Peripheral Nerve Injury Repair Using Synthetic Conduits or Processed Nerve

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, *HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

Note: Bioengineered Skin and Soft Tissue Substitutes is addressed separately in medical policy 00572.

Note: Microwave Tumor Ablation is addressed separately in medical policy00569.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the use of processed nerve allografts (e.g.,Avance nerve allograft) for the repair and closure of peripheral nerve gaps up to 70 mm when direct primary repair is not feasible (see Policy Guidelines) to be **eligible for coverage.****

Based on review of available data, the Company may consider the use of synthetic nerve conduits (e.g., NeuraGen synthetic conduit [Integra]) for the repair and closure of peripheral nerve gaps in the following scenarios (see Policy Guidelines):

- 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 or major nerve with a gap not exceeding 6 mm.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers all other uses of processed nerve allografts and synthetic nerve conduits for individuals with peripheral nerve gaps to be **investigational.***

Policy Guidelines

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

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

Nerve wraps are bioresorbable surgical implants designed to protect and support peripheral nerve healing following end-to-end repair with no gap (e.g., Axoguard®‡ Nerve Protector by AxoGen, indicated for the repair of peripheral nerve injuries where there is no gap, derived from porcine source). These devices provide a physical barrier that purports to reduce scar formation, reduce mechanical irritation, and promote a favorable environment for nerve regeneration. These materials are addressed in - Bioengineered Skin and Soft Tissue Substitutes (see Related Policies).

Contraindications

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

Background/Overview

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. 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. Functional regeneration of injured nerves requires peripheral nerve surgery to allow axon regrowth and remyelination.

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. 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.

Alternative Treatments
Allogenic nerve grafts (Avance, AxoGen, Inc) are derived from human donors and are generally used to bridge gaps resulting from peripheral nerve injuries that are > 5 mm. Allogenic grafts are preferred for their potential to minimize donor site morbidity, as they eliminate the need for autografts. Allogenic grafts also address the challenge of obtaining a sufficient graft length as they are available in multiple lengths and diameters; this is particularly relevant in cases where the injury site is extensive. Before transplantation, allografts undergo processing to ensure immunological compatibility and reduce the risk of rejection, allowing for successful integration into the recipient's nervous system.

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. 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. Conduits are generally used for nerve gap repairs of < 5 mm.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
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 are subject to these regulations.

Avance nerve graft (Axogen) is a sterile, processed human nerve allograft that is indicated for the repair of peripheral nerve discontinuities to support axonal regeneration across the gap. A proprietary cleansing process removes specific proteins, cells, and cellular debris but spares the extracellular matrix (ECM), providing structural support for cellular migration and regenerating axons.[5,] Avance is available in multiple lengths from 5 to 70 mm, and multiple diameters. The allograft is stored frozen with a shelf life of up to three years, but upon thawing, it must be transplanted within 12 hours. Surgical implantation of the allograft connects the distal and proximal ends of a severed peripheral nerve via suturing. Post-surgery, the allograft is revascularized and remodeled into the patient's own tissue.

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

Axoguard nerve connector®‡ is a semi-translucent coaptation aid designed for connector-assisted repair of a transected nerve with a gap up to 5 mm.

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

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

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

The Neurotube (Synovis Micro) is an absorbable woven polyglycolic acid mesh tube designed for primary or secondary peripheral nerve repair or reconstruction.(Synovis Micro) It received FDA 510k approval on August 28, 1998, for the indication of peripheral nerve injuries where the nerve

gap is more than or equal to 8 mm, but less than or equal to 30 mm.(Neurotube FDA 510(k)). The device is contraindicated for anyone with a known allergy to polyglycolic acid. The walls of the Neurotube are corrugated for strength and flexibility, preventing the tube from collapsing under normal physiological soft tissue pressures.

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

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

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

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

as processed nerve allografts and synthetic nerve conduits are being investigated to provide improved treatment alternatives.

Summary of Evidence

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

For individuals with peripheral nerve injury requiring repair and closure of the nerve gap who receive synthetic nerve conduits, the evidence includes 3 meta-analyses, 8 RCTs (2 comparing NeuraGen to allograft, 1 comparing Neurotube to autologous vein grafting, and 4 comparing conduit [1 Neurolac, 1 Polyhydroxybutyrate {PHB}, 1 polyglycolic acid {PGA}, and 1 silicone tube] to direct surgical repair), 1 non-randomized clinical trial, 1 comparative retrospective cohort study, 1 comparative case series, and 1 non-comparative case series. The evidence base consisted primarily of peripheral nerve injuries to the fingers or upper extremities. NeuraGen was evaluated in 3 studies, and all other

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

2025 Input

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

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

Clinical input noted that synthetic conduit repair is best used to repair digital nerve injuries with gaps <15 mm. Data shows that outcomes under these conditions are similar to allograft nerve repair. For digital nerve injuries with gaps 15-25 mm, conduit repair yields acceptable outcomes but inferior to allograft repair. Conduit repair should only be used in these circumstances if allograft nerve is not available. Any gap exceeding 25 mm is not appropriate for conduit repair. There are insufficient data to support the use of conduit repair for major nerves (any nerve aside from digital nerves) and collective experience and opinion of the group is that conduit repair is not appropriate for major nerves except for very short gaps (<5-6 mm).

Conduit-assisted repair as a technique for tension-relief is appropriate for any nerve repair where there is thought to be mild to moderate tension at the repair site (where tension is displaced off of the nerve ends and onto the conduit as a technique for tension-relief). There are no high-quality human studies examining conduit-assisted repair as a tension-relieving strategy. This is a commonly accepted practice and one frequently employed in situations where there is moderate tension at a repair site. Experience shows that this is a viable technique for relieving tension and helps facilitate nerve repairs that may otherwise be infeasible. For larger nerves (any nerve aside from digital nerves), there are few data to support the use of conduits and our collective experience does not support the use of conduits for this indication, except for the specific application of conduit-assisted repair for tension-relief. It may be reasonable to use conduits for repair of very short gaps (<5-6 mm) for major nerves, with no consistent practice pattern in that regard.

Supplemental Information

Practice Guidelines and Position Statements

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

National Institute for Health and Care Excellence (NICE)

In 2017, NICE published guidance on processed nerve allografting to repair peripheral nerve discontinuities. The evidence base evaluated by NICE included the RCT by Means et al (2016) and the non-randomized trial by He et al (2013), which are discussed in this medical reference policy. NICE also evaluated two other smaller case series, which were not included in our evidence review due to the availability of higher-quality evidence. The following were among the recommendations issued:

- Current evidence on the safety and efficacy of processed nerve allografts to repair peripheral nerve discontinuities is adequate to support the use of this procedure for digital nerves, provided that standard arrangements are in place for clinical governance, consent, and audit.
- The evidence on the safety of processed nerve allografts to repair peripheral nerve discontinuities in other sites raises no major safety concerns. However, current evidence

on its efficacy in these sites is limited in quantity. Therefore, for indications other than digital nerve repair, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research.
- This procedure should only be done by surgeons with training and experience in peripheral nerve repair.
- Patient selection should take into consideration the site, type of nerve (motor, sensory, mixed), and the size of the defect.
- NICE encourages further research into processed nerve allografts to repair peripheral nerve discontinuities. This should include information on the type of nerve repaired, the anatomical site, the size of the defect, patient-reported outcome measures, functional outcomes, time to recovery, and long-term outcomes (12 months to 18 months).

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

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

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

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

NCT05343143[a]	NeuraGen 3D Pilot Study	10	July 2024 (terminated)

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

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Policy History

Original Effective Date: 08/01/2025
Current Effective Date: 08/01/2025
05/01/2025 Medical Policy Committee review
05/13/2025 Medical Policy Implementation Committee approval. New policy.
Next Scheduled Review Date: 05/2026

Coding

The five character codes included in the Louisiana Blue Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)ǂ, copyright 2024 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	64910, 64912, 64913, 64999
HCPCS	C9352, C9355
ICD-10 Diagnosis	All Related Diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and

C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.