Noncontact Warming Therapy, Ultrasound Therapy and Fluorescence Imaging for Wounds (for Tennessee Only)

Policy Number: CS132TN.K
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Instructions for Use

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Related Policies
None

Application

This Medical Policy applies to Medicaid and CoverKIds in the state of Tennessee.

Coverage Rationale

Warming therapy or noncontact normothermic wound therapy (NNWT) and low frequency ultrasound therapy are unproven and not medical necessary for treating wounds due to insufficient evidence of efficacy.

Noncontact real-time fluorescence wound imaging for bacterial presence is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
0598T	Noncontact real-time fluorescence wound imaging, for bacterial presence, location, and load, per session; first anatomic site (e.g., lower extremity)
0599T	Noncontact real-time fluorescence wound imaging, for bacterial presence, location, and load, per session; each additional anatomic site (e.g., upper extremity) (List separately in addition to code for primary procedure)

CPT Code	Description
97610	Low frequency, non-contact, non-thermal ultrasound, including topical application(s), when performed, wound assessment, and instruction(s) for ongoing care, per day

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HCPCS Code	Description
A6000	Noncontact wound-warming wound cover for use with the noncontact wound- warming device and warming card
E0231	Noncontact wound-warming device (temperature control unit, AC adapter and power cord) for use with warming card and wound cover
E0232	Warming card for use with the noncontact wound warming device and noncontact wound warming-wound cover

Description of Services

Warming therapy or noncontact normothermic wound therapy (NNWT) uses a noncontact wound cover and a warming unit to apply radiant heat and maintain 100% relative humidity in a wound. The intent is to raise the wound temperature to increase blood flow and oxygen to the wound.

Low frequency or low energy ultrasound using the Mist Therapy® System has been developed to provide simultaneous cleansing and debridement of wounds. Treatment with this device involves holding an ultrasonic handset 1 cm away from the wound and applying a saline solution to the handset, generating a saline mist that is designed to carry low levels of ultrasonic energy into the wound. According to the device manufacturer, this treatment promotes healing of acute, traumatic, and chronic wounds by stimulating cellular activities that contribute to healing and by cleaning the wound surface.

The MIST Therapy® System is a noncontact, low-frequency ultrasound debridement device that has been developed to promote healing of chronic wounds by removing yellow slough, tissue exudates, fibrin, and bacteria from the wound surface. The main components of the MIST Therapy® System are an ultrasound generator; a handheld ultrasound transducer; and a single-use, disposable applicator with a bottle reservoir for sterile saline. The transducer tip vibrates 40,000 times per second to generate ultrasound waves at 40 kilohertz (kHz) that are carried to the wound via a saline mist. In addition to wound cleaning, ultrasonic energy has been proposed as a means of stimulating angiogenesis, growth factor production, and other cellular activities that contribute to wound healing.

MolecuLight i:X® is a handheld fluorescence imaging device for real-time detection of bacteria in wounds; the violet light illumination captures and documents the presence of bacteria in the wound and surrounding areas. The device provides clinicians with information about the fluorescent characteristics of a wound to assist them in making improved diagnostic and treatment decisions. Despite FDA approval, additional robust clinical studies need to be completed to determine the safety and efficacy of this device. While some evidence exists for the predictive characteristics of the method compared to conventional wound cultures, the clinical significance of the method in improving care and patients' outcomes is unclear.

Clinical Evidence

Warming Therapy

The safety and efficacy of warming therapy or noncontact normothermic wound therapy (NNWT) for the treatment of chronic wounds has not been established in the published medical literature. Limitations of the existing studies include small samples, a lack of controls and/or randomization, and short follow-up times.

Yue et al. (2018) conducted a systematic review to assess the effects of local warming therapy (LWT) in treating chronic wounds. The inclusion criteria included randomized controlled trials (RCTs) that recruited people with chronic wound(s) (pressure ulcers, venous leg ulcers, arterial ulcers, and diabetic foot ulcers) comparing the effects of LWT with standard wound care or other wound-healing interventions. Primary outcomes included time to healing assessed using appropriate survival analysis, proportion of people with diabetic foot ulcers undergoing amputation of the lower limb at any level, including single toes, and proportion of wounds with complete healing. Secondary outcomes consisted of change in wound size, with change

expressed as absolute change or relative change; healing rate; quality of life measured by a validated scale. No RCTs comparing the effects of LWT with standard wound care or other wound-healing interventions amongst people with chronic wound(s) were found. It was not possible to undertake a meta-analysis. The authors concluded that this review highlights the lack of robust evidence for the use of LWT in the treatment of chronic wounds. Thus, no definitive conclusions regarding using LWT for treating chronic wounds can be drawn from this review.

Thomas et al. (2005) conducted a randomized controlled comparative study on forty-one patients with a stage 3 or stage 4 truncal pressure ulcer > 1.0 cm(2). The experimental group was randomized to a radiant-heat dressing device and the control group was randomized to a hydrocolloid dressing, with or without a calcium alginate filler. They were followed until healed or for 12 weeks. Eight patients (57%) in the experimental group had complete healing of their pressure ulcer compared with 7 patients (44%) with complete healing in the control group (p = .46). The authors concluded that although a 13% difference in healing rate between the two arms of the study was found, this difference was not statistically significant. This was a small sample size study.

A randomized pilot study was performed by Karr (2003) to evaluate the use of NNWT in the treatment of wounds associated with osteomyelitis. The study consisted of two arms. The control arm (n = 11) received standard wound care, which resulted in complete ulcer healing at an average of 127 days. The treatment arm (n = 5) received NNWT, which resulted in complete ulcer healing at an average of 59 days, or 54% faster than in the control arm. The authors concluded that although NNWT is not a direct treatment for osteomyelitis, this new treatment option results in accelerated healing of wounds associated with osteomyelitis. However, this difference did not reach statistical significance, and median wound healing times did not differ between groups (Karr, 2003).

Ellis et al. (2003) evaluated 33 patients with full-thickness pressure sores who were randomized to receive standard care or radiant heat therapy with a Warm-Up® device. The Warm-Up® device eradicated bacteria in 6 patients within 2 weeks of starting treatment compared to none in the standard care group. The significance of this study is limited by small sample size.

Low Frequency Ultrasound

Evidence for the use of low frequency ultrasound to treat wounds consists of studies that lack adequate sample sizes and proper control groups. Further controlled trials with larger sample sizes are necessary to demonstrate that low frequency ultrasound is beneficial for health outcomes in patients with wounds.

Mei and Zhang (2021) performed a review on the advances in biological application of and research on low frequency sonophoresis (LFS) technology. In the review, safety and application prospects for wound healing, repair, and regeneration of fibroblasts, cartilage tissue, ligaments, and tendons were addressed. The authors concluded that due to different LFS parameters and treatment regimens used in various studies, the basis for clinical applications was difficult to summarize, however, results of two studies support the role of LFS as an adjuvant therapy to promote healing. The available evidence is limited with overall poor-quality methodology and design, and diversity in reporting outcome measures. Therefore, no conclusions can be made regarding the relative efficacy, effectiveness, or safety of treatment. Further investigation is needed before clinical usefulness of this procedure is proven.

A randomized, double-blind, sham control, single-center study was conducted by Rastogi et al. (2019) to compare the efficacy of noncontact low-frequency airborne ultrasound therapy with sham therapy added to standard treatment in patients with neuropathic, clinically infected, or noninfected DFU (wound size > 2 cm2), Wagner grades 2 and 3. Fifty-eight patients received ultrasound or sham therapy for 28 days dosed daily for 6 days then twice a week for 3 weeks along with standard of care. The duration of wound was 15.8 ±11.2 weeks and 12.1 ±10.9 weeks and wound area of 11.3 ±8.2 cm2 and 14.8 ±13.8 cm2 (p = .507) in the ultrasound and sham groups, respectively. A > 50% reduction in wound area was observed in 97.1% and 73.1% patients (p = .042) in ultrasound and sham groups, respectively. Wound contraction was faster in the first 2 weeks with ultrasound therapy, 5.3 cm2 , compared with 3.0 cm2 (p = .025) with sham treatment. Wound area reduction of 69.4 ±23.2% and 59.6 ±24.9% (p = .126) was observed at 4 weeks in the ultrasound and sham groups, respectively. The authors concluded that low-frequency noncontact ultrasound is a useful adjunctive treatment to hasten wound healing in patients with chronic neuropathic DFUs. The limitations include a small sample size, a short follow-up, and single-center study.

Messa et al. (2019) conducted a retrospective review for patients undergoing lower extremity wound treatment with direct, low-frequency (22.5 kHz), high-intensity (~60 W/cm2) ultrasonic debridement. The study included 82 wounds in 51 patients. Primary outcomes included wound healing assessed by the percentage of wound reduction up to 180 days post ultrasound

treatment, readmission rates and reoperation rates. Average wound age at initial presentation was 1013 days with an average wound size of 9.0cm x 7.4cm. At 180-days post-debridement, 60% of wounds had completely healed. Readmission for wound healing (70%) was primarily for further debridement (41%). Wound infection (30%) was the most common readmission for wound complications (30%). Reoperations primarily consisted of treatments for further wound healing 96%. The authors concluded that the use of direct, low-frequency, high-intensity, ultrasonic debridement is a safe and reliable adjunctive therapy for the management of wounds. The study had a small sample size and no comparison group.

A randomized controlled trial was conducted by Murphy et al. (2018) to compare changes in wound size and appearance and health complication rates in patients with vasculopathy and lower-extremity wounds treated with or without low-frequency contact ultrasound debridement (LFCUD). Seventy patients with vasculopathy and lower-extremity wounds of mixed etiology were enrolled in the trial; 68 completed the study. Patients were randomized to receive LFCUD plus usual care (n = 33) or usual care (n = 37) at 4 weekly visits and were followed for up to 12 weeks. The main outcome measures included closed wounds, change in wound surface area (WSA), and wound appearance by the revised Photographic Wound Assessment Tool (revPWAT). After 4 weekly LFCUD treatments, patients in the LFCUD group had significantly better wound appearance compared with the control group treated only with usual care. LFCUD-treated wounds also had a significant reduction in WSA over 4 weeks that was not found in the usual care group. LFCUD treatment was also associated with a greater number of healed wounds and fewer instances of wound deterioration. The authors concluded that weekly LFCUD applications to patients with significant vasculopathy resulted in superior healing outcomes when compared with current usual wound care practice.

Bekara et al. (2017) conducted a systematic review to describe, evaluate, and compare three recently developed methods for the management of chronic wounds: hydrosurgery (Versajet), ultrasound therapy (the MIST therapy device), or plasma-mediated bipolar radio-frequency ablation therapy (Coblation). In January 2016, an electronic database search was conducted of MEDLINE, PubMed Central, and Embase for articles concerning these three innovative methods for the management of chronic wounds. A total of 389 references were identified by our search strategy, and 15 articles were included. The authors extracted data regarding the number and age of patients, indications, operating time, number of procedures, costs, wound healing time, decrease in exudation, perioperative blood loss, bacterial load, and the occurrence of complications. The 15 articles included studies that involved 563 patients who underwent hydrosurgery (7 studies), ultrasound therapy (6 studies), or Coblation (2 studies). Six randomized controlled trials were included that compared the use of a scalpel or curette to hydrosurgery (2 studies) or ultrasound therapy (6 studies). The authors concluded that hydrosurgery, in addition to being a very precise and selective tool, allowed significantly faster debridement. Ultrasound therapy provided a significant reduction of exudation, and improved the wound healing time. However, no comparative study dedicated to Coblation was identified. Despite the obvious clinical interest on this topic, their review of the current literature revealed a lack of prospective randomized studies comparing these devices with each other or with standard techniques, particularly for Coblation and hydrosurgery.

Cullum and Liu (2017) performed a systematic review to investigate whether ultrasound helps to heal or improve the symptoms of venous leg ulcers. Eleven randomized controlled trials (RCTs) involving a total of 969 participants were found. Eight studies compared ultrasound with use of no ultrasound for venous leg ulcers and the other three compared ultrasound with sham ultrasound. Seven out of the eleven studies were at high risk of bias, one study was at low risk of bias and bias could not be determine in three studies due to poor reporting. The authors found that the results of one study (337 participants) suggested that high-frequency ultrasound may be associated with more adverse events such as pain and skin redness (moderate quality evidence). The two studies that evaluated low-frequency ultrasound did not report whether participants experienced side effects. It is also uncertain whether either high- or low frequency ultrasound affects participants' quality of life. The outcomes of adverse effects, quality of life and cost were not reported for low-frequency ultrasound treatment. The authors concluded that it is uncertain whether therapeutic ultrasound (either high or low frequency) improves the healing of venous leg ulcers. They rated most of the evidence as low or very low quality due to risk of bias and imprecision. Most of the studies did not have many participants, had short follow-up times, and had poor study design.

A systematic review to examine ultrasound (US) for the treatment of chronic wounds, therapeutic efficacies, and clinical considerations was conducted by Alkahtani et al. (2017). Forty studies were included. The authors found that the evidence for the effectiveness of US for pressure ulcers is limited. Randomized controlled trials conducted showed no significant differences between the treatment groups. Low-frequency US techniques have been used in combination with standard wound care medications for treatment of purulent wounds. The findings of these studies showed the therapeutic effectiveness of US technique as an adjunctive or alternative treatment for purulent wound. Ultrasound to treat diabetic wound studies had a lack of strong evidence due to insufficient sample size, short follow-up period, non-random allocation to treatment arms, non-blinded outcomes evaluation, poor description of control, and concurrent interventions. The review found that therapeutic efficacy of

the low-frequency low-dose US technique in chronic venous leg ulcers can shorten the healing period of open wound. The authors concluded that although early studies have been relatively promising, the main challenge for developing US-based techniques as standard treatment options for different wounds is defining an exact dose-response for each wound. Further controlled trials with larger sample sizes are necessary.

Chang et al. (2017) performed a systematic review of current clinical evidence on the use of low-frequency (20-60 kHz) ultrasound in chronic wounds. Twenty-five studies were included. The authors found the current body of evidence supports the use of low frequency ultrasound as adjunctive therapy at least 3 times a week in the treatment of chronic wounds. The majority (21 of 25 studies) of the evidence is limited by study design, representing mostly level 3 to level 5 evidence. One of the major limitations of the study was its inability to discern the efficacy of treatment on different types of wound etiology due to the lack of sufficient study numbers for the pooling of data. More well-designed clinical trials are needed.

Wagner et al. (2017) performed a retrospective study to examine the effect of noncontact low-frequency ultrasound (NLFU) on deep tissue pressure injury (DTPI), both hospital-acquired and those present on admission (POA). Medical records from 44 adult patients with a DTPI treated with NLFU were reviewed; 22 had a hospital acquired DTPI (HADTPI) and 22 had DTPI POA. Data were collected from the medical records including demographic and relevant clinical characteristics, DTPI measurements, and DTPI evolution/resolution. All patients with HADTPI and DTPI POA treated with NLFU exhibited a statistically significant decrease in injury size from initiation to discontinuation of NLFU therapy (24.6 cm vs 14.4 cm). No statistically significant difference in wound resolution was found between HADTPI versus DTPI POA (27% vs 18%). Mean size of both HADTPI and DTPI POA decreased significantly from 15.9 to 13.4 cm. by NLFU therapy. Wounds were classified as resolved at completion of treatment in 23% (10 out of 44) of all treated patients. Of all patients with the potential to be resolved (not discharged early or expired) 63% (10 out of 16) had wounds classified as resolved. The authors concluded that study findings suggest that NLFU is a viable and promising treatment option for both HADTPI and DTPI POA. Future studies are needed to confirm these results and to examine efficacy and feasibility of DTPI across care settings.

In 2015, members of the Association for the Advancement of Wound Care (AAWC), Wound Healing Society, and the Canadian Association for Enterostomal Therapy formed the International Consolidated Guidelines Taskforce to update the AAWC Venous Ulcer Guidelines to the collaborative, intersociety, endorsed International Consolidated Venous Ulcer Guideline. This clinical practice guideline contains systematically developed recommendations intended to optimize patient care and assist physicians and other health care practitioners and patients to make decisions about appropriate health care for venous ulcer (VU) clinical care (Couch et al., 2017).

Recommendations include the following:

- Low frequency ultrasound may support healing, reduce pain, and improve QOL of non-healing venous or mixed etiology venous ulcers.
- Use ultrasound stimulation in combination with adequate patient-appropriate compression and moisture-retentive dressings to add possible VU healing benefit, but be aware that limited evidence supports cost effectiveness, enduring benefit, or parameters of application.
- Warming therapy has insufficient evidence of healing efficacy to inform VU management decisions about its use as an adjunct to optimal patient-appropriate compression and moisture-retentive dressings.

White et al. (2015) compared non-contact low-frequency ultrasound (NLFU) in addition to standard of care (SOC) 3 times a week, with SOC alone at least once-weekly in a single-site, blinded randomized control trial. Thirty-six randomized patients with chronic venous ulcers completed treatment (17 NLFU + SOC, 19 SOC). NLFU plus SOC patients showed a -47 % change in wound area; SOC, -39 % change; with a difference of -7.4 %. The median number of infections per patient was two in both groups and the change in quality of life (QoL) scores were not significant. Non-contact low-frequency ultrasound plus SOC patients reported a substantial mean reduction in pain score of -14.4 points, SOC patients' pain scores reduced by -5.3; with a difference of -9.1. The authors concluded that the results demonstrated the importance of high-quality wound care and that outcome measures favored NLFU + SOC over SOC, but the differences were not statistically significant. The significance of this study is limited by small sample size and a short follow-up period.

Tricco et al. (2015) examined systematic reviews that focused on interventions to treat complex wounds. Ninety-nine systematic reviews of wound care interventions were included in this overview of systematic reviews; 54 were systematic reviews with meta-analysis results and 45 were systematic reviews without a meta-analysis. Six categories of complex wounds were examined: venous leg ulcers, diabetic foot/leg ulcers, pressure ulcers, mixed arterial/venous leg wounds, unspecified mixed

complex wounds, and infected surgical wounds. The duration of treatment ranged from 2 days to 160 months and the duration of follow-up ranged from 2 days to 195 months. Based on data from systematic reviews including a meta-analysis with an AMSTAR score ≥ 8, various interventions for complex wounds were identified. These included bandages or stockings (multi-layer, high compression) and wound cleansing for venous leg ulcers; Four-Layer bandages for mixed arterial/venous leg ulcers; biologics, low frequency, low intensity noncontact ultrasound, and hydrogel dressings for diabetic leg/foot ulcers; hydrocolloid dressings, electrotherapy, air-fluidized beds, and alternate foam mattresses for pressure ulcers; and silver dressings and ultrasound for mixed complex wounds. Moderate to low quality review evidence found topical negative pressure and vacuum-assisted closure could be used for surgical wound infections. The authors concluded that various interventions can be utilized for treatment of varying types of complex wounds, but that few treatments were consistently effective across all outcomes.

A prospective, randomized, controlled, multi-center trial was conducted by Gibbons et al. (2015) to compare percent wound size reduction, proportions healed, pain, and quality-of-life (QOL) outcomes in patients randomized to standard care (SC) alone (n = 40) or SC and 40 kHz noncontact low-frequency ultrasound (NLFU) treatments (n = 41) 3 times per week for 4 weeks. One hundred and twelve individuals with documented venous stasis, a venous insufficiency and ulceration (VLU) greater than 30 days duration, measuring 4 cm2 to 50 cm2, and demonstrated arterial flow were enrolled. Index ulcers were 56 % recurrent, with a median duration of 10.3 months and median ulcer area of 11.0 cm2. All participants received protocol-defined SC compression (30 to 40 mm Hg), dressings to promote a moist wound environment, and sharp debridement for a minimum of 1 time per week. Ulcer measurements were obtained weekly using digital planimetry. Pain and QOL scores were assessed at baseline and after 4 weeks of treatment using the visual analog scale and the Short Form-36 Health Survey. After 4 weeks of treatment, the average wound size reduction was 61.6 % ±28.9 in the NLFU + SC compared to 45 % ±32.5 in the SC group. Reductions in median and absolute wound area as well as pain scores were also significant. The authors concluded that NLFU therapy with guideline defined standard VLU care should be considered for healing VLUs not responding to SC alone. They stated that the results of this study warrant further research on barriers to healing and the changes occurring in the tissue of the wound. This was not a blinded study.

In a 2014 study by Beheshti and colleagues, 90 participants with venous leg ulcers were randomized to receive standard treatment (consisting of compression therapy) and high frequency ultrasound, standard treatment and MIST® ultrasound therapy, or standard treatment alone. Study endpoints included the mean time duration of wound healing, edema, pain, size of ulcers and recurrence rate of the ulcers. In the two ultrasound groups, therapy was administered 3 times per week until the wound healed. Wound size, pain and edema were assessed at baseline ad after 2 and 4 months. Mean time duration of complete wound healing was 8.13 months in the standard treatment group, 6.10 months in the high frequency ultrasound group, and 5.70 months in the MIST ultrasound group. Edema was mild to severe in all groups at the first visit following treatment. After 4 months, the edema was less in both ultrasound groups when compared to the standard treatment group; however the difference of edema between the two ultrasound groups was not significant. Pain degree was also found to be decreased in the ultrasound groups compared to the standard treatment group, but again no significant differences were found between the two ultrasound groups. Six months following treatment, the venous leg ulcers recurred in 4 participants in the standard treatment group, and 2 participants in each of the ultrasound groups. Although the authors noted improvement in edema, a decrease in pain and less recurrence in the ultrasound groups when compared to compression therapy, there were no significant differences between the high frequency ultrasound and the MIST ultrasound groups. Further studies with longer follow-up are needed.

A randomized, controlled clinical study was conducted by Olyaie et al. (2013) to compare the effectiveness of standard treatment and standard treatment plus either high frequency or noncontact low frequency ultrasound when treating chronic wounds, including venous leg ulcers. It was noted that a total of 90 people participated in the study, including 47 men and 43 women. It was also noted that the average age for the participants was 38.3-year-old. Out of the 90 participants it was noted that 30 participants received standard care. Standard care was defined as follows: multilayered compression bandaging (40 mm Hg of pressure at the ankle graduated to 17 mm Hg to 20 mm Hg below the knee), nonadherent dressing, and regular debridement. Standard care dressing changes and ultrasound therapy were provided three times per week for 3 months or until healed. It was noted that 30 participants received standard treatment plus high-frequency ultrasound, which was delivered at 1-3 MHz for 5 to 10 minutes. The remaining 30 participants received standard treatment plus low-frequency ultrasound, which was delivered at 40 kHz for 4-10 minutes. The final results of this study were reported to show that the outcome of both methods of the ultrasound therapy was better than standard care alone. The result of this one study does not provide sufficient clinical data, to change the current unproven status of the use of low frequency ultrasound for the treatment of wounds. Additional studies and randomized trials are required to support and confirm the long- and short-term findings of this lone study.

Yao et al. (2012) conducted a randomized clinical study designed to determine the effects of non-contact low frequency ultrasound (NCLF-US) devices when used for the treatment of chronic non-healing wounds. Subjects were randomly assigned to one of three groups: application of NCLF-US thrice per week (Group 1), NCLF-US once per week (Group 2) and the control (Group 3) that received no NCLF-US. All subjects received standard wound care plus offloading for a total of 4 weeks. Percent area reduction (PAR) of each wound compared to baseline was evaluated weekly. Twelve DFU patients, 2 (16·7%) type 1 and 10 (83·3%) type 2 diabetics, with an average age of 58 ±10 years and a total of 12-foot ulcers were enrolled. Group 1 showed significant wound area reduction at weeks 3, 4 and 5 compared to baseline, with the greatest PAR, 86% ($p < 0·05$); Groups 2 and 3 showed 25% PAR and 39% PAR, respectively, but there were no statistically significant differences between Group 2 and Group 3 over time. Based on the information provided by this small, randomized study demonstrated that NCLF-US is an effective in treating neuropathic diabetic foot ulcers through at least in part, inhibiting pro-inflammatory cytokines in chronic wound and improving tissue regeneration. Therapeutic application of NFLU three times per week allows for the best wound area reduction. The results of this study must be confirmed in a larger trial.

Watson et al. (2011) assessed the clinical effectiveness of weekly delivery of low dose, high frequency therapeutic ultrasound in conjunction with standard care for hard to heal venous leg ulcers in a multicenter, two arm randomized controlled trial. The study included 337 patients with at least one venous leg ulcer of > 6 months' duration or > 5 cm (2) area and an ankle brachial pressure index of ≥ 0.8. The study evaluated weekly administration of low dose, high frequency ultrasound therapy for up to 12 weeks plus standard care compared with standard care alone. The two groups showed no significant difference in the time to healing of the reference leg ulcer. After adjustment for baseline ulcer area, baseline ulcer duration, use of compression bandaging, and study center, there was still no evidence of a difference in time to healing. There was no difference in time to complete healing of all ulcers, with median time to healing of 328 days with standard care and 365 days with ultrasound. There was no evidence of a difference in rates of recurrence of healed ulcers (17/31 with ultrasound vs 14/31 with standard care). There was also no difference between the two groups in health-related quality of life; both for the physical component score and the mental component score, but there were significantly more adverse events in the ultrasound group. The authors concluded that low dose, high frequency ultrasound administered weekly for 12 weeks during dressing changes in addition to standard care did not increase ulcer healing rates, affect quality of life, or reduce ulcer recurrence.

Driver et al. (2011) performed a meta-analysis and summarized the effects of a noncontact low-frequency ultrasound (NLFU) therapy on healing of chronic wounds. The meta-analysis included 8 published studies that reported effects of NLFU on wound size and healing rate of chronic wounds in 444 patients. Mean time to healing was 8.2 weeks, with 42% of wounds healed by 12 weeks. The wound volume was reduced by 79.7% over a mean of 12 weeks. According to the authors, noncontact low-frequency ultrasound for treatment of chronic wounds was associated with consistent and substantial wound size reductions, as well as favorable rates of healing. However, the quality of the evidence was limited by small patient numbers and lack of appropriate comparison groups.

Voigt et al. (2011) conducted a systematic review and meta-analysis to examine low-frequency (20-30 kHz) ultrasound delivered at either low or high intensity. The objective of the review was to determine whether low-frequency ultrasound used as an adjunctive therapy improves the outcomes of complete healing and reduction of size of chronic lower limb wounds. Eight randomized controlled trials were identified. Three of these trials were unpublished papers presented at conferences. Results demonstrated that early healing (at ≤ 5 months) in patients with venous stasis and diabetic foot ulcers was favorably influenced by both high and low-intensity ultrasound delivered at a low frequency-either via contact or noncontact techniques. However, according to the authors, the quality of the evidence is in general of lower quality for both types of ultrasound, and especially for low-frequency low-intensity noncontact ultrasound because of significant biases. The authors stated that although it appears from the meta-analysis performed that low-frequency low-intensity noncontact ultrasound is more effective at complete healing than standard of care, the quality of the evidence as it relates to biases was poor.

Cullum et al. (2010) assessed whether ultrasound (US) increases the healing of venous leg ulcers by searching several databases for randomized controlled trials (RCTs) comparing US with no US. Two authors independently assessed the search results and selected eligible studies. Details from included studies were summarized using a data extraction sheet, and double-checked. Eight trials were included; all had unclear, or high, risks of bias, with differences in duration of follow-up, and US regimens. Six trials evaluated high frequency US and five of these reported healing at 7 - 8 weeks. Significantly more patients healed with US than without it at 7 - 8 weeks, but later assessments at 12 weeks showed the increased risk of healing with US was no longer statistically significant. One poor-quality study of high-frequency US found no evidence of an effect on healing after three weeks' treatment. Two trials evaluated low frequency US and reported healing at different time points. Both trials reported no evidence of a difference in the proportion of ulcers healed with US compared with no US: both were significantly

underpowered. The authors concluded that the trials evaluating US for venous leg ulcers are small, poor-quality, and heterogeneous. They state that there is no reliable evidence that US hastens healing of venous ulcers. There is a small amount of weak evidence of increased healing with US, but this requires confirmation in larger, high-quality RCTs. They conclude that there is no evidence of a benefit associated with low frequency US.

Al-Kurdi et al. (2008) reviewed results from 8 small trials (average enrollment 44 patients) with comparator treatments of either sham ultrasound or standard of care. Studies had either a medium or high risk of bias, which indicates a reduction in study validity. Typical study limitations included lack of allocation concealment and failure to report baseline characteristics, randomization methods, and blinding of outcome assessors. The authors concluded that the available evidence suggests that there may be a benefit from ultrasound therapy in healing venous leg ulcers, however due to the poor quality of the studies; these results need to be interpreted with caution.

The National Institute for Health and Care Excellence (NICE) guideline for diabetic foot problems prevention and management recommends one or more of the following as standard care for treating diabetic foot ulcers: offloading; control of foot infection; control of ischemia; wound debridement; and wound dressings. NICE recommends that negative pressure wound therapy should be considered after surgical debridement for diabetic foot ulcers, on the advice of the multidisciplinary foot care service. Dermal or skin substitutes as an adjunct to standard care can be considered when treating diabetic foot ulcers, only when healing has not progressed, and on the advice of the multidisciplinary foot care service (NICE, 2019).

In a National Institute for Health and Clinical Excellence (NICE) guidance for MIST Therapy® System for the Promotion of Wound Healing in Chronic and Acute Wounds, NICE states that the MIST Therapy® System shows potential to enhance the healing of chronic, hard-to-heal, complex wounds, compared with standard methods of wound management. However, the amount and quality of published evidence on the relative effectiveness of the MIST Therapy® System is not sufficient, at this time, to support the case for routine adoption of the MIST Therapy® System (NICE, 2011, Reaffirmed June 2016).

Clinical Practice Guidelines

Association for the Advancement of Wound Care (AAWC)

The AAWC released a guideline on the care of pressure ulcers. While noncontact ultrasound therapy was included as a potential second-line treatment if first-line treatments failed to induce wound healing, the strength of the evidence supporting this decision was low (Level C), indicating that there is limited evidence for this technology (AAWC, 2010).

In an updated 2015 guideline for venous ulcers (VU), the AAWC indicates that low frequency ultrasound may support healing, reduce pain, and improve QOL of non-healing venous or mixed etiology venous ulcers (moderate strength of rating). The AAWC also indicates that ultrasound stimulation may be used in combination with adequate patient-appropriate compression and moisture-retentive dressings to add possible VU healing benefit but be aware that limited evidence supports enduring benefit or parameters of application (AAWC, 2015).

American Podiatric Medical Association

The American Podiatric Medical Association in collaboration with the Society for Vascular Surgery and the Society for Vascular Medicine developed a 2016 clinical practice guideline for the management of diabetic foot. Their recommendations do not include warming therapy, noncontact normothermic wound therapy (NNWT) or low frequency ultrasound for the treatment of wounds (Hingorani et al. 2016).

Noncontact Real-Time Fluorescence Wound Imaging

The safety and efficacy of handheld, noncontact imaging devices that can visualize fluorescent bacteria and measure wound surface area in real-time has not been established in the published literature. Despite FDA approval on the MolecuLight i:Xdevice, additional robust clinical studies need to be completed to determine the safety and efficacy of this device. While some evidence exists for the predictive characteristics of the method compared to conventional wound cultures, the clinical significance of the method in improving care and patients' outcomes is unclear.

A clinical evidence assessment by ECRI suggests the evidence for the use of the MolecuLight i:X Fluorescence Imaging System is inconclusive. While the evidence might suggest the MolecuLight i:X Fluorescence Imaging System may be helpful for

identification of wounds with bacterial loads, additional RCTs are needed to confirm the safety and efficacy of the device (ECRI 2021).

With five years of published research on bacterial fluorescence imaging (MolecuLight *i:X* device), Farhan and Jeffery (2021) summarized and analyzed the validity of the procedure and compared it to the current standard of care; clinical assessment and microbiological analysis. They highlighted the benefits that could be obtained through the use of this technology as well as the limitations and the feasibility of incorporating this novel procedure into the standard of care. The authors concluded that fluorescence imaging technology has certain ingrained limitations. The first is that the violet excitation light is unable to penetrate more than 1 mm to 1.5 mm into the skin [74,75]. While this enables the detection of some subsurface bacteria, the presence of bacteria deeper within the wound tissue may not be visible, including deep tunneling infection. Furthermore, the fluorescence signals associated with bacteria cannot provide a numerical estimate for the bacterial load other than indicating it is ≥ 104 CFU/g. Nor is it able to determine the specific bacterial species or the antibiotic susceptibility of these microorganisms. This would require microbiological analysis using swab or tissue samples. Finally, there are certain bacterial and yeast species that are not detectable when colonizing a wound on their own as described above. For these reasons, the authors concluded that fluorescence imaging should not take the place of the current standard of care which involves the use of CSS supplemented with microbiological analysis when necessary, but instead acts as an additional tool in the clinician's toolbox for diagnosis. Using fluorescence imaging can vastly improve wound assessment when used together with CSS. When the microbiological analysis is required to identify specific bacterial species, quantitative loads, and/or resistance markers present, then fluorescence imaging can aid microbiological sample collection analysis by guiding sampling location to a region positive for red or cyan fluorescence to avoid false-negative culture reports. Further research is needed to specifically on healing rates surrounding the use of fluorescence imaging.

A National Institute for Health and Care Excellence (NICE) Medtech innovation briefing [MIB212] concluded that there is limited evidence to show whether MolecuLight i:X reduces wound closure time or improves antibiotic stewardship (2020).

Le et al. (2020, included in ECRI report above), conducted a prospective multicenter observational study on the use of MolecuLight i:X for 350 participants. Wounds underwent clinical signs and symptoms (CSS) assessment using the International Wound Infection Institute (IWII) checklist immediately followed by fluorescent imaging with the MolecuLight device. CSS assessment missed approximately 85% of bacterial loads that were greater than 10^4 CFU/g which can be indicative of infection. The authors found the use of the MolecuLight device resulted in higher sensitivity and accuracy of the detection of the bacteria. Limitations of the study included underreporting of bacteria diversity with the culture analysis, limited experience by clinicians in using the MolecuLight device and funding of the study by MolecuLight, Inc. The authors recommend the MolecuLight device be used in combination with CSS assessment and that evidence from larger longitudinal studies would be beneficial.

Farhan and Jeffery (2020) conducted a single-center observational study to assess the MolecuLight i:X device for efficacy in pediatric burn wounds and the overall feasibility of the device. Ten patients were recruited and the device was utilized on sixteen different wounds to assess for the presence or absence of clinical signs and symptoms of infection; swabs were obtained to confirm the findings. The authors found the device demonstrated ability to visually identify significant bacterial growth and high compliance for use of the device. These findings may pave the way for including bacterial fluorescence imaging use into the pediatric burn population.

Chew and associates (2020) stated that early diagnosis of wound infections are crucial as they have been shown to increase patient morbidity and mortality. These researchers examined the use of MolecuLight i:X to identify infections in acute open wounds in hand trauma. In a prospective cohort study, data was collected from patients who attended the hand trauma unit over a 4-week period before having surgery. Wounds were inspected for clinical signs of infection and auto-fluorescence images were taken using the MolecuLight i:X device. Wound swabs were taken and results interpreted according to report by microbiologist. Auto-fluorescence images were interpreted by a clinician blinded to the microbiology results. A total of 31 patients were included and data collected from 35 wounds; 3 wounds (8.6 %) showed positive clinical signs of infection, 3 (8.6 %) were positive on auto-fluorescence imaging and 2 (5.7 %) of wound swab samples were positive for significant infection. Auto-fluorescence imaging correlated with clinical signs and wound swab results for 34 wounds (97.1 %). In 1 case, the clinical assessment and auto-fluorescence imaging showed positive signs of infection but the wound swabs were negative. The authors concluded that auto-fluorescence imaging in acute open wounds may be useful to provide real-time confirmation of bacterial infection and thus guide management.

A pilot study performed by Pijpe et al. (2019) compared the detection of bacteria in burn wounds between an bacterial fluorescence imaging device MolecuLight i:X and standard microbiological swabs. A total of 14 patients with 20 wounds participated in the study. Wounds were swabbed three times: once with a standard swam, once with a high-fluorescent area swab, and a finally with a non-fluorescent (nF) area swab. Proportion agreement of the microbiological results was calculated and the accuracy of the device to detect relevant bacteria was assessed. The diagnostic accuracy of the bacterial fluorescence imaging device to detect relevant bacteria in burn wounds was moderate and the reliability was equal to standard swabbing. Further research in larger sample sizes is needed for safety and efficacy of the fluorescence imaging device.

Raizman et al. (2019) conducted a prospective comparative study aimed to assess the accuracy, clinical incorporation and documentation capabilities of a handheld bacterial fluorescence imaging device (MolecuLight *i*:X). In a clinical trial, trained clinicians digitally measured and captured fluorescence images to assess for presence moderate to heavy loads of bacteria in 50 wounds. The results showed wound measurement was accurate 95%. A positive signal for bacterial fluorescence was demonstrated 72%. Sampling of wounds was found to under-report bacterial loads relative to fluorescence-guided curettage samples.

In a pilot study, Serena et al. (2019) evaluated 19 wounds for diagnostic accuracy of wound bacteria when bacterial fluorescence imaging (MolecuLight i:X) was used in combination with clinical evaluation of signs and symptoms (CSS). CCS criteria for wounds to determine the presence or absence of moderate-to-heavy bacterial loads was done using the NERDS (non-healing, exudate, red and bleeding surface or granulation tissue, debris and smell) and STONEES (size, temperature, osteomyelitis, new areas, exudate, erythema, and smell) method. Then fluorescence images of the wound were acquired along with determination of bacterial presence or absence. Biopsies were obtained under local anesthetic and sent to lab for confirmation; all lab staff was blinded to the wound's assessment outcomes. 4 out the 19 patients (21%) were identified as positive (for moderate-to-heavy bacterial loads) based on clinical signs and symptoms alone. The use of fluorescence imaging in combination with CSS assessment led to 2.5–3.2-fold improvements in reported diagnostic accuracy measures as compared with CSS assessment alone. The authors concluded the data in this pilot study suggests that current standard of care assessment for wounds fails to identify many wounds with moderate-to-heavy bacterial loads, leaving patients with undetected and untreated bacteria. The addition of bacterial fluorescence imaging improved sensitivity and accuracy of assessments for detecting moderate-to-heavy bacterial loads. Limitations of this study included small sample size thus not statistically significant and lack of follow-up. Future larger sample studies are needed.

In a prospective observational study, Hurley et al. (2019) swabbed 43 wounds from 33 patients. The authors wanted to establish the accuracy of the wound imaging device at detecting bacteria. All data was collected in the outpatient wound care clinic setting. Patients over 18 were recruited with a variety of wounds; participants on antibiotics for wound infection were excluded. Images from the wounds were captured with the handheld fluorescent device; upon visualization of bacteria, areas of red or cyan fluorescence indicating bacteria were swabbed and sent to the lab for culture and sensitivity testing. Of the swabs taken, 95.4% were positive for bacteria growth and nine different species of bacteria were identified. Limitations included device incompatibility for wounds with active bleeding, dressings that contained silver (a potent antimicrobial) and sample size. Despite these limitations, the authors concluded the device as safe, effective and accurate for use. Further research should be directed to its application in other environments such as preoperative and perioperative settings.

Twenty patients with burn wounds were photographed under both a standard light and violet light illumination to compare presentations of obvious infection signs and symptoms. Microbiology swab samples were obtained; the fluorescence images were used to guide swabs to where the bacteria were collecting. Four patients did not have bacterial contamination based on their images and swab results, sixteen patients showed growth of Staphylococcus aureus, Pseudomonas aeruginosa, or other bacteria and nine of the patients, by definition, had infections. Blumenthal and Jeffery (2018) found the prospective comparative study to show the efficacy of the MolecuLight i:X is evident due to the microbiology results correlating to the images. With these early results and guidance of swab samples, the MolecuLight i:X may be able to detect bacterial load before an infection and subsequent graft failure, thereby shortening lengths of hospital stay and improving overall healing. Further research with well-designed studies is needed to test the device in terms of being an early intervention tool.

Rennie et al. (2017, included in the ECRI report above) conducted a prospective cohort study where 60 lower chronic limb wounds were imaged for bacterial fluorescence using the MolecuLight i:X imaging device. Point-of-care bacterial fluorescence imaging illuminates a wound with 405nm light, triggering bacteria to produce red fluorescence and enabling real-time bacterial concentration. Regions positive for red fluorescence were sampled by either biopsy or curettage for bacterial presence and

analysis. The authors found fluorescence imaging of wounds offers clinicians' real-time information on the wound's bacteria which can potentially influence treatment decisions.

For information on current clinical trials studying the use of MolecuLight i:X and bacterial growth, go to www.clinicaltrials.gov. (Accessed March 16, 2022)

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Warm-Up® Active Wound Therapy (Augustine Medical, Inc.) received 510(k) approval from the FDA on March 28, 1997 as a wound and burn occlusive heated dressing. Refer to the following website for more information (use product code MSA): http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed April 22, 2022)

The Mist Therapy® System is regulated by the FDA as a Class II device and is classified as an ultrasound wound cleaner. This device was approved via the FDA 510(k) process in April 2004. In May 2005, FDA granted marketing clearance to Celleration for the MIST Therapy® System 5.1 with an expanded indication. The approved indication for use is to produce "a low-energy ultrasound-generated mist to promote wound healing through wound cleansing and maintenance debridement by the removal of yellow slough, fibrin, tissue exudates, and bacteria". In 2014 the FDA approved the UltraMIST® System (K140782), a smaller, sleeker, and user-friendly design. Refer to the following website for more information: http://www.accessdata.fda.gov/cdrh_docs/pdf5/K050129.pdf. (Accessed April 22, 2022)

Refer to the following website for additional devices (use product code NRB): https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed April 22, 2022)

The U.S. Food and Drug Administration (FDA) cleared The MolecuLight i:X® device under its 510(k) premarket notification process as substantially equivalent to predicate devices. For additional information refer to the following: https://www.accessdata.fda.gov/cdrh_docs/pdf19/K191371.pdf. (Accessed April 22, 2022).

Refer to the following website for additional devices (use product code QJF or FXN): http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed April 22, 2022)

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Policy History/Revision Information

Date	Summary of Changes
12/01/2022	**Title Change** • Previously titled *Warming Therapy and Ultrasound Therapy for Wounds (for Tennessee Only)* **Coverage Rationale** • Added language to indicate noncontact real-time fluorescence wound imaging for bacterial presence is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy [previously addressed in the Medical Policy titled *Omnibus Codes (for Tennessee Only)*] **Applicable Codes** • Added CPT codes 0598T and 0599T [previously addressed in the Medical Policy titled *Omnibus Codes (for Tennessee Only)*] **Supporting Information** • Updated *Description of Services*, *Clinical Evidence*, *FDA*, and *References* sections to reflect the most current information • Archived previous policy version CS132TN.J

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

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