APPENDIX to Urinary Incontinence Outpatient Treatment Policy

Prior Authorization Requirements

This service (or procedure) is considered **medically necessary** in certain instances and **investigational** in others (refer to policy for details).

For instances when the indication is **medically necessary**, clinical evidence is required to determine **medical necessity**.

For instances when the indication is **investigational**, you may submit additional information to the Prior Authorization Department.

Within five days before the actual date of service, the Provider MUST confirm with Blue Shield of California / Blue Shield of California Life & Health Insurance Company (Blue Shield) that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should also be directed to the Prior Authorization Department. Please call 1-800-541-6652 or visit the Provider Portal www.blueshieldca.com/provider.

Evidence Basis for the Policy

Rationale

Urinary incontinence, also referred to as urinary voiding dysfunction, is defined as the involuntary loss of bladder control. Based on expert opinion, there is an estimated 25 million individuals in the United States that are, or have been, affected by urinary incontinence (National Association for Continence [NAFC], 2009). Additionally, urinary incontinence affects 10% to 30% of all adults and 35% of individuals older than 60 years of age (National Committee for Quality Assurance [NCQA], 2009; Fong & Nitti, 2010). The incidence of urinary incontinence in women is two times greater than that in men (Fong and Nitti, 2010), with a prevalence of 30% to 60% in women over the age of 60 (NAFC, 2009). Nearly 6% to 10% of nursing home admissions are attributable to urinary incontinence (Morrison & Levy, 1989) and 43% to 77% (median 58%) of all nursing home residents are incontinent (Offermans et al., 2009). Despite its consequences, it is often under recognized and under treated. Many patients do not report incontinence to their primary care providers due to embarrassment or misconceptions regarding treatment (American Urological Association [AUA], 2013).

Urinary incontinence is not considered a disease, but a symptom that may be caused by a variety of conditions that directly or indirectly affect bladder control (Hayes Inc., 2011). Predisposing factors for urinary incontinence include genetics, congenital defects, spinal stenosis, spinal cord injury, and neurological abnormalities (e.g., stroke, multiple sclerosis, Parkinson's disease). Risk factors in women for the development of urinary incontinence in women include pregnancy, childbirth, parity, hysterectomy, pelvic radiation, pelvic organ prolapse and menopause (Deng, 2011). Risk factors in men included benign prostatic hyperplasia (BPH), benign prostatic enlargement, and prostatectomy (Shaban et al., 2010). Other risk factors include smoking, obesity, advanced age, urinary tract infections, medications (e.g., diuretics, sedative-hypnotics and alpha blockers), and the presence of comorbid diseases (e.g., congestive heart failure and chronic pulmonary disease, diabetes and cardiovascular disease). Dementia is also associated with urinary incontinence.

Initial evaluation of urinary incontinence should include a focused history and physical exam, prostate and rectal tone (in men), examination for pelvic organ prolapse (in women), focused stress test (i.e., cough and demonstrate involuntary urine loss from the urethral meatus), urinalysis, and culture if indicated. One or more validated questionnaires that ask about lifestyle and medical history (Donovan et al., 2005), such as the Incontinence Quality of Life (I-QOL) questionnaire (Patrick, 1997), should be completed. The clinician may request that the patient keep a bladder diary to record urinary leakage episodes to determine the extent of the incontinence (AUA, 2011). In some cases, a referral to a urologist is warranted and additional diagnostic studies may be ordered such as uroflowmetry, radiography, ultrasonography, determination of postvoid residual urine, pad tests, cystoscopy, and multichannel urodynamic testing (Fong and Nitti, 2010; Shaban et al., 2010).

The essential elements involved in the storage and emptying cycles of normal urination include “inhibition and contraction” of smooth muscle of the bladder wall (detrusor), “afferent signaling from the urothelium, contraction and relaxation of the smooth and striated sphincter muscles and a complex series of central, peripheral, and autonomic nervous neuronal signals” (DuBeau et al., 2013). The average bladder can hold 350 milliliters (ml) to 550 ml of urine. Most individuals will feel like they need to urinate when there is about 200 ml of urine in the bladder (Resnick, 2011).

According to the American Urological Association (AUA) (2013), urinary incontinence is generally the result of either bladder or urethral dysfunction. Bladder dysfunction includes urge incontinence or overflow incontinence. Urethral dysfunction includes stress incontinence (anatomic dysfunction due to mobility of the bladder neck) or intrinsic sphincter deficiency (ISD) (due to bladder neck dysfunction). There are also other commonly used classifications of urinary incontinence. Incontinence may also occur due to a non-urologic cause which is usually reversible when the underlying problem is treated. More uncommon causes of incontinence include urinary fistulae or ectopic ureteral orifices.

Bladder Dysfunction

Bladder dysfunction causes urge or overflow incontinence, as described below:

Urge Incontinence

Urge incontinence is described as the sudden leakage or gush of urine after suddenly feeling the need or urge to urinate, for no apparent reason (Walsh, 2012). According to the AUA (2013):

> Urge incontinence occurs when the bladder pressure is sufficient to overcome the sphincter mechanism. Elevated bladder or detrusor pressure tends to open the bladder neck and urethra. An elevation in detrusor pressure may occur from intermittent bladder contractions (detrusor over activity) or because of an incremental rise in pressure with increased bladder volume (poor compliance).

Urge incontinence may be the result of bladder cancer or inflammation, bladder outlet obstruction, bladder stones, infection, nervous system diseases (e.g., multiple sclerosis) or injuries (e.g., spinal cord injury or stroke). In men, it may be due to BPH or bladder outlet obstruction for an enlarged prostate). Urge incontinence is also known as a spastic bladder, detrusor instability, detrusor hyperreflexia, irritable bladder and overactive bladder (OAB). The amount of leakage in patients with urge incontinence is variable, depending on the patient's ability to suppress the contraction (AUA, 2013).

Overactive Bladder

Overactive bladder is a newer term that describes patients with frequency or urgency with or without urge incontinence. This type of voiding dysfunction occurs when abnormal nerves send signals to the bladder at the wrong time, and causes the bladder muscles to contract without warning (National Kidney and Urologic Diseases Information Clearinghouse [NKUDIC], 2010). The symptoms of OAB include any or all of the following: urinary frequency (bothersome urination eight or more times a day or two more times at night), urinary urgency the sudden, strong need to urinate immediately), urge incontinence (leakage or gushing of urine that follows a sudden strong urge), and nocturnal awakening (two or more times at night to urinate) (Walsh, 2012).

Overflow Incontinence

Overflow incontinence occurs at extreme bladder volumes or when the bladder volume reaches the limit of the bladder's viscoelastic properties. The loss of urine is driven by an elevation in detrusor pressure. Overflow incontinence is seen when there is incomplete bladder emptying caused either by obstruction (e.g., tumors, urinary stones) or poor bladder contractility (e.g., weak bladder muscles caused by nerve damage from diabetes). Obstruction is rare in women but can result from severe pelvic prolapse or following surgery for stress incontinence. “Patients with overflow incontinence will complain of constant dribbling and they may also describe as extreme frequency” (AUA, 2013).

Urethral Dysfunction

Stress Urinary Incontinence

Urethral dysfunction or stress urinary incontinence is described as the involuntary loss of urine from the urethra due to an increase in intra-abdominal pressure. With stress incontinence, a laugh, sneeze, cough, heavy lifting, or anything else that puts added strain on the bladder can trigger urine leakage. It is usually caused by weakness in the pelvic muscles brought on by

childbirth, surgery, or menopause. Men may sometimes experience stress incontinence following prostate cancer surgery, but symptoms are much more common in women. It is the most common type of urinary incontinence in women (Walsh, 2012). Stress incontinence most often occurs because of either urethral hypermobility or ISD.

Incontinence with hypermobility has been called anatomic incontinence, because the incontinence is due to malposition of the sphincter unit (AUA, 2013). Poor bladder support by the pelvic muscles results in the opening and descent of the urethra when abdominal pressure is increased. Urethral mobility is classified as type I or II hypermobility, type III non-mobility, or normal according to the degree of change of posterior urethrovesical angle that occurs with straining maneuvers as assessed during fluoroscopy. The degree of urethral mobility is diagnosed by estimation at the time of the physical exam, cotton-swab test, or imaging. Sphincter function is diagnosed by examination, Valsalva leak point pressure, or urethral pressure profile.

The following are the classifications of stress urinary incontinence (Green, 1962; McGuire, 1981):

- Type I - The bladder neck and urethra are open and slightly hypermobile, and the urethra moves down less than 2 cm when stressed. Type I patients have little or no sign of cystocele. On diagnostic testing patients have a Valsalva Q-Tip angle less than 30 degrees an abdominal leak point pressure (ALPP) greater than 120 cm H2O.
- Type II - The bladder neck and urethra are closed and hypermobile, and the urethra moves down more than 2 cm when stressed. Patients who have cystocele inside the vagina have Type IIA stress incontinence. When cystocele is outside the vagina, it is classified as Type IIB. On diagnostic testing patients have a Valsalva Q-Tip angle greater than 30 degrees and ALPP more than 90 cm H2O.
- Type III (severe) - The urethral sphincter is very weak due to a non-functional proximal urethra that remains open all of the time. Type III stress incontinence may also be referred to as ISD. On diagnostic testing patients have a Valsalva Q-tip angle less than 30 degrees and ALPP less than 60 cm H2O.

Intrinsic Sphincter Deficiency

Intrinsic sphincter deficiency (ISD) is a condition in which the urethral sphincter is unable to adapt and generate enough resting urethral closing pressure to retain urine in the bladder. The anatomic support is normal but the urethra cannot remain closed (remains open all the time) due to a lack of mucosal seal mechanism. Inadequate bladder outlet resistance during times of physical activity results in involuntary urine loss. This may be caused by a prior surgery for stress incontinence and changes in the urethral tissues from aging. Other causes include myelodysplasia, trauma, and radiation (AUA, 2013).

Other Classifications of Urinary Incontinence

- Transient incontinence: Leakage that occurs temporarily because of a situation that will pass (e.g., infection, taking a new medication, delirium, atrophic vaginitis, pharmacologic reasons, excessive urine production, colds with coughing) (NKUDIC, 2010).

- Mixed incontinence: Describes a combination of different types of urinary incontinence, most commonly, stress and urge incontinence. Many studies have shown that mixed incontinence is the most common type of urine loss in women (NKUDIC, 2010).
- Functional or environmental incontinence: Described as the inability to hold urine (untimely urination) due to reasons other than neuro-urologic and lower urinary tract dysfunction (Vasavada et al., 2013). These conditions include physical disability, external obstacles, or problems in thinking or communicating that prevent a person from reaching a toilet (National Kidney and Urologic Diseases Information Clearinghouse [NKUDIC], 2010).
- Post-prostatectomy incontinence: Development of stress incontinence, total (dripping faucet) incontinence, and detrusor instability after prostatectomy surgery. Both stress incontinence and total incontinence are caused by injury to the urethral sphincter muscle during surgery. Damage to the nerve and muscle fibers of the bladder itself, causing "spasms", urgency, and urge causes detrusor instability.

Accurate diagnosis of the type of urinary incontinence is important for the appropriate selection of treatment options. Because urinary incontinence is a symptom of several disorders, the treatment choices vary considerably depending on the underlying disorder (Hayes Inc., 2011). First line, conservative (non-surgical) treatments may include pelvic muscle exercises (e.g., Kegel exercises), bladder training exercises (e.g., distraction, relaxation, and scheduled voiding), fluid restriction and dietary modification, weight loss, pessaries, and pharmacologic treatment (e.g., anticholinergics/antimuscarinics [primary treatment for urge incontinence], musculotropic relaxants, alpha-adrenergics, duloxitene, topical estrogen, and tricyclic antidepressants). Botulinum toxin has also been injected into the detrusor muscle with some success, although it can sometimes cause post treatment urinary retention. See Blue Shield Pharmacy Policy: Botulinum Toxin B. Second-line treatments may include electrical stimulation, neuromodulation, periurethral bulking agents, surgery, or augmentation cystoplasty.

The following are descriptions and a review of the literature on some of the various techniques (non-surgical and surgical) for urinary incontinence.

Periurethral Bulking Agents

Periurethral bulking agents have been widely used for incontinence in women, however, men have also been treated, typically those with post-prostatectomy incontinence. Periurethral bulking agents are substances injected periurethrally to increase tissue bulk around the urethra. Improvement in stress incontinence is achieved by increasing resistance to the outflow of urine. Bulking agents may be composed of collagen, synthetic materials, or autologous fillers. The procedure is performed suburethrally through a cytstoscope, with a spinal needle inserted percutaneously or transvaginally with cystoscopic control. The bulking agent is injected into the periurethral tissue as a liquid which solidifies into a spongy material to bulk the urethral wall. Bulking up the bladder neck effectively closes the lumen of the urethra, which improves urethral coaptation and restores the mucosal seal mechanism of continence. Bulking agents may be injected over a course of several treatments until the desired effect is achieved. Adverse events with these agents are usually uncommon and relatively minor (e.g., dysuria [most common], urinary urgency, transient urinary retention and acute urinary retention). Unfortunately, most of

the available bulking agents lose their effectiveness over time, and repeat injections are needed every 6 to 18 months (depending on the bulking agent used).

Biocompatibility, durability, and absence of migration are key factors in the success of bulking agents. Several periurethral bulking agents are approved by the U.S. Food and Drug Administration (FDA) and have been studied in randomized trials that established safety and efficacy for the treatment of stress urinary incontinence due to ISD (Agency for Health Care Policy and Research [AHCPR], now Agency for Healthcare Research and Quality [AHRQ]), 1996; Carcos et al., 2005**;** Ghoniem et al., 2009; Ghoniem et al., 2010; Lightner et al., 2001; Mayer et al., 2007). Other than Contigen®, approval is only for use in adult women. Contigen is the only bulking agent currently approved by the FDA for use in men and women.

The following section discusses various injectable bulking agents used for the treatment of urinary incontinence (FDA-approved, non-FDA-approved, and those products not requiring FDA approval).

FDA-Approved Periurethral Bulking Agents

Cross-Linked Collagen (Contigen®)

Glutaraldehyde cross-linked [GAX] bovine collagen (i.e., Contigen®) (C.R. Bard, Covington, GA). Contigen was the first bulking agent to received premarket approval (PMA) approval for urinary incontinence, in 1993. A supplemental approval in 2009 limited the device's indication to treatment of urinary incontinence due to ISD in patients (men or women) who have shown no improvement in incontinence for at least 12 months. At that time, Contigen was modified and marketed under the trade name Contigen Bard Collagen Implant. Once injected, the bovine collagen begins to degrade within 12 weeks and completely degrades in 9 to 19 months. A month before the first treatment, the patient must undergo a skin test to exclude hypersensitivity. Collagen is slowly absorbed over time, and symptoms may recur, requiring additional injections.

Carbon-Coated Beads or Spheres (e.g., Durasphere™)

Durasphere (pyrolytic carbon-coated zirconium oxide spheres) (Advanced UroScience, St. Paul, MN) was approved by the FDA in 1999 for the treatment of ISD in women >/= 21 years of age. In 2002, bead modifications and a trade name revision to Durasphere EXP were made, and is also indicated in the treatment of adult women with stress urinary incontinence due to ISD.

Calcium Hydroxylapatite, CaHA (Coaptite®)

In 2005, Coaptite (BioForm Medical, Inc., San Mateo, CA), spherical particles of calcium hydroxylapatite suspended in a gel carrier, was approved for soft tissue augmentation in the treatment of stress urinary incontinence due to ISD in adult females. It is contraindicated in patients with a significant history of urinary tract infections without resolution, current or acute conditions of cystitis or urethritis, or fragile urethral mucosal lining.

Polydimethylsiloxane (Macroplastique®)

In 2006, Macroplastique® Implants (silicone elastomer/polydimethylsiloxane) (Uroplasty Inc., Minnetonka, MN) were given PMA by the FDA. Macroplastique is composed of polydimethylsiloxanc particles suspended in a polyvinylpyrrolidone (PVP) carrier gel and is permanently implanted. It is indicated for transurethral injection in the treatment of adult women

diagnosed with stress urinary incontinence primarily due to ISD. Macroplastique is contraindicated in patients with acute urogenital tract inflammation or infection, and fragile urethral mucosal lining (e.g., post-radiation therapy, post-surgery to the bladder neck).

Ethylene Vinyl Alcohol Copolymer (EVA, e.g., URYX™ marketed as Tegress™)

In 2004, URYX® (Genyx Medical, Inc., Aliso Viejo, CA), vinyl alcohol copolymer implants, was approved. In 2005, approval was given to market the device under the trade name Tegress™ (C.R. Bard, Covington, GA) for the treatment of stress urinary incontinence due to ISD in adult women. Following reports of adverse effects (i.e., reports of up to 37% erosion rates), Tegress was voluntarily withdrawn from the market by CR Bard as of January 31, 2007 (Hurtado et al., 2007).

Non-FDA-Approved Periurethral Bulking Agents

Dextranomer/hyaluronic (Dx/HA, Zuidex™) with an injection system (Implacer™)

The Zuidex-Implacer (Q-MED, Uppsala, Sweden) is a system to inject Dx/HA in the outpatient clinic without the need for endoscopy. An industry-sponsored (Q-Med) randomized non-inferiority trial that compared the Zuidex/Implacer system to Contigen conducted in North America was published by Lightner and colleagues in 2009. Patients were blinded to treatment group. The primary study outcome was the proportion of women who had an equal to or greater than 50% reduction in urinary leakage on provocation testing from baseline to 12 months after the final treatment (up to three treatments were permitted). The primary outcome was achieved by 65% of Zuidex-treated women compared to 84% in the Contigen group; non-inferiority of Zuidex was not established. The study is limited by a high rate of missing data; primary outcome data were missing for 35% of randomly assigned patients.

An open multicenter study from Europe reported a 12-month 77% positive response rate (reduction >/= 50% for provocation test urinary leakage) with the Dx/HA Zuidex-Implacer system in 142 women who met strict inclusion/exclusion criteria (Chapple et al., 2005). Similar to the North American trial, this study had a high dropout rate, (24%), as well as an unrepresentative patient population and lack of a comparison group. Twenty-one women recruited as part of this study were followed for a mean of 6.7 years after treatment with the Zuidex-Implacer system (Lone et al., 2010). At this long-term follow-up, 7 of 21 (33%) were continent of urine, but 6 of the 7 had undergone other continence procedures since their Zuidex injections.

Polyacrylamide Hydrogel (Bulkamid®)

Bulkamid® (Contura International, Denmark) is a gel containing 2.5% cross-linked polyacrylamide and 97.5% apyrogenic water. Findings from a multicenter European case series were published by Lose and colleagues in 2010. A total of 135 adult women with symptomatic stress (n = 67) or mixed (n = 68) incontinence for at least 12 months and at least one episode of incontinence per day were included. Ninety-eight (73%) completed the 12-month follow-up; four additional patients were excluded from the per-protocol analysis due to protocol violations. The primary outcome was response to treatment, defined as patients self-reporting that they considered themselves “improved” or “cured.” The response rate at 6 and 12 months was 71% and 66%, respectively. Corresponding cure rates were 16% and 24%. The study lacked a

comparison group with which to compare these outcomes; a comparison group is particularly important with a subjective outcome such as the one used in the study. There were 32 treatment-related adverse effects including 2 cases of urinary retention requiring hospitalization and 10 cases of urinary tract infection.

Polytetrafluoroethylene (Teflon®)

Polytetrafluoroethylene (Teflon®) has also been investigated as an implant material for the treatment of female stress urinary incontinence. However, the FDA has not approved Teflon use because of possible local and distant migration of the particles into the lymph nodes, lung, and brain. No published clinical trials were identified.

Periurethral Bulking Agents That Do Not Require FDA Approval

Autologous fat and autologous ear chondrocytes have also been used as periurethral bulking agents; autologous substances do not require FDA approval. Another explored alternative is cellular therapy with myoblasts, fibroblasts, or stem cells (muscle-derived or adipose-derived).

Autologous Fat and Autologous Ear Chondrocytes

These are other materials that have been used as bulking agents but have not demonstrated sustained effectiveness comparable to cross-linked collagen or carbon-coated beads. In a randomized, double-blind clinical trial of 56 female patients that compared periurethral injections of autologous fat (treatment group) to saline (placebo group), Lee and colleagues (2001) found that periurethral fat injections did not appear to be more efficacious than placebo for treating stress incontinence. At 3 months, only 6 of 27 patients (22.2%) in the treatment group and 6 of 29 (20.7%) in the placebo group were cured or improved. In addition, one death occurred as a result of a pulmonary fat embolism. In another clinical trial of 32 female patients, Bent and colleagues (2001) reported that 50% of patients remained dry for 12 months after receiving a single outpatient injection of harvested autologous auricular cartilage. While autologous substances have a non-immunogenic advantage, their use may be limited by resorption and fibrous replacement along with local discomfort associated with harvesting procedures.

Autologous Cellular Therapy

In 2007, Strasser et al. published the first randomized study on autologous cell therapy for treating stress urinary incontinence. This study has been widely cited as an important advance in the field. However, in September 2008, the Lancet published a statement that they were retracting publication of this study due to ethical and quality concerns (Kleinert & Horton, 2008). The Lancet retraction states “our view, the conclusions of this official investigation pinpoint so many irregularities in the conduct of their (Strasser et al.) work that, taken together, the paper should be retracted from the public record.” Because of this retraction, findings from this study will no longer be cited as evidence in this policy.

Professional Society and Systematic Reviews (Periurethral Bulking Agents)

In 2005 (reaffirmed 2009), the American College of Obstetricians and Gynecologists (ACOG) issued a practice bulletin on urinary incontinence in women. The practice bulletin included a recommendation for injection of bulking agents (i.e., collagen, carbon-coated beads, and fat) as

second-line therapy or in women with urinary incontinence who are ineligible for surgery. This recommendation was based on limited or inconsistent scientific evidence.

In 2010, the Society of Obstetricians and Gynaecologists of Canada Urogynaecology Committee published a guideline on the evaluation and treatment of recurrent urinary incontinence after pelvic floor surgery (Lovatsis et al., 2010). The guideline recommends that conservative management be used as first-line therapy. It also stated that patients with significantly decreased urethral mobility may be managed with periurethral bulking agents as one of several treatment options.

In a systematic review by the International Consultation on Incontinence on Surgical Treatment of Stress Incontinence in Men, Herschorn et al. (2010) stated the following regarding urethral bulking agents:

> Bulking agents remain the most minimally invasive treatment for post-RP [radical prostatectomy] incontinence after conservative measures. All agents for which there is peer-reviewed data available, show only modest success rates with low cure rates. Effects tend to deteriorate over time. It remains to be seen if improvements in outcomes can be achieved with alternative agents, or if the concept of urethral bulking has achieved its maximal benefit with the agents available now.

A 2012 Cochrane review (Kirchin et al., 2012) assessed the effects of periurethral or transurethral injection therapy on the cure or improvement of urinary incontinence in women in 14 randomized controlled trials (RCTs) with sample sizes ranging from 30 to 355 patients that included bulking agents in at least one of the study arms. All trials included women with a urodynamic diagnosis of stress incontinence, and seven trials limited eligibility to stress incontinence due to ISD. The studies varied in the type of bulking agent and comparison intervention used (e.g., two bulking agents, bulking agents to surgery, bulking agent to pelvic floor exercise, placebo comparison group). Several studies required that women had experienced incontinence for a specified period of time (e.g., 3 months, 6 or 12 months, and/or had already used conservative therapy). The authors stated that data from the trials were not suitable for pooling due to heterogeneity among studies and no clear conclusions could be drawn regarding the comparison of bulking agents. Insufficient evidence was found to show superiority of mid-urethral or bladder neck injection. They concluded that further comparative randomized trials with long-term follow-up, involving a placebo or conservative treatment arm, are required before injection therapy can be recommended as a standard first-line treatment for stress incontinence.

A 2011 systematic review by Davila identified 20 studies meeting their inclusion criteria (prospective clinical studies or RCTs conducted among women with stress urinary incontinence and published in English). Nine studies (total n = 682) evaluated the bulking agent cross-linked collagen. Rates of patients considered cured or improved in individual studies ranged from 21% to 81% at 12 months, 7% to 52% at 2 years, and 30% to 43% at more than 4 years. There were 8 trials (n = 507) using cross-linked polydimethylsiloxane injection. Cure rates ranged from 20% to 71% at 12 months and 18% to 40% at long-term follow-up up to 60 months. The authors concluded that bulking agents have demonstrated effectiveness at 1 year, but results, particularly with older agents, diminish over time, and repeated injections can restore or enhance improvement.

Summary

In conclusion, several FDA-approved periurethral bulking agents have proven to be effective in treating stress urinary incontinence due to ISD when specific selection criteria are met. Cross-linked collagen is the most established bulking agent that is currently available. The evidence on cross-linked collagen is sufficient to conclude that it is effective in some patients who fail conservative treatment and therefore, is a reasonable alternative to more risky surgical procedures. These bulking agents are not FDA-approved for urge incontinence and are considered investigational. Results from available trials suggest that carbon-coated spheres, calcium hydroxylapatite, and polydimethylsiloxane have efficacy for treating stress urinary incontinence that is similar to cross-linked collagen. For other agents, such as autologous cellular therapy, autologous fat, autologous ear chondrocytes, and Teflon, there are few RCTs and little evidence of efficacy.

Transurethral Radiofrequency Energy Collagen Micro-Remodeling

In 2005, Novasys Medical® Inc., (Newark, CA) received clearance to market the Renessa® transurethral radiofrequency system through the FDA 510(k) process. The device is indicated for the transurethral treatment of female stress urinary incontinence due to urethral hypermobility in women who have failed conservative treatment and who are not candidates for surgical therapy. In 2013, Verathon Medical (Bothell, WA) acquired Renessa by Novasys Medical, and rebranded it as the Lyrette™ transurethral SUI system.

The Renessa procedure is a minimally invasive, non-surgical in-office or outpatient treatment option for stress urinary incontinence that involves passing a specially designed four-needle radiofrequency probe through the urethral opening into the urethra and then into the bladder. Once the probe is in position, a small balloon is inflated to keep it in position during the procedure. Radiofrequency energy is then delivered for 60 seconds to the four needles which are deployed from the probe into the tissue of the bladder neck and upper urethra. Tissue temperatures of 65 to 75 centigrade are generated; at this temperature, focal microscopic denaturation of collagen occurs. The procedure is repeated nine times so that collagen is denatured at 36 tissue sites. Upon healing, the treated area is less compliant and more resistant to leaks.

In 2008, the California Technology Assessment Forum (CTAF) (Karliner, 2008) completed a review of radiofrequency remodeling for the treatment of female stress urinary incontinence. The evidence for Renessa consisted of a RCT with 12-month follow-up and post-hoc analysis (Appell et al., 2007) and two observational pilot studies (Lenihan et al., 2005; Appell et al., 2006). The author advised that while radiofrequency micro-remodeling (Renesssa) for stress urinary incontinence does not show as high success rates as the gold standard approaches (Burch procedure and tension-free vaginal tape), it does demonstrate a good safety profile and moderate improvement in objective urinary leakage and quality of life, particularly for women with moderate-to-severe stress urinary incontinence. The CTAF Assessment concluded:

> Radiofrequency micro-remodeling with the Renessa system meets CTAF TA [Technology Assessment] criteria 1-5 for safety, efficacy and improvement in health outcomes for the treatment of moderate to severe female stress urinary incontinence (as defined as a specified score below 60 on the IQOL [Incontinence Quality of Life Scale])

in non-pregnant women who are either not able or not willing to undergo surgery for their stress urinary incontinence treatment

In a prospective, single-arm clinical trial, Elser et al. (2009) performed a 12 month multicenter study of transurethral radiofrequency remodeling (Renesssa) in 136 women with stress urinary incontinence caused by bladder outlet hypermobility who had failed non-surgical treatment and were not candidates for surgical therapy. Efficacy, based on the percentage of patients with a 50% or greater reduction from baseline in daily incontinence episodes, was reported in 68 (50%) patients. Of the 75 evaluated at 12 months, 69% (38% of 136) reported at least a 50% reduction in leaked urine (median of 15 g) from baseline, and 45% (25% of 136) were dry. No serious adverse events were reported. The authors concluded that at 12 months, treatment of stress urinary incontinence with surgical of transurethral radiofrequency remodeling resulted in significant improvements in activity-related leaks and quality of life.

Eighteen-month and 3-year follow-up data have been published. Sixty-three of 136 (46%) women who received treatment completed the 18-month follow-up, and data were available on 60 women (44% of the study population) (Elser et al., 2010). Thirty-one of the 60 evaluable women (61.7%) reported a reduction of at least 50% from baseline in leaks due to activity. In an intention-to-treat (ITT) analysis of data from all 136 participants (last observation carried forward), 46.7% reported at least a 50% reduction in leaks from baseline. A total of 41 women (30% of the study population) completed the 3-year follow-up evaluation (Elser et al., 2011). According to diary data, available for 39 women, 24 (62%) reported at least a 50% reduction in leaks per day. The authors advised that transurethral collagen denaturation seems to be a low-risk, office-based procedure that results in durable quality-of-life improvements in a significant proportion of women for as long as 3 years. While the ITT analysis had multiple imputations of missing data; 60% of women had at least a 50% reduction in leaks. The study was limited by a low long-term follow-up rate and lack of a control or comparison group.

There is a non-randomized clinical trial recruiting participants with the ClinicalTrials.gov identifier of NCT01455779, sponsored by Novasys Medical, Inc. The purpose of this study is to demonstrate the treatment efficacy of the Renessa System in women most likely to be treated in an office setting for the condition of stress urinary incontinence, secondary to urethral hypermobility. The estimated completion date is March 2014.

In summary, while the evidence from well-conducted, RCTs on transurethral radiofrequency tissue remodeling for stress incontinence is limited in quantity and quality, there is some available evidence to suggest that the Lyrette system (formerly Renessa) provides benefits for carefully selected patients.

Acupuncture

Acupuncture is the practice of piercing the skin with needles at specific body sites to induce anesthesia, to relieve pain to alleviate withdrawal symptoms of substance abusers, or to treat various non-painful disorders. The placement of needles into the skin is dictated by the location of meridians. These meridians are thought to mark patterns of energy flow throughout the human body. Acupuncture may be performed with or without electrical stimulation.

A review published by the World Health Organization (WHO) (2003) evaluated controlled clinical trials published up to 1998 and early 1999 and categorized disorders according to evidence. According to the report, acupuncture may be appropriate for numerous conditions; however, urinary incontinence was not mentioned.

A randomized, placebo-controlled trial compared the efficacy of acupuncture treatment versus placebo for OAB with urge incontinence in 74 women (Emmons et al., 2005). At 4 weeks, women in both groups had significant decreases in the primary outcome measurement of number of incontinent episodes (59% for treatment; 40% for placebo) without a significant difference in the change between the groups. Both groups also had an improvement in the urinary distress inventory and incontinence impact questionnaire scores.

In 2006, the National Institute for Health and Clinical Excellence (NICE) issued a guideline on the management of urinary incontinence in women. Acupuncture was not discussed in the guideline specifically. However, NICE advised that complementary therapies are not recommended for the treatment of urinary incontinence or OAB.

A review examined the effect of complementary therapies (such as herbal remedies, acupuncture and hypnotherapy), behavioral therapies (bladder training and timed and prompted voiding), pelvic floor muscle training and some over-the-counter preparations on urinary incontinence, urgency and OAB symptoms (Christofi & Hextall, 2007). The authors concluded, "Many of the therapies, however, lack a solid evidence base with regard to their efficacy and few have been subjected to robust randomized trials."

In the European Association of Urology (EAU) Guidelines on urinary incontinence (Thet al., 2011), acupuncture was not discussed as a treatment option for men or women with urinary incontinence.

At this time, there is insufficient evidence in the published, peer-reviewed scientific literature to conclude that acupuncture is effective for the treatment of all types of urinary incontinence.

Adjustable Continence Therapy (ACT®, ProACT™)

The ACT® system (Uromedica, Inc., Plymouth, MN) is an implantable device developed as a minimally invasive option for treatment-resistant or recurrent stress urinary incontinence in women after one or more failed incontinence surgeries, although the optimal treatment sequence has not been established (Hayes Inc., 2010). The device is not proposed for first-line therapy or for use in women with diminished cognitive function, urinary retention, urge incontinence, or other types of conditions associated with the involuntary leakage of urine.

The ACT system consists of two balloon implants constructed from silicone elastomer, similar to the materials used to construct artificial urinary sphincter (AUS) devices. Each balloon is connected via short tubing to an injectable titanium port. The balloons are fully implanted bilaterally and positioned at the level of the bladder neck using a paraurethral/vaginal approach with the aim of coapting the urethra and restoring continence. Each balloon is attached via a conduit to a postoperatively adjustable port placed in a subcutaneous pocket in each labia majora. The implantation of the ACT system takes 30 to 60 minutes to perform under general, spinal, or local anesthesia using digital and fluoroscopic guidance. A cystoscopy confirms implant positioning and the absence of any perforation. Outpatient balloon pressure adjustments

may be performed at 6 weeks if continence has not been achieved, and then monthly if necessary (Hayes Inc., 2010).

The published results of a multicenter uncontrolled U.S. pivotal trial (NCT00113555; Aboseif et al., 2009), a published report on outcomes in a subgroup of patients from the trial (Aboseif et al., 2010) and two European small uncontrolled case series (Wachter et al., 2008; Kocjancic et al., 2010) suggest the ACT system may be a reasonable treatment option for women with severe and protracted stress urinary incontinence after other unsuccessful surgical procedures. However, long-term safety outcomes have not been established and the best published studies reported adverse effects including balloon migration, transient urinary obstruction, and balloon leakage ranging from 21% to 39% (Hayes Inc., 2010).

A similar device known as ProACT™ (Uromedica, Inc., Plymouth, MN) is a percutaneously implanted balloon device used to apply adjustable pressure on the urethra to control involuntary leakage of urine in men with severely symptomatic and persistent incontinence due to weakness of the intrinsic sphincter muscle following prostate surgery. The balloon implants and connections are similar to the ACT device. The balloons are fully implanted bilaterally and positioned on each side of the bladder neck proximal to the remnant external sphincter (in post-prostatectomy patients) or at the level of the membranous urethra (in post-TURP patients) when there is residual prostate tissue. The procedure is performed with guidance imaging with cystoscopy and fluoroscopy and takes approximately 20 minutes under anesthesia. A urethrogram confirms the implant positioning once the balloons are inflated. Outpatient adjustments may be performed every 4 weeks.

At this time, the long-term safety of the ProACT system has not been established. The best studies published suggest a learning curve for the device implantation, and increased risk for bladder injury, and a frequent need for revision procedures and removals. The clinical efficacy of the ProACT system for improving stress urinary incontinence has not been fully evaluated, and is limited by weak study designs (Hayes Inc., 2011).

The ACT and ProACT system are commercially available in countries throughout Europe and South America, Canada, New Zealand and Australia. However, the FDA declined to approve the PMA application for the ACT device, and in April 2010, a formal appeal by the device manufacturer to the FDA was denied (Hayes Inc., 2011). The future of the ACT system in the United States is uncertain. A pivotal clinical trial of the ProACT device (NCT00277095) for FDA review was due for completion in 2009; however, it has been extended beyond that date. No study results have been posted.

Biofeedback

Biofeedback is added to the treatment of urinary incontinence to help the patient learn to control and coordinate the contraction of sphincter muscles (i.e., skeletal muscles) which are under voluntary control. In particular, biofeedback is often used to enhance training in pelvic floor muscle exercises.

Biofeedback for urinary incontinence in men and women is discussed in the Blue Shield Medical Policy: Biofeedback. The Biofeedback policy summarizes:

> Numerous RCTs have evaluated biofeedback as a treatment of urinary incontinence in women. The methodology of the studies has varied, and many were not able to isolate the potential contribution of biofeedback. Several RCTs described above that evaluated PFMT [pelvic floor muscle training] with and without the addition of biofeedback did not find a benefit when biofeedback was added to PFMT or behavioral therapy. A meta-analysis of RCTs evaluating biofeedback and/or verbal feedback as part of urinary incontinence treatment found improvement in some outcomes (e.g., improvement or cure) but not others (e.g., cure, leakage episodes). There is a lack of consistent evidence from well-designed trials that biofeedback is an effective treatment of urinary incontinence, whether as part of an outpatient program or unsupervised in the home.

A few RCTs on biofeedback for post-prostatectomy incontinence have been completed, with mixed results. Some studies report a significant improvement in symptoms with biofeedback, but others do not. This evidence is insufficient to determine whether biofeedback improves health outcomes for patients with post-prostatectomy incontinence whether as part of an outpatient program or unsupervised in the home.

Biofeedback as a treatment for urinary incontinence is considered investigational due to insufficient evidence to permit conclusions concerning the impact of this procedure on net health outcomes. Specifically the value of adding biofeedback to a program of pelvic muscle exercises has not been demonstrated.

See the Blue Shield Medical Policy, Biofeedback, for further detail and literature reviews.

Biomagnetic Therapy

Biomagnetic therapy has been investigated for various conditions including chronic pain conditions (e.g., diabetic neuropathy, musculoskeletal pain, and osteoarthritis), and more recently, the treatment of urinary incontinence. Biomagnetic therapy involves the static use of magnetic fields using a variety of devices including necklaces, bracelets, insoles, sleeves, headbands, or mattress pads. It is a non-invasive approach proposed to promote analgesia by the use of static magnets. This type of therapy has been also referred to as magnetic therapy, magnetherapy, magnotherapy, static magnetic field therapy, or therapeutic magnets.

In 2005, But and colleagues examined the efficacy of functional magnetic stimulation (FMS) compared to placebo for treating 39 women with mixed urinary incontinence. The women were randomly assigned to the FMS group (23 patients) or to the placebo group (16 patients). Functional magnetic stimulation was continuously applied at 18.5 Hz day and night for 2 months. Conventional urodynamic studies were performed before and after stimulation. Outcome measures assessed were clinical (daytime frequency, nocturia, pad use, pad weight) and urodynamic variables (first sensation of bladder filling, maximum cystometric capacity, maximum urethral closure pressure), and patient subjective assessment (visual analogue scale). The authors advised that 18 of the 23 women receiving FMS reported improvement in symptoms after FMS with an average success rate of 41.9%. The success rate in the placebo group was significantly lower at 22.9%. The authors concluded that FMS “was useful and safe for treating women with mixed urinary incontinence.”

In 2005, Quek examined the acute effects of static magnetic stimulation on urodynamic parameters and reviewed the data on its use in the management of urinary incontinence. Based on the data reviewed, cure rates for stress incontinence immediately after a course of perineal magnetic stimulation ranged from 12.5 to 52.9% with good improvement occurring in 32% to 41%. However the effect seemed temporary and dependent on the number of sessions. The author advised that overall, the data had to many variations in terms of treatment protocols, patient mix, and symptom severity to determine which group of patients might benefit the most and what the optimal stimulation parameters were for each condition. While there were reported mean reductions in leak parameters that were statistically significant, these may not always be clinically satisfactory. Additionally, the beneficial effects also appeared to be temporary and continuous treatment would probably be required. The author concluded that further trials were needed "to determine the optimum stimulation protocols for different situations and to compare magnetic stimulation with other forms of conservative pelvic floor therapy."

At this time, there are no randomized studies that have shown significant benefits from biomagnetic therapy for urinary incontinence.

Pelvic Floor Stimulation

Pelvic floor stimulation (PFS) is proposed as a nonsurgical treatment option for women and men with urinary incontinence. This approach involves either electrical stimulation of pelvic floor musculature or extracorporeal pulsed magnetic stimulation.

Electrical Stimulation of Pelvic Floor Muscles

Pelvic floor electrical stimulation (PFES) as a treatment of urinary incontinence refers to electrical stimulation of the pudendal nerve. It is an approach thought to work through three different mechanisms:

- Direct stimulation of motor nerves supplying the pelvic floor and external urethral sphincter which results in muscle contraction thereby strengthening the muscles
- Exhausting afferent sensory nerves from the bladder thereby suppressing overactive bladder contractions
- Blocking irritative bladder symptoms via the gate control theory

Patients receiving electrical pelvic floor stimulation may undergo treatment in a physician's office or physical therapy facility, or may undergo initial training in a physician's office followed by home treatment with a rented or purchased pelvic floor stimulator.

Several electrical stimulators have been cleared by the FDA. In March 2006, the MyoTrac Infiniti™ (Thought Technology, Ltd., Quebec, Canada), a non-implanted electrical stimulator for treating urinary incontinence, was cleared for marketing by the FDA through the 510(k) process. Predicate devices, also used to treat urinary incontinence, include the Pathway™ CTS 2000 (The Prometheus Group, Dover, NH) and the InCare® PRS (Hollister Inc., Libertyville, IL).

Women with Urinary Incontinence

A Blue Cross Blue Shield Technology Evaluation Center (TEC) Assessment (2000a) concluded that there was insufficient evidence that electrical pelvic floor stimulation improved health

outcomes compared to placebo or other behavior therapies in women with stress, urge, or mixed incontinence.

Several RCTs comparing PFES to sham treatment found no significant difference in outcomes between arms (Jeyaseelan et al., 2000; Amaro et al, 2005; Amaro et al., 2006). Other RCTs demonstrated no significant benefit of electrical stimulation compared with pelvic floor exercises, biofeedback-assisted training, or placebo (Goode et al., 2003; Wille et al., 2003; Wang et al., 2004) for stress, urge, and post-prostatectomy incontinence.

In 2008, Castro and colleagues in Brazil published an RCT comparing treatment with pelvic floor muscle training, electrical stimulation or vaginal cones, or a no-treatment control group in women with proven urodynamic stress urinary incontinence that did not have urge incontinence. All of the active interventions consisted of three sessions a week, which were conducted at a urogynecology clinic under the supervision of a trained physical therapist. The intervention continued for 6 months, at which time outcomes were measured. Outcome assessment was blinded, but patients were not blinded to treatment group and ITT analysis was not used. A total of 118 women were randomized, and 17 (14%) withdrew from the study; the loss of patients was similar in the four groups. There were 101 women who completed the study and were included in the analysis. This included 26 women in the pelvic floor muscle training group, 27 in the electrical stimulation group, 24 in the vaginal cones group, and 24 in the untreated group. The primary outcome was the proportion of women with a negative pad test (i.e., less than 2 grams' weight). At 6 months, outcomes were similar in the three treatment groups, but significantly fewer women in the no-treatment group had a negative pad test. The numbers of women with negative pad tests were 12 (46%) in the pelvic floor muscle training group, 13 (48%) in the electrical stimulation group, 11 (46%) in the vaginal cone group, and 2 (8.0%) in the untreated control group. Findings in the no-treatment group could be due, at least in part, to a placebo effect. Moreover, the interventions in this study differ from most other studies in that they continued for 6 months and that all sessions were supervised by a trained professional.

Several more recent systematic reviews have been published. In 2010, the Health Technology Assessment program in the United Kingdom published a review of studies on non-surgical treatments for women with stress urinary incontinence (Imamura et al., 2010). The investigators identified eight RCTs comparing electrical stimulation to no active treatment; a sham control was used in six of the studies. A pooled analysis of study findings (all comparison groups combined) did not find a statistically significant difference between groups in cure rate, which was 6% in each group (odds ratio [OR]: 1.10, 95% CI: 0.41 to 2.94). Moreover a pooled analysis of cure rates from the 5 studies comparing electrical stimulation to pelvic floor muscle training did not show a significant difference between groups; the cure rates were 24% and 11%, respectively (OR: 2.65, 95% CI: 0.82 to 8.60). When the comparison was limited to studies comparing electrical stimulation to no active treatment, there was a higher rate of improvement with electrical stimulation (37% versus 14%, OR: 3.93, 95% CI: 1.43 to 10.8). Due to the lack of a sham intervention group, a placebo effect of electrical stimulation cannot be ruled out. The authors of the systematic review concluded that there is insufficient evidence to recommend electrical stimulation on a routine basis for treatment of stress urinary incontinence.

In addition, a systematic review of published literature on electrical pelvic floor stimulation was published by Shamliyan and colleagues in 2008. The literature review was funded by the AHRQ

and conducted by the University of Minnesota Evidence-based Practice Center. The review included RCTs conducted among women with stress and urge urinary incontinence, OAB with urge incontinence, or minimal urinary incontinence. Study quality was analyzed using the following criteria: participant selection; length and loss of follow-up; use of ITT analysis; masking of the treatment status; randomization scheme; adequacy of randomization and allocation concealment; and justification of sample sizes. Results of 12 RCTs did not find that electrical stimulation cured or improved urinary incontinence in women better than sham stimulation or pelvic muscle training. Two of the 12 trials that assessed continence at 6 months or longer follow-up failed to show statistically significant benefit from electrical stimulation compared with continence services or medications. Other RCTs demonstrated no significant benefit of electrical stimulation compared with pelvic floor exercises, biofeedback-assisted training, or placebo.

In conclusion, findings from multiple RCTs and meta-analyses of RCTs have not found that electrical stimulation used to treat urinary incontinence in women consistently improved the net health outcome compared to placebo or other conservative treatments.

Men with Post-Prostatectomy Urinary Incontinence

Two systematic reviews of RCTs were published in 2012 (Campbell et al., 2012; Zhu et al., 2012). The review by Zhu and colleagues (2012) focused on pelvic floor electrical stimulation used to treat post-prostatectomy urinary incontinence. The authors identified four RCTs with 210 men that provided sufficient data on clinical outcomes. A pooled analysis of data from three trials did not find a statistically significant benefit of electrical stimulation on continence levels compared to control within 3 months of prostatectomy (risk ratio [RR]: 1.21; 95% CI: 0.96-1.54). Similarly, a pooled analysis of data from all four trials did not show a statistically significant benefit of electrical stimulation on continence levels 6 to 12 months after prostatectomy (RR: 1.03: 95% CI: 0.88-1.20). The second systematic review was a Cochrane review (Campbell et al., 2012) that addressed the more general issue of conservative management of post-prostatectomy urinary incontinence. The reviewers identified three RCTs evaluating electrical stimulation compared to no stimulation or sham stimulation for postoperative treatment of incontinence. In a pooled analysis, the short-term (3-month) rate of incontinence was lower in the group that received electrical stimulation than in the control group (76% versus 90%, respectively). The pooled-RR was 0.84 (95% CI: 0.74 to 0.94). The authors stated that there were too few data to evaluate the long-term impact of electrical stimulation on rates of incontinence.

In 2011, Goode and colleagues published the results of a randomized trial comparing behavioral therapy alone to behavioral therapy in combination with biofeedback and pelvic floor electrical stimulation. The trial included 208 men with urinary incontinence persisting at least 1 year after radical prostatectomy. Men with pre-prostatectomy incontinence were excluded. Participants were randomized to one of three groups; 8 weeks of behavioral therapy (pelvic floor muscle training and bladder control exercises) (n = 70), behavioral therapy plus biofeedback and electrical stimulation (n = 70), and a delayed-treatment control group (n = 68). The biofeedback and electrical stimulation intervention, called “behavior-plus”, consisted of in-office electrical stimulation with biofeedback using an anal probe and daily home pelvic floor electrical stimulation. After 8 weeks, patients in the two active treatment groups were given instructions

for a maintenance program of pelvic floor exercises and fluid control and were followed up at 6 and 12 months. The primary efficacy outcome was reduction in the number of incontinent episodes at 8 weeks, as measured by a 7-day bladder diary. A total of 176 of 208 (85%) randomized men completed the 8 weeks of treatment. In an ITT analysis of the primary outcome, the mean reduction in incontinent episodes was 55% (28 to 13 episodes per week) in the behavioral therapy group, 51% (from 26 to 12 episodes per week) in the behavior-plus group, and 24% (from 25 to 20 episodes per week) in the control group. The overall difference between groups was significantly significant (p = 0.001), but the behavior-plus intervention did not result in a significantly better outcome than behavioral therapy alone. Findings were similar on other outcomes. For example, at the end of 8 weeks, there was a significantly higher rate of complete continence in the active treatment groups (11 of 70, 16% in the behavior group and 12 of 70, 17% in the behavior-plus group) than the control group (4 of 68, 6%), but the group receiving biofeedback and electrical stimulation did not have a significantly higher continence rate than the group receiving behavioral therapy alone. The study did not isolate the effect of pelvic floor electrical stimulation. However, the combined intervention of biofeedback and electrical stimulation along with behavioral therapy did not result in better outcomes than behavioral therapy alone.

In 2010, Yamanishi and colleagues published findings of a study comparing electrical stimulation to a sham control group. This trial, conducted in Japan, was a double-blind trial in which 56 men with severe post-prostatectomy urinary incontinence were randomized to receive active (n = 26) or sham (n =3 0) electrical stimulation. All men performed pelvic floor muscle training. Active or sham electrical stimulation was performed until incontinence was resolved or until the end of the study at 12 months. A total of 47 patients (22 in the active stimulation group and 25 in the sham group) completed the 12-month study. The continence rate, defined as loss of 8 gm or less of urine during a 24-hour pad test, was the primary efficacy outcome. There was a statistically significantly higher rate of continence at 1, 3, and 6 months in the active stimulation group compared to the sham group, but the difference between groups was not statistically significant at 12 months. Rates of continence in the active electrical stimulation group were 8 (36%), 14 (63%), 18 (81%), and 19 (86%) at 1, 3, 6, and 12 months, respectively. Corresponding rates in the sham group were 1 (4%), 4 (16%), 11 (44%), and 17 (86%). Findings of the 24-hour pad tests were also reported in several other ways. Differences in the amount (number of grams) of daily leakage were not significantly different between groups at any follow-up time point. For example, after 1 month, the mean amount of leakage was 210 gm in the active treatment group and 423 in the sham group, $p>0.05$. Change in the amount of daily leakage from baseline differed significantly between groups at 1 month (-528 gm in the active treatment group and -257 gm in the sham group, $p<0.01$) but not at the other follow-up time points.

In conclusion, there are a few small RCTs evaluating electrical pelvic floor muscle stimulation as a treatment of post-prostatectomy urinary incontinence in men that report improvements on some outcomes with electrical stimulation. These studies tended to be limited by failure to isolate the effect of electrical simulation and/or lack of a sham comparison or comparison to an accepted treatment. Two pooled analyses of RCTs were identified; one found short-term benefit of electrical stimulation and the other did not find a statistically significant short- or long-term benefit.

Magnetic Stimulation of Pelvic Floor Muscles (PFMS)

Pelvic floor magnetic stimulation has been used to stimulate both autonomic and somatic nerve pathways in the pelvis region to improve urinary continence. It has been used in the treatment of OAB (detrusor instability), for stress incontinence and to promote micturition in an arcflexic bladder. The variation in the amplitude and frequency of electrical pulse is purported to mimic and stimulate the different physiologic mechanisms of the voiding response.

The NeoControl® Pelvic Floor Therapy System (formerly Neotonus Inc., and currently marketed by Kitalpha Med Ltd., [Munchen, Germany]) was cleared by the FDA in June of 1998 and was the first product utilizing extracorporeal magnetic innervation (ExMI). During extracorporeal magnetic stimulation (EMS) therapy, a focused, time-varying magnetic field penetrates into the perineum and activates the motor neurons of the pelvic floor muscles. The pelvic muscles contract and relax with each magnetic pulse, thereby strengthening the muscles. The goal of this therapy is the rehabilitation of the pelvic floor musculature to reduce urinary incontinence (Kitalpha Med Ltd., 2009).

In general, a licensed urologist or gynecologist performs the EMS procedure in an office visit. The patient is sits fully clothed in a treatment chair while the electromagnetic field is generated from a magnetic stimulator that is located beneath the pelvic floor and controlled by an external power unit. Additional armchair devices include the Magstim® Rapid (Magstim Co. Ltd., Whitland, South West Wales), BioCon-2000™ (Mcube Technology Co., Ltd., Seoul, Korea), and Magther Incontinence Therapy System (EMD Medical Inc., Ankara, Turkey). Treatment sessions typically last 20 to 30 minutes and are performed twice a week for an 8-week period. Although the patient can sense the muscle contractions, EMS is generally not painful and anesthesia is not required (Hayes Inc., 2011). Alternatively, continuous treatment may be conducted at home using a small EMS device (Pulsegen™; Power of Nature LLC, San Rafael, CA), which is inserted into specially designed undergarments (Hayes Inc., 2011).

Women with Urinary Incontinence

A Blue Cross Blue Shield TEC Assessment (2000b) did not identify any RCTs evaluating electromagnetic pelvic floor stimulation for treating adults with incontinence. Several RCTs have subsequently been published. For example, in 2009, Gilling and colleagues in New Zealand published an RCT comparing magnetic stimulation using the Neocontrol chair to a sham treatment. The sham treatment involved inserting a thin aluminum plate in the chair to prevent penetration of the magnetic field. The study included 70 women, 35 in each group, with stress or mixed urinary incontinence. Treatment in both groups consisted of three treatment sessions per week for 6 weeks. There was no significant difference in the active versus sham treatment group in the primary outcome measure, change from baseline in the 20-minute pad test result from baseline to 8 weeks after the start of treatment (2 weeks after finishing treatment). At 8 weeks, the mean change in the 20-minute pad test was 20.1 mL in the treatment group and 7.5 mL in the control group. The groups also did not differ significantly in the 20-minute pad weight or quality-of-life measure at the 6-month follow-up. Data from 29 (83%) women in the active treatment group and 26 (74%) women in the sham group were available at 6 months; all participants appear to be included in the 8-week outcome analysis.

The AHRQ systematic review of 12 RCTs (Shamliyan et al., 2008) referenced earlier did not show magnetic or electrical stimulation cured or improved urinary incontinence in women better than sham stimulation or pelvic muscle training. Two of the 12 trials that assessed continence at six months or longer follow-up failed to show statistically significant benefit from electrical stimulation compared with continence services or medications.

In 2012, Wallis and colleagues in Australia published a single-blind RCT comparing magnetic progression-free survival (PFS) to a sham intervention in 122 women at least 60 years-old who had urinary incontinence for 6 months or more. Magnetic stimulation was provided via an undergarment that had 15 magnetic disks of 800 to 1,200 Gauss each sewn into the cotton bands on the outside of the garment. For the sham intervention, the undergarments were the same, but the magnets were replaced by inert metal disks of the same size and weight. Women were instructed to wear the undergarments at least 6 consecutive hours during the day and at least 6 hours at night. Outcomes were reported after 12 weeks of garment use. A total of 101/122 (83%) of women completed at least 4 weeks of the intervention and provided data for the efficacy analysis. At 12 weeks, the study did not find any statistically significant differences between groups on any of the efficacy outcomes, which included frequency of incontinence severity and quality-of-life measures. For example, the median change in frequency of incontinence episodes (time period not specified) was 0.75 in the magnetic stimulation group and 0.5 in the sham group, $p = 0.68$. The magnetic undergarments used in this study do not appear to be approved by the FDA for treating urinary incontinence.

Hayes Inc. (2011) evaluated the evidence surrounding EMS for the treatment of urinary incontinence from a number of controlled and uncontrolled studies. The authors advised there was evidence that EMS could safely reduce the frequency of incontinence episodes and improve quality of life for women with urinary incontinence. However, the effects were short-term, and some studies failed to find an effect of EMS. The authors cited limitations of the studies including small sample size, no sham control group, and a lack of long-term follow-up. Additionally, definitive patient selection criteria for EMS for the treatment of urinary incontinence have not been established. Hayes reviews of newer published studies on EMS, in 2012 and 2013, did not result in any change to the conclusions of the 2011 report.

Men with Post-Prostatectomy Urinary Incontinence

As stated above, the 2000 TEC Assessment did not identify any RCTs evaluating electromagnetic pelvic floor stimulation for treating adults with incontinence. One RCT was identified in literature updates. In 2004, Yokoyama and colleagues reported findings from a 3-arm randomized trial from Japan conducted in men with post-prostatectomy urinary incontinence. A total of 36 men (12 in each group) were randomized to receive extracorporeal magnetic pelvic floor stimulation (Neocontrol® chair), functional electrical stimulation, or pelvic floor exercises The primary outcome was pad weight testing for up to 6 months after the 1-month treatment period. At 1 month after catheter removal, pad weight was significantly lower in the electrical stimulation group than the control group; at 2 months, pad weight was significantly lower in the magnetic stimulation group compared to the control group; and, beginning at 3 months, there were no significant differences in pad weight. There were no significant differences between groups in quality-of-life measures at any follow-up point.

Practice Guidelines and Position Statements

The 2006 NICE guideline on the management of urinary incontinence in women stated that "perineometry or pelvic floor electromyography as biofeedback should not be used as a routine part of pelvic floor muscle training," but that "electrical stimulation and/or biofeedback should be considered in women who cannot actively contract pelvic floor muscles in order to aid motivation and adherence to therapy." This conclusion regarding use of electrostimulation is based on expert opinion.

In December 2007, the National Institutes of Health (NIH) convened a Consensus Development Conference, Prevention of Fecal and Urinary Incontinence and subsequently released a statement. Included in this statement was the following regarding pelvic floor muscle training and magnetic or electrical stimulation: "Inconsistent low-level evidence from twelve randomized controlled trials did not show that magnetic or electrical stimulation cured or improved urinary incontinence in women better than did sham stimulation or pelvic floor muscle training."

In 2012, the European Association of Urology (EAU) published clinical guidelines on the management of urinary incontinence (Thet al., 2012). The guidelines do not recommend treatment or urinary incontinence with electrical stimulation using surface electrodes alone, and do not recommend treatment with magnetic stimulation.

Summary

In conclusion, findings from multiple RCTs have not found that electrical pelvic floor stimulation used to treat urinary incontinence in women consistently improved net health outcomes compared to placebo or other conservative treatments. Moreover, there is insufficient evidence on the efficacy of electrical pelvic floor stimulation in the treatment of post-prostatectomy incontinence in men, and on the efficacy of magnetic pelvic floor stimulation for treating stress, urge or mixed urinary incontinence in men or women. Thus, pelvic floor stimulation as a treatment of urinary incontinence is considered investigational.

Posterior Tibial Nerve Stimulation

Posterior tibial nerve stimulation (PTNS) is a technique of electrical neuromodulation used for treating urinary incontinence or voiding dysfunction. While the posterior tibial nerve is located near the ankle, it is derived from the lumbar-sacral nerves (L4-S3), which control the bladder detrusor and perineal floor. The procedure for PTNS consists of the insertion of a needle above the medial malleolus into the posterior tibial nerve followed by the application of low-voltage (10 milliamps [mA], 1 to 10 hertz [Hz] frequency) electrical stimulation that produces sensory and motor responses (i.e., a tickling sensation and plantar flexion or fanning of all toes). Non-invasive PTNS has also been delivered with surface electrodes. Altering the function of the posterior tibial nerve with PTNS is believed to improve voiding function and control. The recommended course of treatment is an initial series of 12 weekly 30 minute office-based sessions followed by an individualized maintenance treatment schedule.

Posterior tibial nerve stimulation is less invasive than traditional sacral nerve neuromodulation (see Blue Shield Medical Policy: Sacral Nerve Neuromodulation/Stimulation), which has been successfully used in the treatment of urinary dysfunction but requires implantation of a permanent device. In sacral root neuromodulation, an implantable pulse generator that delivers

controlled electrical impulses is attached to wire leads that connect to the sacral nerves, most commonly the S3 nerve root that modulates the neural pathways controlling bladder function.

In July 2005, the Urgent® PC Neuromodulation System (Uroplasty, Inc., Minnetonka, MN) received 510(k) marketing clearance from the FDA for percutaneous tibial nerve stimulation to treat patients suffering from urinary urgency, urinary frequency, and urge incontinence. The device was cleared as a class II nonimplanted, peripheral nerve stimulator for pelvic floor dysfunction" because it was considered to be substantially equivalent to the previously cleared percutaneous Stoller afferent nerve system (PerQ SANS System) in 2001 (K992069, UroSurge, Inc.).

Overactive Bladder

Randomized Controlled Trials

Two key RCTs that evaluated PTNS for treating patients diagnosed with OAB syndrome have been published. In 2009, Peters and colleagues published an industry-sponsored non-blinded comparison of PTNS and extended-release tolterodine (Detrol LA) in women with OAB syndrome (the OrBIT trial). The study included 100 patients (50 per group); more than 90% were women. Study participants were identified at 11 centers between June 2006 and September 2008. Subjects had to have symptoms of OAB, with at least eight voids per 24 hours; the mean daily voids for those entering the study were 12.3. A total of 87 of the 100 (87%) patients completed the study and voiding diary data were available for 84 patients, 41 of 50 (82%) in the PTNS group and 43 of 50 (86%) in the tolterodine group.

The primary outcome was the non-inferiority of PTNS in the mean reduction in the number of voids per 24 hours after 12 weeks of treatment. Non-inferiority was defined as no more than a 20% difference in the mean void reduction. Study findings showed non-inferiority of PTNS based on results for 84 patients. The decrease in number and standard deviation (SD) of voids per day was 2.4 (4.0) in the PTNS group and 2.5 (3.9) in the tolterodine group.

The study also reported a number of secondary outcomes, and findings on these were mixed. There were no statistically significant differences in the PTNS and tolterodine groups for other symptoms recorded in the voiding diary; this includes mean change in episodes of nocturia (-0.7 and -0.6, respectively), episodes of moderate to severe urgency per day (-2.2 and -2.9, respectively), and episodes of urge incontinence per day (-1.0 and -1.7, respectively). In other secondary outcomes, 35 of 44 patients (79.5%) in the PTNS group and 23 of 42 (54.8%) in the tolterodine group reported symptom improvement or cure. This difference was statistically significant (p=0.01), favoring the PTNS group. However, the proportion of patients reporting symptom improvement (excluding the 3 patients reporting that they were cured) did not differ significantly between groups, 34 of 44 (77.3%) of those receiving PTNS and 21 of 42 (50%) receiving tolterodine. For the adverse event data, responses were obtained in person for the PTNS group in conjunction with their weekly treatment sessions and over the phone for the medication group, using standard checklists. It is not clear how response to treatment or quality of life data were collected.

Limitations of the OrBIT trial included the lack of blinding of patients and providers and the lack of comparative data beyond the end of the initial 12-week treatment period. Moreover, there was

no sham or placebo group to mitigate the potential bias due to subjective outcomes. In addition, the authors did not clearly define criteria for “improvement” or “cure”, a key secondary outcome, and did not report the extent of compliance with medical therapy and used different methods of data collection in the two groups for adverse event outcomes and possibly also for other self-report outcomes.

In 2010, MacDiarmid and colleagues reported 1-year follow-up data for patients from the OrBIT trial that had been assigned to the PTNS group and had responded to the initial course of treatment, defined as reporting symptom improvement at 12 weeks. Thirty-three of the 35 responders were included. They received a mean of 12.1 (SD=4.9) additional treatments between the 12-week and 12-month visits, and there was a median of 17 days between treatments. Data were available for 32 of the 33 (97%) participants at 6 months and 25 of the 33 (76%) participants at 12 months. The mean reduction in number of voids per day from baseline (the original primary outcome of the study) was 3.2 (SD=3.7) at 6 months and 2.8 (SD=3.7) at 12 months. Other voiding diary outcomes at 12 months, based on 25 responses, were mean changes in nocturia episodes of -0.8, in episodes of moderate to severe urgency per day of -3.7, and in episodes of urge incontinence per day of -1.6. As noted above, this analysis was limited in that no data from the tolterodine group were available to compare long-term outcomes. Another limitation was not all patients in the PTNS group were included in the follow-up analysis, only PTNS responders were eligible. A potential bias is that the initial subjective outcome measure may be subject to the placebo effect. Moreover, patients in the PTNS group who responded to initial treatment may be particularly susceptible to a placebo response and/or may represent those with the best treatment response. Thus, these individuals may also be susceptible to a placebo response during maintenance treatments, especially treatments offered on an as-needed basis. It is important that long-term response data from RCTs reflect the patient population at the beginning of the study.

The second key RCT on OAB syndrome, also industry-sponsored, was published by Peters and colleagues in 2010. This study, known as the SUmiT trial, had a sham-comparison group. Prior to conducting the trial, the researchers performed a pilot study in healthy volunteers to determine the adequacy of a sham PTNS intervention (Peters et al., 2009). Findings were that 10 of 30 volunteers (33%) correctly identified the sham procedure. This percentage is below the 50% that could be expected by chance; the investigators concluded that the procedure was a feasible sham. The SUmiT trial included patients with OAB syndrome. Eligibility criteria included a score of at least 4 on the OAB questionnaire (OAB-q) short form for urgency, self-report bladder symptoms lasting at least 3 months, and having failed conservative care. Data were collected from 23 centers in the United States. A total of 220 patients were randomly assigned, 110 to the PTNS group and 110 to the sham group. Both groups received 12 weekly 30-minute intervention sessions. In the sham group, a blunt (placebo) instrument was used to simulate the location and sensation of needle electrode insertion in active treatment. An inactive PTNS surface electrode was used and also two active transcutaneous electrical nerve stimulation (TENS) surface electrodes. The TENS unit was used to deliver low-level sensation to simulate the PTNS intervention. The 12-week course of treatment was completed by 103 of 110 (94%) in the PTNS group and 105 of 110 (95%) in the sham group.

The primary study outcome was response to treatment based on a single-item global response assessment (GRA) variable at 13 weeks. Possible responses were that symptoms were markedly worse, moderately worse, mildly worse, the same, slightly improved, moderately improved, or markedly improved. The proportion of patients who responded to treatment based on the GRA (i.e., answered that symptoms were moderately or markedly improved) was 60 of 110 (54.5%) in the PTNS group and 23 of 110 (20.9%) in the sham group; this difference was statistically significant, p less than 0.001. Intention-to-treat analysis was used for the primary endpoint only. Several secondary outcomes also favored the PTNS group. The mean reduction in a symptom severity score (a lower score indicates less severity) was 36.7 (SD=21.5) in the PTNS group and 29.2 (SD=20.0) in the sham group, p=0.01. Similarly, the mean reduction in a quality of life scale, the SF-36 (a higher score indicates higher quality of life), was 34.2 (SD=21.3) in the PTNS group and 20.6 (SD=20.6) in the sham group, p=0.006.

For the four voiding diary variables used, there was a statistically significant difference between groups favoring PTNS. The mean change from baseline in the number of voids per day was -2.4 (SD=2.5) in the PTNS group and -1.5 (SD=2.4) in the sham group (difference between groups 0.9 voids per day, p=0.01). The mean change in nocturia episodes was -0.7 (SD=1.2) in the PTNS group and -0.3 (SD=1.4) in the sham group (difference between groups 0.4 nighttime voids, p=0.04). The mean change in moderate to severe urgency per day was -3.7 in the PTNS group and -2.0 in the sham group (difference between groups 1.7 episodes, p<0.001). Finally, the mean change in urge incontinence episodes was -1.3 in the PTNS group and -0.3 in the sham group (difference between groups was one episode per day, p<0.002). (Standard deviations were not reported for the latter two outcomes).

Advantages of the SUmiT trial were that it included a sham comparison and the primary endpoint analysis was ITT. A limitation was that the primary outcome, the GRA, was a single-item subjective measure. For the more objective measures, the voiding diary variables, there was statistically significantly greater benefit with PTNS compared to sham treatment; however, the clinical significance of the difference between the PTNS and sham groups was unclear (e.g., on average, there was one fewer episode of urge incontinence a day in the PTNS group). In addition, as in the OrBIT trial, the SUmiT trial only reported comparative data immediately following the initial course of treatment; the study did not evaluate the long-term effectiveness of PTNS. Unlike medication which can be taken on an ongoing basis, PTNS involves an initial 12-week course of treatment followed by maintenance therapy, which to date has not been well-defined. Therefore, the assumption cannot be made that short-term treatment effects will be maintained.

As with the ORBIT trial, there was a SUMIT extension study including only those patients who had been assigned to the PTNS group and initially responded to treatment. That is, the extension study did not collect additional follow-up data from patients in the PTNS group who failed to meet the 12-week primary effectiveness endpoint or from patients assigned to the sham-control group. Among the 110 patients assigned to the PTNS group, 60 were initial responders and 50 of these entered the extension study (Peters et al., 2012; Peters et al., 2013). Data were available on 34 patients at 24 months and 29 patients at 36 months. After enrolling in the extension study, patients underwent a 14-week transitional protocol consisting of two treatments with a 14-day interval, two treatments with a 21-day interval and then one treatment after another 28 days.

Following this 14-week period, a personal treatment plan was developed for each patient. The PTNS treatments were delivered based on the patient's reporting of symptoms; patients knew that PTNS sessions were available to them as needed when their symptoms increased. Between 6 and 36 months, patients received a median of 1.1 PTNS treatments per month. In a per protocol analysis, compared to baseline, 28 of 29 patients (97%) who completed the 36-month follow-up met the primary efficacy endpoint of moderate or marked improvement in overall bladder symptoms on the GRA. In addition, compared to baseline, all voiding diary measures were significantly improved in this group of patients at every 6-month follow-up. As mentioned previously in the discussion of the ORBIT extension study, the SUMIT extension study was limited by a lack of follow-up data on the control group and a lack of follow-up data on all participants in the treatment group. This design cannot rule out biases such as a placebo effect and/or that these responders represent the best response rather than the mean response.

Several other RCTs have been published; none reported on the efficacy of PTNS beyond 12 weeks. Three trials used a parallel group design. In 2010, Finazzi-Agro and colleagues from Italy was a double-blind RCT that included 35 female patients who had urge incontinence and detrusor overactivity on urodynamic testing. Patients were randomly assigned to 30-minute PTNS sessions three times per week for 4 weeks (n=18) or sham treatment (n=17). One patient dropped out of the PTNS group and two patients dropped out of the sham group; analysis was not ITT. The primary outcome, percent responders at 4 weeks (defined as at least 50% reduction in incontinent episodes) was attained by 12/17 (71%) in the PTNS group and 0/15 (0%) in the sham group. Also in 2010, Schreiner and colleagues in Brazil randomized 51 women older than 60 years who complained of urge urinary incontinence to 12 weeks of conservative treatment (Kegel exercises and bladder training) alone (n=26) or conservative treatment plus 12 weekly sessions of PTNS (n=25). The response rate at 12 weeks, defined as a reduction of at least 50% in the number of incontinence episodes reported by the patient in a bladder diary, was 76% in the PTNS group and 27% in the conservative treatment only group; p=0.001. Blinding was not discussed.

In 2012, Gungor Ugurlucan and colleagues in Turkey published findings of an RCT comparing transvaginal electrical stimulation (ES) (n=38) and PTNS (n=21) in women with OAB. The ES protocol consisted of 20-minute treatments three times a week for 6 to 8 weeks. Percutaneous tibial nerve stimulation was performed with an Urgent PC device used for twelve 30-minute weekly sessions. A total of 52 of 59 (88%) patients completed the study. The authors assessed numerous outcome variables and did not specify primary outcomes or adjust p values for multiple comparisons. Four bladder diary variables were reported. From baseline to the end of the treatment period, the groups did not differ significantly at the $p<0.05$ level in mean change in urgency episodes, nocturia or incontinence episodes. For example, the mean number of urgency episodes was 2.9 (SD: 4.1) at baseline and 1.6 (SD: 0.5) after treatment in the ES group and 2.0 (SD: 3.1) at baseline and 1.3 (SD: 0.5) after treatment in the PTNS group, p=0.54. There was a statistically significant difference in daytime frequency. The mean daytime frequency was 7.8 (SD: 2.7) at baseline and 5.8 (SD: 1.9) after treatment in the ES group and 7.6 (SD: 2.6) at baseline and 7.4 (SD: 2.9) in the PTNS group (p=0.03). The authors reported that a significantly higher proportion of patients in the ES group described themselves as cured, but they did not provide proportions or p values.

One randomized trial, published in 2013, used a crossover design. This study, by Vecchioli-Scaldazza and colleagues in Italy, included 40 women with OAB. The treatments were PTNS (twice weekly for 6 weeks) and medication (oral solifenacin succinate 5 mg/day for 40 days), given in random order, with a 6-week wash-out period between treatments. Group A received medication first and Group B received PTNS first. The primary efficacy outcome was reduction in the number of voids in a 24-hour period. Thirty of the 40 patients (75%) completed the study. The number of daily voids significantly decreased after each treatment compared to before treatment. In Group A, the mean number of daily voids pre-medication was 11.6 (SD: 1.6) and post-medication was 10.0 (SD: 2.1), $p=0.004$. The mean number of voids pre-PTNS was 11.5 (SD: 1.1) and post-PTNS was 8.5 (SD: 2.3), $p<0.001$. In Group B, the mean number of voids pre-medication was 11.4 (SD: 1.4) and post-medication was 10.4 (SD: 1.8), $p=0.008$. The mean number of voids pre-PTNS was 11.4 (SD: 1.4) and post-PTNS was 9.4 (SD: 1.9), $p<0.001$. In addition, secondary outcomes including nocturia urge incontinence and voided volume significantly improved after each treatment compared to pre-treatment values. The authors did not directly compare the efficacy of medication and PTNS.

Systematic Reviews

A review by Hayes Inc. (2008) evaluated the peer-reviewed scientific evidence from 1966 through 2008 (15 studies) on the use of PTNS for patients (including women and children) with OAB, urinary frequency syndrome, urinary incontinence, non-obstructive urinary retention, and/or pelvic floor pain. The authors advised there was some evidence from uncontrolled studies indicating that PTNS may be a safe and effective treatment for adult patients with urinary frequency, urgency, and urge incontinence. Additionally, the treatment was easily appliable and minimally invasive, without significant side effects. However, due to limitations of the studies including the lack of sham or alternative treatment modalities, and small sample size; the level of evidence was weak. Further, there were unresolved issues regarding the percentage of patients that would benefit from PTNS and the rate at which maintenance treatment should be provided. Subsequent annual reviews of the literature by Hayes, including 2012, did not result in any change to the conclusions of the 2008 report.

A Blue Cross Blue Shield TEC Assessment on PTNS for treatment of voiding dysfunction was completed in December 2010. At that time, initial findings from the OrBIT and SUmiT trials had been published, as well as 1-year findings on ORBIT responders. The Assessment concluded that PTNS as treatment for voiding dysfunction does not meet the TEC criteria due to insufficient data on durability of treatment. The Assessment stated that, although there is sufficient evidence from three RCTs to establish a short-term benefit for PTNS, the evidence is not sufficient to permit conclusions on the long-term efficacy of PTNS treatment.

In 2012, Monga and colleagues performed a systematic review regarding the evidence for a variety of electrical stimulation therapies for the treatment of urinary tract symptoms. Sixteen of the studies evaluated PTNS including 13 prospective case series, and 3 randomized comparative studies. The authors reported that median mean reductions in incontinence episodes and voiding frequency were similar for implanted sacral nerve stimulation and PTNS. However, the authors advised that additional long-term follow up studies were required to validate the ability of PTNS to produce a sustained effect (Monga et al., 2012)

In 2012, three systematic reviews of the literature on PTNS for treating OAB were published (Burton et al., 2012; Levin et al., 2012; Moossdorff-Steinhaurser & Berghmans, 2013). Only one of the three systematic reviews, by Burton and colleagues (2012), conducted pooled analyses of study results. The Burton review identified six RCTs, the ORBIT and SUMIT trials (Peters et al., 2009; Peters et al., 2010) and trial by Finazzi-Agro and colleagues (2010), all discussed above, as well as three RCTs only published as abstracts with sample sizes between 16 and 32 patients. A meta-analysis of data from four trials (two of which were abstracts) comparing PTNS to sham treatment found a significantly higher risk of successful treatment with PTNS (RR: 7.02, 95% CI: 1.69 to 29.17). The CI was wide, indicating a lack of precision in the pooled estimate. The SUMIT trial contributed 220 of 289 patients (76%) in the pooled analysis.

An editorial comment by Wein (2013) of the systematic reviews discussed above by Burton et al. (2012) and Levin et al. (2012) noted that after the initial 10 to 12 weeks of treatment, “success” (no consistent definition) rates of 37% to 93% were described. However, both studies cited or implied the need for the following:

- Long-term success studies (certainly over the initial treatment course, preferably over 12 months);
- A more specific characterization of the influence of simultaneous behavioral and lifestyle modifications;
- A calculation of cost-effectiveness; and
- More definitive statements as to the requirement for ongoing therapy, both type and frequency.

Also in 2012, the AHRQ Effective Health Care Program published a comparative effectiveness review on the broader topic of nonsurgical treatments for urinary incontinence in adult women (Shamliyan et al., 2012). The review identified four reports of RCTs comparing PTNS and no active treatment in patients with OAB. Two of the four articles reported 12-week results of the sham-controlled SUMIT trial; one of these included a subgroup of SUmiT participants and was only published as an abstract. The other two studies consisted of the Finazzo-Agro et al. RCT, (2010) which reported outcomes at 4 weeks and the Schriner and et al. RCT, (2010) which reported outcomes at 12 weeks. The AHRQ report included a pooled analysis of data from three studies that found statistically significantly greater improvement in urinary incontinence in the PTNS compared to control group (RR: 1.9, 95% CI: 1.1 to 3.2). This pooled analysis included a total of 405 patients; 220 in the SUMIT trial, 150 in the SUMIT trial sub-analysis and 35 in the Finazzo-Agro trial. A limit of the analysis was that the 150 patients in the SUMIT sub-analysis were included twice. The AHRQ report did not discuss evidence on the efficacy of PTNS beyond 12 weeks.

Case Series

Initial research has also been published on a shortened treatment protocol (weekly 30-minute sessions for 6 weeks) using the Urgent PC device. A study by Yoong and colleagues in the U.K. included 43 women with OAB refractory to medication (Yoong et al., 2010). Thirty women (68%) responded to the initial course of treatment. Response was defined as a 50% reduction in symptoms and 25% improvement in quality of life. Two-year follow-up data on 23 of 30 (67.5%) responders were reported in 2012. Additional PTNS sessions were available to women

on an as-needed basis. Women received a median of 8.4 treatments per year with a median of 64 days between treatments. Among the 23 women, the mean daily frequency was 11.8 at baseline, 6.9 at 6 weeks and 6.5 at 2 years ($p<0.05$ compared to baseline at both time points). Findings were similar for other outcome measures. This analysis lacks a control group. The shortened protocol has not yet been evaluated in a randomized trial.

Neurogenic Bladder

In 2011, two case series evaluating PTNS in patients with multiple sclerosis (MS) were published. One study, by Gobbi and colleagues (2011) in the United Kingdom included twelve 30-minute treatment sessions with the Urgent PC device. The study included 21 patients with MS who had lower urinary tract symptoms unresponsive to anticholinergics. Overall, urinary symptoms significantly improved at the end of treatment. For example, median daytime frequency decreased from nine to six episodes per day, $p=0.04$ and median nocturia decreased from three to one episode per night, $p=0.002$. The other case series was conducted in France by de Seze and colleagues (2011) and used a different protocol. Participants underwent 1 in-clinic treatment session and were then given a TENS device for in-home tibial nerve stimulation; they were told to use the device 20 minutes a day for 3 months. A total of 70 individuals with MS and OAB refractory to medication participated in the study. Compared to baseline, there was a statistically significant reduction in OAB symptoms. For example, the proportion of continent patients increased from 26% to 45% ($p=0.005$). Both studies were limited by lack of control groups and lack of long-term follow-up; the French study used a different device and different protocol than in the other PTNS studies.

Practice Guidelines and Position Statements

The 2005 (reaffirmed 2009) American College of Obstetricians and Gynecologists practice bulletin on treatment of urinary incontinence in women does not address PTNS or other types of nerve stimulation.

In 2012, the American Urological Association (AUA) and the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (Gormley et al., 2012) published a guideline on diagnosis and treatment of non-neurogenic OAB in adults. The guideline included a statement that clinicians may offer PTNS as a third-line treatment option in carefully selected patients. The statement was rated as Grade C, indicating that the balance of benefits and risks/burdens are uncertain.

Summary

In conclusion, PTNS is a technique of electrical neuromodulation used for treating voiding dysfunction. All of the available RCTs are small and short in duration, and have other methodologic weaknesses. The RCTs report short-term (up to 12 weeks) improvements on measures of urinary incontinence, but the long-term effectiveness and the optimal maintenance regimen are poorly defined. Up to 36 months of data are available for some patients enrolled in RCTs who responded to an initial course of treatment. These patients are highly selected and a placebo response to the original and additional treatments cannot be ruled out. Long-term data are needed that reflect the patient population in an RCT that was initially randomized to the treatment and control groups. Systematic reviews of the evidence have found short-term

improvements with PTNS and have not identified evidence of long-term effectiveness. Until the durability of PTNS has been demonstrated in well-designed long-term comparative studies and its clinical impact more clearly shown, its efficacy for treating chronic urinary dysfunction remains uncertain. Thus, PTNS for treating voiding dysfunction (urinary incontinence) is considered investigational**.**

Pudendal Nerve Stimulation for Urinary Incontinence (e.g., BION® device)

Another electrical neuromodulation approach recently reported for the treatment of urinary incontinence is the implantation of the BION® device (Advanced Bionics Corp., Valencia, CA) . This rechargeable device is a self-contained, battery-powered, telemetrically programmable, current-controlled mini-neurostimulator with an integrated electrode. It is 27 x 3.3 mm and can be implanted adjacent to the pudendal nerve. Subjects qualify for implantation after a positive percutaneous screening test (PST). A PST is considered positive if stimulation results in an increase of more than half in the bladder volume at the first involuntary detrusor contraction or the maximum cystometric capacity. After a successful PST the Bion can be implanted at its target location, adjacent to the pudendal nerve at Alcock's canal; it is implanted with a specially developed tool kit (Bosch, 2006).

The results obtained with the BION device in a pilot study of female patients with refractory

detrusor overactivity incontinence were reported by Groen and colleagues in 2005. Five of six patients had failed sacral nerve neuromodulation. Six of 14 patients responded to the PST and received an implant. After 6 months of follow-up the mean number of incontinence episodes decreased from 6.2 to 2.4 per day (Groen et al., 2005). The authors concluded that pudendal nerve neuromodulation may reduce the degree of detrusor over-activity incontinence, even in patients in whom sacral neuromodulation fails. Clinical trials of the Bion device involving more patients are underway.

Spinelli et al. (2005) stated pudendal nerve stimulation had beneficial effects on numerous pelvic floor function impairments including urinary and/or fecal incontinence, retention, and constipation. The researchers performed a staged procedure similar to that of sacral neuromodulation to place tined lead near the pudendal nerve, using neurophysiological guidance that allowed accurate pudendal nerve stimulation through either perineal or posterior approach. The researchers named this approach, chronic pudendal nerve neuromodulation (CPNN). A total of 15 neurogenic patients (8 males, 7 females) with symptoms of urge urinary incontinence due to neurogenic over-active bladder underwent CPNN. All patients had complete neurophysiological and urodynamic evaluation at baseline and follow-up and were asked to complete voiding and bowel diary for 7 days. During screening, average number of incontinent episodes per day decreased from 7 (+/- 3.3) to 2.6 (+/- 3.3) ($p < 0.02$, paired t-test). Eight patients became continent, two improved by more than 88 % (from nine to once daily incontinence episodes) and two patients reduced the number of incontinence episodes by 50 %. The implantable pulse generator (IPG) was subsequently implanted in those 12 patients. Three patients without improvement did not continue to second stage. In implanted patients with 6 months follow-up, urodynamic evaluation showed an objective improvement in the maximum cystometric capacity which increased from 153.3 (+/- 49.9) to 331.4 (+/- 110.7 ml) ($p < 0.01$, paired t-test). The maximum pressure decreased from 66 (+/- 24.3) to 36.8 (+/- 35.9 cm H2O) (p

= 0.059, paired t-test). Eight patients reported significant improvement in bowel function. The authors concluded that CPNN is feasible and neurophysiological guidance was mandatory to place the lead near the pudendal nerve either using perineal or posterior approach. However, the researchers advised that further studies must be carried out to identify the best stimulation parameters and to verify the long-term results.

Seif and colleagues (2005) investigated the BION microstimulation system as an alternative therapeutic option for patients with anti-cholinergic resistant OAB in two patients. After the BION(R)-implantation, patient 1 showed a reduction in incontinence episodes by 31.5 % a day and patient 2 had lowered voiding frequencies from 12.6 to 7 a day. The postoperative urodynamic investigations confirmed these clinical results. The authors concluded that the BION-system and CPNN “seem to be alternatives to sacral neuromodulation, however, patient selection is difficult as subchronic stimulation for a longer period of time is not possible so far.”

A randomized clinical trial regarding the battery-powered BION device for the chronic treatment of refractory urinary urge incontinence sponsored by Boston Scientific Corporation that was projected for completion in 2012, however it currently ongoing as of June of 2013.

While studies involving pudendal serve stimulation suggest an increase in efficacy over sacral neuromodulation; long-term studies are not yet available (Bosch, 2006). At this time, the evidence regarding pudendal nerve stimulation (BION device) for the treatment of urinary incontinence is insufficient to determine its clinical utility and effect on long-term health outcomes.

Transvaginal Radiofrequency Micro-Remodeling

In 2002, the SURx® Transvaginal System (Surx Inc., Livermore, CA) received marketing clearance through the FDA 510(k) process. According to the FDA, the device "is indicated for shrinkage and stabilization of female pelvic tissue for treatment of Type II stress urinary incontinence due to hypermobility in women not eligible for major corrective surgery." Use of the SURx Transvaginal System involves making an incision through the vagina lateral to the urethra, exposing the endopelvic fascia. Radiofrequency energy is then applied over the endopelvic fascia in a slow sweeping manner, resulting in blanching and shrinkage of the tissue. As of 2006, the SURx is no longer marketed in the United States.

Dmochowski and colleagues (2003) reported on a multi-institutional prospective case series of 120 consecutive women with urinary stress incontinence that underwent transvaginal radiofrequency bladder neck suspension. Enrolled patients had failed at least a 3-month trial of conservative therapy, including most commonly, pelvic floor muscle exercises or pelvic floor stimulation. Follow-up examinations at 1, 3, 6, and 12 months consisted of a history, physical examination, and urodynamic studies. In addition, each patient completed a voiding diary and quality-of-life questionnaire. A cure was defined as a negative Valsalva maneuver; improvement was defined as decreased daily episodes of pad use. A total of 73% of patients were considered cured or improved at 12 months. More than 68% of patients reported satisfaction with the treatment. The authors concluded that the results were encouraging and that a 73% 12-month success rate suggested that this procedure had applicability for women with refractory incontinence who did not wish to undergo a more complicated surgical procedure. Ross and colleagues (2002) conducted a multicenter, prospective single-arm study that included 94 women

with stress incontinence. At 1 year, the objective cure rate was 79%, based on a negative leak point pressure. Assessment of quality of life was also significantly improved. Larger controlled studies with longer follow-up were needed to further evaluate this procedure. As noted in a review of laparoscopic bladder neck suspension, initial promising results at 12 months declined to a 30% success rate at 45 months (McDougall et al., 1999). These authors suggested that any new surgical technique for the treatment of stress incontinence should have more than 2 years of follow-up.

In 2007, Buchsbaum and colleagues published a retrospective follow-up of the transvaginal RF procedure in 18 patients, 11 with genuine stress urinary incontinence and 7 with mixed incontinence. At an unspecified time greater than 3 months following treatment, 6 of the 18 patients reported no urine loss and were satisfied with the outcome, 2 patients were lost to follow-up, and 10 reported continuing symptoms of incontinence. The relation between diagnosis (i.e., genuine stress-induced or mixed incontinence) and outcome was not presented.

In 2008, CTAF completed a review of radiofrequency remodeling for the treatment of female stress urinary incontinence. The authors found, “radiofrequency micro-remodeling using the SURx system has not been directly compared to either a sham procedure or a gold-standard surgical approach to SUI, nor has it been studied in an RCT.” In conclusion, the evidence for SURx did not meet the CTAF criteria.

The ACOG recommendations on treating urinary incontinence in women (reaffirmed in 2009) do not mention transvaginal radiofrequency remodeling.

In conclusion, the evidence is insufficient to support efficacy of transvaginal radiofrequency micro-remodeling (e.g., SURx) for the treatment of female stress urinary incontinence because well-designed, large-population, randomized, controlled clinical trials are lacking.

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program (FEP)) prohibit Plans from denying Food and Drug Administration (FDA) - approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

Type	Number	Description
CPT	51715	Endoscopic injection of implant material into the submucosal tissues of the urethra and/or bladder neck
	53860	Transurethral radiofrequency micro-remodeling of the female bladder neck and proximal urethra for stress urinary incontinence
	64566	Posterior tibial neurostimulation, percutaneous needle electrode, single treatment, includes programming
	90901	Biofeedback training by any modality
	90911	Biofeedback training, perineal muscles, anorectal or urethral sphincter, including EMG and/or manometry
	97014	Application of a modality to 1 or more areas; electrical stimulation (unattended)
	97032	Application of a modality to 1 or more areas; electrical stimulation (manual), each 15 minutes
	97810	Acupuncture, 1 or more needles; without electrical stimulation, initial 15 minutes of personal one-on-one contact with the patient
	97811	Acupuncture, 1 or more needles; without electrical stimulation, each additional 15 minutes of personal one-on-one contact with the patient, with re-insertion of needle(s) (List separately in addition to code for primary procedure)
	97813	Acupuncture, 1 or more needles; with electrical stimulation, initial 15 minutes of personal one-on-one contact with the patient
	97814	Acupuncture, 1 or more needles; with electrical stimulation, each additional 15 minutes of personal one-on-one contact with the patient, with re-insertion of needle(s) (List separately in addition to code for primary procedure)
HCPC	E0740	Incontinence treatment system, pelvic floor stimulator, monitor, sensor and/or trainer
	E0745	Neuromuscular stimulator, electronic shock unit
	E0746	Electromyography (emg), biofeedback device
ICD9 Procedure	None	

Type	Number	Description
ICD9 Diagnosis	All Diagnoses	
Place of Service	Hospital Outpatient/Surgicenter Nursing Home/Convalescent Home Patient's Home Skilled Nursing Facility (SNF) / Extended Care Facility	

Tables

N/A

Definitions

Detrusor instability - A bladder that contracts and empties out urine even though it is not full, or when the person does not intend to urinate.

Intrinsic sphincter deficiency (ISD) - A poor or non-functioning urethral outlet muscle.

Neuromodulation - The electrical stimulation of a nerve.

Overactive Bladder (OAB) - Describes patients with frequency or urgency with or without urge incontinence. This type of voiding dysfunction occurs when abnormal nerves send signals to the bladder at the wrong time, and causes the bladder muscles to contract without warning.

Periurethral - An area around the urethra, which is the natural channel or tube through which urine passes from the bladder to outside the body.

Sacral nerve stimulation - A permanent implantable device that stimulates the neural pathways controlling bladder function.

Urinary incontinence - The involuntary loss of urine. More than one type may be present at any given time. Types of urinary incontinence include:

- **Stress incontinence -** The most common type of urinary incontinence diagnosed in women. It is associated with a lack of anatomical support (e.g., hypermobility) of the urethra in women, or a deficiency of the intrinsic urethral closure mechanism in either sex. It occurs with activities that cause an increase in intra-abdominal pressure (e.g. sneezing, coughing, and lifting).
- **Urge incontinence -** Also known as spastic bladder, overactive bladder or reflex incontinence. The uncontrolled loss of urine that is preceded by a strong, unexpected urge to void. It is unrelated to position or activity. Urge incontinence is generally due to detrusor over activity.

- **Overflow incontinence -** The result of obstruction or weakened bladder muscles causing over-distention of the bladder. May lead to incomplete emptying of the bladder and the dribbling of urine.
- **Mixed incontinence -** A result of a combination urinary incontinence types, most commonly, stress and urge incontinence.
- Functional incontinence - Occurs when a person recognizes the need to urinate, but cannot physically make it to the bathroom in time due to limitations in moving, thinking or communicating. This is the most common type of incontinence among elderly patients.

Urinary Incontinence Severity Grades - Classification grading system of symptoms.

- **Grade 0 -** Continent
- **Grade I -** Patient loses urine with sudden increase in prone position but not in supine
- **Grade II -** Patient loses urine with physical stress (walking; changing from a reclining to a standing position; sitting up in bed)
- **Grade III -** Patient with total incontinence; urine loss unrelated to physical activity and/or position

Urinary retention - The inability to completely empty the bladder of urine.

Urinary urgency-frequency - An uncontrollable urge to urinate resulting in very frequent, small volumes.

Index / Cross Reference of Related BSC Medical Policies

The following Medical Policies share diagnoses and/or are equivalent BSC Medical Policies:

- Sacral Nerve Neuromodulation/Stimulation
- Electrical Stimulation for Pain and Other Conditions
- Neuromuscular, Functional, and Threshold Electrical Stimulation
- OnabotulinumtoxinA, (Botox®) (Pharmacy/Medication Policy)

Key / Related Searchable Words

- ACT
- Acupuncture
- Adjustable continence therapy
- Athena pelvic muscle trainer
- Biofeedback
- Biomagnetic therapy
- Botox
- Coaptite
- Contigen
- Deflux

- Durasphere
- Extracorporeal electromagnetic stimulation
- Injectable bulking agents
- Lyrette system
- Pelvic floor stimulation
- Pelvic muscle trainer devices
- Electrical pelvic floor stimulation
- Gyneflex
- Kegelmaster
- Macroplastique
- Periurethral bulking agents
- PMFT
- Posterior tibial nerve stimulation
- PTNS
- Renessa system
- Stress incontinence
- SUI
- SURx
- Teflon
- Transvaginal radiofrequency bladder neck suspension
- Transurethral radiofrequency energy collagen
- UI
- Urge incontinence
- Urgent PC neuromodulation system
- Urinary incontinence

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Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
1/11/2008	New Policy Adoption of BCBSA MPP 7.01.106. Content enhanced by merging BSC policies Urinary Incontinence Treatment and Endoscopic Injections for Urinary Incontinence, Codes updated. Policy title change. Prior policy title Urinary Incontinence Treatment.	Medical Policy Committee
3/1/2009	Coding Update	Administrative Review
4/2/2010	Policy Revision with position change	Medical Policy Committee
4/14/2010	Coding Update	Administrative Review
10/29/2010	Coding Update	Administrative Review

Effective Date	Action	Reason
1/21/2011	Coding Update	Administrative Review
1/12/2012	Coding Update	Administrative Review
7/3/2013	Policy revision with position change	Medical Policy Committee

The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.

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