Medical Coverage Policy

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Coverage Policy Number **0403**

Male Sexual Dysfunction Treatment: Non-pharmacologic

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Related Coverage Resources

Collagenase clostridium histolyticum
Sildenafil (Viagra®)
Vardenafil
Avanafil

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This Coverage Policy addresses devices and procedures used in the treatment of erectile dysfunction.

Coverage Policy

Coverage for male sexual dysfunction varies across plans. Refer to the customer's benefit plan document for coverage details.

If coverage is available for the treatment of male sexual dysfunction, the following conditions of coverage apply.

Vacuum Erection Device

A vacuum erection device is considered medically necessary for the treatment of erectile dysfunction.

Penile Prosthesis

Surgical implantation of a penile prosthesis is considered medically necessary for the treatment of erectile dysfunction when ALL of the following criteria are met:

- erectile dysfunction has persisted for at least six months
- a comprehensive history and physical exam, including appropriate laboratory testing, has been completed
- there is failure, contraindication or intolerance to conservative medical management including FDA pharmacological therapy (e.g., oral PDE5 inhibitors, intracavernosal injection, intraurethral medication) and/or a vacuum erection device

Surgical reimplantation of a medically necessary penile prosthetic device, following the medically necessary removal of a penile prosthesis, is considered medically necessary when benefit coverage is available.

Removal of a penile prosthesis is considered medically necessary for ANY of the following indications:

- infection
- mechanical failure
- urinary obstruction
- intractable pain

A penile prosthesis for ANY other indication is considered not medically necessary.

Not Covered Procedures

Each of the following procedures for the treatment of erectile dysfunction is considered experimental, investigational or unproven:

- venous occlusive surgery (e.g., venous ligation)
- nerve grafting during or after a radical prostatectomy (e.g., sural nerve, genitofemoral nerve)
- extracorporeal shock wave therapy (ESWT)
- application of amniotic-derived allografts to nerve bundles during a radical prostatectomy (e.g., AmnioFix®, BioDFence® G3)

General Background

Erectile dysfunction (ED) (i.e., impotence) is defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance. ED usually has a physical cause in older men and is treatable at all ages. An age correlation exists for the prevalence of ED, however it is not an inevitable part of the aging process. Burnett and Ramasamy report the worldwide prevalence is 1%–10% for men younger than the age 40, up to 15% for men age 40–49, up to 30% for men age 50–59, up to 40% for men age 60–69, and 50%–100% for men between age 70–90. Additionally, it is estimated that in 1995, there were more than 152 million men worldwide who experienced ED. The 2025 prevalence projection was that approximately 322 million men would have ED. They report that the trend is maintained irrespective of racial/ethnic background or geographic region (Burnett and Ramasamy, 2021).

There are multiple causes of organic ED including disease processes, trauma, drug and alcohol use/abuse, as well as smoking. ED may occur as a result of an underlying medical condition, such as diabetes, kidney disease, hormonal imbalance, multiple sclerosis, atherosclerosis, vascular disease or neurological disease. Injury to the penis, spinal cord, prostate, bladder, and pelvis may also cause ED due to damage to nerves smooth muscles, arteries or fibrous tissue of the corpora cavernosa. Surgery, especially radical prostate or bladder surgery can injure the nerves and arteries near the penis resulting in ED. One of the side effects of medications, such as

antihypertensive drugs, antihistamines, antidepressants, tranquilizers, histamine-receptor antagonists for treatment of gastric ulcers, opiates, and appetite suppressants is ED. Peyronie's disease, which causes scarring of the fibrous tissue of the penis, and priapism (i.e., persistent, abnormal erection of the penis) are also associated with ED. Other possible contributing factors of ED include smoking, which affects blood flow, and hormonal abnormalities. Psychological factors (e.g., stress, anxiety, depression, and low self-esteem) cause 10–20% of ED cases (Hellstrom, 2022; McVary, 2007; Rosen, et al., 2005; Fazio, et al., 2004; Morales, 2003).

Men with symptoms of ED should have a complete medical, sexual, and psychosocial history taken along with a physical examination and selective laboratory testing. Patients should be informed that ED is a risk factor for underlying cardiovascular disease and other health conditions that may warrant further evaluation and treatment. The laboratory tests that are routinely performed as a part of an ED evaluation are serum testosterone, glucose/hemoglobin A1c, and in some cases serum lipids. No routine serum study is likely to alter ED management. However, serum studies may provide information on the etiology of ED and reveal the presence of additional conditions that require treatment. In addition, a prostate specific antigen (PSA) may be appropriate in some men with ED (American Urological Association [AUA], 2018). Vascular flow to the corpora cavernosa may be evaluated using a penile doppler examination. Color duplex ultrasonography, which measures cavernous artery diameter and pressures, may also be used to assess venous leakage. According to the American Association of Clinical Endocrinologists (AACE), "occasionally, the measurement of nocturnal penile tumescence and rigidity is useful, especially to distinguish between psychologic and organic erectile dysfunction" (AACE, 2003).

The method of treatment for ED is dependent upon the etiology of the condition. Psychologically-based ED, without organic cause (e.g., secondary to depression, anxiety, stress) may dissipate with psychotherapy and/or behavioral therapy. Organic ED can occur as a secondary condition to several diseases and/or their treatment. Treatment of underlying diseases such as diabetes mellitus, hypertension, heart disease and endocrine conditions (e.g., hypogonadism, hyperprolactinemia, and thyroid disorders), and cessation or modification of prescription medications (e.g., antihypertensives) may be indicated. Discontinuing alcohol consumption and illicit drug use, and/or making lifestyle modifications (e.g., avoiding smoking, maintaining ideal body weight and engaging in regular exercise) may reverse ED. Treatment of Peyronie's disease resulting in severe curvature may involve the concomitant use of incision/grafting and prosthesis insertion due to the significant incidence of erectile dysfunction following surgery on the penis for Peyronie's plaques (Taylor and Levine, 2007). There is some controversy regarding testosterone replacement therapy, which includes oral preparations, intramuscular injections, topical gels, and transdermal preparations. Topical gels are the most commonly prescribed forms of testosterone replacement (Brant, et al., 2007; McVary, 2007; Seftel, et al., 2004; Morales, 2003).

Treatment algorithms for erectile dysfunction (ED) involve using medical therapies such as phosphodiesterase type 5 (PDE5) inhibitors, intracavernosal injection therapy of vasoactive agents, as well as vacuum erection devices (Chung, 2019). Current practice guidelines suggest that the choice of PDE5 inhibitor should be based upon on the patient's preferences, including cost, ease of use, and adverse effects (AUA, 2018). Oral agents (e.g., PDE-5 inhibitors) are successful in 70–80% of men. With the availability of oral agents and minimally invasive options, surgical implantation typically occurs when these less invasive options are unavailable, unsuccessful or provide inadequate erective function (Chung, 2019; Brant, et al., 2007; McVary, 2007; Sadeghi-Nejad, 2007; Jain and Terry, 2006; Carson, 2005; Fazio, et al., 2004; Morales, 2003).

In addition to the surgically implanted prostheses, other procedures may be recommended for ED that is refractory to medical therapy. Vascular surgical procedures include penile arterial bypass or revascularization and venous ligation for the treatment of vasculogenic ED. For those with ED unresponsive to nonsurgical treatments, vascular surgery may be the preferred treatment option that offers the possibility of spontaneous, unaided erections. The success rates for arterial revascularization are low but reasonable success rates may be achieved in young, nonsmoking, otherwise healthy men with recently acquired ED due to a focal arterial occlusion. Techniques to improve the veno-occlusive mechanism with ligation of the dorsal, cavernous, and crural veins have been largely abandoned in favor of medical therapies (PDE-5 inhibitors) (Lazarou, 2021). Sural nerve grafting has been proposed as a surgical intervention for ED that occurs in association with radical prostatectomy. The Nesbit and Lue procedures are established for the correction of penile deformities caused by Peyronie's disease. Extracorporeal Shock Wave Therapy (ESWT) has also been proposed as a treatment for Peyronie's disease.

Vacuum Erection Device
An alternative treatment for erectile dysfunction is a vacuum erection device (VED). This device functions as an external aid; however, some users may find it difficult to use. The device causes an erection by creating a partial vacuum, drawing blood into the penis, engorging and expanding it. The device has three components: a plastic cylinder, in which the penis is placed; a pump that draws air out of the cylinder; and an elastic band that is placed around the base of the penis to maintain the erection when the cylinder is removed.

Penile Prosthesis
When nonsurgical therapies have proven ineffective, a penile prosthesis may be surgically implanted. Since surgery destroys the corpus cavernosum of the penis, this procedure precludes any future pharmacological treatment (Morales, 2003).

Complications of penile prostheses include erosion of the device, mechanical failure and the possibility of infection. Device extrusion, migration, urinary obstruction and prolonged or intractable pain are other potential risks. The average infection rate post-operatively ranges from 2–4% over a two year period, with most infections becoming evident during the first year. Some bacterial species can lie indolent for as long as two years before causing clinical signs of infection. Men with diabetes, spinal cord injuries or urinary tract infections have an increased risk of prosthesis-associated infections. If the infection cannot be successfully treated with antibiotics, it may be necessary to remove the prosthesis. Replacement with a new prosthesis should be delayed after removal of an infected prosthesis to allow adequate healing and eradication of the offending microorganism (Hellstrom, 2022).

U.S. Food and Drug Administration (FDA): There are two types of mechanical devices for treatment of erectile dysfunction: external penile rigidity devices and penile rigidity implants. Both are regulated by the FDA. External penile rigidity devices are classified by the FDA as Class II medical devices and are exempt from the premarket notification requirements of the 510(k) process (FDA, 2004). Examples of these devices are the Rejoyn Vacuum Therapy System (Rejoyn Medical Systems, Nevada City, CA) and Osbon Erecaid™ Vacuum Therapy (Timm Medical Technologies, Dodge City, KS).

Penile rigidity implants are either noninflatable (i.e., semirigid rods) or inflatable. Noninflatable devices are classified by the FDA as Class II medical devices and consist of a pair of semi-rigid rods or cylinders that are surgically implanted in the corpora cavernosa. The purpose of the device is to provide adequate penile rigidity for intercourse. This classification includes the following designs (FDA, 2000):

- rod prosthesis: a flexible, solid cylinder of polymer material
- malleable prosthesis: a flexible polymer cylinder that incorporates an internal metal core
- single-hinged prosthesis: a highly flexible material that enables the user to position the penis downward for concealment
- multiple-hinged prosthesis: a series of hinged segments, encapsulated in a polymer sheath

The Spectra™ (AMS Men's Health/Boston Scientific) and the Genesis® Penile Prosthesis (Coloplast, Minneapolis, MN) are examples of rigid penile prostheses.

Inflatable devices are classified by the FDA as Class III medical devices and consist of paired cylinders, surgically implanted inside the penis, which can be expanded using pressurized fluid. Tubes connect the cylinders to a reservoir filled with radiopaque fluid implanted in the abdomen and a subcutaneous pump implanted in the scrotum. The user inflates the cylinders by pressing on the small pump, located under the skin in the scrotum (FDA, 2020). The AMS 700™ (Boston Scientific) and the Titan® (Coloplast, Minneapolis, MN) are examples of inflatable penile prostheses.

Literature Review - Penile Prostheses: Due to the nature of these devices, outcomes reported in studies evaluating their effectiveness are largely self-reported and subjective (e.g., patient satisfaction questionnaires). Objective outcome measures that have been reported in the medical literature include rate of mechanical failures and defects, and complications. Published evidence supports improved patient satisfaction with the use of penile implants when compared to sildenafil or intracavernous injections (Rajpurkar, et al., 2003); improved quality of

life (Ferguson, et al., 2003); and improved erectile function (Mulhall, et al., 2003). Patient satisfaction has been reported to range from 71% to 91.2% with the use of implantable penile prostheses (Paranhos, et al., 2010; Knoll, et al., 2009; Israilov, et al., 2005; Minervini, et al., 2006; Zermann, et al., 2006; Ferguson, et al., 2003). Wilson et al. (2007) reported an estimated mechanical revision rate of 79.4% for device survival at 10 years compared to 71.2% at 15 years. The authors also noted with newer devices a 10-year mechanical survival and freedom from mechanical breakage increased to 88.6% and 97.9%, respectively. In general, the medical literature indicates these devices are safe and effective for the treatment of ED for a carefully selected subset of individuals whose condition is organic in nature and have failed more conservative treatment.

Vascular Surgery
Patients who are considered for vascular surgical therapy typically have appropriate preoperative evaluation, which may include the combined injection and stimulation (CIS) test, dynamic infusion pharmaco-cavernosometry and cavernosography (DICC), duplex ultrasonography, and possibly arteriography. Penile arterial reconstructive surgery, also referred to as penile arterial bypass or revascularization, is one intervention that has the potential to cure patients with ED. During penile revascularization procedures, an arterial blockage is bypassed usually by anastomosing the inferior epigastric artery to the dorsal artery of the penis. Young men without other vascular risk factors (e.g., diabetes, high blood pressure, lipid disorders, cigarette smoking), who have ED due to pure artery blockage, are ideal candidates for this procedure. For posttraumatic arteriogenic ED in young patients, surgical penile revascularization has a 60–70% long-term success rate (Hatzimouratidis, et al., 2018).

Penile Vein Ligation
Venous ligation is a surgical procedure used to treat veno-occlusive ED, or erectile failure caused by venous insufficiency. The procedure involves the removal or ligation of the veins leaving the corpora cavernosa. Penile vein ligation techniques range from dorsal and accessory vein ligation to complete ligation and excision of the dorsal, cavernous, and crural veins. Surgery of the penile venous system has been reported to have some efficacy in patients with venous leakage. However, the tests necessary to establish this diagnosis have been incompletely validated. Therefore, it is difficult to select patients who will have a predictably good outcome. In general, the long-term benefits of venous ligation surgery have been limited. Success rates within the first year range from 23–80% but consistently decrease on longer follow-up (Rao and Donatucci, 2001).

Literature Review - **Penile Vein Ligation:** Studies in the published peer-reviewed medical literature evaluating penile vein ligation for venogenic ED include case series primarily with small sample sizes. A larger series by Hsu et al. (2010) compared patients with veno-occlusive dysfunction who were treated with a venous stripping surgical method (n=178) with patients who were treated without this surgery (n=163). At an average follow-up of 7.7 years, there were no statistically significant differences in outcomes between the surgery and control groups as measured by the International Index of Erectile Function (IIEF-5) scores.

Cayan (2008) reported a series of 26 patients who underwent penile venous surgery with crural ligation for primary venous leakage. Postoperatively complete improvement in erectile function occurred in 11 men (42.3%), partial improvement occurred in eight (30.8%), and erectile function remained unchanged in seven (26.9%). Earlier case series have reported success rates of 31%–60% (Berardinucci, et al., 1996; Kim and McVary, 1995).

Nerve Graft During or After a Radical Prostatectomy
Despite advances in radical prostatectomy procedures, ED remains a significant postoperative complication. When both neurovascular bundles are spared during radical prostatectomy (RP), potency rates of up to 70% have been reported, but rates of 30–60% have been observed. For intentional resection of both neurovascular bundles, the return of erectile function is the exception (Kim, et al., 2001). Nerve grafting has been proposed as an intervention during or after a RP to prevent ED associated with the procedure. Some of the nerves studied include the sural nerve, ilioinguinal nerve and genitofemoral nerve.

In nerve grafting, a portion of the nerve is harvested and then anastomosed to the divided ends of the cavernous nerves which are resected during a radical prostatectomy.

Literature Review - Nerve Graft: There is limited data in the scientific peer-reviewed literature regarding the long-term outcomes of nerve grafting (e.g., sural nerve, genitofemoral nerve) during or after a radical prostatectomy. An RCT by Davis et al. (2009) compared outcomes of patients who underwent unilateral nerve-sparing radical prostatectomy with a sural nerve graft (n=66) to those who had unilateral nerve-sparing radical prostatectomy alone (n=41). At 24-month follow-up, there was no significant difference in the return of erectile function for the sural nerve graft group versus the control group (p=0.962).

Nonrandomized controlled comparison studies and case series have also evaluated the safety and effectiveness of nerve grafting during or after a radical prostatectomy (Souza Trindade, et al., 2017; Siddiqui, et al., 2014; Satkunasivam, et al., 2009; Hanson, et al., 2008; Zorn, et al., 2008; Nelson, et al., 2006; Sim, et al., 2006; Porpiglia, et al., 2005; Kim, et al., 2001). Study populations have ranged from 10–40 with a follow-up range of 12–36 months. Small sample sizes have limited the generalizability of results. In addition, the results of these studies have not consistently shown a statistically significant difference in erectile function after nerve grafting.

Souza Trindade, et al. (2017) described a novel penile reinnervation technique using four sural nerve grafts and end-to-side neurorraphies connecting bilaterally the femoral nerve and the cavernous corpus and the femoral nerve and the dorsal penile nerves. Patients (n=10) who had undergone radical prostatectomy (RP) at least two years previously were included and underwent penile reinnervation. A total of 60% of patients were able to achieve full penetration, on average, 13 months after reinnervation surgery. The four patients not achieving penetration after three years after reinnervation surgery, all developed flaccid or semi-rigid erections, suggesting that partial reinnervation occurred. Limitations of the study included the small patient population, lack of a control group and short term follow-up. Randomized controlled studies with large patient populations and long term follow-up are needed. No health disparities were identified by the investigators.

Extracorporeal Shock Wave Therapy (ESWT)
ESWT is a noninvasive treatment that involves delivery of low- or high-energy shock waves via a device to a specific site within the body. These pressure waves travel through fluid and soft tissue; their effects occur at sites where there is a change in impedance, such as the bone/soft-tissue interface.

Peyronie's Disease (PD): PD is a localized connective tissue disorder of unknown cause, and is characterized by the formation of inelastic fibrous plaques within the tunica albuginea or erectile tissue of the penis. For many patients, PD results in sexual problems due to the difficulty in attaining and/or maintaining erections. In a significant number of patients, the disorder improves or resolves spontaneously. Medical therapies, including antioxidants (such as vitamin E and potassium aminobenzoate) and corticosteroids injected directly into the plaque, lack adequate scientific support. Medical treatment options for PD typically include oral or intralesional drug therapy. Surgical management is considered for patients who have penile deformity compromising sexual function and whose PD has persisted for more than 12 months, and is refractory to medical therapy (Brant, et al., 2021).

ESWT has been investigated as a treatment option for PD. Various hypotheses about its mechanism of action exists, including direct damage to the plaque resulting in an inflammatory reaction with increased macrophage reaction leading to plaque lysis, improved vascularity resulting in plaque resorption, and the creation of contralateral scarring of the penis resulting in "false" straightening (Taylor and Levine, 2007). There is a lack of standardization regarding issues such as shockwave dosage, energy levels and number of sessions required for a therapeutic effect in patients with PD. Currently, the treatment of PD is not a U.S. Food and Drug Administration (FDA)-approved indication for ESWT.

Literature Review – ESWT for PD: The use of ESWT for the treatment of PD has been examined in several RCTs, systematic review/meta-analysis and observational studies. Gao et al. (2016) conducted a meta-analysis of the evidence on ESWT for PD (n=6 studies/443 patients). Data was extracted from RCTS (n=3 studies/238 subjects), case-control studies (n=2 studies/111 subjects), and one cohort study (n=94 subjects). The primary outcomes were lessening of plaques and improvement of penile curvature. Secondary outcomes included relief and complete remission of pain, and improvement of sexual function. Follow-up ranged from four weeks to six months. Pooling data showed statistically significant pain relief and remission of pain ($p<0.0001$) after ESWT. A decrease of penile plaque was also observed (p=0.02). However, insignificant differences were found in improvement of penile curvature (p=0.06) and sexual function (p=0.18) between ESWT and placebo groups. A

meta-analysis of RCTs only showed similar results for all parameters. Study limitations include the short-term follow-up in trials and the inclusion of low-quality evidence. The authors concluded that although the results of this meta-analysis suggests that ESWT may be an effective and relatively safe choice for PD patients with penile plaque and painful erection, the efficacy of ESWT could be very limited in patients with penile curvature and ED.

Chitale et al. (2010) randomized men with Peyronie's disease to receive ESWT (n=16) or sham (n=20). Inclusion requirements were stable penile deformity secondary to PD, recent onset of painless deformity of the penis on erection, and stable for > six months; pain and/or angulation of the penis on erection; difficult intercourse due to penile curvature, and partner dissatisfaction; a degree of ED (partial) associated with penile deformity; palpable plaque along the penis with penile deformity; aged > 18 years. The exclusion criteria were: congenital curvature of the penis; previous treatment for PD (surgical/medical); patients on warfarin and patients with total ED in need of therapy for ED. Primary outcome measures were the difference in the angle of deformity and the difference in IIEF score before and after treatment. Secondary outcome measures included the difference in VAS scores before and after treatment. At six months of follow-up there was no significant difference in the mean change between the control and intervention groups on any outcome measure. The study is limited by its small sample size. Results do not support the effectiveness of ESWT for PD.

Palmieri et al. (2009) conducted an RCT comparing ESWT as a treatment for PD with a duration of less than 12 months (n=50) to placebo (n=50). At 24 weeks, the mean visual analog scale (VAS) score was reported to be significantly lower in both groups compared to baseline. Mean plaque size and mean curvature degree were significantly higher in the placebo group compared to baseline and ESWT values. Study limitations include small sample size, restricted inclusion criteria, and short-term follow-up.

In general, the evidence evaluating the safety and efficacy of ESWT for PD consists of observational studies and case series with relatively small sample sizes (n=44–325) and short-term follow-up (di Mauro, et al., 2019; De Berardinis, et al., 2010; Poulakis, et al., 2006; Srirangam, et al., 2006; Strebel, et al., 2004; Hauck, et al., 2004). These studies have yielded inconsistent results.

Vasculogenic ED: Low-intensity ESWT (LI–ESWT) has recently been investigated as a treatment for patients with mild to severe ED resulting from altered blood flow to the penis. Low-intensity extracorporeal shockwave therapy (Li-ESWT) is noninvasive and uses acoustic waves, which can pass through tissue and be focussed to target specific areas or organs to induce the desired effects (Young Academic Urologists Men's Health Group, 2017). LI–ESWT is thought to induce mechanical stress and cellular microtrauma which results in the development of new blood vessels in the treated tissue of the corpora cavernosa. LI–ESWT aims to restore the erectile mechanism in order to enable natural or spontaneous erections. Patients who might be offered LI–ESWT include those with vasculogenic ED amenable to microvascular surgery.

Literature Review – ESWT for Vasculogenic ED
Evidence in the published peer-reviewed medical literature evaluating ESWT for ED includes RCTs, cohort studies and systematic reviews/meta-analyses.

Vinay et al. (2021) conducted a double-blind, sham controlled, randomized controlled trial that assessed the effect of electromagnetic LI-ESWT on the erectile function of vascular phosphodiesterase type 5 inhibitor (PDE5I) refractory ED patients. Included patients were predominantly, middle-aged men with a high prevalence of multiple cardiovascular risk factors with a history of ED of more than six months refractory to PDE5I drugs. Patients (n=80) were randomized to LI-ESWT (n=40) or sham treatment (n=40). All patients in the active LI-ESWT group and 36 sham treated patients completed the study protocol (n=76). All patients in the study stopped using ED drugs during study protocol and follow-up, with a wash-out period of two months. The LI-ESWT group received 5000 shocks once a week for four weeks using the RENOVA® electromagnetic device (Direx Group, Wiesbaden, Germany). The sham group was treated with a device probe, identical to the treatment group, but without shockwaves. Outcomes measured the response to treatment at one, three and six months after the last session using the following questionnaires: index of erectile function–erectile function domain (IIEF-EF), erection hardness score (EHS) (> 2), sexual encounter profile (SEP2 and SEP3) and global assessment question (GAQ1). In each of the four LI-EWST sessions and three post-treatment evaluations, patients were questioned about the use of ED drugs. At one month, there were not any significant differences between the groups in any of the EF questionnaire scores. At the three month follow-up, there was a significant difference in the median

change of the IIEF-EF score for active and sham groups in favor of the LI-ESWT group (p=0.004). There were not any significant differences between groups regarding the percentage of men with an EHS > 2 or the number of positive answers to SEP2, SEP3 and GAQ1 during the three month evaluation. At the six month follow-up, there were significant differences between the groups in EHS > 2 and positive answers to GAQ-1 in favor of the LI-ESWT group (p=0.028 and p=0.011, respectively). SEP2 and SEP3 positive answers did not present significant differences between groups. No adverse events were observed during the study. Author noted limitations included: small patient population, penile hemodynamics were not measured to diagnose vasculogenic ED or to confirm the improvement of cavernous blood inflow or penile rigidity and the short-term follow-up. The authors concluded that the study showed that penile electromagnetic shockwave therapy may improve erectile function, to a modest extent, on certain patients that do not respond to PDE5I. However, randomized sham controlled trials with long-term follow-up is needed to compare different ED etiologies and protocol characteristics. No health disparities were identified by the investigators.

Ortac et al. (2021) reported on a prospective, single-blinded, placebo randomized controlled trial that compared outcomes in ED patients after ESWT and placebo treatment. Included patients were age 18–75 with a diagnosis of mild ED (IIEF-EF score = 17–25) which was confirmed by Penile Doppler ultrasonography (US) at least six months prior to study. The study was comprised of a four week washout phase, a four week treatment phase, and a 48-week follow-up Patients (n=66) were randomized to ESWT (n=44) or placebo (n=22). Mean age of ESWT and the placebo group was 42.32±9.88 and 39.86±11.64 (p=0.374) respectively. The ESWT group received 3000 shock wave pulses once a week using the DUOLITH® SD1 shock wave generator. The placebo group also received treatment once a week, however no shocks were given during treatment. Outcomes measured changes from baseline in patient-reported outcomes of erectile function (International Index of Erectile Function domain scores [IIEF-EF]), as well as erection hardness and duration (Sexual Encounter Profile diary [SEP] and Global Assessment Questions [GAQ]). Safety was assessed throughout the study. Follow-up occurred at three months (V3), six months (V4) and 12 months (V5). Only treatment responders were evaluated at V4 and V5. At the three-month follow-up, mean IIEF-EF scores were significantly higher in ESWT patients than in placebo patients (p=0.003) and IIEF-EF scores of ESWT patients remained high during the six month follow-up. A subgroup analyses indicated that the improvement of ED by ESWT detected at month three was independent of age, BMI, and ED duration. However, at six months follow-up, the beneficial effect of ESWT seemed to decline in patients with a BMI ≥ 30, in patients older than 35 years and in patients with ED history ≥ 12 months. The percentage of patients reporting both successful penetration (SEP2) and intercourse (SEP3) in more than 50% of attempts was significantly higher in the ESWT patients compared to placebo patients (p=0.001). One safety event (pain) and headache (1) occurred in the placebo group. A total of 12 adverse events were reported by ESWT patients (n=10) which included headache (2), fatigue and nausea (1), nausea and headache (1), dysuria (1), fatigue and tiredness (2), headache and fatigue (1), and mild fever (1). No adverse event occurring at the sites of treatment was reported. Author noted limitations included that the study was single-blinded, (which might introduce a potential for investigator bias), small patient population and only responders were included in the open-label extension study (V4, V5). The study concluded that ESWT significantly improved the erectile function of relatively young patients with vasculogenic mild ED when compared to placebo for up to six months. However, additional research with large randomized controlled trials are needed to define subgroups of ED patients that will benefit the most from ESWT and to establish treatment protocols. No health disparities were identified by the investigators.

Shendy et al (2021) conducted a randomized controlled trial that assessed the effectiveness of low-intensity extracorporeal shockwave therapy (Li-ESWT) in the management of mixed vasculogenic and neurogenic erectile dysfunction in diabetic patients. Included patients were age 41–55 with a body mass index < 30 kg/m2 suffering from type-2 DM diabetic neuropathy as confirmed by nerve conduction study, and mild to moderate ED lasting for at least six months. All patients had controlled DM. Patients (n=42) were randomly assigned to one of two groups: shock wave group (n=21) treated with Li-ESWT plus pelvic floor exercises (PFE) and control group (n=21) treated with pelvic floor muscle exercise and sham shock wave therapy. Li-ESWT sessions were delivered twice a week (3,000 shock waves) for three weeks, and repeated again after three weeks rest period. Pelvic floor exercises consisted of Kegel exercises three times daily for six weeks. The outcomes measured were improvement in International Index of Erectile Function (IIEF-5) and the penile Doppler parameters for the evaluation of penile perfusion of the two cavernous arteries. The assessment was done before and three months after treatment. IIEF-EF increased significantly in the study group (p<0.001), but not in the control group

(p=0.194). Peak systolic velocity increased significantly in the two groups; however, the post-treatment peak systolic velocity was significantly higher in the study group compared to the control group (p<0.001, for both arteries). Author noted limitations were the small patient population and the short-term follow-up. The authors concluded that Li-ESWT appears to be an effective and safe noninvasive option for the treatment of diabetic patients with erectile dysfunction. The combination of Li-ESWT and PFE can improve the vasculogenic and neurogenic elements of diabetic ED, however studies with long-term follow-up are needed to confirm the effectiveness of Li-ESWT to be approved for the treatment of DM-related ED. No health disparities were identified by the investigators.

Ladegaard et al (2021) investigated treating men with ED following robotic nerve-sparing radical prostatectomy (RARP) with Li-ESWT in a placebo randomized controlled trial. Men (n=38) from the Region of Southern Denmark (covering 1.2 million people) with ED for more than six months following nerve-sparing RP with an International Index of Erectile Function (IIEF-5) score < 22, no impaired EF prior to RP (no use of 5-PDEi, ICI or other erectogenic aid) and without active cancer or radiation therapy to the pelvic area were included. Participants were randomized into an active A group (n=20) and a placebo/sham B group (n=18). Each study arm had treatment once a week for five weeks using the handheld Duolith SD1 machine (Storz Medical, Switzerland) with 4,000 shock impulses. Outcomes were assessed by international validated questionnaires, Erection Hardness Score (EHS) and IIEF-5. Follow-up occurred at four weeks and 12 weeks following treatment. A significant increase was observed in EHS in group A at four and 12 weeks (p=0.033 and p=0.019, respectively). Group A had a significantly higher IIEF-5 score than group B at 12 weeks of follow-up. (p=0.026). However, the difference between groups in IIEF-5 score was not statistically significant at four weeks of follow-up. The study did not prohibit the use of erectile aids and the small patient population were noted as limitations by the authors. An additional limitation is that the population studied only included men from the Region of Southern Denmark and the results may not be applicable to other races or ethnic groups. The authors concluded that there was slight increase in mean IIEF-5 and EHS in men with ED following RARP treated with Li-ESWT. However, future research in Li-ESWT following RP is needed and should focus on initial timing of treatment, stratification of ED subgroups most susceptible to treatment, the efficiency of Li-ESWT in combination with other treatment modalities and defining the most optimal time for shockwave application.

Sramkova et al. (2020) evaluated the treatment outcome of Li-ESWT for ED in single-blind, randomized controlled trial. Included patients had mild to severe vasculogenic ED lasting for at least six months, were partial responders to PDE5i and had a stable partner with regular sexual activity at least twice a week. All patients were heterosexual and white European. The median patient age was 54 (range: 40–70). Patients (n=60) were randomized into two age-matched groups: Group A received treatment with PiezoWave2 unit (R.Wolf and Elvation Medical) and Group B received placebo. After a 4-week wash-out period, treatment consisted of four sessions with 6,000 shockwaves. Efficacy of treatment was measured according to the International Index of Erectile Function (IIEF-5), Erectile Hardness Score (EHS), questions 2 and 3 of the Sexual Encounter Profile (SEP 2, SEP 3) and Global Assessment Question (GAQ) scores at baseline and four and 12 weeks following treatment. The patient's and partner's subjective satisfaction were also evaluated. The quality of erection according to the IIEF-5 and EHS at four and 12 weeks was clinically significant in favor of the treatment group (p=0.049 and p <0.001; p=0.030 and p<0.001, respectively). At 12 weeks, the GAQ, SEP 2, SEP 3, patient's satisfaction and partner's satisfaction reached clinical significance in favor of the treatment group (p<0.001, p=0.05, p<0.001, p <0.001, p <0.001); respectively). The author noted limitations of the study included the small patient population, short follow-up and the single blind study design. An additional limitation is that the population studied only included heterosexual white European men and the results may not be applicable to other races or ethnic groups. The authors concluded that Li-ESWT significantly improves erectile function. However, additional studies are needed, before considering this treatment as the new standard for the treatment of ED.

Baccaglini et al. (2020) conducted a randomized controlled trial that compared the early introduction of phosphodiesterase-5 inhibitor (PDE5i) with a combination of LiESWT and phosphodiesterase-5 inhibitor (PDE5i) in patients submitted to radical prostatectomy (RP). Patients aged ≤ 75 years presenting preoperatively with an IIEF-5 score > 18 and in a stable heterosexual relationship for at least three months were included. Patients underwent a bilateral nerve-sparing RP and agreed to discontinue PDE5i use at the end of the protocol for the last assessment of erectile rehabilitation. Patients (n=92) were randomized into the experimental group (n=46) or the control group (n=46). Both groups started tadalafil at a dose of 5 mg/day right after the removal of the transurethral catheter, and the experimental group received 2,400 shocks/session-week using Renova (DIREX

Group). The control group did not receive placebo ESWT. The primary outcome measured the statistical difference in erectile function using the International Index of Erectile Function short form (IIEF-5), the end point was ≥ 4-point difference in favor of the experimental group at last follow-up. The authors noted that this specific cutoff has been proven to represent the minimal clinically important difference (MCID) in the EF domain of the IIEF scale. The secondary outcome measured the rate of patients reaching orgasm and the erectile hardness score at last follow-up. Adverse events and continence status was also evaluated. At last follow-up (10 weeks), 77 patients were assessed and included in the final analysis, 36 in the experimental group 41 in the control group. A difference between groups was detected when accessing the final median IIEF-5 score (12.0 vs 10.0; p=0.006). However, the primary clinical endpoint considering a difference ≥ 4-point between the arms was not reached. When performing an exploratory analysis comparing the proportion of those individuals with an IIEF-5 score ≥ 17, no difference between groups was noted. There were no significant differences noted between groups in postoperative complications or continence. The erectile hardness score and proportion of patients reaching orgasm were ruled out from the protocol because the investigators could not find any additional benefit for these tools after applying IIEF-5 in the protocol. Author acknowledged limitations included: the machine used Renova (DIREX Group) does not have the sham probe making the blinding process unfeasible; the early period after RP that assessed the IIEF-5 could have limited the spontaneous recovery of EF; PDE5i use was discontinued at the last session, which may have interfered in the penile vascular rehabilitation; some benefits of LiESWT could have disappeared after the washout period; the study protocol included only one session per week for the experimental group, possibly a more intensive application could achieved better results. Additional limitations were short term follow-up and small patient population. The population studied only included heterosexual men and the results may not be applicable to other races or ethnic groups. In conclusion, the study was unable to demonstrate clinical benefits on erectile function. The authors concluded that more studies are needed before any recommendation on this topic. No health disparities were identified by the investigators.

Dong et al. (2019) conducted a systematic review and meta-analysis of seven randomized controlled trials (RCT's) (n=522 patients) to evaluate the efficacy of Li-ESWT by comparing the changes in the International Index of Erectile Function erectile function domain (IIEF-EF) and the Erection Hardness Score (EHS) to sham therapy in men with ED. The authors noted that men treated with Li-ESWT showed significant improvement in pooled mean IIEF-EF and EHS scores from baseline to follow-up compared to sham therapy ($p<0.00001$ and $p<0.00001$, respectively). Study limitations included small sample size, short term follow up and no unified protocol using Li-ESWT in treating ED. The authors concluded that additional well designed RCTs are needed in the future.

A systematic review and meta-analysis of 10 RCT's (n=873 patients) conducted by Sokolakis et al. (2019) concluded that when Li-ESWT was compared to sham, Li-ESWT significantly improved the IIEF-EF and EHS scores along with penile hemodynamics ($p<0.0001$, $p=0.0009$, $p<0.00001$, respectively). The mean follow-up was 5.12 months, with a range of 1–12 months. Acknowledged study limitations included the lack of consistency in outcome measures, specified dose intensities (low, medium, high ESWT) and short-term follow-up. The study concluded that larger multi-centric RCTs with longer than one year follow-up are needed.

Fojecki et al. (2017) assessed the outcome of linear low intensity-ESWT (LLi-ESWT) on ED at six and at 12 months from a randomized, double-blinded, sham-controlled trial. The advantage of linear ESWT compared with focused ESWT is that the usage of the linear probe delivers shock waves (SW) to a wider area of the corpora cavernosa, which limits movements of the probe during treatment. In this study, subjects with ED (n=126) were randomized into two groups to compare LLi–ESWT to sham treatment for ED. Group A (n=63) was assigned to a phase one sham for five weeks and phase two LLi–ESWT for five weeks. Group B (n=63) was assigned to phase one and phase two of LLi–ESWT (10 weeks). The inclusion criteria were; age over 40 years, complaints of ED and in a stable relationship for greater than six months. The primary outcome measure was an increase of at least five points in the IIEF-EF (△IIEF-EF score). The secondary outcome measure was an increase in the erectile hardness scale (EHS) score to at least a three in men with a score no higher than two at baseline. Patients (n=27) were excluded from final analysis for not returning questionnaires (n=23) or dropping out (n=4). Linear regression of the △IIEF-EF score from baseline to 12 months included 95 patients (n=95). The success rate based on the main outcome parameter (△IIEF-EF score ≥ 5) was 54% in group A vs. 47% in group B ($p=0.28$). Improvements based on changes in the EHS score in groups A and B were 34% and 24%, respectively ($p=0.82$). The differences between groups were not clinically significant. The limitations of the study included the lack of dosage related studies and the study design. Only the short-term effects of sham treatment were

assessed, because all participants received active treatment in the second phase. The authors concluded that exposure to two cycles of linear Li-ESWT for ED is not superior to one cycle at six and at 12-month follow-ups and further studies are needed.

Kalyvianakis and Hatzichristou (2017) reported their results of a double-blinded, randomized, sham-controlled trial that assessed the effectiveness of low-intensity extracorporeal shockwave therapy (Li-ESWT) in patients with vasculogenic erectile dysfunction. Patients met inclusion criteria if they were at least 18 years old, had vasculogenic ED for at least six months, and were partial responders to PDE5 inhibitors. Following a four week washout period, the baseline International Index of Erectile Function erectile function domain (IIEF-EF) score had to be at least six (mild to moderate ED) to 21 (moderate and severe ED). Patients (n=46) were randomly assigned to receive Li-ESWT (n=30) or a sham procedure (n=16). All patients underwent penile triplex ultrasonography by the same investigator immediately before and three months after treatment. The primary outcome measured was the changes in peak systolic velocity and resistance index as measured by triplex ultrasonography at baseline and three months after treatment. Secondary outcomes measured were changes in the IIEF-EF score from baseline to one, three, six, nine, and 12 months after treatment and the percentage of patients reaching a minimal clinically important difference during the same period for the two groups. IIEF-EF minimal clinically important differences for the active vs sham group were observed for 56.7% vs 12.5% (p=0.005) at one month, 56.7% vs 12.5% (p=0.003) at three months, 63.3% vs 18.8% (p=0.006) at six months, 66.7% vs 31.3% (p=0.022) at nine months, and 75% vs 25% (p=0.008) at 12 months. Mean peak systolic velocity increased by 4.5 and 0.6 cm/s in the Li-ESWT and sham groups, respectively (p<0.001). Limitations included the small sample and strict inclusion criteria that do not reflect everyday clinical practice.

Clavijo et al. (2017) conducted a systematic review and meta-analysis of the evidence (n=7 RCTs/602 subjects) evaluating the efficacy of Li-ESWT for ED. RCTs were eligible for inclusion if they were published in the peer-reviewed literature and assessed erectile function outcomes using the IIEF-EF score. Estimates were pooled using random-effects meta-analysis. The average follow-up period was 19.8 weeks. A statistically significant improvement in pooled change in IIEF-EF score was found from baseline to follow-up in men undergoing Li-ESWT compared to those undergoing sham therapy (p<0.0001; between-group difference, p=0.047). Limitations of the review include the small sample size and short follow-up period in individual studies. It was also noted that data on PDE5i use during ESWT treatment was available in only five of seven studies. Although these results suggest that ESWT is more effective than sham therapy for ED, additional well-designed RCTs comparing ESWT to standard ED treatments are needed to establish the role in the treatment algorithm for ED.

Another systematic review and meta-analysis (n=14 studies/833 subjects) performed by Lu et al. (2017) evaluated the Li-ESWT for patients with ED. The evidence reviewed included RCTs (n=7 studies) which were used for meta-analysis and cohort studies (n=7 studies). No limitation was placed on the severity of ED or use of PDE-5i during treatment with Li-ESWT in studies. Follow-up occurred up to 12 months. The overall meta-analysis of the data showed that Li-ESWT improved the IIEF significantly overall in the treatment groups (p<0.0001). Different Li-ESWT setup parameters (energy flux density [EFD], number of pulses), and different treatment protocols, including treatment frequency and length of course, resulted in differences in reported efficacy. Results showed that studies using the highest EFD (> 0.2 mJ/mm2) reported significantly increased IIEFs (p<0.0001). Sub-group analysis (n=3 RCTs) showed that the IIEF of patients with mild ED increased significantly after Li-ESWT (p<0.0001), which did not occur for patients in the severe and moderate categories (p=0.30 and p=0.49, respectively). No adverse effects were reported. Acknowledged limitations of the meta-analysis were the inclusion of lower level evidence (i.e., cohort studies) and individual study deficiencies such as missing information as to details of randomization and treatment protocol.

Olsen et al. (2014) conducted a prospective, randomized blinded, placebo-controlled study (n=112) comparing LI-ESWT to sham treatment for ED. Both participants and physicians were blinded to treatment allocation. A total of 105 men with organic ED for at least six months who had responded to PDE-5 inhibitors were enrolled in this study. Additional inclusion requirements were an Erection Hardness Score (EHS) < 2 and an Index of Erectile Function (IIEF-15) score < 20. Exclusion criteria were psychogenic ED, neurological pathology and pelvic radiation or recovery from cancer within the past five years. The participants were assessed by EHS and IIEF-erectile function domain at baseline and at five weeks. Men in the placebo group (n=54) were offered LI-ESWT 10 weeks after study. The blinded part of the study was terminated at this point. The active placebo group (n=52) was assessed at five, 12 and 24 weeks after treatment. At five weeks of follow-up 29 men (57%) in the active

group had an EHS of 3–4, which made it possible for them to have full sexual intercourse; three men (6%) had an EHS of 1–2, and 19 (37%) showed no change in ED. In the placebo group, five men (9%) had an EHS of 3–4, seven (13%) an EHS of 1–2 and 42 (78%) had experienced no change. The difference between the two groups was statistically significant at the EHS levels 0 and 3–4 (p=0.0001).The EHS response rate was 80% at week 12 and 70% at week 24 in the active group. In the active placebo group, the EHS response rate was 85% at week 12 and 75% at week 24. Between weeks 12 and 24, the number of men who achieved improved EHS scores (3–4) decreased in both groups. There was no significant difference between the two groups in terms of IIEF-erectile function domain after week five. This study is limited by its short-term follow-up and unblinding after five weeks. Study results suggest a short-term treatment effect however, this effect was not maintained throughout the follow-up period.

Vardi et al. (2012) performed a randomized, double-blind, sham controlled study (n=77) of men with organic ED who were PDE-5 inhibitor responders. After a one-month PDE-5 inhibitor washout period, 67 men were randomized in a 2:1 ratio to receive 12 sessions of Li-ESWT (n=40) or sham therapy (n=20). The primary outcome was erectile function measured by the IIEF-EF, with treatment success defined as a 5-point or greater score improvement. Secondary outcomes included an increase in EHS and an improvement in penile blood flow. The 9-week treatment period was comprised of two treatment sessions per week for three weeks that were repeated after a three-week no treatment interval. Follow-up occurred one month after the final treatment session at which time erectile function and penile hemodynamics were reassessed while the men were still not taking PDE-5 inhibitors. At 13 weeks of follow-up, men in the treated group had a 5-point or greater increase in IIEF-EF than those in the sham group (p=0.0001). The treated men had significantly improved mean scores in the IIEF subcategories of Sexual Desire (p=0.0348) and Overall Satisfaction (p=0.0054). Penile hemodynamics improved significantly in the treated group (p=0.0001). Study limitations are short-term follow-up and small sample size. Additional data are needed to confirm the efficacy suggested by these results.

Although preliminary results appear promising, additional well-designed studies with long-term follow-up are needed to establish safety and effectiveness of ESWT for the treatment of ED.

Amniotic-Derived Allografts
Amniotic membrane-derived allografts are harvested from human placenta tissue soon after birth. The allografts are minimally manipulated, cleaned, dehydrated and sterilized and is available in sheets, wraps, particulate, and membrane configurations. Amniotic membrane-derived allografts are hypothesized to be effective in improving potency outcomes post radical prostatectomy. Dehydrated human amnion/chorion membrane (dHACM) is a human allograft comprised of laminated amnion and chorion membranes derived from the placenta.

U.S. Food and Drug Administration (FDA): Amniotic membrane is a banked human tissue regulated by the American Association of Tissue Banks® (AATB) and does not require FDA approval. However, the manufacturer must meet specific FDA regulations for the collection, processing, and selling of human cell, tissue, and cellular and tissue-based products (HCT/Ps). (FDA, 2021).

Literature Review – Amniotic-Derived Allografts: Evidence in the published peer-reviewed medical literature evaluating the use of an amniotic-membrane derived allograft wrapped around the nerve bundles during a radical prostatectomy includes observational studies with retrospective data collection.

Noël et al. (2022) assessed the functional and oncological outcomes of applying amniotic or dehydrated human amnion/chorion membrane (dHACM) on preserved neurovascular bundles (NVBs) during a nerve sparing (NS) robot-assisted laparoscopic prostatectomy (RALP) for prostate cancer. Five-hundred and ninety-nine patients underwent placement of a dHACM graft (AmnioFix by MiMedx, Marietta, GA, USA) and 529 patients were followed-up for a median of 42 months. Full NS was performed in 74% (391/529), no patient had a non NS procedure. The number of patients with positive surgical margins (PSM) was 86 (16%), and the overall biochemical recurrence (BCR) in the entire cohort was 10%. Postoperatively, 434 (82%) were sexually active. Median time to potency was 119 (37–420) days and time to continence was 42 (23–91) days. Days to return of potency was significantly higher in the full NS group (p=0.003) compared to the partial NS group. However, return to continence or American Urological Association (AUA) scores was independent of NS degree with dHACM. Author acknowledged limitations included the study design as an observational study with retrospective data without a control group. The authors concluded that the findings of the study indicated that the application of

amniotic membrane/dHACM allowed for the return of potency at an average time of three months, with an overall shorter period for continence recovery. Additional long term randomized control trials with large patient populations are needed to validate the outcomes of the study and establish the efficacy of the placement of dHACM graft on potency. No health disparities were identified by the investigators.

Razdan et al (2019) conducted a retrospective matched longitudinal cohort study that assessed the potency outcomes in two systematically controlled, non-randomized, matched, homogenous patient cohorts, which either underwent intervention (INT) with placement of dehydrated human amniotic membrane (dHAM) around nerve bundles (NVB) during robotic-assisted laparoscopic radical prostatectomy (RALP) or did not (CON). The intervention group (n=700) had dHAM allograft (Amniofix™) wrapped around the NVB while the CON (n=700) did not. Potency was defined as the ability to have satisfactory penetrative intercourse > 50% of time with Sexual Health Inventory for Men (SHIM) score of ≥ 17 with or without of phosphodiesterase-5 inhibitors. Follow-up was performed at one year. INT had a significantly higher percentage of patients becoming potent ($p<0.005$) compared to CON every quarter post-surgery. A significantly higher ($p<0.005$) percentage (93.1%) of INT regained potency versus CON (87.1%) at the one year follow-up. With advancing age, the return to potency was delayed in both the groups, age being an independent predictor of return to potency. dHAM use was not associated with any membrane-related adverse effects or allergic reactions. Limitations noted by the authors included potential for placebo effect and recall bias during telephonic interviews due to the retrospective non-blinded study design. The authors concluded that a randomized prospective blinded study with different operators would eliminate the bias emanating out of a single surgeon, the same nerve-sparing technique, and single center study. No health disparities were identified by the investigators.

Ogaya-Pinies et al. (2018) conducted a retrospective analysis of prospectively collected data that evaluated if using dehydrated human amnion/chorion membrane (dHACM) allograft wrapped around the neurovascular bundles (NVB) during a robotic-assisted radical prostatectomy (RARP) accelerates the return of potency. Patients were divided into two similar groups using a 1:3 proportion, the dHACM group (n=235) and the control group or group 2 (n=705). The dHACM group underwent RARP, with bilateral placement of dHACM graft (AmnioFix® by MiMedx,® Marietta, GA, USA) around the NVBs. The control group or group 2 did not receive the allograft. Minimum follow-up was 12 months. Postoperative outcomes were analyzed between propensity-matched dHACM graft (group 1) and non-graft groups (group 2). Potency was defined as the ability to achieve and maintain satisfactory erections firm enough for sexual intercourse, with or without the use of PDE-5 inhibitors. The mean time to potency was significantly lower in group 1 (2.37 months) versus group 2 (3.94 months) ($p<0.0001$). The potency recovery rates were superior for group 1 at all early time points measured except at 12 months. At 12-months post-RARP potency recovery rates did not differ between groups. The authors concluded that patients who received the dHACM wrap had faster return to potency when compared to those who didn't receive the allograft. Additionally, the results indicate that dHACM placement at the site of the prostatic NVB does not increase the risk of biochemical recurrence after RARP, neither in the presence of positive surgical margin, extra-prostatic disease nor high Gleason score. Author noted limitations included the lack of prospective randomization and potential placebo bias could have altered the outcome. No health disparities were identified by the investigators.

Patel, et al. (2015) conducted a propensity-matched observational study with retrospective data collection that assessed if placing dehydrated human amnion/chorion membrane allograft nerve wrap around the prostatic neurovascular bundle during nerve-sparing (NS) robot-assisted laparoscopic prostatectomy(RARP) accelerates early return to continence and potency. Patients (n=58) in group 1 received dHACM (AmnioFix; MiMedx Group, Marietta, GA, USA) and propensity matched patients (n=58) in group 2 did not receive dHACM. There was no significant difference between the groups in the return of continence or potency at eight weeks ($p=0.373$; $p=0.132$, respectively) but the mean time to continence and potency was significantly quicker in group 1 patients when compared to group 2 ($p=0.033$; $p=0.007$, respectively). Limitations noted by the authors included the observational, retrospective study design which is subject to patient recall bias. The authors concluded that graft placement enhanced the meantime to continence and potency and that postoperative Sexual Health Inventory for Men (SHIM) scores were higher in the dHACM group at maximal follow-up (mean score 16.2 vs 9.1). Additional long term randomized control trials with large patient populations are needed to validate the outcomes of the study and establish the efficacy of the placement of dHACM graft on potency. No health disparities were identified by the investigators.

There is insufficient evidence in the published peer-reviewed medical literature to support the application of amniotic derived allograft to nerve bundles during a radical retroperitoneal prostatectomy.

Professional Societies/Organizations
American Academy of Family Physicians (AAFP): According to the AAFP, oral phosphodiesterase-5 inhibitors are the first-line treatments for ED. Second-line treatments include alprostadil, vacuum devices and when all other options are ineffective surgically implanted penile prostheses are an option (Rew et al., 2016).

American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE): AACE and ACE issued a guideline on the evaluation and treatment of male sexual dysfunction. The guideline supports the use of vacuum pump devices and internal implanted penile prostheses in the treatment of ED (AACE, 2003).

American Urological Association (AUA): In 2018, the AUA published revised guidelines on erectile dysfunction. According to the guidelines, men may choose to begin with the least invasive option, however any type of treatment as an initial treatment is a valid choice. The clinician is responsible to ensure that the man and his partner fully understand the benefits and risks/burdens associated with the choice and be informed of all the treatments (e.g., vacuum erection device, penile prosthesis) that are not contraindicated for the patient. The AUA also recommended against penile venous surgery and considered ESWT investigational.

National Comprehensive Cancer Network® (NCCN): According to the 2022 NCCN guidelines for prostate cancer, recovery of erectile function is directly related to factors such as age at radical prostatectomy, preoperative erectile function and the degree of preservation of the cavernous nerves. Replacement of resected nerves with nerve grafts has not been shown to be beneficial.

Use Outside of the US
The Canada Urology Association (CUA) recommended a stepwise progression from oral agents through second- and third-line therapies. After reversible causes of ED are ruled out, the recommended first line therapy is a trial of oral medication. If oral treatment fails, patients should be counselled regarding proper use of the medication and may need a dose adjustment. The second-line therapies, although more invasive than oral agents, are generally well-tolerated and effective and include injection therapy, urethral therapy and vacuum erection device. Penile implant surgery remains the third-line therapy and is an important option for men. Not all nonsurgical options need to fail prior to considering placement of a penile prosthesis. However, all nonsurgical options should be discussed with the patient prior to considering surgical intervention. At this time, the CUA recommended against low-intensity shockwave treatment (Li-SWT) as a treatment option for patients with ED. Additionally, regenerative approaches for treating ED, such as stem cell therapy (SCT), platelet rich plasma and amniotic fluid matrices are not currently approved for use outside of clinical trials and remain experimental (Domes, et al., 2021).

The European Association of Urology (EAU) guidelines on male sexual dysfunction states that if drug treatment fails, patients should be offered an alternative therapy such as intracavernosal injection therapy or the use of a vacuum erection device. The surgical implantation of a penile prosthesis may be considered in patients who do not respond to pharmacotherapy or who prefer a permanent solution to their problem. In regards to shockwave therapy and erectile dysfunction, the current data is still limited and clear recommendations cannot be given (Hatzimouratidis, et al., 2019).

In addition, the EAU guidelines on penile curvature state that the mechanism of action involved in extracorporeal shock wave lithotripsy is unclear. According to the EAU, extracorporeal shock wave treatment may only be used to treat penile pain (Hatzimouratidis, et al., 2019). However, the cited evidence supporting this statement consists of a single placebo-controlled RCT (Palmieri et al., 2009) described previously.

According to the National Institute for Health and Care Excellence (NICE), (2003), “current evidence on the safety of extracorporeal shockwave therapy (ESWT) for Peyronie's disease appears adequate. However, the evidence on the efficacy does not appear adequate to support the use of this procedure without special arrangements for consent and for audit or research.”

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD	National	Diagnosis and Treatment of Impotence (230.4)	This is a longstanding national coverage determination.
LCD	CGS Administrators, LLC and Noridian Healthcare Solutions, LLC	Vacuum Erection Devices (VED) (L34824)	1/1/2020

Note: Please review the current Medicare Policy for the most up-to-date information.
(NCD = National Coverage Determination; LCD = Local Coverage Determination)

Coding Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Vacuum Erection Device

Considered medically necessary when criteria in the applicable policy statements listed above are met and only when benefit coverage is available for the specific item:

HCPCS Codes	Description
L7900	Male vacuum erection system
L7902	Tension ring, for vacuum erection device, any type, replacement only, each

Penile Prosthesis

Considered medically necessary when criteria in the applicable policy statements listed above are met and only when benefit coverage is available for the specific service/item:

CPT®* Codes	Description
54400	Insertion of penile prosthesis; non-inflatable (semi-rigid)
54401	Insertion of penile prosthesis; inflatable (self-contained)
54405	Insertion of multi-component, inflatable penile prosthesis, including placement of pump, cylinders, and reservoir

HCPCS Codes	Description
C1813	Prosthesis, penile, inflatable
C2622	Prosthesis, penile, non-inflatable

Penile Prosthesis Removal

Considered medically necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
54406	Removal of all components of a multi-component, inflatable penile prosthesis without replacement of prosthesis
54408	Repair of component(s) of a multi-component, inflatable penile prosthesis
54410	Removal and replacement of all component(s) of a multi-component, inflatable penile prosthesis at the same operative session
54411	Removal and replacement of all components of a multi-component inflatable penile prosthesis through an infected field at the same operative session, including irrigation and debridement of infected tissue
54415	Removal of non-inflatable (semi-rigid) or inflatable (self-contained) penile prosthesis, without replacement of prosthesis
54416	Removal and replacement of non-inflatable (semi-rigid) or inflatable (self-contained) penile prosthesis at the same operative session
54417	Removal and replacement of non-inflatable (semi-rigid) or inflatable (self-contained) penile prosthesis through an infected field at the same operative session, including irrigation and debridement of infected tissue

Considered Experimental/Investigational/Unproven:

CPT®* Codes	Description
37790	Penile venous occlusive procedure
55899†	Unlisted procedure, male genital system
64912††	Nerve repair; with nerve allograft, each nerve, first strand (cable)
64913††	Nerve repair; with nerve allograft, each additional strand (List separately in addition to code for primary procedure)
64999†††	Unlisted procedure, nervous system

HCPCS* Codes	Description
Q4100	Skin substitute, not otherwise specified
Q4138	Biodfense dryflex, per square centimeter
Q4140	Biodfense, per square centimeter
Q4145	Epifix, injectable, 1 mg
Q4148	Neox cord 1K, Neox cord rt, or clarix cord 1K, per square centimeter
Q4156	Neox 100 or clarix 100, per sq cm, per square centimeter

†**Note: Considered Experimental/Investigational/Unproven when used to report extracorporeal shock wave therapy for the treatment of erectile dysfunction.**

††**Note: Considered Experimental/Investigational/Unproven when used to report the application of amniotic-derived allografts to nerve bundles during a radical prostatectomy.**

†††**Note: Considered Experimental/Investigational/Unproven when used to report sural nerve grafting during radical prostatectomy.**

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