Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 9/1/24**
(See policy history boxes for previous effective dates)

Title: Nerve Graft with Radical Prostatectomy

Description/Background

ERECTILE DYSFUNCTION
Erectile dysfunction is a common problem after radical prostatectomy. In particular, spontaneous erections are usually absent in men whose prostate cancer required bilateral resection of the neurovascular bundles as part of the radical prostatectomy procedure.

Treatment
A variety of noninvasive treatments are available, including vacuum constriction devices and intracavernosal injection therapy. However, spontaneous erectile activity is preferred by individuals. Studies have reported results from bilateral and unilateral nerve grafts, the latter involving resection of 1 neurovascular bundle.

There has been interest in sural nerve grafting to replace cavernous nerves resected during prostatectomy. The sural nerve is considered expendable and has been extensively used in other nerve grafting procedures, such as brachial plexus and peripheral nerve injuries. As applied to prostatectomy, a portion of the sural nerve is harvested from 1 leg and then anastomosed to the divided ends of the cavernous nerve. Reports also indicate use of other nerves (eg, genitofemoral nerve) for grafting.

Regulatory Status:

A nerve graft in association with radical prostatectomy is a surgical procedure and as such is not subject to regulation by the U.S. Food and Drug Administration (FDA).

Several nerve cuff products have been cleared for marketing by FDA through the 510(k) process. FDA product code: JXI. An example of a human tissue nerve graft product, the Avance® nerve graft (AxoGen), is regulated by the FDA under the 21 CFR Part 1271 regulations for Human Cellular and Tissue-based Products (HCT/P).

Medical Policy Statement

Unilateral or bilateral nerve graft is considered experimental/investigational in individuals who have had resection of one or both neurovascular bundles as part of a radical prostatectomy. It has not been scientifically demonstrated to improve patient clinical outcomes as a conventional treatment.

Inclusionary and Exclusionary Guidelines

N/A

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.):

64999

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.

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the 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.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the

intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

NERVE GRAFTING

Clinical Context and Therapy Purpose

Individuals with prostate cancer may undergo treatment with prostatectomy or prostate radiation therapy. Several studies have reported racial disparities among individuals with low-risk prostate cancer.[1] African American individuals enrolled in active surveillance programs have been shown to have a higher risk of disease progression than White individuals. For African American individuals in the low-to-intermediate risk categories, there have been reports of increased risk of biochemical recurrence after treatment. While reasons for clinical disparities in this population are still being investigated, studies suggest that disparities in prostate cancer health outcomes can be minimized when health care access is equal.

The purpose of nerve grafting in patients who have radical prostatectomy is to provide a treatment option that is an alternative to or an improvement on existing therapies.

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

Populations

The relevant population of interest is individuals who have radical prostatectomy with resection of neurovascular bundles.

Interventions

The therapy being considered is nerve grafting in association with radical prostatectomy.

Comparators

The relevant comparator is prostatectomy without nerve grafting.

Outcomes

The outcomes of interest are functional outcomes, quality of life, and treatment-related morbidity.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Randomized Controlled Trial

One RCT evaluating nerve grafting to reduce risk of erectile dysfunction has been published; findings were reported by Davis et al (2009).[2] The trial included individuals ages 65 years or younger with normal self-reported baseline erectile function selected for a unilateral nerve sparing radical prostatectomy with preservation of 1 neurovascular bundle. All patients had unilateral neurovascular bundle removal, and individuals were randomized to receive or not to receive sural nerve grafting after removal. The primary outcome was potency 2 years postsurgery, defined as the ability to have intercourse with or without erectile dysfunction medication. All patients received the same early erectile dysfunction therapy, including medication and mechanical devices. The investigators sought to detect an absolute difference of 20% between groups (graft, 60% potency rate versus no graft, 40% potency rate). A sample of 200 individuals was originally planned to provide 80% power. However, after 107 individuals were randomized, a preplanned interim analysis of evaluated individuals found similar potency rates between groups. The data monitoring committee stopped the trial based on its estimate of less than a 5% chance that additional recruitment would result in a significant difference between groups. Endpoint data were available for 66 individuals. Potency was achieved in 32 (71%) of 45 sural nerve graft individuals and 14 (67%) of 21 control individuals (p=.78). Trialists concluded that unilateral sural nerve graft did not result in an absolute improvement of 20% between groups, but that a smaller effect could not be ruled out. A limitation of the trial was that it was unblinded, which could have impacted self-report of potency because individuals knew the procedure they received.

Observational Studies

The literature also includes 2 retrospective cohort studies and 3 case series.[3,4,5,6,7] The cohort studies are described below.

The cohort study by Kung et al (2015)[3] included 38 patients who underwent nerve grafting after radical prostatectomy and a random sample of 53 control patients who had open prostatectomy without nerve grafting. Control patients had unilateral or bilateral nerve-sparing prostatectomy, or non-nerve sparing prostatectomy. Complete urinary incontinence, no erectile capacity at baseline, and follow-up data less than 12 months were study exclusion criteria. Unilateral nerve grafting (n=29) and unilateral nerve sparing (n=10) patients did not differ significantly between groups (p>.05) on various outcomes, including urinary continence, erections sufficient for sex, spontaneous erections, and use of erectile dysfunction medications. Bilateral nerve grafting (n=9) and bilateral non-nerve sparing (n=10) patients had similar outcomes (p>.05). This study lacked randomization and blinding, and subgroup analyses included small numbers of patients.

The second cohort study, published by Namiki et al (2007), included 113 patients: 19 had unilateral nerve sparing plus sural nerve graft, 60 patients had unilateral nerve-sparing with no grafting, and 34 patients had bilateral nerve sparing surgery.[4] Function was assessed using validated questionnaires and, at 2 years, no difference in sexual function scores was found between the unilateral nerve graft and bilateral nerve sparing patients. At 3 years, similar percentages of patients in the unilateral nerve graft (25%) and bilateral nerve-sparing (28%)

groups considered their sexual function as fair or good. Urinary function returned to baseline continence in the unilateral nerve graft and bilateral nerve-sparing groups at 6 months and in the unilateral nerve-sparing group at 12 months. Baseline sexual function differed between groups, which could have biased study findings: the nerve grafted and bilateral nerve-sparing patients reported higher baseline function than the unilateral nerve sparing group.

SUMMARY OF EVIDENCE

For individuals who have radical prostatectomy with resection of neurovascular bundles who receive nerve grafting, the evidence includes a randomized controlled trial, cohort studies, and case series. Relevant outcomes are functional outcomes, quality of life, and treatment-related morbidity. The RCT did not find that unilateral nerve grafting was associated with a statistically significant improvement in potency rates at 2 years postsurgery. Cohort studies also did not result in better outcomes with nerve grafting. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

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

Clinical Input Received From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, Blue Cross Blue Shield Association received input from 4 academic medical centers while their policy was under review in 2008; no input was received from physician specialty societies. Input from these 4 centers agreed that this procedure is considered investigational.

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 Comprehensive Cancer Network

The National Comprehensive Care Network guidelines on the treatment of prostate cancer (V.3.2024) states: “Replacement of resected nerves with nerve grafts has not been shown to be beneficial” for recovery of erectile function after radical prostatectomy.[1]

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

N/A

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
Unpublished			
NCT01770340	Nerve Grafting With an Allograft During Radical Prostatectomy - Extended Follow-up in a Prospective Randomized Trial	30	Jul 2020 (terminated)

Government Regulations

National: There is no national coverage determination on this topic.

Local: There is no local coverage determination on 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

N/A

References

1. National Comprehensive Cancer Network. Prostate Cancer. Clinical practice guidelines in oncology, V.3.2024. prostate.pdf (nccn.org) Accessed 4/9/24.
2. Davis JW, Chang DW, Chevray P et al. Randomized phase II trial evaluation of erectile function after attempted unilateral cavernous nerve-sparing retropubic radical prostatectomy with versus without unilateral sural nerve grafting for clinically localized prostate cancer. Eur Urol. May 2009; 55(5):1135-44. PMID 18783876
3. Kung TA, Waljee JF, Curtin CM, et al. Interpositional nerve grafting of the prostatic plexus after radical prostatectomy. Plast Reconstr Surg Glob Open. Jul 2015;3(7):e452. PMID 26301141
4. Namiki S, Saito S, Nakagawa H et al. Impact of unilateral sural nerve graft on recovery of potency and continence following radical prostatectomy: 3-year longitudinal study. J Urol. Jul 2007; 178(1):212-6. PMID 17499797
5. Rabbani F, Ramasamy R, Patel MI et al. Predictors of recovery of erectile function after unilateral cavernous nerve graft reconstruction at radical retropubic prostatectomy. J Sex Med. Jan 2010; 7(1 pt 1):166-81. PMID 19686422

6. Siddiqui KM, Billia M, Mazzola CR, et al. Three-year outcomes of recovery of erectile function after open radical prostatectomy with sural nerve grafting. J Sex Med. Aug 2014;11(8):2119-2124. PMID 24903070
7. Souza Trindade JC, Viterbo F, Petean Trindade A, et al. Long-term follow-up of treatment of erectile dysfunction after radical prostatectomy using nerve grafts and end-to-side somatic-autonomic neurorraphy: a new technique. BJU Int. Jan 17 2017. PMID 28093890

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 4/9/24 the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
11/1/12	8/21/12	8/21/12	Joint policy established
3/1/15	2/17/15	2/27/15	Routine review References and rationale updated
7/1/16	4/19/16	4/19/16	Routine review
9/1/16	6/21/16	6/21/16	Routine review
9/1/17	6/20/17	6/20/17	Routine review References and rationale updated
9/1/18	6/19/18	6/19/18	Routine maintenance
9/1/19	6/18/19		Routine maintenance
9/1/20	6/16/20		Routine maintenance
9/1/21	6/15/21		Routine maintenance
9/1/22	6/21/22		Routine maintenance
9/1/23	6/13/23		Routine maintenance (jf) Vendor Managed: NA Last line of the Medical Policy statement updated from old verbiage to updated language. Removed safe and effective, added: “This therapy has not been scientifically demonstrated to improve patient clinical outcomes”.
9/1/24	6/11/24		Routine maintenance (jf) Vendor Managed: NA

Next Review Date: 2nd Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: NERVE GRAFT WITH RADICAL PROSTATECTOMY

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered
BCNA (Medicare Advantage)	See Government Regulations 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.