
Medical Policy



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***Current Policy Effective Date: 7/1/26**
(See policy history boxes for previous effective dates)

Title: Peripheral Nerve Injury Repair Using Synthetic Conduits or Processed Nerve Allografts

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.

Medical Policy Statement

The use of processed nerve allografts for the repair and bridging of peripheral nerve gaps is established when criteria are met.

The use of synthetic nerve conduits for the repair and closure of peripheral nerve gaps is established when criteria are met.

Inclusionary and Exclusionary Guidelines

Inclusions:

The use of **processed nerve allografts** for the repair and closure of peripheral nerve gaps up to 70 mm when:

- Direct repair is not feasible for individuals with large nerve gaps, segmental nerve loss or chronic and complex injuries **OR**
- There is insufficient donor material for autografting.

The use of **synthetic nerve conduits** for the repair and closure of peripheral nerve gaps when:

- Repair of digital nerve injuries with gaps <15 mm; **OR**
- Repair of digital nerve injuries with gaps 15-25 mm, where allograft nerve is not available; **OR**
- Repair of major nerves with small gaps not exceeding 6 mm, where allograft nerve is not available; **OR**
- In the context of conduit-assisted repair as a technique for tension-relief at the peripheral nerve repair site.

Exclusions:

- Allograft and conduit repair in a surgical field with active infection.
- Synthetic conduits in individuals with a history of an allergic reaction or sensitivity to any component of the synthetic conduit (e.g., bovine, porcine, or chondroitin materials).
- All other uses of processed nerve allografts and synthetic nerve conduits for individuals with peripheral nerve gaps not meeting above criteria.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

64910	64912	64913	64999	C9352	C9355
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Other codes (investigational, not medically necessary, etc.):

N/A

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

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 > 5 mm.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 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

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 helps to reduce scar formation, reduce mechanical irritation, and promote a favorable environment for nerve regeneration. These materials are addressed in Bioengineered Skin and Soft Tissue Substitutes (see Related Policies).

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. The author's concluded that processed nerve allografts were clinically superior to conduits for long gap reconstructions. The second RCT comparing allograft to NeuraGen found that S2PD favored the Avance allograft group at 1-year follow-up. In this pilot study, the author's concluded that patients whose digital nerve reconstructions were performed with processed nerve allografts had significantly improved and had more consistent functional sensory outcomes compared with hollowed conduits. 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. The authors found that processed

nerve allografts offer effective means of reconstructing a digital nerve gap. 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 ($\geq$ 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. Many of the included trials have limitations, and the substantial heterogeneity in patient and intervention characteristics makes it challenging to compare outcomes reliably across studies. Additionally, substantial interventional, comparator, and outcome heterogeneity across the evidence base makes 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. Although the available evidence demonstrates a clear need for more thorough investigation the evidence is sufficient 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). The second RCT comparing Avance allograft to NeuraGen found that S2PD favored the allograft group at 1-year follow-up. One RCT compared Neurotube conduit to an autologous vein conduit and found similar outcomes at a 2-year follow-up. 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. 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. One other meta-analysis found comparable pooled rates of S2PD and M2PD across assessed interventions. The third meta-analysis found that meaningful recovery ($\geq$ 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. Although the available evidence demonstrates the need for more thorough investigation of surgical options and trends. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Rationale

Evidence reviews assess 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 individuals 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. The following is a summary of the key literature to date.

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 >5 mm. These allografts spare individuals with nerve injuries the need to harvest autologous grafting material and negate the potential for donor site defects.

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. 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.

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 repairs 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 statistics, 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 article, 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 ($\geq$ 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 ($\leq$ 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 1 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	•	
Battiston et al 2005	•	
Bushnell et al 2008	•	
Chiriac et al 2012		•
Guo et al 2013	•	•
Haug et al 2013		•
He et al 2015	•	
Karabekmez et al 2009	•	•
Kusuhara et al 2019	•	
Leckenby et al 2020		•
Lohmeyer et al 2014	•	•
Lohmeyer et al 2009		•
Lohmeyer et al 2007	•	
Mackinnon and Dellon 1990	•	
Means et al 2016	•	•
Neubrech et al 2016	•	
Rbia et al 2019	•	•
Rinker and Liao 2011	•	
Rinker et al 2015		
Rinker et al 2017	•	
Safa et al 2020		•
Saeki et al 2018		•
Salomon et al 2016		•
Schmauss et al 2014	•	
Taras et al 2011	•	•
Taras et al 2013	•	•
Thomsen et al 2010	•	
Zuniga et al 2017		•

* Only trials of processed nerve allograft or synthetic nerve conduit are reported.

M-A: meta-analysis; SR: systematic review.

Table 2. SR & M-A Characteristics for Processed Nerve Allograft and Synthetic Conduit

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Zhang et al (2023)	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: 0.5to 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 10years
Lans et al (2023)	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	Total: 1559 (5-475)Autograft: 670 Allograft: 711 Synthetic conduit: 178	Case series, cohort studies, and clinical trials	NR

			Synthetic conduit:10.8mm-14mm Autograft:12mm-75mm			
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M-A: meta-analysis; NR: not reported; SR: systematic review.

Table 3. 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 $\geq$ S3, mean(95% CI)	Semmes-Weinstein monofilament testing good rating (SWMF)
Zhang et al (2023)				
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: 5 Autograft: 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: 8.80 (7.63 to 9.97) End-to-side coaptation: 8.28 (6.69 to 9.88)	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)

I^2 (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)	Mackinnon and Dellon Classification $\geq$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% 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.		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%) 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)	
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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 7.5 mm; $p<.05$). The authors also found that 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 4. Summary of Key RCT Characteristics for Processed Nerve Allograft

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Isaacs et al (2023)	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 NerveGuide (Integra LifeSciences) (n=108)
Means et al (2016)	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 5. 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)					
Avance (n=112)	Short gaps (15-25mm): 7.3 (2.8) Long gaps (15-25mm): 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%)	Avance (n=112)
NeuraGen (n=108)	Short gaps (5-14 mm): 7.5 (3.1) Long gaps (15-25mm): 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)	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 6 and 7) 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 6. 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)	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)					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 7. 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)				6. Not intent to treat analysis		
Means et al (2016)				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.

^aAllocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.

^bBlinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.

^cSelective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.

^dData 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.

^ePower key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.

^fStatistical 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 in follow-up and were 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 8. Summary of Key Nonrandomized Trials OR Observational Comparative Study Characteristics for Processed Nerve Allograft

Study	Study Type	Country	Dates	Participants	Intervention	Comparator	Follow-Up
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Rbia et al (2019)	Case series	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)	Single-blind, non-randomized clinical trial	China	NR	Patients who required direct suturing of nerve defect 1 to 5cm in length and required nerve transplantation	Processed nerve allograft(n=72)	Direct surgical repair or autograft (n=81)	6 months
Ducic et al (2012)	Retro-spective 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 9. 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)	At 12 months:			
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)				
Processed human acellular nerve allograft (n=72)		Pre-op: 20 (0) 1 month: 18.5 (3.8)		Mild wound pain: 6 (8%)

		3 months: 14.4 (6.3) 6 months: 12.8 (6) Excellent to good rate: 65.28% (51.98-78.93%)		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)				
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 were not 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 (% $\geq$ 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 10. Summary of Key Case Series Characteristics for Processed Nerve Allograft

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

Table 11. 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)	Processed nerve allograft(Avance)	$\geq$ S3: 77%	$\geq$ M3: 36%	1 (.8%) (surgical site infection)

Safa et al (2019)	Processed nerve allograft(Avance)	≥S3: 81%	≥M3: 66%	Revision: 39 (3%)Any adverse event: 39 (3.7%) (most commonly neuroma at their pair site and infection)Serious adverse event: 23 (2.1%) <i>No adverse events were determined to be related to the treatment product</i>
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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 and wraps through the 510k process.

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. 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. 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. 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. 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 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 is an absorbable woven polyglycolic acid mesh tube designed for primary or secondary peripheral nerve repair or reconstruction. 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. 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.

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 repairs 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. 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). 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 12. Comparisons of Trials/Studies Included in SR & MA for Synthetic Nerve Conduits

Study	Thomson et al (2022)
Aberg et al 2009	•
Bertleff et al 2005	•
Boeckstyns et al 2013	•
Lundborg et al 2004	•
Weber et al 2000	•

Table 13. SR & M-A Characteristics for Synthetic Nerve Conduits

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Thomson et al (2022)	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 14. 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)	1 RCT	1 RCT	2 RCTs	5 RCTs	5 RCTs
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: 0.03 (-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
I^2 (p)	NA	24 months: NA 12 months: 66 (=0.09)	5 years: NA 2 years: 0% (.66) 1 year: 100% (<.00001)	0% (.75)	0% (.64)

BMRC: British Medical 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, 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. 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 18months 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 15 and 16. 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 15 and 16. 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 15. 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	US	20	NR	N=220 adults with acute or subacute (< 24 weeks old) digital nerve injuries	processed nerve allograft (Avance) (n=112)	NeuraGen NerveGuide (Integra LifeSciences) (n=108)
Means et al (2016)	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)
Vs. autologous vein conduit						
Rinker et al (2011)	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)	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)	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)	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)	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)	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)
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NR; not reported; RCT: randomized controlled trial.

Table 16. 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)	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%)
p-value for difference	NS for all comparisons		NS for all comparisons		
Vs. direct surgical repair					
Boeckstyns et al (2013)					
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	No surgical complications of infection, extrusion of the

				months was superior in the direct surgical repair group, including the muscle force and grip strength sub-domains	conduit or other local adverse reaction, or development of a chronic regional pain syndrome
Aberg et al (2009)	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) Div V abduction: 1: 6 (100%)			
p-value for difference	.12	.19			
Bertleff et al (2005)	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)	s2PD at last visit; median (IQR)	SWMF at last median (IQR)	BMRC Classification, at 5 years	Composite Instrument Rosen-Score, mean (SD)	Complicationsn (%)
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)	0%

				1 year: 0.5 (0.5) Cold intolerance: 0.5 (0.33 to 0.67)	
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)	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: 9.6 Gaps > 8 mm: 13.1		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%)
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 estimated 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 17 and 18) 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 17. 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)	5. Baseline information on gap length not reported				
Rinker et al (2011)	5. Single-center study				
Aberg et al (2009)	5. Single-center study				
Bertleff et al (2005)	5. Baseline information on gap length not reported				
Lundborg et al (2004)	5. Single-center study; baseline information on gap length, not reported				

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

^aPopulation 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.

^bIntervention 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.

^cComparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

^dOutcomes 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.

^eFollow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 18. 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)		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)		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)		1. Participants not blinded				
Bertleff et al (2005)		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)		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)		1. Unclear if participants were blinded		1. High loss to follow-up or missing data	1. Power calculations not reported	

				6. Not intent to treat analysis		
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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 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 19. 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)	Case series	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)	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)	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 20. 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)	86		
Artificial conduit (n=48)	36 (75%) (60% to 86%)	S0: 7 (17%) S1: 5 (12%) S2: 3 (7%) S3: 14 (33%) S4: 13 (31%)	Any Adverse Event: 70% Serious Adverse Event: 21%
Autologous nerve (n=38)	28 (73.7%) (57% to 87%)	S0: 2 (29%) S1: 0 S2: 0 S3: 4 (57%) S4: 1 (14%) <i>Only non-historic participants reported (n=7)</i>	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.

Wangenstein 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%). 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 greater percentage 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 21. Summary of Key Case Series Characteristics for Synthetic Nerve Conduit

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

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

Study	Treatment	Sensory Outcome	Motor Score	Complications
Wangenstein 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;

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.

CLINICAL INPUT FROM PHYSICIAN SPECIALTY SOCIETIES, ACADEMIC MEDICAL CENTERS AND EXTERNAL STAKEHOLDERS (PRACTICING CLINICIANS AND RESEARCH BASED EXPERTS IN THE FIELD)

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 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.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they are 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 their 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).

Ongoing and Unpublished Clinical Trials

Some currently ongoing trials that might influence this review are listed in Table 23.

Table 23. 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 SM)	15	Dec 2026
NCT01526681	Registry of Avance® Nerve Graft's Utilization and Recovery Outcomes Post Peripheral Nerve Reconstruction (RANGER®)	3126	Nov 2028
Unpublished			
NCT01809002	Comparison of Processed Nerve Allograft and Collagen Nerve Cuffs for Peripheral Nerve repair	220	Aug 2021
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)
NCT05339594a	Registry of Avance® Nerve Graft's Utilization and Recovery Outcomes Post Peripheral Nerve Reconstruction	5000	Dec 2025 (Terminated)

NCT: national clinical trial.

^aDenotes industry-sponsored or cosponsored trial.

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 24). 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 24. 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

Government Regulations

National:

There is no NCD related to this topic.

Local:

There is no LCD related to this topic.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Nerve Fiber Density Testing
 - Allografts for Nerve Repair (retired)
 - Cryoablation or Cryoneurolysis of Peripheral Nerves
 - Skin and Tissue Substitutes
-

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through March 2026, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
7/1/25	4/15/25		Joint policy established. Vendor managed: N/A (ds)
7/1/26	4/21/26		Routine policy maintenance, formatting changes made. No change in status. Vendor managed: N/A (ds)

Next Review Date: 2nd Qtr. 2027

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN:	Revised:
BCBSM:	Revised:

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: PERIPHERAL NERVE INJURY REPAIR USING SYNTHETIC CONDUITS OR
PROCESSED NERVE ALLOGRAFTS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered per policy
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.
- Duplicate (back-up) equipment is not a covered benefit.