly relevant in cases where the injury site is extensive. Before transplantation, allografts undergo processing to ensure immunological compatibility and reduce the risk of rejection, allowing for successful integration into the recipient's nervous system. [5,]
Synthetic nerve conduits are hollow tubular structures designed to bridge nerve gaps caused by injury or trauma, providing a supportive environment for the regrowth of damaged nerve fibers.[6,] They are available in various biocompatible materials, lengths, and diameters and are designed to degrade over time. The conduits serve as guidance channels for regenerating nerves, facilitating directional growth, and preventing scar tissue formation.[3,] Conduits are generally used for nerve gap repairs of < 5 mm.[4,]

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 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.

Processed Nerve Allograft

Clinical Context and Therapy Purpose

The purpose of processed nerve allografts in individuals with peripheral nerve injuries is to provide a treatment option that is an alternative to or an improvement on existing standard therapies such as autologous nerve grafting in injuries where the discontinuity is >5mm. These allografts spare individuals with nerve injuries the need to harvest autologous grafting material and negate the potential for donor site defects.

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

Populations

The relevant population of interest is individuals with peripheral nerve injuries requiring the repair and closure of peripheral nerve gaps generally >5mm.

Interventions

The therapy being considered is processed, nerve allografts (Avance, Axogen, Inc). Avance nerve graft is a sterile, processed human nerve allograft that is indicated for the repair of peripheral nerve discontinuities to support axonal regeneration across the gap.[5,] A proprietary cleansing process removes specific proteins, cells, and cellular debris but spares the extracellular matrix (ECM),

providing structural support for cellular migration and regenerating axons.[5,] Avance is available in multiple lengths from 5 to 70 mm, and multiple diameters. The allograft is stored frozen with a shelf life of up to three years, but upon thawing, it must be transplanted within 12 hours. Surgical implantation of the allograft connects the distal and proximal ends of a severed peripheral nerve via suturing. Post-surgery, the allograft is revascularized and remodeled into the patient's own tissue.

Comparators

To repair peripheral nerves, standard therapies include direct microsurgical repair with nerve sutures in small gaps, or autologous nerve grafting when direct suturing is not possible due to the size of the gap.

Outcomes

The outcomes of interest are improvements in sensory recovery (British Medical Research Council [BMRC] grade, Semmes Weinstein Monofilament [SWMF] testing, 2-point static and moving discrimination [S2PD and M2PD]), function (BMRC grade, Rosen Model Instrument [RMI]), quality of life (Disability of the Arm and Shoulder [DASH] questionnaire), and treatment-related morbidity. Outcome scales and interpretation are reported in the Appendix.

The S2PD test measures the narrowest gap at which two separate points applied to the skin can be distinguished as two rather than one. S2PD evaluates innervation density, which is important for assessing hand function, particularly precision sensory grip and constant touch. The M2PD test is performed similarly, except the assessor moves the points over the skin surface rather than performing the test at a static location. Normal values are ≤5 mm for the S2PD and ≤ 2 mm for M2PD tests, and lower scores indicate a more positive result. The SWMF test measures touch pressure in a standardized way using filaments of variable diameters and pressing them in the assessment area just to the point of bending; sensation with lower diameters indicates a better result. These tests are often used as components of composite sensory and motor outcomes scale such as the RMI or BRMC grade. On the BMRC scale, meaningful recovery was generally defined as an S3 or M4 rating or better.

Follow-up at 1 year is of interest to adequately assess sensory and functional recovery where there are sizable nerve discontinuities at the time of surgery and to allow for the identification of delayed adverse events.

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

Two meta-analyses evaluated processed nerve allografts (PNA) and synthetic nerve conduits for peripheral nerve injuries to fingers or peripheral nerve injuries in various locations (finger, hand, upper extremity, head, neck, or lower extremity).[7,8,] The characteristics of the meta-analyses are provided in Table 3, and the results are provided in Table 4. The meta-analysis of peripheral nerve injuries of the finger found similar ranges in pooled sensory and motor outcomes between PNA, autograft,

synthetic conduits, or direct surgical repair. The meta-analysis of injuries to various peripheral nerve locations showed that more patients treated with PNA or autograft had meaningful sensory recovery compared to synthetic nerve conduits. However, conduit repairs and direct surgical repair would only apply to short nerve gap repairs so all treatment groups were not applicable across all gaps and nerve types in the included studies. Both analyses showed substantial heterogeneity for all pooled estimates. This variability, along with differences in patient populations (e.g. nerve gap length, location of nerve injury, cause and number of injuries, and the time from injury to nerve repair), limit drawing conclusions from these findings.

Zhang et al (2023) included a total of 66 studies which pooled data on PNA, synthetic conduits (polyglycolic acid [PGA] conduit or collagen conduit), autografting (muscle-in-vein graft, vein graft, or autologous nerve graft), and direct surgical repair (end to end or end to side coaptation) for the treatment of peripheral nerve defects of the finger.[7,]Treatment groups varied substantially by the size of the nerve defect treated. The authors provided pooled estimates for static 2-point discrimination test (S2PD), moving 2-point discrimination test (M2PD), Mackinnon and Dellon modified British Medical Research Council (BMRC) scale, and Semmes-Weinstein monofilament (SWMF) testing stratified by each of these treatment categories. The proportion of significant recovery, defined as achieving a level of S3 or higher on the Mackinnon and Dellon scale, was consistent across various studies. On average, PNA showed a recovery rate of 78%, PGA and collagen-based synthetic nerve conduits exhibited recovery rates of 74% and 83%, respectively. The recovery rates ranged from 77% to 84% for the three different types of autografts. In surgical procedures, end-to-end and end-to-side direct repairs demonstrated recovery rates of 79% and 98%, respectively. The pooled estimates had overlapping confidence intervals for all interventions and reported outcomes, but no statistical comparison between groups was made. High heterogeneity, according to the I^2 statistic, was observed for all pooled within-group estimates for all outcome measures. In addition to this statistical heterogeneity, the studies had significant variations in nerve gap length, type of injury, number of injuries, and time of injury to repair. The included body of evidence had methodological shortcomings due to pooling data from many case reports or series and fewer comparative studies or RCTs. Reporting on outcomes by length of injury and type of injury is insufficient in the meta-analysis to determine the relative impact on each treatment group. Most included studies did not report complications, but in a pooled analysis,14 studies reported neuroma (artificial conduit: 2 articles, n=3; autograft repair: 7 articles, n=7; and direct surgical repair: 3 articles, n=4), cold stimulation in 13 studies (autograft repair: 10 articles, n=47; nerve sutures: 3 articles, n=3), 17 studies reporting paresthesia (artificial conduit: 3 articles, n=1; autograft repair:11 articles, n=14; and nerve sutures: 3 articles); post-operative infections 6 studies (artificial conduit: 3 articles, n=5; nerve allograft: 2 articles, n=4; autograft repair:1 articles, n=1); 13 articles reported pain (artificial conduit: 2 articles, n=1; nerve allograft: 3 articles, n=9; autograft repair: 6 articles, n=12; and nerve sutures: 2 articles, n=1).

Lans et al (2023) included 35 studies comparing processed nerve allograft, synthetic nerve conduit, and autograft for treating peripheral nerve defects in the hand, arm, head and neck, or lower extremity.[8,] Although nerve repairs involving the lower extremities and the head or neck areas were part of the study, they only constituted 1.3% and 2%, respectively of the overall study population. The studies on allografts and autografts covered a similar range of nerve gap lengths, whereas synthetic conduits were limited to studies with nerve gaps less than 1.5 cm. The meaningful recovery rate (≥ S3 on the BMRC scale) was significantly higher in the allograft (82%) and autograft (72%) groups than in the synthetic conduit group (62%). Subgroup analyses of meaningful recovery rate by gap length (≤30 mm or >30 mm) and motor type (sensory or motor) revealed no differences between the allograft and autograft groups. All reported estimates had high heterogeneity, but the I^2 values were not reported for the primary endpoint of overall meaningful sensory recovery by repair type. In addition to this statistical heterogeneity, the studies had significant variations in nerve gap length, type of injury, number of injuries, and time of injury to repair. The included body of evidence had methodological shortcomings due to pooling data from many case reports or series and fewer comparative studies or RCTs. Reporting on outcomes by injury type is insufficient in the meta-analysis to determine the relative impact on each treatment group.

Table 2. Comparisons of Trials/Studies Included in SR & MA for Processed Nerve Allograft and Synthetic Conduit

Study	Zhang et al (2023)*	Lans et al (2023)*
Arnaout et al 2014[9]	●	
Battiston et al 2005[10]	●	
Bushnell et al 2008[11]	●	
Chiriac et al 2012[12]		●
Guo et al 2013[13]	●	●
Haug et al 2013[14]		●
He et al 2015[15]	●	
Karabekmez et al 2009[16]	●	●
Kusuhara et al 2019[17]	●	
Leckenby et al 2020[18]		●
Lohmeyer et al 2014[19]	●	●
Lohmeyer et al 2009[20]		●
Lohmeyer et al 2007[21]	●	
Mackinnon and Dellon 1990[22]	●	
Means et al 2016[23]	●	●
Neubrech et al 2016[24]	●	
Rbia et al 2019[25]	●	●
Rinker and Liau 2011[26]	●	
Rinker et al 2015[27]		
Rinker et al 2017[28]	●	
Safa et al 2020[29]		●
Saeki et al 2018[30]		●
Salomon et al 2016[31]		●
Schmauss et al 2014[32]	●	
Taras et al 2011[33]	●	●
Taras et al 2013[34]	●	●
Thomsen et al 2010[35]	●	
Zuniga et al 2017[36]		●

*Only trials of processed nerve allograft or synthetic nerve conduit are reported.
M-A: meta-analysis; SR: systematic review.

Table 3. SR & M-A Characteristics for Processed Nerve Allograft and Synthetic Conduit

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Zhang et al (2023)[7]	1990 to 2019	66	Patients with finger peripheral nerve injury. Range of nerve gaps treated by group: Allograft: 0.5 to 5 cm Synthetic conduit: 0.5 to 3 cm Autograft: 0.5 to 9 cm Direct surgical repair: <.05, tension-free coaptation possible	2446 (3-218)	Case reports, case series, cohort studies, and clinical trials	6 months to 10 years
Lans et al (2023)[8]	1980 to 2020	35	Patients with peripheral nerve injuries affecting their hands, arms, head, neck, or lower extremities. Range of nerve gaps treated by group: Allograft: 11mm-70mm Synthetic conduit: 10.8mm-14mm Autograft: 12mm-75mm	Total: 1559 (5-475) Autograft: 670 Allograft: 711 Synthetic conduit: 178	Case series, cohort studies, and clinical trials	NR

M-A: meta-analysis; NR: not reported; SR: systematic review.

Table 4. SR & M-A Results for Processed Nerve Allograft and Synthetic Conduit

Study	Static 2-point discrimination (S2PD [mm])	Moving 2-point discrimination (M2PD [mm])	Mackinnon and Dellon Classification ≥S3, mean (95% CI)	Semmes–Weinstein monofilament testing good rating (SWMF)
Zhang et al (2023)[7],				
66 studies	Allograft: PNA: 7 Synthetic conduit: PGA Artificial Conduit: 4 Collagen artificial conduit: 8 Autograft: Autograft, MIV: 3 Autograft, Vein: 8 Autograft, Nerve: 18 Direct surgical repair: End-to-end coaptation: 11 End-to-side coaptation: 4	Allograft: PNA: 4 Synthetic conduit: Artificial conduit: 5Autograft: Autograft repair (MIV, vein graft): 7 Autologous nerve graft: 6 Direct surgical repair: 4	Allograft: PNA: 6 Synthetic conduit: PGA Artificial Conduit: 3 Collagen artificial conduit: 9 Autograft: Autograft, MIV: 4 Autograft, Vein: 8 Autograft, Nerve: 14 Direct surgical repair: End-to-end coaptation: 18 End-to-side coaptation: 4	Allograft: PNA: 6 Synthetic conduit: Artificial conduit: 5 Autograft: Autograft repair (MIV, vein graft): 6 Autologous nerve graft: 10 Direct surgical repair: 5
Pooled effect (95% CI)	Allograft: PNA: 7.88 (6.32 to 9.43) Synthetic conduit: PGA Artificial Conduit: 6.71 (4.46 to 8.96) Collagen artificial conduit: 8.10 (6.15 to 10.06) Autograft: Autograft, MIV: 8.07 (5.02 to 11.12) Autograft, Vein: 8.33 (6.13 to 10.52) Autograft, Nerve: 8.46 (7.41; 9.50) Direct surgical repair: End-to-end coaptation:	Allograft: PNA: 5.82 (4.51 to 7.12) Synthetic conduit: Artificial conduit: 5.84 (4.16 to 7.51) Autograft: Autograft repair (MIV, vein graft): 7.06 (5.58 to 8.54) Autologous nerve graft: 5.53 (4.52 to 6.55) Direct surgical repair: 4.91 (3.72 to 6.09)	Allograft: PNA: 0.78 (0.66 to 0.88) Synthetic conduit: PGA Artificial Conduit: 0.74 (0.53 to 0.91) Collagen artificial conduit: 0.83 (0.67 to 0.95) Autograft: Autograft, MIV: 0.83 (0.58 to 0.99) Autograft, Vein: 0.77 (0.61 to 0.90) Autograft, Nerve: 0.84 (0.66 to 0.97) Direct surgical repair: End-to-end coaptation: 0.79 (0.68 to 0.88) End-to-side coaptation: 0.98 (0.85 to 1.00)	Allograft: PNA: 0.86 (0.73 to 0.96) Synthetic conduit: Artificial conduit: 0.64 (0.28 to 0.94) Autograft: Autograft repair (MIV, vein graft): 0.61 (0.40 to 0.80) Autologous nerve graft: 0.91 (0.80 to 0.99) Direct surgical repair: 0.87 (0.73 to 0.97)

Study	Static 2-point discrimination (S2PD [mm])	Moving 2-point discrimination (M2PD [mm])	Mackinnon and Dellon Classification ≥S3, mean (95% CI)	Semmes–Weinstein monofilament testing good rating (SWMF)
	8.80 (7.63 to 9.97) End-to-side coaptation: 8.28 (6.69 to 9.88)			
***P* (p)**	Allograft: PNA: 96% (<.01) Synthetic conduit: PGA Artificial Conduit: 97% (<.01) Collagen artificial conduit: 88% (<.01) Autograft: Autograft, MIV: 85% (<.01) Autograft, Vein: 96% (<.01) Autograft, Nerve: 93% (<.01) Direct surgical repair: End-to-end coaptation: 91% (<.01) End-to-side coaptation: 94% (<.01)	Allograft: PNA: 88% (<.01) Synthetic conduit: Artificial conduit: 95% (<.01) Autograft: Autograft repair (MIV, vein graft): 86% (<.01) Autologous nerve graft: 52 (.06) Direct surgical repair: 73 (.01)	Allograft: PNA: 68% (<.01) Synthetic conduit: PGA Artificial Conduit: 66% (.05) Collagen artificial conduit: 81% (<.01) Autograft: Autograft, MIV: 66% (.03) Autograft, Vein: 72% (<.01) Autograft, Nerve: 90% (<.01) Direct surgical repair: End-to-end coaptation: 94% (<.01) End-to-side coaptation: 37% (.19)	Allograft: PNA: 68% (<.01) Synthetic conduit: Artificial conduit: 89% (<.01) Autograft: Autograft repair (MIV, vein graft): 89 (<.01) Autologous nerve graft: 88 (<.01) Direct surgical repair: 85 (<.01)
Lans et al (2023)[8,]			**Mackinnon and Dellon Classification ≥S3, mean (95% CI)**	**Complications, n (%)**
35 studies			Allograft: 19 Synthetic conduit: 5 Autograft: 21	N studies varies by event
Pooled effect (95% CI)			Total: Allograft: 81.9% Synthetic conduit: 62.2% Autograft: 71.8% *Meaningful recovery was significantly greater for allograft and autograft compared to conduit (p=.031 and p=.033, respectively)* Short Nerve Gap (sensory): Allograft: 87.1% Autograft: 81.6%	Revision surgery: Allograft: 3 (6%) Synthetic conduit: 5 (6%) Autograft: NR Symptomatic neuroma: Allograft: 1 (3%) Synthetic conduit: NR Autograft: NR Pain: Allograft: 2 (19%) Synthetic conduit: 2 (38%) Autograft: 2 (21%)

Study	Static 2-point discrimination (S2PD [mm])	Moving 2-point discrimination (M2PD [mm])	Mackinnon and Dellon Classification ≥S3, mean (95% CI)	Semmes–Weinstein monofilament testing good rating (SWMF)
			Short Nerve Gap (motor): Allograft: 70.4% Autograft: 69.9% Long Nerve Gap (sensory): Allograft: 72.6% Autograft: 57.2% Long Nerve Gap (motor): Allograft: 52.6% Autograft: 50.5% *No significant differences were reported between allograft and autograft groups for meaningful recovery rates stratified by nerve gap distance.*	Infection: Allograft: 7 (1%) Synthetic conduit: 4 (5%) Autograft: 1 (4%) Altered sensibility: Allograft: 1 (33%) Synthetic conduit: 3 (26%) Autograft: 1 (13%) Donor-site neuroma: Allograft: NR Synthetic conduit: NR Autograft: 1 (14%) Donor-site pain: Allograft: NR Synthetic conduit: NR Autograft: 1 (14%)
I^2 (p)			Heterogeneity for non-subgroup analyses was NR Sensory: Allograft: 95% Synthetic conduit: 90% Autograft: 96.3% Motor: Allograft: 85% Synthetic conduit: NR Autograft: 93.8% *All reported estimates have significant heterogeneity but did not report identically for the outcomes above (not stratified by gap length)*	

CI: confidence interval; M-A: meta-analysis; MIV: muscle in vein; NNT: number needed to treat; NR: not reported; PGA: polyglycolic acid; PNA: processed nerve allograft; RR: risk ratio; SR: systematic review.

Randomized Controlled Trials

Isaacs et al (2023) published the results of a multicenter, double-blind RCT comparing conduit and processed nerve allograft (PNA) for peripheral nerve repairs of the fingers.[37,] Study characteristics and results are summarized in Tables 5 and 6. A total of 220 participants were recruited who were randomized 1:1 to PNA (n=112, Avance allograft, AxoGen, Inc) or to NeuraGen nerve conduit (Integra Lifesciences); 183 patients completed at least 1 acceptable post-surgery visit between 6 and 15 months post-repair. The primary endpoint was static 2-point discrimination (S2PD), and the authors determined that to achieve 80% power in the larger gap group and 95% power in the shorter gap group, a total of 88 subjects needed to be enrolled. The mean patient age was 38.5 years, and baseline characteristics were similar between groups. A higher proportion of patients treated with PNA for nerve gap distances between 15 and 25 mm achieved superior mean S2PD scores at the last follow-up (6.1mm vs 7.5mm; p<.05). The authors also found a greater percentage of participants receiving PNA had a return of protective sensation on the Semmes Weinstein Monofilament (SWMF) recovery in both short (5 to 14 mm) and long (15 to 25 mm) gaps (p<.05), but no difference in the mean

or median values at last follow-up. No significant differences were noted in M2PD evaluations at the last follow-up. Complications occurred in 17 patients treated with PNA and 10 patients whose nerve gaps were bridged with conduits; the most common complications were infection, wound healing problems, and the need for surgical re-intervention. Physician satisfaction was high in both groups but was statistically significantly greater in the PNA group for handling properties of the implant, ability to properly size the implant, and overall satisfaction (p<.05), with no differences observed for the ease of implantation for the devices. Limitations of the study include evaluating patients who had follow-up appointments from 6 to 15 months rather than the desired 12-month follow-up period, not adjusting statistical significance for multiple comparisons, and limitations in describing the baseline level of discontinuities and etiology of injuries in each group (Tables 7 & 8) (NCT01809002).

Means et al (2016) reported the results of a multicenter, double-blind pilot RCT comparing hollow collagen conduits to PNA for peripheral nerve repairs of the fingers.[23,] Study characteristics and results are summarized in Tables 5 and 6. A total of 23 participants were recruited who were randomized 3:2 to processed nerve allograft (n=14, Avance allograft, Axogen, Inc) or to hollow collagen nerve conduit (n=9, Neurogen, Neuromatrix, or Neuroflex, Stryker Orthopedics); 5 patients were lost to follow-up before 12-month assessment (22%). The primary endpoint was s2PD. The mean patient age was 42 years in the PNA group and 38 years in the conduit group, with average nerve gap lengths of 12.8±4.6 and 12.2±4.5, respectively. At 12 months follow-up, participants treated with PNA had a greater improvement on S2PD testing compared to conduit (5mm versus 8 mm; p<.05). The authors also reported a non-significant difference favoring PNA on M2PD testing at 12 months follow-up (5mm versus 7 mm; p>.05). No significant differences in the rate of participants achieving S3+ or S4 on medical research council classification (MRCC) was observed between groups. SWMF testing revealed that at 12 months, the PNA group had more favorable results (3.6 mm versus 4.4mm; p<.05), and all patients in the PNA group had recovery of protective sensation compared to 75% in the conduit group. Disability of the Arm, Shoulder, and Hand (DASH) assessment yielded no significant differences between groups, as did the mean pain intensity (p>.05). Study limitations included a small sample size with no power calculations in determining the number of participants needed to recruit to detect a difference in S2PD, and high loss to follow-up with a greater proportion in the PNA group (NCT00948025).

Table 5. Summary of Key RCT Characteristics for Processed Nerve Allograft

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Isaacs et al (2023); RECON[37,]	US	20	NR	N=220 adults with acute or subacute (< 24 weeks old) nerve injuries to the finger	processed nerve allograft (Avance) (n=112)	NeuraGen Nerve Guide (Integra LifeSciences) (n=108)
Means et al (2016)[23,]	US	4	NR	N=23 adults who sustained a peripheral nerve injury to the finger requiring surgical repair of at least 1 nerve (gap length ≥5 and ≤ 20 mm)	processed nerve allograft (Avance) (n=14)	Hollow nerve conduits (NeuroGen, NeuroMatrix, or NeuroFlex) (n=9)

NR; not reported; RCT: randomized controlled trial.

Table 6. Summary of Key RCT Results for Processed Nerve Allograft

Study	s2PD at last visit; mean (SD) mm	SWMF at last visit, mean (SD)	M2PD at last visit, mean (SD), mm	DASH, mean (SD)	Complications, n (%)
Isaacs et al (2023)[37,]					
Avance (n=112)	Short gaps (15-25 mm): 7.3 (2.8) Long gaps (15-25 mm): 6.1 (3.3)	Short gaps: 4 (1) Long gaps: 4 (1.3)	Short gaps: 6.9 (3.2) Long gaps: 7 (3.1)		17 (15%)
NeuraGen (n=108)	Short gaps (5-14 mm): 7.5 (3.1) Long gaps (15-25 mm): 7.5 (2.4)	Short gaps: 3.8 (1) Long gaps: 3.3 (1.5)	Short gaps: 7.1 (3) Long gaps: 7.8 (3.4)		10 (9.3%)
p-value for difference	<.05 for gaps > 12 mm	<.05 for return of protective sensation rate favoring PNA in short (90% vs. 93%) and long gaps (70% vs. 80%)			
Means et al (2016)[23,]	At 12 months:	At 12 months:	At 12 months:	At 12 months:	
Avance (n=14)	5 (1)	3.6 (0.7)	5 (1)	5 (6.5)	1 (7%)
NeuraGen (n=9)	8 (5)	4.4 (1.4)	7 (5)	8 (6.3)	2 (22%)
p-value for difference	<.05, favoring PNA	NS	NS	P=.32	

BMRC: British Medical Research Council; CI: confidence interval; HR: hazard ratio; IQR: interquartile range; M2PD: moving 2-point discrimination; NNT: number needed to treat; NR: not reported; NS: non-significant; OR: odds ratio; PGA: polyglycolic acid; PNA: processed nerve allograft; RCT: randomized controlled trial; RR: relative risk ; S2PD: static 2-point discrimination; SD: standard deviation; SWMF: Semmes-Weinstein Monofilament testing.

The purpose of the study limitations tables (see Tables 7 and 8) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement.

Table 7. Study Relevance Limitations for Processed Nerve Allograft

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Isaacs et al (2023)[37,]	5. Baseline information on gap length, location and cause of discontinuity not reported				1. Protocol specified 12 month evaluation period but patients included if they had follow-up at any time point between 6 to 16 months
Means et al (2016)[23,]					1. Not sufficient duration for benefit

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 for Processed Nerve Allograft

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Isaacs et al (2023)[38,]				6. Not intent to treat analysis		
Means et al (2016)[23,]				1. High loss to follow-up or missing data	1. Power calculations not reported	

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 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 Studies

Three non-randomized comparative studies were identified, including 1 case series and 2 non-randomized clinical trials that evaluated PNA.[25,15,39,] Rbia et al (2019) published a case series of patients who underwent peripheral nerve injury reconstruction of the finger with either Avance PNA (n=18) or Neuragen collagen nerve conduit (n=19) from 2005 to 2015 at a single center in the Netherlands in adult patients who underwent 1 or more nerve reconstructions with a nerve gap after resection (Table 9)[25,]. The mean age at surgery was 38 years in the collagen conduit group and 41 years for patients treated with PNA; gap lengths in the conduit and PNA groups were 14 mm and 18.4 mm, respectively. The primary outcome of S2diPD was reported as a mean of 9.8±3.8 mm at 12 months follow-up in the conduit group and 8.5±3.7 in PNA (Table 10). Excellent sensory recovery was reported in 48% of collagen conduit implantations and 39% of PNA patients. No significant differences in S2PD or degree of sensory recovery by Mackinnon classification were observed. At 12 months follow-up, the authors reported no instances of graft rejection or extrusion of conduit. The rate of other adverse events was low and included one instance each of neuroma and allodynia with complex regional pain syndrome in the PNA group and one infection in the collagen conduit implanted group (p=.378). Limitations of the study include lack of randomization and blinding, absence of power calculations, and retrospective nature of the study.

He et al (2013) conducted a multicenter, single-blinded, non-randomized controlled trial of acellular nerve allografting (n=72) compared standard direct surgical repair or, in cases where the gap was > 10 mm, autograft (n=81) of the damaged nerve.[15,] The mean age of patients was 33±11.1 years in the allograft group and 36.9±13.4 years in the control group (p=.047); the mechanism of injury (cut, contusion, avulsion, squeeze, or electrical) also varied between groups. The mean length of the nerve graft was 1.8±.82 cm (range 1 to 5 cm). Seven participants (4%) were lost to follow-up and not included in the analysis. Power calculations suggested that 70 patients needed to be recruited in each group to have 80% power at a 95% significance level to detect an expected ±15% difference in the primary outcome of the SWMF test. All surgeries were reported as successful. In both neural and patient-level assessments, S2PD scores were significantly different between groups, with the control

group having fewer excellent reconstruction outcomes (p<.01) (Table 10). Only 78 patients were included in the safety evaluation, which found that 6 patients (8%) had mild wound pain for 2 weeks post operation and 3 patients (4%) had mild redness; no reports of pain, itching, local erythema, urticaria, rash or other allergic symptoms were observed at 1-month follow-up. At 6-month follow-up, two patients had required secondary tenolysis (8%). Limitations of the study include lack of randomization and single-blinding, imbalanced baseline patient characteristics, and short duration of follow-up.

Ducic et al (2012) published a retrospective cohort study of patients treated with either Avance PNA (n=8), NeuraGen conduit repair (n=27) compared to autograft (n=11) or end-to-end direct surgical repair (n=8) for upper extremity peripheral nerve reconstruction.[39,] Participants were treated from 2003 to 2009 and were evaluated using the Quick Disability of the Arm, Shoulder, and Hand (QuickDASH) questionnaire. The average age of participants was 46.4 years of age, and the nerve gap length within each group was highly variable but not compared statistically (mean range 0 mm to 37.5 mm). Minimum follow-up was greater than 2 years, although the timing of outcome assessment is unclear. QuickDASH scores did not vary significantly between groups (P=.56), and no complications were reported. Limitations of the study include the retrospective nature of the study design, imbalanced baseline characteristics, and a lack of statistical analysis for between-group comparisons of interest.

Table 9. Summary of Key Nonrandomized Trials OR Observational Comparative Study Characteristics for Processed Nerve Allograft

Study	Study Type	Country	Dates	Participants	Intervention	Comparator	Follow-Up
Rbia et al (2019)[25,]	Case series	the Netherlands	2005-2015	Review of patients with peripheral nerve injury to the fingers who underwent reconstruction with either Neuragen nerve conduit or Avance allograft	Processed nerve allograft (Avance) (n=18)	Neuragen nerve conduit (n=19)	Mean 477 days for the PNA group and 432 days for the conduit group
He et al (2013)[15,]	Single-blind, non-randomized clinical trial	China	NR	Patients who required direct suturing of nerve defect 1 to 5 cm in length and required nerve transplantation	Processed nerve allograft (n=72)	Direct surgical repair or autograft (n=81)	6 months
Ducic et al (2012)[39,]	Retrospective cohort	US	2003-2009	Consecutive upper-extremity nerve repair	Processed nerve allograft (Avance) (n=8)	Conduit repair (NeuraGen) (n=27) Autograft repair (n=11) Direct surgical repair (n=8)	Mean of 130 to 250 weeks

NR: not reported; PNA: processed nerve allograft.

Table 10. Summary of Key Nonrandomized Trials OR Observational Comparative Study Results for Processed Nerve Allograft

Study	Mackinnon and Dellon classification, n (%)	S2PD, mean (SD) mm	QuickDASH, mean (SD)	Complications, n (%)
Rbia et al (2019)[25,]	At 12 months:			

Study	Mackinnon and Dellon classification, n (%)	S2PD, mean (SD) mm	QuickDASH, mean (SD)	Complications, n (%)
Processed nerve allograft (Avance) (n=18)	Excellent: 7 (39%) Good: 10 (55%) Poor: 1 (6%)	8.5 (3.7)		Neuroma: 1 (6%) Allodynia w/ complex regional pain syndrome: 1 (6%)
Neuragen nerve conduit (n=19)	Excellent: 9 (48%) Good: 5 (26%) Poor: 5 (26%)	9.8 (3.8)		Infection: 1 (5%)
p-value for difference	NS difference between groups for each comparison	NS		
He et al (2013)[15,]				
Processed human acellular nerve allograft (n=72)		Pre-op: 20 (0) 1 month: 18.5 (3.8) 3 months: 14.4 (6.3) 6 months: 12.8 (6) Excellent to good rate: 65.28% (51.98-78.93%)		Mild wound pain: 6 (8%) Mild redness: 3 (4%) Secondary tenolysis: 2 (3%)
Direct surgical repair (n=81)		Excellent to good rate: 64.2% (NR)		
p-value for difference		p=.839 for between-group comparison; for the allograft group, mean S2PD values at 3 and 6 months post-operation were significantly better than 1-month post-op (p<.05).		
Ducic et al (2012)[39,]				
Conduit repair (n=27)			33 (15.3)	0%
Allograft repair (n=8)			19.8 (10.4)	0%
Autograft repair (n=11)			22.5 (11.1)	0%
Direct surgical repair (n=8)			14 (1.3)	0%
p-value			NS difference between groups (p=.56)	No infection, dehiscence, or seroma were reported in treated patients from all groups.

BMRC: British Medical Research Council; CI: confidence interval; HR: hazard ratio; IQR: interquartile range; M2PD: moving 2-point discrimination; NNT: number needed to treat; NR: not reported; NS: non-significant; OR: odds ratio; PGA: polyglycolic acid; PNA: Processed decellularized nerve allograft; RCT: randomized controlled trial; RR: relative risk; S2PD: static 2-point discrimination; SD: standard deviation; SWMF: Semmes-Weinstein Monofilament testing.

Observational studies

Many observational case reports and case series are available on treating peripheral nerve discontinuities with processed nerve allografts.[40,41,42,13,34,18,38,28,43,44,29,45,46,16,27,29,47,] Because higher quality evidence is available, only larger studies (N≥75) with commercially available interventions and longer-term follow-up over 6 months were summarized.

Leckenby et al (2020) performed a single-center, retrospective review of outcomes from Avance PNA for peripheral nerve injuries from April 2009 to October 2017.[18,] A total of 129 patients with 171 nerve allografts met the study inclusion criteria (Table 11). The mean age of surgery was 45 years (range 18

to 82 years) with an average follow-up period of 13 months. On the BMRC sensory rating scale, 77% of patients achieved a sensory outcome score of S3 or above, and 36% achieved a motor score of M3 or above and were deemed to have meaningful recovery (MR) (Table 12). Longer grafts and grafts used in lower limbs were associated with poorer outcomes compared to shorter grafts and grafts of the upper extremity (p<.05). Median numeric rating scale pain scores decreased from a pre-operative value of 7 (range 3 to 10) to 3 (range 0 to 7; p<.05). The authors noted that no patient developed a higher level of pain or diminished level of sensation in the post-surgical observation period.

Safa et al (2019) published results from the multi-center, Retrospective Avance Nerve Graft utilization, Evaluations, and outcomes in peripheral nerve injury Repair (RANGER) registry.[45,] The study is ongoing, but at the time of publication, 385 subjects with 624 nerve repairs had sufficient follow-up and were included in the outcome analysis (Table 11). The mean patient age was 42 years (range 6 to 83 years), and although injuries to regions other than the upper extremity were eligible for inclusion, only 28 (7.3%) of patients had lower extremity nerve repairs, and 4 (1%) had repairs of nerves in the head and neck region. The mean follow-up time was 417 days (range 120 to 3,286 days). Overall, 82% MR was achieved across sensory, mixed, and motor nerves in gaps up to 70mm. No adverse events were reported over the study period. For upper extremity repair, significant differences were noted in the mechanism of injury between complex injuries (74%), lacerations (85%), and neuroma resections (100%; p=.03) and by the gap length (MR: <15 mm, 91%; 15-29 mm, 84%; 30-49 mm, 78%; 50-70mm, 69% (p<.05) (Table 12). By body region, MR was reported in 83% of the upper extremity, 53% of the lower extremity, and 100% of head/neck repairs (p=.01). Assessment of MR found no differences according to nerve type, time-to-repair discontinuity, and smoking status. Overall, there were reoperations in 31 subjects (8%), and adverse events were reported in 39 subjects (3.7%) drawn from the safety population, which included a total of 1041 subjects, many of which weren't yet included in the outcome evaluation population due to lack of sufficient follow-up.

A sub-group analysis using data from the RANGER registry retrospectively compared outcomes between Avance PNA and synthetic conduits (manufacturer unspecified) in a matched cohort.[48,] Participants were matched based on patient characteristics, medical history, mechanism of injury, and time to repair for nerve gaps up to 25 mm across eight study centers. A total of 49 individuals treated with synthetic nerve conduits were compared to 113 individuals treated with PNA. Significant differences were observed in the rate of meaningful recovery (% ≥S3, 61% vs. 88%; p =.0001) and s2PD (12.2 vs. 9.7; p =.018), both favoring the PNA group. When outcomes were further stratified by nerve gap length (<14 mm and 15–25 mm), the PNA group continued to demonstrate superior results (p <.05).

Table 11. Summary of Key Case Series Characteristics for Processed Nerve Allograft

Study	Country	Participants	Follow-Up
Leckenby et al (2020)[18,]	US	Adult patients treated with processed nerve allograft (Avance) (n=129)	Mean: 13 months (range: 6 to 38 months)
Safa et al (2019); RANGER[45,]	US	Multicenter registry patients treated with processed nerve allograft (Avance) (n=385)	Mean: 417 days (range: 120 to 3,286)

Table 12. Summary of Key Case Series Results for Processed Nerve Allograft

Study	Treatment	Mackinnon-Dellon Score, Sensory (% with meaningful recovery)	Mackinnon-Dellon Score, Motor(% with meaningful recovery)	Complications, n (%)
Leckenby et al (2020)[18,]	Processed nerve allograft (Avance)	≥S3: 77%	≥M3: 36%	1 (.8%) (surgical site infection)
Safa et al (2019)[45,]	Processed nerve allograft (Avance)	≥S3: 81%	≥M3: 66%	Revision: 39 (3%) Any adverse event: 39 (3.7%) (most commonly neuroma at the repair site and infection) Serious adverse event: 23 (2.1%) *No adverse events were determined to be related to the treatment product*

Section Summary: Processed Nerve Allograft

For individuals with peripheral nerve injury requiring repair and closure of the nerve gap who receive processed nerve allografts, the evidence includes 2 meta-analyses, 2 randomized controlled trials (RCTs) comparing allograft to collagen conduit repair with NeuraGen, 1 comparative case series, 1 retrospective cohort study, 1 case series, and 1 registry study. All studies, with the exception of 1 non-randomized controlled trial, used Avance allografts. The evidence base consisted primarily of peripheral nerve injuries to the fingers or upper extremities. Relevant outcomes were sensory and motor function changes, quality of life, and treatment-related morbidity. In 1 RCT that compared allograft to NeuraGen synthetic conduit, allograft patients had a greater return of protective sensation rate on the static 2-point discrimination (S2PD) score but did not differ on overall S2PD score or other outcome measures. The second RCT comparing allograft to Neuragen found that S2PD favored the Avance allograft group at 1-year follow-up, but no differences were noted in moving 2-point discrimination (M2PD), Semmes Weinstein Monofilament (SWMF) test, or the Disability of the Arm and Shoulder (DASH) questionnaire. Limitations in the RCT evidence base included a lack of intention to treat (ITT) analysis, high loss to follow-up, lack of reporting power calculations, and insufficient follow-up duration. Three non-randomized comparative studies found no difference between NeuraGen (n=2) and direct surgical repair (n=2) in sensory or functional outcomes and complications compared to allograft. One meta-analysis found comparable pooled rates of S2PD and M2PD across assessed interventions, including allograft, autograft, artificial conduits, and direct surgical repair, but all estimates had extreme heterogeneity. Another meta-analysis found that meaningful recovery (≥S3 on the British Medical Research Council [BMRC] recovery grading system) was significantly higher in allograft and autografting than for synthetic conduits. Data from the ongoing Avance registry study suggested durability of outcomes and safety at more than 2 years of follow-up. There is an absence of comparison of Avance to autografting in the included literature, which is a significant limitation as this is the current standard of care for repairing peripheral nerve gap discontinuities larger than 5 mm. Additionally, substantial interventional, comparator, and outcome heterogeneity across the evidence base make it challenging to compare outcomes across studies reliably. Randomized comparisons of allograft to autograft with sufficient follow-up using validated outcome measures are needed to evaluate the relative risk-benefit of allografting. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Synthetic Nerve Conduits

Clinical Context and Therapy Purpose

The purpose of nerve conduits in individuals with peripheral nerve injuries is to provide a treatment option that is an alternative to or an improvement on existing standard therapies, such as direct surgical repair for shorter nerve gaps and autologous nerve grafting in injuries larger than 5 mm.

These synthetic devices spare individuals with nerve injuries the need to harvest autologous grafting material and negate the potential for donor site defects as well as protect the area of injury by blocking external inhibitory factors during axon regeneration. The FDA has approved multiple synthetic nerve conduits through the 510k process, including some for which this reference medical policy found no peer-reviewed, published research meeting the PICO (Population, Intervention, Comparison, Outcome) criteria.

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

Populations
The relevant population of interest is individuals with peripheral nerve injuries requiring the repair and closure of peripheral nerve gaps.

Interventions
The therapy being considered are synthetic nerve conduits (NeuraGen [Integra, Lifesciences], Neuroflex [Stryker Orthopedics], Neurolac [Polyganics, BV], Neurotube [Synovis Micro]) for peripheral nerve injuries requiring nerve gap repair and closure.

NeuraGen is a resorbable hollow nerve conduit designed for the repair of peripheral nerve discontinuities where gap closure is achievable by flexion of the extremity.(Integra, Lifesciences) The device received FDA 510k approval on April 24, 2014.(NeuraGen FDA 510(k)) It provides a protective environment for peripheral nerve repair after injury.(NeuraGen® Nerve Guide (integralife.com) The NeuraGen Nerve Guide is designed to be an interface between the nerve and surrounding tissue, creating a conduit for axonal growth across a nerve gap. NeuraGen's semi-permeable type 1 collagen membrane allows for controlled resorption, appropriate nutrient diffusion, and retention of representative Nerve Growth Factor. It is available in different lengths and diameters to meet varied implantation needs. Conduits are generally used most commonly for nerve gap repairs of < 1 cm.[4,]

Neuroflex is a resorbable, flexible type I collagen conduit that encases peripheral nerve injuries and protects the neural environment.(Stryker Neuroflex) It is designed to prevent the ingrowth of scar tissue and the formation of neuromas. The corrugated walls of the conduit allow it to bend up to approximately 60 degrees without forming an occlusion. The device received FDA 410k approval on April 03, 2014, and is indicated for peripheral nerve discontinuities where gap closure can be achieved by flexion of the extremity or at the end of the nerve in the foot to reduce the formation of symptomatic or painful neuroma. (Neuroflex FDA 510(k)) The device is available in differing lengths and diameters.

Neurolac is a synthetic nerve guide designed for the reconstruction of peripheral nerve discontinuities up to 20 mm.(Polyganics B.V.) It received FDA 510k approval on October 20, 2011 and is indicated for the reconstruction of a peripheral nerve discontinuity up to 20 mm in patients who have sustained a complete nerve division.(Neurolac FDA 510(k)) Neurolac provides guidance and protection to regenerated axons and prevents the ingrowth of fibrous tissue into the nerve gap during nerve regeneration. It retains its initial mechanical properties up to 10 weeks, providing support and protection to the healing nerve, and after this period, rapid loss of mechanical strength and gradual reduction in mass occurs. The final degraded products are resorbed, metabolized, and excreted by the body. Neurolac is available in different internal diameters, making it suitable for small nerves that require precise suturing in a small and defined area.

The Neurotube (Synovis Micro) is an absorbable woven polyglycolic acid mesh tube designed for primary or secondary peripheral nerve repair or reconstruction.(Synovis Micro) It received FDA 510k approval on August 28, 1998, for the indication of peripheral nerve injuries where the nerve gap is more than or equal to 8 mm, but less than or equal to 30 mm.(Neurotube FDA 510(k)). The device is contraindicated for anyone with a known allergy to polyglycolic acid. The walls of the Neurotube are

corrugated for strength and flexibility, preventing the tube from collapsing under normal physiological soft tissue pressures.

Comparators

To repair peripheral nerves, standard therapies include microsurgical repair with nerve sutures in small gaps or when direct suturing is not possible due to the size of the gap, autologous nerve grafts are used. Several studies compared processed nerve allografts and synthetic conduits either as part of a systematic review and meta-analysis or a primary study. These studies are reported in detail in the section on processed nerve allografts and summarized in this section on synthetic nerve conduits.

Outcomes

The outcomes of interest are improvements in sensory recovery (British Medical Research Council [BMRC] grade, Semmes Weinstein Monofilament [SWMF]testing, 2-point static and moving discrimination [S2PD and M2PD]), function (BMRC grade, Rosen Model Instrument), quality of life (Disability of the Arm and Shoulder [DASH] questionnaire), and treatment-related morbidity. Outcome scales and interpretation are reported in the Appendix.

The S2PD test measures the narrowest gap at which two separate points applied to the skin can be distinguished as two rather than one. S2PD evaluates innervation density, which is important for assessing hand function, particularly precision sensory grip and constant touch. The M2PD test is performed similarly, except the assessor moves the points over the skin surface rather than performing the test at a static location. Normal values are ≤ 5 mm for the S2PD and ≤ 2 mm for M2PD tests, and lower scores indicate a more positive result. The SWMF test measures touch pressure in a standardized way using filaments of variable diameters and pressing them in the assessment area just to the point of bending; sensation with lower diameters indicates a better result. These tests are often used as components of composite sensory and motor outcomes scale such as the RMI or BRMC grade. On the BMRC scale, meaningful recovery was generally defined as an S3 or M4 rating or better.

Follow-up at 1 year is of interest to adequately assess sensory and functional recovery where there are sizable nerve discontinuities at the time of surgery and to allow for the identification of delayed adverse events.

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

Two meta-analyses evaluated processed nerve allografts (PNA) and synthetic nerve conduits for peripheral nerve injuries to fingers or peripheral nerve injuries in various locations (finger or hand, upper extremity, head and neck, and lower extremity).[7,8,] The meta-analyses are relevant to both the first and second PICO and are summarized in more detail in the previous section on processed nerve allografts (Tables 2-4).The meta-analysis of peripheral nerve injuries of the finger found similar ranges in pooled sensory and motor outcomes between PNA, autograft, synthetic conduits, or direct

surgical repair. The meta-analysis of injuries to various peripheral nerve locations showed that more patients treated with PNA or autograft had meaningful sensory recovery compared to synthetic nerve conduits. However, conduit repairs and direct surgical repair would only apply to short nerve gap repairs so all treatment groups were not applicable across all gaps and nerve types in the included studies. Both analyses showed substantial heterogeneity for all pooled estimates. This variability, along with differences in patient populations (e.g. nerve gap length, location of nerve injury, cause and number of injuries, and the time from injury to nerve repair), complicates drawing conclusions from these findings.

The Cochrane Collaboration published another meta-analysis of bioengineered nerve conduits and wraps for repairs of peripheral nerves of the upper extremity.[49,] The authors included only RCTs or quasi-RCT experimental studies and found 5 which included the desired interventions and had follow-up periods of at least 12 months. A total of 213 participants were included in the studies, which compared nerve reconstruction with artificial wraps or conduits to standard repair either with direct end-to-end epineural repair or with autologous nerve grafting.(Table 14) Sensory recovery assessed with the British Medical Research Council (BMRC) grading scale was higher in the wrap or conduit group than in standard repair with very low certainty of evidence on Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) at 12 months (mean difference [MD],.03; range, -0.43 to 0.49) and 24 months follow-up (MD,.01; 95% CI, -0.06 to 0.08). (Table 15) Rosen model instrument (RMI) comparisons between conduit or wrap versus standard repair revealed no between-group differences through 24 months (MD, -0.17; 95% CI, -0.38 to 0.05; p=.13) and was determined to have low certainty of evidence; findings at 5 years follow-up in a single study found a greater improvement in the conduit or wrap group, but the estimate also had low certainty of evidence (MD, 0.23; 95% CI, 0.07 to 0.38). The rate of adverse event occurrence may be greater in patients treated with nerve wraps or conduits than with standard techniques, but the evidence had a GRADE rating reflected a very low certainty of evidence (risk ratio [RR], 7.15; 95% CI, 1.74 to 29.42). The authors also sought BMRC muscle strength scores, which were not reported in the included studies. The authors concluded that based on the currently available high-quality evidence, the use of currently available nerve repair devices is not supported over the standard of care due to heterogeneity in included participants, the pattern of injury, timing of repair, timing of outcome assessment, and choice of outcome measurement scales.

Table 13. Comparisons of Trials/Studies Included in SR & MA for Synthetic Nerve Conduits

Study	Thomson et al (2022)[49,]
Aberg et al 2009[50,]	●
Bertleff et al 2005[51,]	●
Boeckstyns et al 2013[52,]	●
Lundborg et al 2004[53,]	●
Weber et al 2000[54,]	●

Table 14. SR & M-A Characteristics for Synthetic Nerve Conduits

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Thomson et al (2022)[35,]	2000-2018	5	Patients with peripheral nerve repairs of the upper limb	213 (12-98)	RCTs or quasi-RCTs	12 months to 5 years

Table 15. SR & M-A Results for Synthetic Nerve Conduits

Study	BMRC sensory grading	Semmes–Weinstein monofilament test	Rosen Model Instrument Score	Adverse Events (any grade)	Further surgery (device removal/revision)
Thomson et al (2022)[49,]	1 RCT	1 RCT	2 RCTs	5 RCTs	5 RCTs

Study	BMRC sensory grading	Semmes–Weinstein monofilament test	Rosen Model Instrument Score	Adverse Events (any grade)	Further surgery (device removal/revision)
5 studies (n=256)	5 years or 24 months: 1 (n=28) 12 to 24 months: 1 (n=11)	24 months: 1 (n=19) 12 months: 2 (n=65)	5 years: 1 (n=28) 2 years: 2 (n=60) 1 year: 2 (n=65)	5 studies (n=256)	5 studies (n=256)
MD (95% CI)	5 years: 03 (-0.43 to 0.49) 12 to 24 months: 0.93 (-0.09 to 1.95) NS difference at any time point between groups	24 months: 0.01 (-0.06 to 0.08) 12 months: 0.05 (−0.07 to 0.17) NS difference at any time point between groups	5 years: 0.23 (0.07 to 0.38) 2 years: -.17 (-0.38 to 0.05) 1 year: -2.29 (-2.49 to -2.29), favors the conduit group at 5 years	RR: 7.15 (1.74 to 29.42), favors standard repair	RR: 7.61 (1.48 to 39.02), favors standard repair
P **(p)**	NA	24 months: NA 12 months: 66 (=.09)	5 years: NA 2 years: 0% (.66) 1 year: 100% (<.00001)	0% (.75)	0% (.64)

BMRC: British Meidcal Research Council; CI: confidence interval; MIV: muscle in vein; NA: not applicable; NNT: number needed to treat; PGA: polyglycolic acid; PNA: processed nerve allograft; RMI: Rosen Model Instrument; RR: risk ratio.CI: confidence interval; NNT: number needed to treat.

Randomized Controlled Trials

Eight RCTs were identified that compared nerve conduits to processed nerve allografting (n=2), autologous vein conduit (n=1), or direct surgical repair(n=5) and are presented based on comparator. [37,23,52,26,50,51,53,54,]

Processed Nerve Allograft

The preceding section on processed nerve allografting reported the two trials that compared nerve conduits to allografts.[37,23,] Isaacs et al (2023) compared Avance allograft to NeuraGen synthetic conduit and found that allograft patients had a greater return of protective sensation rate on the static 2-point discrimination (S2PD) as well as overall S2PD score for gaps > 12mm. No other differences were noted in moving 2-point discrimination (M2PD), Disability of the Arm and Shoulder (DASH) questionnaire score, or complications between groups. Means et al (2016) compared Avance allograft to Neuragen in peripheral nerve finger repairs and found that S2PD favored the Avance group at 1-year follow-up, but no differences were noted in M2PD, Semmes Weinstein Monofilament (SWMF) test, or DASH score. Limitations in the RCT evidence base included a lack of intention to treat (ITT) analysis, high loss to follow-up, lack of reporting power calculations, and insufficient follow-up duration.

Autologous Vein Conduit

Rinker et al (2011) published the findings from a multicenter, single-blind RCT comparing polyglycolic acid nerve conduit with autogenous vein conduits for the repair of digital nerves gaps ≤3 cm.[26,] A total of 42 patients were randomized 1:1 to nerve conduit (n=41, Neurotube, Synovis Life Technologies, Inc) or to autogenous vein conduit (n=35); 5 patients were lost to follow-up before 6-month evaluation and not included in the analysis. The mean patient age was 33 years in the PGA conduit group and 38 years in the vein conduit group, with mean nerve gap lengths of 9.1±4.6 mm and 10.3±4.8 MMS, respectively. Reported baseline characteristics were balanced between groups. The primary endpoint was 2-point discrimination testing, and the authors calculated that to detect a predicted mean difference of 25% with 80% power at the 95% confidence level, a total of 28 participants needed to be enrolled. No differences in static or moving 2-point discrimination were observed at 6 months follow-up between groups (Table 17). A subgroup analysis based on gap length (< 10 mm and ≥ 10 mm) also found no statistically significant between-group differences. A numerically greater number of complications occurred in the synthetic conduit group (8%) compared

to the vein conduit group (3%), but no statistical comparison was reported. These events in the PGA conduit group included 2 implant extrusions and 1 infection, with 1 infection in the vein conduit group. Limitations included a lack of intention to treat analysis and higher loss to follow-up for 12-month post-operative estimations.

Direct Surgical Repair

Five RCTs compared various synthetic nerve conduits (Neurolac [n=1], NeuraGen [n=1], PHB conduit [n=1], PGA conduit [n=1] or silicone conduit [n=1]) to direct surgical repair of peripheral nerve injuries of the hand or upper extremity. [52,50,51,53,54,] One RCT found that direct surgical repair performed better than Neuragen on the motor domain components of the Rosen score at 1 year follow-up, but no significant differences were noted in this or other outcomes at 2 years of follow-up.[52,] Another RCT reported that cold intolerance favored the silicone conduit group over conventional repair, but the other elements of the Rosen composite score were not significantly different between groups.[53,] A third RCT found that conduit repair did not improve overall S2PD or M2PD, but when stratified for gaps <4mm and gaps >8mm, the conduit group outperformed standard repair on M2PD.[54,] No significant differences were noted between the conduit and direct surgical repair in 2 remaining RCTs.[50,51,]

Boeckstyns et al (2013) reported the results from a multicenter, single-blind RCT comparing repair with a nerve conduit to direct suture repair for acute lacerations of mixed sensory-motor (ulnar and median) nerves.[52,] Study characteristics and results are summarized in Tables 16 and 17. In total, 43 participants were recruited who were randomized 1:1 to nerve conduit (n=23, Neuragen, Integra Lifesciences) or to direct surgical repair (n=21); 11 of which were lost to follow-up before the final evaluation at 24-months follow-up and not included in the analysis. The mean patient age was 37 years in the conduit group and 33 years in the direct suture group. The operated nerves for the conduit group included 11 median and 12 ulnar nerves, with one patient having both median and ulnar nerve repair; in the direct suture group, 13 median and 8 ulnar nerves were repaired. No surgical complications of infection, extrusion of the conduit or other local adverse reaction, or development of a chronic regional pain syndrome were reported. No electrophysiological measures differed between the two treatment groups at 24-month follow-up, but at 12 months, differences in the distal motor latency and compound muscle action potential were observed, which favored direct surgical repair. Composite Rosen-Score did not vary between groups at 12 or 24-month follow-up, but the components of the motor domain (muscle force and grip strength) and overall motor domain scores favored direct surgical repair at the 12-month evaluation. Limitations include not reporting the baseline nerve gap distance a high loss to follow-up (25%), no power calculations reported, and absence of trial registration or protocol publication.

Aberg et al (2009) reported a prospective, assessor-blinded pilot RCT comparing resorbable polyhydroxybutyrate (PHB) to conventional end-to-end repair in wrist and forearm nerve discontinuities.[50,] Twelve patients were randomized 1:1 to either PHB (n=6) or conventional repair (n=6); 1 patient in the PHB group was lost to follow-up (17%). Reported baseline characteristics were balanced between the two study arms. No significant difference was noted in BMRC sensory or BMRC motor scores at 18 months follow-up although the PHB group tended to have a numerically greater level of sensory and muscle recovery (Table 17). Limitations to this study were the small sample size, lack of power calculations, lack of participant blinding, no intent to treat analysis, and absence of information on the length of nerve discontinuity in each treatment group.

Bertleff et al (2005) conducted a multicenter, double-blind RCT comparing Neurolac nerve guide (Polyganics, B.V.) with standard reconstruction techniques in individuals with traumatic peripheral nerve lesions of the hand. [51,] Thirty patients with 34 nerve injuries were included and randomized 1:1 to either Neurolac (n=20) or standard of care reconstruction (n=13). No significant differences were observed on S2PD or M2PD through 12-month follow-up. Two patients in the Neurolac group (10%) needed revision surgery due to a rupture of the repaired tendon and the development of tenolysis. Limitations to this trial included lack of power calculations, uncertainty regarding participant

blinding, no intention to treat analysis, absence of comparative effect calculation, and absence of information on nerve gap length at baseline.

Lundborg et al (2004) published the results of a multicenter, double-blind RCT comparing silicone tube conduit and conventional microsurgery for transection of the median or ulnar nerve at the wrist or forearm.[53,] Study characteristics and results are summarized in Tables 16 and 17. Thirty participants were recruited who were randomized 1:1 to silicone tube (n=17) or to standard end-to-end epineural suturing (n=13). Outcomes were assessed at 3-, 6- and 12-month follow-ups and then yearly through 5-year follow-ups; 2 participants were lost to follow-up at the 5-year assessment 1 in each of the study arms. Outcome assessors were blinded through 1-year follow-up but not for yearly assessments after this time. The primary endpoint was BMRC grading for sensory recovery with a secondary outcome of Rosen-score. Patients ranged from 12 to 72 years of age, with an overall mean age of 33 years. No description of nerve discontinuity length within each group was reported. Early results 1 year follow-up showed a significant difference for cutaneous touch and pressure thresholds favoring the conduit group (p=.03). At 5 years of follow-up, only perceived problems from cold intolerance were significantly different between groups and favored the conduit group over conventional repair (p=.01); all other elements of the Rosen-score were not significant (SWM, s2PD, STI-test, Sollerman test [tasks 4,8 and 10], manual muscle test, grip strength, and hyperesthesia). Limitations of the trial included a lack of blinding for follow-up beyond 1 year, lack of baseline information on nerve discontinuity length for each treatment arm, lack of power calculations reported, and non-ITT analysis.

Weber et al (2000) published the results of a multicenter, double-blind RCT comparing PGA conduit to standard nerve repair for digital nerve reconstruction.[54,] Study characteristics and results are summarized in Tables 16 and 17. A total of 98 participants with 136 nerve transections of the hand were randomized 1:1 to PGA conduit (n=62) or standard surgical repair (n=74). At baseline, patient gender (p=.02) and mean gap length (7.0 mm in the PGA group vs 4.3 mm in the conventional repair group; p=.01) were not balanced between treatment arms. The average length of follow-up was 9.4 months in the PGA conduit patients and 8.1 months in the control group. Sixteen (25%) nerves in the PGA group and 18 (25%) nerves in the control group were lost to follow-up. No significant differences were observed in any outcome when examining the total enrolled study population, but when stratified by length of nerve gap, nerves with gaps of 4 mm or less had better sensation when repaired with a PGA conduit (mean m2PD, 3.7±6.4 mm for PGA conduit versus 6.1 ± 6.33 mm for end-to-end repairs (p=.03). Deficits of 8 mm or greater, which necessitated an autologous nerve graft in the control arm, favored PGA tube on m2PD test (mean, 6.8±3.8 mm for PGA conduit versus 12.9±2.4 mm for conventional repair; p=.001). Three patients in the PGA group had their conduit removed. Limitations of this study include uncertainty regarding the blinding for participants, lack of power calculations, non-ITT analysis, and a high number of participants who were lost to follow-up.

Table 16. Summary of Key RCT Characteristics for Synthetic Nerve Conduit

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Vs. processed nerve allograft (summarized in the previous section)						
Isaacs et al (2023); RECON[37,]	US	20	NR	N=220 adults with acute or subacute (< 24 weeks old) digital nerve injuries	processed nerve allograft (Avance) (n=112)	NeuraGen Nerve Guide (Integra LifeSciences) (n=108)
Means et al (2016)[23,]	US	4	NR	N=23 adults who sustained an injury requiring surgical repair of at least 1 digital nerve (gap length ≥5 and ≤ 20 mm)	processed nerve allograft (Avance) (n=14)	Hollow nerve conduits (NeuroGen, NeuroMatrix, or NeuroFlex) (n=9)

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
Vs. autologous vein conduit						
Rinker et al (2011)[26,]	US	1	NR	N=68 adults with acute digital nerve injuries w/ a gap of less than 3 cm	PGA conduit (Neurotube) (n=36)	Autologous vein conduit (n=32)
Vs. direct surgical repair						
Boeckstyns et al (2013)[52,]	Denmark	6	NR	N=44 adults w/ complete nerve laceration of the median or ulnar nerves in the distal third of the forearm	NeuraGen conduit (n=23)	Direct surgical repair (n=21)
Aberg et al (2009)[50,]	Sweden	1	NR	N=11 adults w/ peripheral nerve injuries of the wrist or forearm damaging the ulnar or median nerves	PHB conduit (n=6)	Direct surgical repair (n=6)
Bertleff et al (2005)[51,]	the Netherlands	5	2002 to 2003	N=34 adults w/ traumatic peripheral nerve lesions	Neurolac conduit (n=21)	Direct surgical repair (n=13)
Lundborg et al (2004)[53,]	Sweden	1	NR	N=30 patients with transection of median or ulnar nerve at the wrist or distal forearm	Silicone conduit (n=17)	Direct surgical repair (n=13)
Weber et al (2000)[54,]	US	5	1994 to 1998	N=102 adults w/ complete division of sensory nerve distal to the wrist crease	PGA conduit (n=46)	Direct surgical repair (n=56)

NR; not reported; RCT: randomized controlled trial.

Table 17. Summary of Key RCT Results for Synthetic Nerve Conduit

Study	S2PD at last visit; mean (SD) mm	SWMF at last visit, mean (SD)	M2PD at last visit, mean (SD), mm	RMI Score, mean (SE)	Complications, n (%)
Vs. autologous vein conduit					
Rinker et al (2011)[26,]	**S2PD, mean (SD) mm**		**M2PD at last visit, mean (SD), mm**		**Complications, n (%)**
PGA conduit	Total: 6 mos: 8.3 (2) Nerve gap <10 mm: 6 mos: 9.6 (1.9) 12 mos: 8.5 (1.9) Nerve gap ≥10 mm: 6 mos: 9.6 (1.9) 12 mos: 8.5 (1.9)		Total: 6 mos: 6.6 (2.3) Nerve gap <10 mm: 6 mos: 5.7 (1.9) 12 mos: 4.9 (1.7) Nerve gap ≥10 mm: 6 mos: 7.7 (2.5) 12 mos: 6.7 (2.4)		3 (8%)
Vein conduit	Total: 6 mos: 8.5 (1.8) Nerve gap <10 mm: 6 mos: 7.7 (1.6) 12 mos: 6.3 (2)		Total: 6 mos: 7.1 (2.2) Nerve gap <10 mm: 6 mos: 5.9 (1.3) 12 mos: 5 (1.3)		1 (3%)

Study	S2PD at last visit; mean (SD) mm	SWMF at last visit, mean (SD)	M2PD at last visit, mean (SD), mm	RMI Score, mean (SE)	Complications, n (%)
	Nerve gap ≥10 mm: 6 mos: 9.3 (1.9) 12 mos: 8.5 (2.5)		Nerve gap ≥10 mm: 6 mos: 8.2 (2.3) 12 mos: 7.8 (3.2)		
p-value for difference	NS for all comparisons		NS for all comparisons		
Vs. direct surgical repair					
Boeckstyns et al (2013)[52],					
NeuraGen conduit				Total: 12 months: 1.55 (0.11) 24 months: 1.85 (0.09) Motor domain: 12 months: 0.51 (0.04) 24 months: 0.60 (0.05)	
Direct surgical repair				Total: 12 months: 1.77 (0.09) 24 months: 2.05 (0.10) Motor domain: 12 months: 0.66 (0.05) 24 months: 0.75 (0.05)	
p-value for difference				The total score was NS, but the Motor domain at 12 months was superior in the direct surgical repair group, including the muscle force and grip strength sub-domains	No surgical complications of infection, extrusion of the conduit or other local adverse reaction, or development of a chronic regional pain syndrome
Aberg et al (2009)[50],	**BMRC Sensory Rating, 18 months**	**Manual Muscle test, 18 months**			
PHB conduit	S4: 1 (20%) S3: 1 (20%) S2: 3 (60%)	Dig II abduction, median (SD): 60 (11) Div V abduction: 2: 3 (60%) 1: 1 (20%) 0: 1 (20%)			
Direct surgical repair	S2: 5 (83%) S0: 1 (17%)	Dig II abduction, median (SD): 40 (13)			

Study	S2PD at last visit; mean (SD) mm	SWMF at last visit, mean (SD)	M2PD at last visit, mean (SD), mm	RMI Score, mean (SE)	Complications, n (%)
		Div V abduction: 1: 6 (100%)			
p-value for difference	.12	.19			
Bertleff et al (2005)[51],	**S2PD at 12 months; mean mm**		**M2PD at 12 months, mean mm**		
Neurolac nerve guide	~9		~8		
Standard of care	~11		~11		
p-value for difference	NS		NS		
Lundborg et al (2004)[53],	**s2PD at last visit; median (IQR)**	**SWMF at last median (IQR)**	**BMRC Classification, at 5 years**	**Composite Instrument Rosen-Score, mean (SD)**	**Complications, n (%)**
Silicone conduit	0.80 (0.6 to 0.93)	0.57 (0.47 to 0.66)	Class, n (%): S2: 5 (31%) S2+: 2 (13%) S3: 5 (31%) S3+: 3 (19%) S4: 1 (6%)	Overall: 5 years: 2.2 (0.8) 2 years: 1.6 (0.2) 1 year: 1.5 (0.2) Cold intolerance: 0.83 (0.67 to 1)	Tube removal due to discomfort: 8 (47%)
Direct surgical repair	0.80 (0.6 to 0.93)	0.52 (0.37 to 0.66)	S2: 3 (25%) S2+: 3 (25%) S3: 3 (25%) S3+: 3 (25%) S4: 0	Overall: 5 years: 2.1 (0.3) 2 years: 1.7 (0.6) 1 year: 0.5 (0.5) Cold intolerance: 0.5 (0.33 to 0.67)	0%
p-value for difference	NS	NS	NR	Continued improvement was shown in both groups since the previous follow-up interval, p<.05. NS difference between groups in the overall score. For cold intolerance, direct surgical repair was favored over conduit, p=.01.	
Weber et al (2000)[54],	**S2PD at last visit; mean (SD) mm**		**M2PD at last visit, mean (SD), mm**		
PGA conduit	All pts: 10.3 Gaps < 4 mm: 7.1 Gaps 5 to 7 mm: 11.7 Gaps > 8 mm: 10.8		All pts: 6.9 Gaps < 4 mm: 3.7 Gaps 5 to 7 mm: 8.9 Gaps > 8 mm: 6.8		Extrusion of PGA conduit: 3 (6.5%)
Direct surgical repair or Autograft	All pts: 9.3 Gaps < 4 mm: 8.3 Gaps 5 to 7 mm:		All pts: 7 Gaps < 4 mm: 5.1 Gaps 5 to 7 mm: 6 Gaps > 8 mm: 12.9		Persistent numbness at donor site: 8 (14%)

Study	S2PD at last visit; mean (SD) mm	SWMF at last visit, mean (SD)	M2PD at last visit, mean (SD), mm	RMI Score, mean (SE)	Complications, n (%)
	9.6 Gaps > 8 mm:13.1				
p-value for difference	NS for all comparisons		All pts: p=.89 Gaps < 4 mm: p=.03 Gaps 5 to 7 mm: p=.12 Gaps > 8 mm: p=.001		

~: indicates esimtated from figure; BMRC: British Medical Research Council; CI: confidence interval; HR: hazard ratio; IQR: interquartile range; M2PD: moving 2-point discrimination; NNT: number needed to treat; NR: not reported; NS: non-significant; OR: odds ratio; PGA: polyglycolic acid; PNA: Processed decellularized nerve allograft; RCT: randomized controlled trial; RMI: Rosen Model Instrument; RR: relative risk ; S2PD: static 2-point discrimination; SD: standard deviation; SWMF: Semmes-Weinstein Monofilament testing.

The purpose of the study limitations tables (see Tables 18 and 19) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement.

Table 18. Study Relevance Limitations for Synthetic Nerve Conduit

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Boeckstyns et al (2013)[52,]	5. Baseline information on gap length not reported				
Rinker et al (2011)[26,]	5. Single-center study				
Aberg et al (2009)[50,]	5. Single-center study				
Bertleff et al (2005)[51,]	5. Baseline information on gap length not reported				
Lundborg et al (2004)[53,]	5. Single-center study; baseline information on gap length, not reported				
Weber et al (2000)[54,]					

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 19. Study Design and Conduct Limitations for Synthetic Nerve Conduit

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Boeckstyns et al (2013)[52,]		1. Participants not blinded		1. High loss to follow-up or missing data 6. Not intent to treat analysis	1. Power calculations not reported	
Rinker et al (2011)[26,]		1. Unclear if participants were blinded		1. High loss to follow-up or missing data 6. Not intent to treat analysis		
Aberg et al (2009)[50,]		1. Participants not blinded				
Bertleff et al (2005)[51,]		1. Unclear if participants were blinded		6. Not intent to treat analysis	1. Power calculations not reported	4. Comparative treatment effects not calculated
Lundborg et al (2004)[53,]		1. Unclear if participants were blinded; outcome assessors not blinded past 1-year follow-up		6. Not intent to treat analysis	1. Power calculations not reported	
Weber et al (2000)[54,]		1. Unclear if participants were blinded		1. High loss to follow-up or missing data 6. Not intent to treat analysis	1. Power calculations not reported	

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 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 Studies

Processed Nerve Allograft

Two non-randomized comparative studies of Neuragen compared to Avance allograft are reported in the process nerve allograft section.[25,39,] In a case series by Rbia et al (2019), 18 patients underwent peripheral nerve reconstruction of the fingers using Avance PNA and 19 with Neuragen collagen nerve conduit. The study reported comparable sensory recovery in both groups with no significant differences. In a retrospective cohort study by Ducic et al (2012), patients with upper extremity peripheral nerve reconstructions were treated using Avance PNA, NeuraGen conduit, autograft, or direct surgical repair. The study found no significant differences in QuickDASH questionnaire scores between the groups.

Autologous Nerve Graft

Saeki et al (2018) reported the results of a multi-center, open-label, non-randomized trial of non-hollow, collagen-filled conduits (n=48) compared to autologous nerve graft (n=38) in individuals with sensory nerve defects of the wrist or more distal location on the upper extremity. [30,] Participants were recruited from 9 centers in Japan from 2010 to 2014. A non-inferiority margin of -25% between collagen conduit and allograft was assigned, and the authors determined that to have 80% power, an estimated 41 participants would be needed in each group. The allograft group contained predominately historical controls (n=31). The two treatment arms differed in the baseline characteristics of mean age (42 in the conduit group versus 36 in the autologous graft group, p=.032) and the mean size of nerve defect (12.6 in the conduit group versus 18.7 in the autologous graft group, p<.0001). At 12 months post-surgery, both groups had similar rates of sensory recovery, assessed by S2PD, of 75% (95% CI, 60% to 86%) for the artificial conduit and 73.7 (95% CI, 57% to 87%). Adverse events were reported in 70% of the nerve conduit patients, with 21% assessed as serious events, and in the autologous grafting group, 86% of participants had at least 1 adverse event, with only 5% deemed as serious. Limitations of the study include lack of randomization and blinding, generalizability of the collagen conduit intervention, use of historical control patients, and imbalanced baseline patient characteristics.

Table 20. Summary of Key Nonrandomized Trials OR Observational Comparative Study Characteristics for Synthetic Nerve Conduit

Study	Study Type	Country	Dates	Participants	Intervention	Comparator	Follow-Up
Synthetic conduit vs. processed nerve allograft (summarized in the previous section)							
Rbia et al (2019)[25,]	Case series	the Netherlands	2005-2015	Review of patients with digital nerve injury who underwent reconstruction with either Neuragen nerve conduit or Avance allograft	Processed nerve allograft (Avance) (n=18)	Neuragen nerve conduit (n=19)	Mean 477 days for the PNA group and 432 days for the conduit group
Ducic et al (2012)[39,]	Retrospective cohort	US	2003-2009	Consecutive upper-extremity nerve repair	Processed nerve allograft (Avance) (n=8)	Conduit repair (NeuraGen) (n=27) Autograft repair (n=11) Direct surgical repair (n=8)	Mean of 130 to 250 weeks
Synthetic conduit vs. autologous nerve graft							
Saeki et al (2018)[30,]	Open-label, non-randomized clinical trial	US	2010-2014	Open or closed traumatic injuries to sensory nerves in the wrist or more distal lesions	Artificial nerve conduit (n=49)	Autologous nerve (n=38; 7 from the current study and 31 from a historical study)	12 months

NR: not reported; PNA: Processed decellularized nerve allograft

Table 21. Summary of Key Nonrandomized Trials OR Observational Comparative Study Results for Synthetic Nerve Conduit

Study	Sensory recovery, n (%) (95% CI)	S2PD, category, n (%)	Complications, n (%)
Saeki et al (2018)[30,]	86		
Artificial conduit (n=48)	36 (75%) (60% to 86%)	S0: 7 (17%) S1: 5 (12%) S2: 3 (7%)	Any Adverse Event:70% Serious Adverse Event:21%

Study	Sensory recovery, n (%) (95% CI)	S2PD, category, n (%)	Complications, n (%)
		S3: 14 (33%) S4: 13 (31%)	
Autologous nerve (n=38)	28 (73.7%) (57% to 87%)	S0: 2 (29%) S1: 0 S2: 0 S3: 4 (57%) S4: 1 (14%) *Only non-historic participants reported (n=7)*	Any Adverse Event:86% Serious Adverse Event:5%
Between-group difference (95% CI)	1.3 (-20 to 22; p=.9)		

BMRC: British Medical Research Council; CI: confidence interval; HR: hazard ratio; IQR: interquartile range; M2PD: moving 2-point discrimination; NNT: number needed to treat; NR: not reported; NS: non-significant; OR: odds ratio; PGA: polyglycolic acid; PNA: Processed decellularized nerve allograft; RCT: randomized controlled trial; RR: relative risk ; S2PD: static 2-point discrimination; SD: standard deviation; SWMF: Semmes-Weinstein Monofilament testing.

Observational Studies

Numerous observational case reports and case series are available on the treatment of peripheral nerve discontinuities with synthetic conduits.[9,11,12,55,56,14,17,21,57,32,58,59,19,22,60,35,] Because higher quality evidence is available, only studies with ≥75 participants, using commercially available interventions and longer-term follow-up over 6 months, were summarized.

Wangensteen et al (2010) reported results from a retrospective chart review of all patients who received Neuragen conduits (Integra Lifesciences) at a single center.[61,] From 2002 to 2007, 96 patients with 126 nerve lesions were repaired; the majority of repairs were to the upper extremity (95%), non-upper extremity repairs were limited (5%). (Table 11). The mean age of the overall population was 33 years (range, 7 to 79 years), and the average nerve gap was 12.8 mm (range 2.5 to 20 mm). The average follow-up period was 256 days, and 40 nerve repairs (32%) were lost to follow-up. The total number of surgical revisions was 11 (9%), with 9 occurring in the upper extremities (8%) and a greaterpercentage in the non-upper extremities (33%). Overall, 43% of patients with either objective or subjective evaluation by electromyography, 2-point discrimination, or Semmes-Weinstein monofilament testing showed post-operative improvement.

Table 22. Summary of Key Case Series Characteristics for Synthetic Nerve Conduit

Study	Country	Participants	Follow-Up
Wangensteen et al (2010)[61,]	US	Patients who underwent nerve repair with a collagen conduit at a single trauma center (NeuraGen) (n=96)	3.5

Table 23. Summary of Key Case Series Results for Synthetic Nerve Conduit

Study	Treatment	Sensory Outcome	Motor Score	Complications
Wangensteen et al (2010)[61,]	Collagen conduit (Neuragen)	67% reported improvement on the SWMF exam 24% of patients improved on 2-point sensory exam	NR	No intra-operative complications Post-operative complications: 3 (3%) (1 case each of erythema around the wound, pulmonary embolism, partial wound dehiscence) 7 (7%) revision surgeries were needed to repair 11 nerves

NR: not reported; SWMF:Semmes-Weinstein monofilament testing;

Section Summary: Synthetic Conduits

For individuals with peripheral nerve injury requiring repair and closure of the nerve gap who receive synthetic nerve conduits, the evidence includes 3 meta-analyses, 8 RCTs (2 comparing NeuraGen to allograft, 1 comparing Neurotube to autologous vein grafting, and 4 comparing conduit [1 Neurolac, 1 Polyhydroxybutyrate {PHB}, 1 polyglycolic acid {PGA}, and 1 silicone tube] to direct surgical repair), 1 non-randomized clinical trial, 1 comparative retrospective cohort study, 1 comparative case series, and 1 non-comparative case series. The evidence base consisted primarily of peripheral nerve injuries to the fingers or upper extremities. NeuraGen was evaluated in 3 studies, and all other synthetic conduits were represented by a single study (Neuromatrix, Neuroflex, Neurotube, Neurolac, PHB conduit, PGA conduit, and collagen-filled conduit). In 1 RCT that compared Avance allograft to NeuraGen, allograft patients had a greater return of protective sensation rate on static 2-point discrimination (S2PD), but did not differ on overall S2PD score or other outcome measures. The second RCT comparing Avance allograft to Neuragen found that S2PD favored the allograft group at 1-year follow-up, but no differences were noted in moving 2-point discrimination (M2PD), Semmes Weinstein Monofilament (SWMF) test, or the Disability of the Arm and Shoulder (DASH) questionnaire. One RCT compared Neurotube conduit to an autologous vein conduit and found similar outcomes at a 2-year follow-up, but at 1-year analysis, the motor domain of the Rosen Model Instrument (RMI) favored the autologous treatment arm. Five other trials compared different types of conduits to direct surgical repair with generally equivalent outcomes; one RCT observed a significant difference in cold intolerance, which favored the synthetic conduit group, and another found that at short (<4 mm) and long nerve gaps (> 8 mm) M2PD was better in the PGA conduit group than in direct surgical repair or autograft. Major limitations identified in the trial evidence base included an absence of participant blinding, lack of intention to treat analysis, high loss to follow-up, absence of power calculations, and short duration of follow-up. Three non-randomized comparative studies found no difference between synthetic conduits and Avance (n=2), direct surgical repair (n=1), or autograft (n=1) in sensory or functional outcomes as well as complications. A Cochrane review found that there is no clear benefit to patients treated with artificial nerve conduits or nerve wraps over direct surgical repair, and that complications may be greater for participants treated with synthetic nerve conduits or wraps. The overall evidence base was considered very uncertain, with few outcomes having more than 1 included study. One other meta-analysis found comparable pooled rates of S2PD and M2PD across assessed interventions, but all estimates had extreme heterogeneity. The third meta-analysis found that meaningful recovery (≥S3 on the British Medical Research Council [BMRC] recovery grading system) was significantly higher in allograft and autografting than for synthetic conduits. No guideline evidence was identified for synthetic nerve conduits for the treatment of peripheral nerve injuries. Many of the included trials have significant limitations, and the substantial heterogeneity in patient and intervention characteristics makes it challenging to compare outcomes reliably across studies. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

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

Practice Guidelines and Position Statements

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

National Institute for Health and Care Excellence (NICE)

In 2017, NICE published guidance on processed nerve allografting to repair peripheral nerve discontinuities. [62,] The evidence base evaluated by NICE included the RCT by Means et al (2016) and the non-randomized trial by He et al (2013), which are discussed in this medical reference policy. NICE

also evaluated two other smaller case series, which were not included in our evidence review due to the availability of higher-quality evidence. The following were among the recommendations issued:

- Current evidence on the safety and efficacy of processed nerve allografts to repair peripheral nerve discontinuities is adequate to support the use of this procedure for digital nerves, provided that standard arrangements are in place for clinical governance, consent, and audit.
- The evidence on the safety of processed nerve allografts to repair peripheral nerve discontinuities in other sites raises no major safety concerns. However, current evidence on its efficacy in these sites is limited in quantity. Therefore, for indications other than digital nerve repair, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research.
- This procedure should only be done by surgeons with training and experience in peripheral nerve repair.
- Patient selection should take into consideration the site, type of nerve (motor, sensory, mixed), and the size of the defect.
- NICE encourages further research into processed nerve allografts to repair peripheral nerve discontinuities. This should include information on the type of nerve repaired, the anatomical site, the size of the defect, patient-reported outcome measures, functional outcomes, time to recovery, and long-term outcomes (12 months to 18 months).

U.S. Preventive Services Task Force Recommendations
Not applicable.

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 24.

Table 24. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04865679[a]	Tolerability and Feasibility Pilot Clinical Study of a Large-Diameter Nerve Cap for Protecting and Preserving Terminated Nerve Ends (REPOSE-XL℠)	15	Dec 2026
NCT01526681[a]	Registry of Avance® Nerve Graft's Utilization and Recovery Outcomes Post Peripheral Nerve Reconstruction	5000	Dec 2025
NCT05339594[a]	REINVENT Registry (Registry of the Nerve Gap Repair From Integra)	350	June 2027
Unpublished			
NCT05199155	Use of a Nerve Regeneration Conduit (NerVFIX®) in the Treatment of Nerve Section of the Wrist	15	Dec 2023 (terminated)
NCT05343143[a]	NeuraGen 3D Pilot Study	10	July 2024 (terminated)

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

Appendix 1

2025 Clinical Input
Objective
Clinical input was sought to help determine whether the use of processed nerve allograft or synthetic nerve conduit in individuals with peripheral nerve injuries requiring repair and closure of a nerve gap

would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input was received from 3 respondents, including 1 specialty society-level response.

Respondents

Clinical input was provided by the following specialty societies and physician members identified by a specialty society or clinical health system:

- American Association of Neurological Surgeons / Congress of Neurological Surgeons
- Nicholas Pulos, MD, Mayo Clinic
- Noah Raizman, MD, The Centers for Advanced Orthopedics

Clinical Input Ratings

Clinical Indication	Respondent	Identified by	Confidence Level That Clinical Use Expected to Provide Clinically Meaningful Improvement in Net Health Outcome: Yes or No	NO: High 5	4	Intermediate 3	2	Low 1	YES: Low 1	Intermediate 2	3	High 4	5	Confidence Level that Clinical Use is Consistent with Generally Accepted Medical Practice: Yes or No	NO: High 5	4	Intermediate 3	2	Low 1	YES: Low 1	Intermediate 2	3	High 4	5
Use of processed nerve allograft in individuals with peripheral nerve injuries requiring repair and closure of a nerve gap	AANS/CNS		Yes										■	Yes										■
	Dr. Nicholas Pulos*	Mayo Clinic	Yes										■	Yes								■		
	Dr. Noah Raizman	The Centers for Advanced Orthopedics	Yes										■	Yes										■
Use of synthetic nerve conduit in individuals with peripheral nerve injuries requiring repair and closure of a nerve gap	AANS/CNS		Yes										■	Yes										■
	Dr. Nicholas Pulos*	Mayo Clinic	Yes										■	Yes										■
	Dr. Noah Raizman	The Centers for Advanced Orthopedics	Yes										■	Yes										■

AANS/CNS: American Association of Neurological Surgeons / Congress of Neurological Surgeons.
* Indicates that conflicts of interest related to the topic where clinical input is being sought were identified by this respondent (see Appendix).

Respondent Profile

#	Respondent	Clinical Specialty	Board Certification
1	American Association of Neurological Surgeons/Congress of Neurological Surgeons	Neurosurgery	
2	Nicholas Pulos, MD, Mayo Clinic, Rochester, MN	Pediatric Hand Surgery	Orthopedic Surgery, Hand Fellowship, Pediatric Upper Extremity Fellowship
3	Noah M Raizman, MD, The Centers for Advanced Orthopedics, Washington, DC	Hand and Peripheral Nerve Surgery	Orthopedic Surgery, Hand Fellowship

Respondent Conflict of Interest Disclosure

#	1) Research support related to the topic where clinical input is being sought		2) Positions, paid or unpaid, related to the topic where clinical input is being sought		3) Reportable, more than $1,000, health care–related assets or sources of income for myself, my spouse, or my dependent children related to the topic where clinical input is being sought		4) Reportable, more than $350, gifts or travel reimbursements for myself, my spouse, or my dependent children related to the topic where clinical input is being sought	
	YES/NO	Explanation	YES/NO	Explanation	YES/NO	Explanation	YES/NO	Explanation
1	NO		NO		NO		NO	
2	Yes	Co-authored several publications on nerve auto and allografts and	NO		NO		NO	

#	1) Research support related to the topic where clinical input is being sought	2) Positions, paid or unpaid, related to the topic where clinical input is being sought	3) Reportable, more than $1,000, health care–related assets or sources of income for myself, my spouse, or my dependent children related to the topic where clinical input is being sought	4) Reportable, more than $350, gifts or travel reimbursements for myself, my spouse, or my dependent children related to the topic where clinical input is being sought
	brachial plexus injuries.			
3	NO	NO	NO	NO

Specialty Society respondents provided aggregate information that may be relevant to the group of clinicians who provided input to the Society-level response.

Clinical Input Responses

Question 1: We are seeking your rationale on whether using processed nerve allograft in individuals with peripheral nerve injuries requiring repair and closure of a nerve gap provides a clinically meaningful improvement in net health outcome. Please respond based on the evidence and your clinical experience.
Please address these points in your response:

- Relevant clinical scenarios (e.g., a chain of evidence) where the technology is expected to provide a clinically meaningful improvement in net health outcome.
- Specific outcomes that are clinically meaningful.
- Any relevant patient inclusion/exclusion criteria or clinical context important to consider in identifying individuals for this indication.
- Key supporting evidence from the authoritative scientific literature (please include PMID).

#	Rationale
1	The use of processed nerve allografts has become a standard part of the options for repair of nerves with gaps that exceed the ability to perform a direct repair. When direct nerve repair is feasible, this is the surgical technique of choice that results in the best outcomes. When the gap exceeds the ability to primarily repair a nerve, the options for repair include autograft nerve repair, allograft nerve repair, and conduit repair. The advantage of allograft nerve repair compared to autograft nerve repair is that it avoids potential donor site morbidity associated with the harvest of nerve autograft. In certain circumstances, nerve allograft has been shown to be equivalent to nerve autograft, while in other scenarios there are not convincing data regarding the comparability of autograft versus allograft. Despite this, when considering risks versus benefits, including the benefit of avoiding donor site morbidity, there is enough evidence for allograft nerve repair to support its inclusion as a standard option for nerve repair when primary repair is infeasible. The maximum available allograft length is 70 mm. For gaps that exceed 70 mm, there are no data supporting the technique of daisy-chaining allografts together (i.e., connecting allografts end to end). On that basis, there are no data to support the use of allografts for gaps that exceed 70 mm. Currently, based on a systematic review, no conclusions concerning differences in outcome using processed nerve allografts versus autograft or conduits can be drawn (PMID: 37383478). Data from the RANGER registry (a prospectively maintained registry of allograft nerve repairs) suggest that allograft nerve repair results in acceptable rates of motor and sensory recovery (PMID: 32101338). The bulk of the data are for digital nerve repairs, where allograft nerve repair has become quite standard and well-supported. In fact, in one survey study, allograft nerve repair was seen as the method of choice for repair of digital nerve injuries, exceeding autograft and conduit repair in surgeon-indicated preference (PMID: 30254826). This is well-supported by the reported good outcomes (sensory recovery) for digital nerves with allografts, with data showing superior outcomes for allografts compared to conduits for larger gaps (PMID: 37530686, 28328632). Thus, the use of allografts is well-supported by both study data and practice patterns for the repair of digital nerves. There are not enough data to draw meaningful conclusions for larger sensory, motor, and mixed nerves. The available data, though with a low sample size and relatively poor study quality, suggest that motor and sensory outcomes for allograft nerve repair of larger nerves are comparable to autograft nerve repair. The data do not support superiority of allograft repair over autograft. Autograft repair should still be considered the gold standard for larger, important sensory, motor, and mixed nerves. However, there are enough data

#	Rationale
	to support the use of allografts as an option, particularly if the patient wants to avoid potential donor morbidity or especially in patients who have multiple injuries making autograft nerve harvest risky or infeasible. Finally, allograft nerve repair has been shown to reduce neuropathic pain (PMID: 32542326, 37775087, 34616638). In scenarios where the main indication for nerve repair is the prevention or treatment of neuropathic pain, allograft nerve repair is a reasonable option and should be available in the set of possible treatment options. As one example, experience and study data show that allograft nerve repair following nerve biopsy dramatically reduces the incidence of long-term neuropathic pain (PMID: 32542326)
2	-For patients with a sensory nerve gap, that is not suitable for direct repair, it is my opinion and experience that patients prefer allograft to autograft reconstruction. The reason for this is that autograft harvest, most commonly from the sural nerve, leaves patients with a sensory deficit over the lateral aspect of their foot. Allograft reconstruction may be performed, as the references note, with either a synthetic nerve conduit or a processed nerve allogaft. The decision to utilize one over the other in my practice is largely based on size of the gap. For gaps less than 1.5cm (the literature above refernces 20mm), a nerve conduit is reasonable. I have some some concern that more rigid nerve conduits may inhibit motion or cause skin problems if used across flexion creases in the fingers. Nerve allografts therefore are indicated for gaps longer than 1.5cm AND may be considered in smaller gaps where a conduit may not be compliant in the soft tissues. -I agree with S2P, M2P, and SWMF as suitable outcome measures in studies looking at clinical outcomes. There is also evidence to support a more simple "Ten's Test" which is patient reported and compares sensation on both sides to each other. -Mixed nerve and motor nerve gaps are not an appropriate indication for the use of nerve allograft except in cases where there is insufficient nerve autograft available. (Nerve autograft is the gold standard for mixed and motor nerve injries and comparable results with allograft have not been achieved in non-industry funded research in humans). Allergies and religious objections would be a paitent exclusion criteria for the use of these adjuncts.
3	Processed Nerve Allograft (PNA) has been shown, in multiple studies and peer-reviewed registry data, to fare comparably to nerve autograft, particularly for sensory nerves and digital nerves, with no donor site morbidity, sacrifice of sensation in other parts of the body, potential neuroma pain, and disfiguring scarring. The cost of the implant is more than made up for by the decreased operative time and hospital resource utilization. Given the ethical issues with sham surgery for harvesting a donor nerve, a randomized clinical trial is not feasible, but registry data is compelling. Allograft has shown excellent results in facial and trigeminal nerve reconstruction as well. Net health outcome includes donor site morbidity.

Question 2: We are seeking your rationale on whether using synthetic nerve conduit in individuals with peripheral nerve injuries requiring repair and closure of a nerve gap provides a clinically meaningful improvement in net health outcome. Please respond based on the evidence and your clinical experience.

Please address these points in your response:

- Relevant clinical scenarios (e.g., a chain of evidence) where the technology is expected to provide a clinically meaningful improvement in net health outcome.
- Specific outcomes that are clinically meaningful.
- Any relevant patient inclusion/exclusion criteria or clinical context important to consider in identifying individuals for this indication.
- Key supporting evidence from the authoritative scientific literature (please include PMID).

#	Rationale
1	Nerve conduits are hollow tubes, or more recently tubes containing an inner matrix, that are designed to bridge a nerve gap and to provide axonal guidance across the gap. While conduits can be used in this fashion to bridge a nerve gap, another use of conduits is in conduit-assisted repairs, where tension is displaced off of the nerve ends and onto the conduit as a technique for tension-relief. Conduits are available for bridging gaps up to 25 mm. There are no high-quality human studies, to our knowledge, examining conduit-assisted repair as a tension-relieving strategy. This is a commonly accepted practice and one frequently employed in situations where there is moderate tension at a repair site. Experience shows that this is a viable technique for relieving tension and helps facilitate nerve repairs that may otherwise be infeasible. As a result, we believe this technique is supported by clinical experience. Additionally, this technique has been studied in animals and

#	Rationale
	found to be a viable technique for tension-relief, supported by the experimental data (PMID: 33356577, 15128129). For digital nerves, especially with short gaps (<15 mm), conduit repair is supported by the available data. In a randomized trial comparing conduit repair to allograft repair for digital nerves, 2 point discrimination was similar at last follow-up in the two groups for gaps <15 mm, with both groups showing a high rate of meaningful sensory return. For gaps 15 mm or greater, allograft repair outperformed conduit repair, though meaningful sensory return was still achieved in a high proportion of patients who underwent conduit repair (PMID: 37530686). Other non-randomized studies have demonstrated superiority of allograft repair but showed similar rates of meaningful sensory return in the conduit repair groups (PMID: 23827446, 33010972). The data support the use of conduits for repair in digital nerves for gaps <15 mm. For gaps 15-25 mm, allograft repair is superior but in cases where allograft nerve may not be available, conduit repair is an acceptable alternative with high rates of meaningful sensory return. For larger nerves (any nerve aside from digital nerves), there are few data to support the use of conduits and our collective experience does not support the use of conduits for this indication, except for the specific application of conduit-assisted repair for tension-relief. It may be reasonable to use conduits for repair of very short gaps (<5-6 mm) for major nerves, with no consistent practice pattern in that regard.
2	As above. The determining factor in using a conduits over allograft is commonly the size of the gap. Conduits are easier to store than allograft, making them popular in certain settings. Conduits can also be used as "nerve wraps" to protect direct nerve-to-nerve coaptations.
3	Conduits have been used for decades for short gap nerve reconstruction as well as to assist nerve repair by better aligning fascicles than can be accomplished with suture fixation. The literature is compelling and compares well to nerve autograft, with some studies showing better recovery of sensation than in autograft. The lack of donor site morbidity is similarly critical.

Question 3: What key clinical features or guidelines are used to best select individuals who might benefit from using processed nerve allograft for repair or closure of peripheral nerve gaps? Are there any unique considerations based on wound etiology (e.g. digital wounds vs. other etiologies) or the distance of nerve gap to be closed or repaired (e.g. ≥5mm)?

#	Rationale
1	Allograft nerve repair can be considered for repair of any nerve injury where direct repair is infeasible. There are no specific cutoff guidelines for length of the nerve gap, except that the maximum allograft length is 7 cm. There are no data to support connecting allografts (daisy-chaining), limiting the maximum gap to 7 cm. When direct repair is possible, it should be utilized with an assessment of tension at the repair sites through range of motion or combined with immobilization to prevent additional tension and rupture of the repair. When direct repair is infeasible, repair with allograft nerve should be considered part of the standard set of options available. Allograft repair is the repair technique of choice for digital nerves when direct repair is infeasible, especially if the gap exceeds 15 mm. If the gap is less than 15 mm, conduit repair is an equally acceptable option. For repairs where management or prevention of neuropathic pain is the primary consideration, allograft repair is the technique of choice, since harvest of autograft introduces the same risk of neuropathic pain at the donor site. As an example, repair of nerve biopsy sites is best achieved with allograft nerve repair. For major sensory nerves covering critical sensory territories, motor, or mixed motor/sensory nerves, autograft repair remains the gold standard. Allograft nerve repair is considered acceptable in these cases, if the patient wishes to avoid the risk of donor site morbidity or in cases where autograft harvest is risky or infeasible, though the patient should be counseled that experience tells us that autograft repair has superior outcomes. Despite this collective experience, the current level of evidence in the literature is not sufficient to make a reasonable comparison.
2	As above. But again: Sensory deficit >1.5cm Patient allergy or objection to source material used in making the conduit.
3	While long gaps (>5cm) and mixed/motor nerves may achieve marginally better results with autograft, the donor site morbidity is substantial, and the overall results with autograft are poor. PNA is indicated in any situation where a tension-free primary coaptation cannot be performed. Indications beyond that are not abundantly clear, and it would be inappropriate for a payor to, in blanket fashion, deny coverage for the use of PNA, as care must be individuated by the operating surgeon.

Question 4: What key clinical features or guidelines are used to best select individuals who might benefit from using synthetic nerve conduit for repair or closure of peripheral nerve gaps? Are there

any unique considerations based on wound etiology (e.g. digital wounds vs. other etiologies), the distance of nerve gap to be closed or repaired (e.g. ≤5mm), or synthetic nerve conduit product?

#	Rationale
1	Synthetic conduit repair is best used to repair digital nerve injuries with gaps <15 mm. Data shows that outcomes under these conditions are similar to allograft nerve repair. For digital nerve injuries with gaps 15-25 mm, conduit repair yields acceptable outcomes but inferior to allograft repair. Conduit repair should only be used in these circumstances if allograft nerve is not available. Any gap exceeding 25 mm is not appropriate for conduit repair. There are insufficient data to support the use of conduit repair for major nerves (any nerve aside from digital nerves) and collective experience and opinion of the group is that conduit repair is not appropriate for major nerves except for very short gaps (<5-6 mm). Conduit-assisted repair as a technique for tension-relief is appropriate for any nerve repair where there is thought to be mild to moderate tension at the repair site.
2	As above. Sensory deficit. Smaller nerve gaps (<2cm) Augmentation of direct end-to-end nerve repairs.
3	Conduits have not been shown to compare favorably to autograft in gaps over 3cm. Other than that, any nerve repair should be a candidate for conduit assisted repair, and any nerve gap should be considered an indication

Question 5: Please describe any contraindications or patient comorbidities of concern for using processed nerve allograft or synthetic nerve conduit in individuals with peripheral nerve injuries requiring repair and closure of a nerve gap.

#	Rationale
1	Both allograft nerve and synthetic conduits are contraindicated in a surgical field with active infection. Synethic conduits are contraindicated for patients with a history of an allergic reaction or sensitivity to any component of the synthetic conduit. As examples, allergic reaction or sensitivity to porcine materials, bovine materials, or chondroitins, depending on the specific conduit.
2	Large mixed and motor nerves are a contra-indication to the use of nerve allografts or synthetic nerve conduits except when there is insufficient source material available for autografting or the conduit is used to augment the nerve coaptations as a wrap.
3	There are none.

Question 6: Is there any key evidence missing from the attached reference list on page 12 that demonstrates clinically meaningful improvement in net health outcome?

#	Rationale
1	PMID: 37383478; 30254826; 32542326; 37775087; 34616638; 23827446; 33010972
2	N.B. The two yes/no bubble queustions on Page 8 I answered strictly for the reconstruction of sensory nerve gaps, NOT motor. Experts may site the RANGER studies to suggest that nerve allograft is a reasonable alternative to autograft for mixed and motor nerve deficits, but this, in my opinion, is not an appropriate use of allograft. Independent studies have repeatedly shown in human studies and animal models that autograft is superior to allograft in restoring motor function. I've summarzied the literature regarding this topic most recently in this article: Saffari S, Shin AY, Pulos N. Nerve Autografts Versus Allografts for Mixed Motor/Sensory Nerve Reconstruction. J Hand Surg Glob Online. 2024 Apr 20;6(5):694-699. doi: 10.1016/j.jhsg.2024.01.025. PMID: 39381403; PMCID: PMC11456634.
3	28495410; 22121093; 32537284; 28328632; 32101338; 31044125; 33010972; 34616638; 32039999; 28336306; 25893633; 36780351; 37051208

Outcome Assessment Instruments:
British Medical Research Council Muscular Strength Grading System [63,]

Grade	Muscular function
M0	No contraction
M1	Flicker/trace contraction
M2	Active movement with gravity eliminated

Grade	Muscular function
M3	Active movement against gravity
M4-	Slight movement against resistance
M4	Moderate movement against resistance
M4+	Strong movement against resistance
M5	Normal/full power

British Medical Research Council Sensory Recovery Grading System [63,]

Grade	Sensory recovery
S0	No sensation
S1	Pain sensation (deep)
S2-	Pain sensation (superficial)
S2	Pain and touch sensation
S2+	Pain and touch sensation with some overreaction
S3	As S2+, without overreaction and w/ static 2PD 15-20mm
S3+	As S3, static 2PD 7-15 mm
S4	As S3, static 2PD <7 mm

Static two-point discrimination scoring (S2PD) [63,]

Measures the innervation density (number of nerves present in an area) by testing the ability to discern the difference between 1 and 2 static pressure points.

Range	Interpretation
1 to 5 mm	Normal
6 to 10 mm	Fair
11 to 15 mm	Poor
One point perceived	Protective sensation only
No points perceived	Anesthetic

Moving 2-point discrimination scoring [63,]

After nerve injury, moving 2-point discrimination returns earlier than static 2-point discrimination. The test is used to determine progress in return of sensation. Seven of 10 correct answers are needed for an accurate response. Two millimeters is considered a normal moving 2-point discrimination distance.

Semmes–Weinstein Monofilament test (SWMF) of pressure threshold [63,]

SWMF is used to evaluate cutaneous pressure thresholds. The detection threshold is the perceived sensation after applying the smallest S/W monofilament at the affected fingertip.

Score	Interpretation
0	untestable
1 (filament marking 6.65)	perception of deep pressure
2 (filament marking 4.56)	loss of protective sensation
3 (filament marking 4.31)	diminished protective sensation
4 (filament marking 3.61)	diminished perception of light touch
5 (filament marking 2.83)	normal perception of touch and pressure

Mackinnon–Dellon scale – Classification of sensory recovery [63,]

Grade	Recovery of Sensation	S2PD (mm)	M2PD (mm)
S0	No recovery of sensation in the autonomous zone of the nerve		
S1	Recovery of deep cutaneous pain sensation within the autonomous zone of the nerve		
S1+	Recovery of superficial pain sensation		
S2	Recovery of superficial pain and some touch sensation		
S2+	As in S2, but with over-response		
S3	Recovery of pain and touch sensation with the disappearance of over-response	>15	>7

Grade	Recovery of Sensation	S2PD (mm)	M2PD (mm)
S3+	As in S3, the localization of the stimulus is good, and there is imperfect recovery of 2-point discrimination (7-12mm)	7 to 15	4 to 7
S4	Complete recovery	2 to 6	2 to 3

Rosen Model Instrument (RMI) Score [64,]

The instrument assesses clinical hand function and has been validated and standardized for evaluation after nerve repair. It consists of 3 domains: sensory (touch thresholds, tactile gnosis, dexterity), motor (muscle function, grip strength), and pain/discomfort (hyperesthesia, cold sensitivity). Each domain produces a score that ranges from 0 to 1, and the total score is the sum of the 3 domains. The maximum total score is 3, which indicates normal sensory and motor function without pain, with lower scores indicating a greater degree of impairment.

Weber 2-point discrimination scale (mm) [63,]

Rating	M2PD		S2PD
Excellent	≤ 4	Or	≤ 6
Good	5 to 7	Or	7 to 15
Poor	≥ 8	Or	≥ 16

QuickDASH [63,]

QuickDASH is a 30-item questionnaire that addresses specific symptoms and disability of the arm during the preceding week and is used to estimate the patient's view of disability.

Item	Scale
1. Open a tight or new jar	1. No difficulty 2. Mild difficulty 3. Moderate difficulty 4. Severe difficulty 5. Unable
2. Do heavy household chores (e.g., wash walls, floors).	
3. Carry a shopping bag or briefcase.	
4. Wash your back.	
5. Use a knife to cut food.	
6. Recreational activities in which you take some force or impact through your arm, shoulder or hand (e.g., golf, hammering, tennis, etc.).	
7. During the past week, to what extent has your arm, shoulder or hand problem interfered with your normal social activities with family, friends, neighbors or groups?	1. Not at all 2. Slightly 3. Moderately 4. Quite a bit 5. Extremely
8. During the past week, were you limited in your work or other regular daily activities as a result of your arm, shoulder or hand problem?	1. Not limited at all 2. Slightly limited 3. Moderately limited 4. Very limited 5. Unable
9. Arm, shoulder or hand pain.	1. None 2. Mild 3. Moderate 4. Severe 5. Extreme
10. Tingling (pins and needles) in your arm, shoulder or hand.	
11. During the past week, how much difficulty have you had sleeping because of the pain in your arm, shoulder or hand? (circle number)	1. No difficulty 2. Mild difficulty3. Moderate difficulty 4. Severe difficulty 5. So much difficulty that I can't sleep

QuickDASH scores are calculated as ([Sum of n responses]/n]-1)*25; questionnaires missing more than 1 item can not be calculated.

Conversion of SMWF and 2PDS to MRCC MR[8,]

SMWF		MRCC	2PDS
Force (g)	**Monofilament No.**	**—**	**—**
100–300	6.10–6.65	S0	Loss of protective sensation
10–60	5.07–5.88	S1	
4–8	4.56–4.93	S2	
0.6–2	3.84–4.31	S3	>15 mm with recovery of pain and touch sensibility

SMWF		MRCC	2PDS
0.16–0.4	3.22–3.61	S3+	7–15 mm
<0.7	1.62–2.83	S4	≤6 mm

References

1. Brattain, K. Analysis of the peripheral nerve repair market in the United States. Magellan Med Technol Consult, Inc. 2014. Available at: http://content.stockpr.com/axogeninc/files/docs/Magellan_Study_-_Analysis_Of_The_Peripheral_Nerve_Repair_Market_In_The_United_States.pdf. Accessed November 15, 2024.
2. Karsy M, Watkins R, Jensen MR, et al. Trends and Cost Analysis of Upper Extremity Nerve Injury Using the National (Nationwide) Inpatient Sample. World Neurosurg. Mar 2019; 123: e488-e500. PMID 30502477
3. Mankavi F, Ibrahim R, Wang H. Advances in Biomimetic Nerve Guidance Conduits for Peripheral Nerve Regeneration. Nanomaterials (Basel). Sep 10 2023; 13(18). PMID 37764557
4. Buncke, G. Peripheral nerve allograft: how innovation has changed surgical practice. Plastic and Aesthetic Research 2022; 9(5).
5. Axogen, Inc. Avance Nerve Graft. Available at: https://www.axogeninc.com/products/avance-nerve-graft/. Accessed, Nov 15, 2024.
6. Parker BJ, Rhodes DI, O'Brien CM, et al. Nerve guidance conduit development for primary treatment of peripheral nerve transection injuries: A commercial perspective. Acta Biomater. Nov 2021; 135: 64-86. PMID 34492374
7. Zhang Y, Hou N, Zhang J, et al. Treatment options for digital nerve injury: a systematic review and meta-analysis. J Orthop Surg Res. Sep 12 2023; 18(1): 675. PMID 37700356
8. Lans J, Eberlin KR, Evans PJ, et al. A Systematic Review and Meta-Analysis of Nerve Gap Repair: Comparative Effectiveness of Allografts, Autografts, and Conduits. Plast Reconstr Surg. May 01 2023; 151(5): 814e-827e. PMID 36728885
9. Arnaout A, Fontaine C, Chantelot C. Sensory recovery after primary repair of palmar digital nerves using a Revolnerv(®) collagen conduit: a prospective series of 27 cases. Chir Main. Sep 2014; 33(4): 279-85. PMID 25169199
10. Battiston B, Geuna S, Ferrero M, et al. Nerve repair by means of tubulization: literature review and personal clinical experience comparing biological and synthetic conduits for sensory nerve repair. Microsurgery. 2005; 25(4): 258-67. PMID 15934044
11. Bushnell BD, McWilliams AD, Whitener GB, et al. Early clinical experience with collagen nerve tubes in digital nerve repair. J Hand Surg Am. Sep 2008; 33(7): 1081-7. PMID 18762101
12. Chiriac S, Facca S, Diaconu M, et al. Experience of using the bioresorbable copolyester poly(DL-lactide-ε-caprolactone) nerve conduit guide Neurolac™ for nerve repair in peripheral nerve defects: report on a series of 28 lesions. J Hand Surg Eur Vol. May 2012; 37(4): 342-9. PMID 21987277
13. Guo Y, Chen G, Tian G, et al. Sensory recovery following decellularized nerve allograft transplantation for digital nerve repair. J Plast Surg Hand Surg. Dec 2013; 47(6): 451-3. PMID 23848418
14. Haug A, Bartels A, Kotas J, et al. Sensory recovery 1 year after bridging digital nerve defects with collagen tubes. J Hand Surg Am. Jan 2013; 38(1): 90-7. PMID 23261191
15. He B, Zhu Q, Chai Y, et al. Safety and efficacy evaluation of a human acellular nerve graft as a digital nerve scaffold: a prospective, multicentre controlled clinical trial. J Tissue Eng Regen Med. Mar 2015; 9(3): 286-95. PMID 23436764
16. Karabekmez FE, Duymaz A, Moran SL. Early clinical outcomes with the use of decellularized nerve allograft for repair of sensory defects within the hand. Hand (N Y). Sep 2009; 4(3): 245-9. PMID 19412640
17. Kusuhara H, Hirase Y, Isogai N, et al. A clinical multi-center registry study on digital nerve repair using a biodegradable nerve conduit of PGA with external and internal collagen scaffolding. Microsurgery. Jul 2019; 39(5): 395-399. PMID 30562848

18. Leckenby JI, Vögelin E. Reply: A Retrospective Case Series Reporting the Outcomes of Avance Nerve Allografts in the Treatment of Peripheral Nerve Injuries. Plast Reconstr Surg. Feb 01 2021; 147(2): 351e. PMID 33177470
19. Lohmeyer JA, Kern Y, Schmauss D, et al. Prospective clinical study on digital nerve repair with collagen nerve conduits and review of literature. J Reconstr Microsurg. May 2014; 30(4): 227-34. PMID 24338485
20. Lohmeyer JA, Siemers F, Machens HG, et al. The clinical use of artificial nerve conduits for digital nerve repair: a prospective cohort study and literature review. J Reconstr Microsurg. Jan 2009; 25(1): 55-61. PMID 19037847
21. Lohmeyer J, Zimmermann S, Sommer B, et al. [Bridging peripheral nerve defects by means of nerve conduits]. Chirurg. Feb 2007; 78(2): 142-7. PMID 17165008
22. Mackinnon SE, Dellon AL. Clinical nerve reconstruction with a bioabsorbable polyglycolic acid tube. Plast Reconstr Surg. Mar 1990; 85(3): 419-24. PMID 2154831
23. Means KR, Rinker BD, Higgins JP, et al. A Multicenter, Prospective, Randomized, Pilot Study of Outcomes for Digital Nerve Repair in the Hand Using Hollow Conduit Compared With Processed Allograft Nerve. Hand (N Y). Jun 2016; 11(2): 144-51. PMID 27390554
24. Neubrech F, Heider S, Otte M, et al. [Nerve Tubes for the Repair of Traumatic Sensory Nerve Lesions of the Hand: Review and Planning Study for a Randomised Controlled Multicentre Trial]. Handchir Mikrochir Plast Chir. Jun 2016; 48(3): 148-54. PMID 27311073
25. Rbia N, Bulstra LF, Saffari TM, et al. Collagen Nerve Conduits and Processed Nerve Allografts for the Reconstruction of Digital Nerve Gaps: A Single-Institution Case Series and Review of the Literature. World Neurosurg. Jul 2019; 127: e1176-e1184. PMID 31003028
26. Rinker B, Liau JY. A prospective randomized study comparing woven polyglycolic acid and autogenous vein conduits for reconstruction of digital nerve gaps. J Hand Surg Am. May 2011; 36(5): 775-81. PMID 21489720
27. Rinker BD, Ingari JV, Greenberg JA, et al. Outcomes of short-gap sensory nerve injuries reconstructed with processed nerve allografts from a multicenter registry study. J Reconstr Microsurg. Jun 2015; 31(5): 384-90. PMID 25893633
28. Rinker B, Zoldos J, Weber RV, et al. Use of Processed Nerve Allografts to Repair Nerve Injuries Greater Than 25 mm in the Hand. Ann Plast Surg. Jun 2017; 78(6S Suppl 5): S292-S295. PMID 28328632
29. Safa B, Shores JT, Ingari JV, et al. Recovery of Motor Function after Mixed and Motor Nerve Repair with Processed Nerve Allograft. Plast Reconstr Surg Glob Open. Mar 2019; 7(3): e2163. PMID 31044125
30. Saeki M, Tanaka K, Imatani J, et al. Efficacy and safety of novel collagen conduits filled with collagen filaments to treat patients with peripheral nerve injury: A multicenter, controlled, open-label clinical trial. Injury. Apr 2018; 49(4): 766-774. PMID 29566987
31. Salomon D, Miloro M, Kolokythas A. Outcomes of Immediate Allograft Reconstruction of Long-Span Defects of the Inferior Alveolar Nerve. J Oral Maxillofac Surg. Dec 2016; 74(12): 2507-2514. PMID 27376182
32. Schmauss D, Finck T, Liodaki E, et al. Is nerve regeneration after reconstruction with collagen nerve conduits terminated after 12 months? the long-term follow-up of two prospective clinical studies. J Reconstr Microsurg. Oct 2014; 30(8): 561-8. PMID 25184617
33. Taras JS, Jacoby SM, Lincoski CJ. Reconstruction of digital nerves with collagen conduits. J Hand Surg Am. Sep 2011; 36(9): 1441-6. PMID 21816545
34. Taras JS, Amin N, Patel N, et al. Allograft reconstruction for digital nerve loss. J Hand Surg Am. Oct 2013; 38(10): 1965-71. PMID 23998191
35. Thomsen L, Bellemere P, Loubersac T, et al. Treatment by collagen conduit of painful post-traumatic neuromas of the sensitive digital nerve: a retrospective study of 10 cases. Chir Main. Sep 2010; 29(4): 255-62. PMID 20727807
36. Zuniga JR, Williams F, Petrisor D. A Case-and-Control, Multisite, Positive Controlled, Prospective Study of the Safety and Effectiveness of Immediate Inferior Alveolar Nerve Processed Nerve Allograft Reconstruction With Ablation of the Mandible for Benign Pathology. J Oral Maxillofac Surg. Dec 2017; 75(12): 2669-2681. PMID 28495410

37. Isaacs J, Nydick JA, Means KR, et al. A Multicenter Prospective Randomized Comparison of Conduits Versus Decellularized Nerve Allograft for Digital Nerve Repairs. J Hand Surg Am. Sep 2023; 48(9): 904-913. PMID 37530686
38. Isaacs J, Browne T. Overcoming short gaps in peripheral nerve repair: conduits and human acellular nerve allograft. Hand (N Y). Jun 2014; 9(2): 131-7. PMID 24839412
39. Ducic I, Safa B, DeVinney E. Refinements of nerve repair with connector-assisted coaptation. Microsurgery. Mar 2017; 37(3): 256-263. PMID 28035702
40. Brooks DN, Weber RV, Chao JD, et al. Processed nerve allografts for peripheral nerve reconstruction: a multicenter study of utilization and outcomes in sensory, mixed, and motor nerve reconstructions. Microsurgery. Jan 2012; 32(1): 1-14. PMID 22121093
41. Cho MS, Rinker BD, Weber RV, et al. Functional outcome following nerve repair in the upper extremity using processed nerve allograft. J Hand Surg Am. Nov 2012; 37(11): 2340-9. PMID 23101532
42. Dunn JC, Tadlock J, Klahs KJ, et al. Nerve Reconstruction Using Processed Nerve Allograft in the U.S. Military. Mil Med. May 03 2021; 186(5-6): e543-e548. PMID 33449099
43. Zhu S, Liu J, Zheng C, et al. Analysis of human acellular nerve allograft reconstruction of 64 injured nerves in the hand and upper extremity: a 3 year follow-up study. J Tissue Eng Regen Med. Aug 2017; 11(8): 2314-2322. PMID 27098545
44. Carlson TL, Wallace RD, Konofaos P. Cadaveric Nerve Allograft: Single Center's Experience in a Variety of Peripheral Nerve Injuries. Ann Plast Surg. Jun 2018; 80(6S Suppl 6): S328-S332. PMID 29847373
45. Safa B, Jain S, Desai MJ, et al. Peripheral nerve repair throughout the body with processed nerve allografts: Results from a large multicenter study. Microsurgery. Jul 2020; 40(5): 527-537. PMID 32101338
46. Peters BR, Wood MD, Hunter DA, et al. Acellular Nerve Allografts in Major Peripheral Nerve Repairs: An Analysis of Cases Presenting With Limited Recovery. Hand (N Y). Mar 2023; 18(2): 236-243. PMID 33880944
47. Jain SA, Nydick J, Leversedge F, et al. Clinical Outcomes of Symptomatic Neuroma Resection and Reconstruction with Processed Nerve Allograft. Plast Reconstr Surg Glob Open. Oct 2021; 9(10): e3832. PMID 34616638
48. Leversedge FJ, Zoldos J, Nydick J, et al. A Multicenter Matched Cohort Study of Processed Nerve Allograft and Conduit in Digital Nerve Reconstruction. J Hand Surg Am. Dec 2020; 45(12): 1148-1156. PMID 33010972
49. Thomson SE, Ng NY, Riehle MO, et al. Bioengineered nerve conduits and wraps for peripheral nerve repair of the upper limb. Cochrane Database Syst Rev. Dec 07 2022; 12(12): CD012574. PMID 36477774
50. Aberg M, Ljungberg C, Edin E, et al. Clinical evaluation of a resorbable wrap-around implant as an alternative to nerve repair: a prospective, assessor-blinded, randomised clinical study of sensory, motor and functional recovery after peripheral nerve repair. J Plast Reconstr Aesthet Surg. Nov 2009; 62(11): 1503-9. PMID 18938119
51. Bertleff MJ, Meek MF, Nicolai JP. A prospective clinical evaluation of biodegradable neurolac nerve guides for sensory nerve repair in the hand. J Hand Surg Am. May 2005; 30(3): 513-8. PMID 15925161
52. Boeckstyns ME, Sørensen AI, Viñeta JF, et al. Collagen conduit versus microsurgical neurorrhaphy: 2-year follow-up of a prospective, blinded clinical and electrophysiological multicenter randomized, controlled trial. J Hand Surg Am. Dec 2013; 38(12): 2405-11. PMID 24200027
53. Lundborg G. Alternatives to autologous nerve grafts. Handchir Mikrochir Plast Chir. Feb 2004; 36(1): 1-7. PMID 15083383
54. Weber RV, Mackinnon SE. Bridging the neural gap. Clin Plast Surg. Oct 2005; 32(4): 605-16, viii. PMID 16139631
55. Dienstknecht T, Klein S, Vykoukal J, et al. Type I collagen nerve conduits for median nerve repairs in the forearm. J Hand Surg Am. Jun 2013; 38(6): 1119-24. PMID 23707012

56. Farole A, Jamal BT. A bioabsorbable collagen nerve cuff (NeuraGen) for repair of lingual and inferior alveolar nerve injuries: a case series. J Oral Maxillofac Surg. Oct 2008; 66(10): 2058-62. PMID 18848102
57. Nakamura Y, Takanari K, Ebisawa K, et al. Repair of temporal branch of the facial nerve with novel polyglycolic acid-collagen tube: a case report of two cases. Nagoya J Med Sci. Feb 2020; 82(1): 123-128. PMID 32273640
58. Takeda S, Kurimoto S, Tanaka Y, et al. Mid-term outcomes of digital nerve injuries treated with Renerve® synthetic collagen nerve conduits: A retrospective single-center study. J Orthop Sci. May 04 2023. PMID 37149481
59. Li Q, Liu Z, Lu J, et al. [Transferring the ulnaris proper digital nerve of index finger and its dorsal branch to repair the thumb nerve avulsion]. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi. Aug 15 2017; 31(8): 992-995. PMID 29806439
60. Patel NP, Lyon KA, Huang JH. An update-tissue engineered nerve grafts for the repair of peripheral nerve injuries. Neural Regen Res. May 2018; 13(5): 764-774. PMID 29862995
61. Wangensteen KJ, Kalliainen LK. Collagen tube conduits in peripheral nerve repair: a retrospective analysis. Hand (N Y). Sep 2010; 5(3): 273-7. PMID 19937145
62. National Institutes for Health and Care Excellence (NICE). Processed nerve allografts to repair peripheral nerve discontinuities [IPG597]. 2017. Available at: https://www.nice.org.uk/guidance/ipg597. Accessed November 15, 2024
63. Wang Y, Sunitha M, Chung KC. How to measure outcomes of peripheral nerve surgery. Hand Clin. Aug 2013; 29(3): 349-61. PMID 23895715
64. Rosén B, Lundborg G. A model instrument for the documentation of outcome after nerve repair. J Hand Surg Am. May 2000; 25(3): 535-43. PMID 10811759

Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Clinical findings (i.e., pertinent symptoms and duration)
  - Activity and functional limitations
  - Reason for procedure/test/device, when applicable
  - Pertinent past procedural and surgical history
  - Past and present diagnostic testing and results
  - Treatment plan (i.e., surgical intervention)
- Consultation and medical clearance report(s), when applicable
- Radiology report(s) and interpretation (i.e., MRI)
- Laboratory results

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed
- Procedure report(s)

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®	64910	Nerve repair; with synthetic conduit or vein allograft (e.g., nerve tube), each nerve
	64912	Nerve repair; with nerve allograft, each nerve, first strand (cable)
	64913	Nerve repair; with nerve allograft, each additional strand (List separately in addition to code for primary procedure)
HCPCS	C9352	Microporous collagen implantable tube (NeuraGen Nerve Guide), per cm length
	C9355	Collagen nerve cuff (NeuroMatrix), per 0.5 cm length

Policy History

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

Effective Date	Action
05/01/2025	New policy.

Definitions of Decision Determinations

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

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

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

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

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

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

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

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

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

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER** **Blue font: Verbiage Changes/Additions**
New Policy **Policy Statement:** N/A	**Peripheral Nerve Injury Repair Using Synthetic Conduits or Processed Nerve Allografts 7.01.177** **Policy Statement:** I. The use of processed nerve allografts for the repair and closure of peripheral nerve gaps up to 70 mm may be considered **medically necessary** when direct primary repair is not feasible. II. The use of synthetic nerve conduits for the repair and closure of peripheral nerve gaps may be considered **medically necessary** in **all** of the following scenarios: A. In the context of conduit-assisted repair as a technique for tension-relief at the peripheral nerve repair site or major nerve with a gap not exceeding 6 mm B. Repair of digital nerve injuries with gaps less than 15 mm C. Repair of digital nerve injuries with gaps 15-25 mm, where allograft nerve is not available D. Repair of major nerves with small gaps not exceeding 6 mm, where allograft nerve is not available III. All other uses of processed nerve allografts and synthetic nerve conduits for individuals with peripheral nerve gaps are considered **investigational**.