BlueCross BlueShield of Louisiana

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Nerve Graft in Association with Radical Prostatectomy

Policy # 00113
Original Effective Date: 06/05/2002
Current Effective Date: 06/25/2013

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.

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 unilateral or bilateral nerve grafts in patients who have undergone resection of one or both neurovascular bundles as part of a radical prostatectomy to be **investigational.***

Background/Overview

Nerve grafting to replace cavernous nerves resected at the time of radical prostatectomy is proposed to reduce the risk of erectile dysfunction after this surgery. The sural nerve is most commonly used in grafting. Erectile dysfunction is a common problem after radical prostatectomy. In particular, spontaneous erections are usually absent in patients whose extent of prostate cancer requires bilateral resection of the neurovascular bundles as part of the radical prostatectomy procedure. A variety of noninvasive treatments are available, including vacuum constriction devices and intracavernosal injection therapy. However, spontaneous erectile activity is preferred by patients. Studies have reported results from bilateral nerve grafts; there are also reports of unilateral grafts when only one neurovascular bundle has been resected.

There has been interest in sural nerve grafting to replace cavernous nerves resected at the time of prostatectomy. The sural nerve is considered expendable and has been used extensively 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 one leg and then anastomosed to the divided ends of the cavernous nerve. Reports are also being published using other nerves, such as the genitofemoral nerve.

FDA or Other Governmental Regulatory Approval

Centers for Medicare and Medicaid Services (CMS)
No national coverage determination.

Rationale/Source

After an initial literature search was performed in 2001, the policy was updated regularly with a literature review using MEDLINE. Most recently, the literature was searched from October 2011 through October 2012. Following is a summary of the literature to date:

The first randomized controlled trial (RCT) that evaluated nerve grafting was published in 2009 by Davis and colleagues. Eligibility criteria included age 65 years or younger, normal self-report baseline erectile function, and scheduled for a unilateral nerve-sparing radical prostatectomy with preservation of one neurovascular bundle. All patients had the other neurovascular bundle removed, and patients were randomly assigned to receive or not receive sural nerve-grafting after its removal. The primary outcome was potency 2 years post-surgery, defined as the ability to have intercourse with or without erectile dysfunction

medication. The investigators estimated that the control group would have a 40% potency rate and powered the study to detect an absolute difference of 20% between groups. All patients received the same early erectile dysfunction therapy including medication and mechanical devices. A sample size of 200 was originally planned to provide 80% power. However, after 107 patients were randomly assigned, a pre-planned interim analysis of evaluable patients found similar rates of potency in the 2 groups; the Data Monitoring Committee estimated that there was less than a 5% chance that there would be a significant difference between groups with additional recruitment and the trial was stopped early. When data collection ended, endpoint data were available for 66 patients who had either achieved potency or had been followed up for 2 years without potency. Potency was achieved in 32 of 45 (71%) sural nerve-graft patients and 14 of 21 (67%) control patients (p=0.78). The authors concluded that unilateral sural nerve-graft did not result in an absolute improvement of 20% in the rate of potency but that a smaller effect cannot be ruled out. A limitation of the study was that it was non-blinded, which could have impacted self-report of potency.

Other than the Davis et al. study, the published literature consists of case series. When the initial literature search was performed, the largest available series included 23 men with a mean of 23-month follow-up. This study, by Kim et al., included men with clinically localized but high-volume prostate cancer such that bilateral resection of the neurovascular bundles was considered necessary. Before surgery, all men reported spontaneous erection. The results were compared to a group of 12 men who were potent preoperatively and had undergone prostatectomy with bilateral nerve resection but who declined nerve-graft placement. Of the 23 men undergoing nerve grafting, 6 (26%) had spontaneous, medically unassisted erection sufficient for sexual intercourse. An additional 6 men (26%) reported 40% to 60% spontaneous erection that was insufficient for intercourse; 4 of these patients were able to have intercourse using sildenafil. Therefore, a total of 10 of the 23 patients were able to have intercourse, either spontaneously or with pharmacologic therapy. A total of 11 men had no clinical response even with the use of sildenafil. Not unexpectedly, all outcomes were significantly better compared to the control group. Side effects of the sural nerve donor site, which included incisional pain and a sensory deficit along the lateral aspect of the foot, were considered tolerable. The authors noted improvement 8 to 12 months postoperatively and accelerated improvement at 12 to 18 months postoperatively.

Subsequent literature searches identified additional case series. The largest published series and those with the longest follow-up are described below:

In 2007, Namiki and colleagues published a series in Japan with 3-year follow-up. A total of 113 patients were evaluated: 19 patients with unilateral nerve-sparing plus sural nerve graft, 60 patients with unilateral nerve-sparing but no grafting, and 34 patients with bilateral nerve-sparing surgery. Sexual function was assessed with validated questionnaires, and at 2 years, there was no difference between the nerve-grafted and the bilateral nerve-sparing patients with regard to sexual function scores. At 3 years, 25% and 28% of patients in the nerve-grafted and bilateral nerve-sparing groups, respectively, considered their sexual function as fair or good. Urinary function returned to baseline in the nerve-grafted and bilateral nerve-sparing groups at 6 months and in the unilateral nerve-sparing group at 12 months. Differences in sexual function were present at baseline with the nerve-grafted and bilateral nerve-sparing patients reporting higher baseline function than the unilateral nerve-sparing group.

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A study by Secin and colleagues had 5-year follow-up. The authors reported results on 44 consecutive patients who underwent bilateral nerve grafting from 1999 to 2004 at Memorial Sloan-Kettering Cancer Center. The overall 5-year recovery of erectile function was 34%, and the rate of consistent function was 11%. None of a number of variables (e.g., age, type of nerve [sural, genitofemoral, ilioinguinal], comorbidities) was significantly associated with recovery of postoperative erectile function.

Sim et al. reported on 2-year results in 41 patients who received unilateral sural nerve grafts following radical prostatectomy when 1 neurovascular bundle was resected. In this series, recovery of erectile function was reported for 63% of patients (based on 24 of 38 patients). This study also reported on erectile function on another group of patients who had unilateral resection at the same institution but without a nerve graft. In this group, which was older and was not matched on key characteristics to the group who received a nerve graft, the erectile function was 26.5% (13 of 49).

A recent case series reviewed the records of 131 men who had unilateral nerve grafts after radical prostatectomy with unilateral neurovascular bundle resection. Men who had prior radiation or hormonal treatment were excluded. Another eligibility criterion was satisfactory erections presurgery as assessed by a 5-point scale (1=full erections; 2=diminished erections, but routinely sufficient for sexual intercourse; 3=partial erections occasionally satisfactory for intercourse; 4=partial erections unsatisfactory for intercourse; and 5=no erections). A total of 49 men received sural nerve grafts, 79 received genitofemoral nerve grafts, and 3 received ilioinguinal nerve grafts. Recovery of erections was evaluated at each follow-up visit according to the 5-point scale (also called 5 levels). The median patient age was 58.7 years, and the median follow-up was 37 months. According to actuarial analysis, the 5-year probability of recovering erections of level 3 or better was 46%. The probability of recovering erections of at least level 2 or level 1 was 34% and 12%, respectively.

Ongoing Clinical Trials
A search of the online ClinicalTrials.gov database in October 2011 did not identify any ongoing trials on nerve grafting but did identify a single-arm pilot study on a related topic, nerve reconstruction in conjunction with robotic-assisted prostatectomy. The study evaluates the use of AVANCE, an allograft tissue product, for nerve reconstruction and is sponsored by the manufacturer of AVANCE. Technical feasibility is the primary outcome, and erectile function is one of the secondary outcomes.

Clinical Input Received Through Physician Specialty Societies and Academic Medical Centers
In response to requests, input was received from 4 academic medical centers while this policy was under review in 2008; no input was received from physician specialty societies. 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. Input from these 4 centers agreed that this procedure is considered investigational as adopted in the policy in May 2008.

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Summary
Nerve-grafting, most commonly using the sural nerve, at the time of radical prostatectomy has been proposed to reduce the risk of postoperative erectile dysfunction. Only one randomized controlled trial that evaluated sural nerve-grafting with radical prostatectomy has been published, and this study did not find that unilateral nerve-grafting was associated with a statistically significant improvement in potency rates 2 years post-surgery. Due to the negative findings of this study, and the lack of other controlled studies evaluating unilateral or bilateral nerve grafting, the technique is considered investigational.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Sural Nerve Graft in Association with Radical Prostatectomy", 7.01.81, 12:2012.
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3. Kim ED, Nath R, Slawin KM et al. Bilateral nerve grafting during radical retropubic prostatectomy: extended follow-up. Urology 2001; 58(6):983-7.
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 2007; 178(1):212-6; discussion 16.
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Coding

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CPT is a registered trademark of the American Medical Association.

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

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Code Type	Code
CPT	64999
HCPCS	No code
ICD-9 Diagnosis	185, 607.84, V45.77, 997.99
ICD-9 Procedure	No code

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05/16/2002	Medical Policy Committee review
06/05/2002	Managed Care Advisory Council approval
06/24/2002	Format revision. Coverage eligibility unchanged.
06/01/2004	Medical Director review
06/15/2004	Medical Policy Committee review. Format revision.
06/28/2004	Managed Care Advisory Council approval
08/02/2006	Medical Director Review
08/09/2006	Medical Policy Committee approval. Format revisions, references and rationale/source updated. Coverage eligibility unchanged.
06/13/2007	Medical Director Review
06/20/2007	Medical Policy Committee approval. Policy updated with literature search. No change to policy statement. Sural removed from title.
06/04/2009	Medical Director Review
06/17/2009	Medical Policy Committee approval. No change to coverage.
06/03/2010	Medical Policy Committee approval
06/16/2010	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/02/2011	Medical Policy Committee review
06/15/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/14/2012	Medical Policy Committee review
06/20/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/06/2013	Medical Policy Committee review
06/25/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 06/2014

*****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 the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated 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.

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