Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 7/1/25**
(See policy history boxes for previous effective dates)

Title: Allografts for Nerve Repair

Description/Background

Nerve Injury

Peripheral nerve injury affects more than 1 million people worldwide and leads to loss or disturbance of sensory and/or motor function mediated by the injured nerve. It is usually caused by traumatic injury (~90%) but may also be caused by surgical procedures (~10%). Approximately 80% of nerve injuries occur in the upper extremities and 10% in the lower extremities. Delays in reinnervation of the associated muscle can lead to a permanent loss of muscle function. Although the distal stump of a damaged nerve degenerates, the proximal segment has the ability to regenerate, restoring nerve function. Therefore, severed peripheral nerves demand prompt surgical exploration and repair. More than 500,000 peripheral nerve repair procedures are performed annually in the United States.

Treatment

Direct suture repair is used for short gaps in a nerve. Autologous nerve graft is the standard of care for repairing nerve gaps of up to 5 cm (centimeters) in length; however, autografts have numerous shortcomings including nerve size mismatch, need for 2 surgical sites, donor site morbidity, limited supply of donor nerve, scarring, and increased recovery time. Nerve gaps in excess of 5 cm require the use of an allograft, which necessitates immune suppression, rendering the patient susceptible to infection and tumor formation.

Collagen nerve wraps and conduits provide an encasement for peripheral nerve injuries and a proposed protection of the neural environment. These are semi-permeable structures that allow diffusion of nutrients and neurotrophic factors into the conduit, but provide a barrier to larger, scar-forming cells.

The use of a nerve guidance, or nerve guide, to allow natural nerve regeneration between nerve stumps (tubulization) has been investigated for more than a century. Currently available nerve guides are either hollow tubes that are sutured to the nerve stumps or open tubes that are wrapped around the damaged nerve and then sutured closed. Nerve guides facilitate nerve repair by aligning the nerve stumps, concentrating growth factors at the injury site, and directing the physical growth of the axons. Nerve guides are made of synthetic or natural materials that are permanent or that degrade sometime after surgery.

New Technology
Nerve allograft transplantation from cadavers offers an alternative without the morbidities associated with autografts, but these grafts are rapidly rejected unless appropriate immunosuppression is achieved.

Recently, commercially available processed nerve allografts are intended for the surgical repair of peripheral nerve discontinuities. Through a proprietary cleansing process for recovered human peripheral nerve tissue, the graft is said to preserve the essential inherent structure of the extracellular matrix while cleansing away cellular and noncellular debris.

Regulatory Status

The FDA issued a 510(k) clearance (K011168) to Integra LifeSciences Corp. for the NeuroGen Nerve Guide as substantially equivalent to previously marketed devices on June 22, 2001. The NeuroGen Nerve Guide is indicated for repair of peripheral nerve discontinuities where gap closure can be achieved by flexion of the extremity.

NOTE: The FDA 510(k) approval lists the product as “NeuroGen”, although the manufacturer lists it as “NeuraGen” Nerve Guide in its announcement of the FDA approval, which was released on July 5, 2001 (Integra LifeSciences Corp., 2001). No mention of it as the NeuroGen Nerve Guide was found on the manufacturer’s site.

In April 2006, the FDA issued a 510(k) clearance (K060952) for Collagen Nerve Wrap that is indicated for the management of peripheral nerve injuries in which there has been no substantial loss of nerve tissue and where gap closure can be achieved by flexion of the extremity.

In January 2014, The FDA issued a 510(k) clearance (K132660) for a nerve cuff composed of a bioabsorbable, extracellular collagen matrix. The nerve cuff is indicated for the repair of peripheral nerve injuries in which there is no gap or where a gap closure is achieved by flexion of the extremity.

Medical Policy Statement

Nerve allografts are considered experimental and investigational for the repair and closure of nerve gaps from peripheral nerve injuries as they have not been scientifically demonstrated to improve patient clinical outcomes.

Inclusionary and Exclusionary Guidelines

Exclusions:
Examples of nerve allografts (this list is not all inclusive):

- Avance®
- AxoGen®
- AxoGUARD®

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:

N/A

Other codes (investigational, not medically necessary, etc.):

64912 64913

Note: Code(s) may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage.

Rationale

Nerve Allografts
Moore et al (2011) compared acellular nerve allograft to nerve isografts and silicone nerve guidance conduits in a 14 mm rat sciatic nerve defect.[1] Three established models of acellular nerve allograft (cold-preserved, detergent processed, and AxoGen®-processed nerve allografts) were compared to nerve isografts and silicone nerve guidance conduits in a 14 mm rat sciatic nerve defect. All acellular nerve grafts were superior to silicone nerve conduits in support of nerve regeneration. Detergent-processed allografts were similar to isografts at 6 weeks post-operatively, while AxoGen®-processed and cold-preserved allografts supported significantly fewer regenerating nerve fibers. Measurement of muscle force confirmed that detergent-processed allografts promoted isograft-equivalent levels of motor recovery 16 weeks post-operatively. All acellular allografts promoted greater amounts of motor recovery compared to silicone conduits. These findings provide evidence that differential processing for removal of cellular constituents in preparing acellular nerve allografts affects recovery *in vivo*.

In 2013, Taras et al investigated the outcomes of digital nerve repairs using processed nerve allograft for defects measuring 30 mm or less.[2] Seventeen patients with 21 digital nerve lacerations in the hand underwent reconstruction with processed nerve allograft. Outcome data for 14 patients with 18 digital nerve lacerations were available for analysis. Postoperative outcome data were recorded at a minimum of 12 months and an average of 15 months. The average nerve gap measured 11 mm (range, 5-30 mm). Outcome measures included postoperative sensory examination as assessed by Semmes-Weinstein monofilaments and static and moving 2-point discrimination. Pain was graded using a visual analog scale

throughout the recovery period. In addition, patients completed the Quick Disabilities of the Arm, Shoulder, and Hand survey before and after surgery. Using Taras outcome criteria, 7 of 18 (39%) digits had excellent results, 8 of 18 (44%) had good results, 3 of 18 (17%) digits had fair results, and none had poor results. At final follow-up, Semmes-Weinstein monofilament testing results ranged from 0.08 g to 279 g. Quick Disabilities of the Arm, Shoulder, and Hand scores recorded at the patient's first postoperative visit averaged 45 (range, 2-80), and final scores averaged 26 (range, 2-43). There were no signs of infection, extrusion, or graft reaction. The data suggest that processed nerve allograft may provide a safe and effective alternative for the reconstruction of peripheral digital nerve deficits measuring up to 30 mm.

According to Boriani et al (2017) although autografts represent the gold standard for peripheral nerve reconstruction, their limited availability, discrepancy of nerve caliber and long surgical times are some drawbacks.[3] Allografts have therefore become a valid alternative option. In particular, acellular nerve allografts (ANAs) rather than fresh allografts do not need immunosuppression and appear to be safe and effective based on recent studies. An innovative method was conceived to obtain ANAs, so as to speed up nerve decellularization, without compromising nerve architecture, and without breaking the asepsis chain. Several detergent-based techniques, integrated with sonication and mechanical stirring, were tested in vitro on rabbit nerves, to identify, by microscopy and immunohistochemistry, the most effective protocol in terms of cell lysis and cellular debris clearance, while maintaining nerve architecture. Furthermore, a pilot in vivo study was performed: ANAs were implanted into tibial nerve defects of three rabbits, and autografts, representing the gold standard, in other three animals. Twelve weeks postoperatively, rabbits were clinically evaluated and euthanasized; grafts were harvested and microscopically and histomorphometrically analyzed. The method proved to be effective in vitro: the treatment removed axons, myelin and cells, without altering nerve architecture. The in vivo study did not reveal any adverse effect: animals maintained normal weight and function of posterior limb during the entire experimental time. A mild fibrotic reaction was observed, macrophages and leukocytes were rare or absent; ANAs regenerated fascicles and bundles were comparable versus autografts. Based on these results, this decellularization protocol is encouraging and deserves deeper investigations with further preclinical and clinical studies.

Yan et al (2018) evaluated whether a hybrid ANA can improve 6-cm gap reconstruction. Rat sciatic nerve was transected and repaired with either 6-cm hybrid or control ANAs.[4] Hybrid ANAs were generated using a 1-cm cellular isograft between 2.5-cm ANAs, whereas control ANAs had no isograft. Outcomes were assessed by graft gene and marker expression (n = 4; at 4 weeks) and motor recovery and nerve histology (n =10; at 20 weeks). Hybrid ANAs modified graft gene and marker expression and promoted modest axon regeneration across the 6-cm defect compared with control ANA ($p<.05$), but yielded no muscle recovery. The authors concluded that control ANAs had no appreciable axon regeneration across the 6-cm defect. A hybrid ANA confers minimal motor recovery benefits for regeneration across long gaps.

In an ongoing observational study on the use and outcomes of processed nerve allografts, Safa et al (2019), reported on motor recovery outcomes for nerve injuries repaired acutely or in a delayed fashion with peripheral nerve allografts (e.g., Avance Nerve Graft, AxoGen).[5] The RANGER database was queried for mixed and motor nerve injuries in the upper extremities, head, and neck area having completed greater than 1 year of follow-up. All subjects with sufficient assessments to evaluate functional outcomes were included. Meaningful recovery

was defined as ≥M3 on the Medical Research Council scale. Demographics, outcomes, and covariate analysis were performed to further characterize this subgroup. The subgroup included 20 subjects with 22 nerve repairs. The mean ± SD (minimum-maximum) age was 38 ± 19 (16-77) years. The median repair time was 9 (0-133) days. The mean graft length was 33 ± 17 (10-70) mm with a mean follow-up of 779 ± 480 (371-2,423) days. Meaningful motor recovery was observed in 73%. Subgroup analysis showed no differences between gap lengths or mechanism of injury. There were no related adverse events. The authors suggest that outcomes compared favorably to historical controls for nerve autograft and exceed those for hollow tube conduit. It appears that peripheral nerve allografts may be considered as a safe option but additional long-term studies are required.

Rbia et al (2019) reported on a single-institution case series and a review of the literature on the outcomes of digital nerve gap reconstruction with the NeuraGen type 1 collagen nerve conduit and the Avance Nerve Graft.[6] Thirty-seven patients were included with a minimal follow-up of 12 months. Primary outcome was postoperative sensory recovery measured by static 2-point discrimination test or the Semmes-Weinstein monofilament test. Secondary outcome measurements were perioperative or postoperative complications. Final outcome data were stratified to grade results as excellent, good, or poor. The mean nerve gap length was 14 ± 4.9 mm for the collagen conduits vs. 18.4 ± 9.3 for nerve allografts. After 12 months, outcomes were graded as excellent sensory recovery in 48% of the collagen conduit repairs and 39% of the nerve allografts (p=.608), good in 26% of the conduits and 55% of the allografts (p=.074), and poor in 26% of the conduits versus 6% of the allografts (p=.091). One neuroma and 1 infection were reported. Graft rejection or extrusion was not observed. The authors concluded that both techniques offer effective means of reconstructing a digital nerve gap <2.5 cm at a minimum of 12 months of follow-up. Future prospective randomized large sample size studies comparing nerve conduits with allografts are needed to perform subgroup analyses and to define their exact role in digital nerve injuries.

SUMMARY OF EVIDENCE

Acellular processed nerve allografts are nerves from deceased human donors that have had their immunogenic components removed using tissue processing techniques. They are stored frozen until implantation and are available in different sizes. Immunosuppressive treatment is apparently not needed. Based on literature review, there has been no comparison between autograft and allograft, as well as autograft with other available clinical alternatives such as nerve guidance, wraps or conduits; there are also no available randomized controlled studies. The evidence is insufficient to determine the effects of this technology on health outcomes.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Recruiting			
NCT01526681	Registry of Avance Nerve Graft's Utilization and Recovery Outcomes Post Peripheral Nerve Reconstruction (RANGER)	5000	Dec 2025

Completed

NCT01809002	Comparison of processed nerve allograft and collagen nerve cuffs for peripheral nerve repair (RECON)	220	Aug 2021

NCT: national clinical trial

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

National Institute for Health and Care Excellence (NICE)[7]
In a NICE interventional procedure guidance document, November 2017, NICE had the following recommendations)

- Current evidence on the safety and efficacy of processed nerve allografts to repair peripheral nerve discontinuities is adequate to support the use of this procedure for digital nerves provided that standard arrangements are in place for clinical governance, consent and audit.
- The evidence on the safety of processed nerve allografts to repair peripheral nerve discontinuities in other sites raises no major safety concerns. However, current evidence on its efficacy in these sites is limited in quantity. Therefore, for indications other than digital nerve repair, this procedure should only be used with special arrangements for clinical governance, consent and audit or research.

Government Regulations

National:

No national coverage determination was identified on this subject.

Local:

No local coverage determination was identified on this subject.

The CMS 2024 Physician Fee Schedule has fees listed for 64912 and 64913. A fee is not a guarantee of payment.

(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

- Ablation of Peripheral Nerves to Treat Pain including Coolief Cooled RF and Iovera System
- Nerve Fiber Density Measurement
- Nerve Graft with Radical Prostatectomy
- Radiofrequency Ablation of the Renal Sympathetic Nerves as a Treatment for Uncontrolled Hypertension

References

1. Moore, A, MacEwan M, Santosa K, et al. Acellular nerve allografts in peripheral nerve regeneration: a comparative study. Muscle Nerve. Aug 2011;44(2):221-234.
2. Taras JS, Amin N, Patel N, and McCabe LA. Allograft reconstruction for digital nerve loss. J Hand Surg Am. Oct 2013;38(10):1965-1971.
3. Boriani F, Fazio N, Fotia C, et al. A novel technique for decellularization of allogenic nerves and in vivo study of their use for peripheral nerve reconstruction. J Biomed Mater Res A. Aug 2017;105(8):2228-2240.
4. Yan Y, Hunter DA, Schellhardt L, et al. Nerve stepping stone has minimal impact in aiding regeneration across long acellular nerve allografts. Muscle Nerve. Feb 2018;57(2): 260-267.
5. Safa B, Shores JT, Ingari JV, et al. Recovery of motor function after mixed and motor nerve repair with processed nerve allograft. Plast Reconstr Surg Glob Open. March 13, 2019;7(3):e2163
6. Rbia N, Bulstra LF, Saffari TM, et al. Collagen nerve conduits and processed nerve allografts for the reconstruction of digital nerve gaps: a single-institution case series and review of literature. World Neurosurg. April 16, 2019;s1878-8750(19)31079-4
7. National Institute for Health and Care Excellence. Processed nerve allografts to repair peripheral nerve discontinuities. Published November 22, 2017.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through June 20, 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
9/1/18	6/19/18	6/19/18	Joint policy established
11/1/18	8/21/18	8/21/18	Redrafted policy to include only E/I services, standard therapies removed.
11/1/19	8/20/19		Routine policy maintenance, updated rationale adding references 5 & 6. No change in policy status.
11/1/20	8/18/20		Routine policy maintenance, updated clinical trials section. No change in policy status.
11/1/21	8/17/21		Routine policy maintenance. No change in policy status.
11/1/22	8/16/22		Routine policy maintenance (ls)
11/1/23	8/15/23		Routine policy maintenance Vendor: N/A (ky)
11/1/24	8/20/24		Routine policy maintenance Vendor: N/A (ky)
7/1/25	4/15/25		A new policy called “Peripheral nerve injury repair using synthetic conduits or processed nerve allografts” is going to April 15, 2025 JUMP. This new JUMP policy will replace this “Allografts for Nerve Repair” policy. Vendor: N/A (ky)

Next Review Date: Policy replaced. Refer to JUMP policy, “Peripheral nerve injury repair using synthetic conduits or processed nerve allografts,” effective 7/1/25

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: ALLOGRAFTS FOR NERVE REPAIR

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered per policy guidelines
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.