Noncontact Warming Therapy, Ultrasound Therapy, and Fluorescence Imaging for Wounds

Policy Number: REHAB 031.19
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➲ Instructions for Use

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Related Policies
None

Coverage Rationale

Warming therapy or noncontact normothermic wound therapy (NNWT) and low frequency ultrasound therapy are unproven and not medically 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 the member specific benefit plan document 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 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)
97610	Low frequency, non-contact, non-thermal ultrasound, including topical application(s), when performed, wound assessment, and instruction(s) for ongoing care, per day

CPT® is a registered trademark of the American Medical Association

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

HCPCS Code	Description
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.

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, diabetic foot ulcers (DFUs) and arterial 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 DFUs 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 therefore 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 participants 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 participants (57%) in the experimental group had complete healing of their pressure ulcer compared with seven participants (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.

Karr (2003) performed a randomized pilot study 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.

Ellis et al. (2003) evaluated 33 participants 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 six participants 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 participants with wounds.

Chen et al. (2023) performed a meta-analysis to evaluate the effect of low-frequency ultrasound as an added treatment for chronic wounds. A systematic literature search, up to May 2022, was performed and 838 subjects with chronic wounds at the baseline of the studies; 412 of them were using the low-frequency ultrasound (225 low-frequency high-intensity contact ultrasound for DFUs, and 187 low-frequency low-intensity non-contact ultrasound for a venous leg wound ulcers), and 426 were using standard care (233 sharp debridement for DFUs and 193 sham treatments for venous leg wound ulcers). Odds ratio (OR), and mean difference (MD) with 95% confidence intervals (CIs) were calculated to assess the effect of low-frequency ultrasound as an added treatment for chronic wounds using the dichotomous, and contentious methods with a random or fixed-effect model. The low-frequency high-intensity contact ultrasound for DFUs had lower non-healed DFUs at ≥ 3 months (OR, 0.37; 95% CI, 0.24-0.56, p < .001), a higher percentage of DFUs area reduction (MD, 17.18; 95% CI, 6.62-27.85, p = .002) compared with sharp debridement for DFUs. The authors concluded that the low-frequency low-intensity non-contact ultrasound for a venous leg wound ulcers had a lower non-healed venous leg wound ulcers at ≥ 3 months (OR, 0.31; 95% CI, 0.15-0.62, p = .001), and higher percentage venous leg wound ulcers area reduction (MD, 18.96; 95% CI, 2.36-35.57, p = .03) compared with sham treatments for a venous leg wound ulcer. The low-frequency ultrasound as an added treatment for DFUs and venous leg wound ulcers had lower non-healed chronic wound ulcers at ≥ 3 months, a higher percentage of chronic wound ulcers area reduction compared with standard care. The authors also stated analysis of outcomes should be with caution because of the low sample size of seven out of 13 studies in the meta-analysis and a small number of studies in certain comparisons. Along with small sample size, additional limitations include possible bias induced by incomplete details including age, gender, and nutritional status of subjects, inclusion of observational studies, as well as missing data from unpublished articles. The findings of this study need to be validated by well-designed studies. [Authors Olyaie et al. (2013), Gibbons et al. (2015), Murphy et al. (2018), and Rastogi et al. (2019), who were previously cited in this policy, are included in this systematic and meta-analysis review.]

Flores-Escobar et al. (2022) conducted a systematic review and meta-analysis of RCTs to investigate the effect of ultrasound-assisted wound (UAW) debridement in participants with DFUs. All selected studies were evaluated using the Cochrane risk of bias tool to assess the risk of bias for randomized controlled trials. A total of eight RCTs met inclusion criteria, with 263 participants. Concerning the healing rate comparing UAW versus the control group, a meta-analysis estimated the pooled OR at 2.22 (95% CI 0.96–5.11, p = 0.06), favoring UAW debridement, with low heterogeneity (x2 = 7.47, df = 5, p = 0.19, I2 = 33%). Time to healing was similar in both groups: UAW group (14.25 ±10.10 weeks) versus the control group (13.38 ±1.99 weeks, p = 0.87). Wound area reduction was greater in the UAW debridement group (74.58% ±19.21%) than in the control group (56.86% ±25.09%), although no differences were observed between them (p = 0.24). UAW debridement showed higher healing rates, a greater percentage of wound area reduction, and similar healing times when compared with placebo (sham device) and standard of care in participants with DFUs, although no statistical differences were observed between groups. The main limitation of this systematic review with meta-analysis is the small sample size of the RCTs included, which limits the generalizability of the results. Another important limitation is heterogeneity between the different RCTs, in terms of the clinical characteristics of the DFUs included (depth, infection, or ischemia), study follow-up time, time of application, and frequency of application associated with the type of ultrasound used (contact or non-contact). Finally, the lack of certain information in the studies is another limitation in evaluating some variables since it prevents the inclusion of some studies in this meta-analysis. Further clinical trials with low risk of bias, using control groups, with clear randomization and blinding of results is needed to determine the clinical relevance of these findings. [Study by Rastogi et al. (2019), which was previously cited in this policy, is included in this systematic review and meta-analysis review.]

Messa et al. (2019) conducted a retrospective case series for participants 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 participants. 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.

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 using 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, and 15 articles were included. The authors extracted data regarding the number and age of participants, 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 participants who underwent hydrosurgery (seven studies), ultrasound therapy (six studies), or Coblation (two studies). Six RCTs were included that compared the use of a scalpel or curette to hydrosurgery (two studies) or ultrasound therapy (six 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. The authors concluded that 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 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 determined 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. RCTs 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. US 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 three 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-Cox 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 participants with a DTPI treated with NLFU were reviewed; 22 had a hospital acquired DTPI (HADTPI) and 22 had DTPI POA. Data was collected from the medical records including demographic and relevant clinical characteristics, DTPI measurements, and DTPI evolution/resolution. All participants 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 participants. Of all participants 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. The findings are limited by lack of a control group receiving a different treatment. Future studies are needed to confirm these results and to examine the efficacy and feasibility of DTPI across care settings.

White et al. (2016) compared non-contact low-frequency ultrasound (NLFU) in addition to standard of care (SOC) three times a week, with SOC alone at least once-weekly in a single-site, blinded randomized control trial. Thirty-six randomized participants with chronic venous ulcers completed treatment (17 NLFU + SOC, 19 SOC). NLFU plus SOC participants showed a -47 % change in wound area; SOC, -39% change; with a difference of -7.4 % ($p = 0.6$). 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 participants reported a substantial mean reduction in pain score of -14.4 points, SOC participants' pain scores reduced by -5.3; with a difference of -9.1 ($p = 0.08$). 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.

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 three 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 four participants in the standard treatment group, and two 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. The findings are limited by lack of masking to group assignment. Further studies with longer follow-up are needed.

Yao et al. (2014) conducted a randomized clinical pilot 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 participants with DFU, 2 (16·7%) with type 1 and 10 (83·3%) with type 2 diabetes, 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 DFUs 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 participants 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.

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. All fluorescence wound imaging devices, regardless of FDA approval, require further clinical studies for evaluation to ensure their safety and efficacy are validated. While some evidence exists for the predictive characteristics of the method compared to conventional wound cultures, the clinical utility of the method in improving care and participants' outcomes is unclear.

Oropallo et al. (2025) conducted a prospective, single-center cohort study aimed to evaluate the association between high bacterial colonization and wound associated pain in venous ulceration using MolecuLight i:X™ for bacterial detection. The authors evaluated 46 adults with venous ulceration of the lower extremity self-reporting a wound-associated pain score of ≥ 4 on a scale of 1 to 10. Before any treatments were performed (e.g., debridement), subjects rated their pain during the study visit, and fluorescence images were captured. Regions of pain and positive fluorescence signals were sketched onto a printed wound image. Fluorescence imaging was repeated post procedurally, and subjects rerated their pain either at the end of the study visit or over the phone the following day. Semiquantitative analysis involved visual estimation of the percentage overlap between regions of fluorescence and pain in the wound bed. Wilcoxon matched pairs signed rank tests and Mann-Whitney t tests assessed changes in pain scores post procedurally. Fluorescence from elevated bacterial loads and biofilm was present in every venous ulcer assessed, usually covering ≤ 50% of the wound bed and commonly colonizing the wound edges. Regions of pain were more extensive than regions of fluorescence within the wound bed, and some degree of overlap was identified in 40 of 46 participants (87%). This overlap was often substantial (29 participants with > 25% overlap and 16 with > 50% overlap). Overall mean pain scores were 8.17 before the procedure and 6.87 after the procedure, corresponding with a 1.30-point reduction that was statistically significant ($p < .0001$). Pain score reduction was higher when participants rerated their pain one day after debridement (3.40-point reduction; $p = .004$).In conclusion, the authors observed that fluorescence signals from clinically significant bacterial colonization and biofilms were commonly present in painful venous lower extremity ulcerations. Regions of patient-reported pain and positive fluorescence frequently overlapped, suggesting a relationship between the two. Wound-associated pain scores were immediately reduced after objectively targeted bacterial removal via real-time fluorescence imaging, with an even greater reduction observed by the next day. The authors concluded that MolecuLight i:X imaging device offers a practical method to enhance the management of venous ulcers through its noninvasive, real-time fluorescent visualization. Understanding the association between chronic bacterial presence and pain in venous ulcers can inform treatment and management strategies, potentially enhancing patient quality of life and satisfaction, promoting healing, and reducing complications. This study has limitations. First, the relatively small sample size may limit the generalization of the results. Data collection was limited to treatment during a single appointment, which does not account for the full scope of wound management. Longitudinal studies should be conducted to establish the role of imaging-informed treatment in the context of consistent, multidisciplinary management of chronic venous ulcers.

Hanson-Viana et al. (2024) conducted a single-center, prospective observational study to investigate the use of real-time fluorescence imaging device, MolecuLight i:X™, as a predictive tool for skin graft integration through detection of common pathogens associated with burn wound infection and graft failure. This study included adult burn patients with previously infected wounds that were deemed clinically and microbiologically clean and were therefore candidates for grafting. Prior to grafting, a fluorescence imaging assessment (blinded to the surgical team) localized areas positive for moderate-high bacterial loads (> 104 CFU/gr). The most common pathogens found in the initial infection were P. aeruginosa (40%), E. coli (16%), and E. cloacae (13%). Intra-operatively, a standard swab sample from the recipient site was collected by the surgical team. Postoperatively, areas positive/negative for fluorescence and areas of graft take and failure were overlapped and measured (cm2) over a 2D schematic. The performance and accuracy of fluorescence imaging and swab sampling in relation to graft outcomes were assessed. A total of 38 participants were enrolled in this study with 73% (n = 28) male, and the mean age was 42 years ±SD13 years. The most common burn causes were direct fire contact (73%, n = 28), electrical (18%, n = 7), and contact burns (8%, n = 3). Six participants had comorbidities: three participants with psychiatric disorders (schizophrenia, depressive disorder, substance withdrawal syndrome), one with hypertension, and

three with type 2 diabetes. The mean total body surface area (TBSA) involvement was 14.5 ±12.4 % [range 0.8 – 40.2%]. Twenty-five of the 38 subjects enrolled had complete graft take while 13 had partial graft losses. There were no total losses. Fluorescence imaging was positive in 100% of losses versus 31% (4/13) of the swab microbiology. Fluorescence imaging was found to have a sensitivity of 86%, specificity of 98%, PPV of 72%, NPV of 99%, and an accuracy of 94% for predicting any type or range of graft loss in the entire cohort. Meanwhile, the sensitivity of microbiology from swab samples was 30%, with a specificity of 76%. The authors concluded that real-time fluorescence imaging of bacterial and biofilm presence and location can identify areas of the wound bed where grafts are most likely to fail or succeed with high sensitivity and specificity. Better diagnostic methods that flag pre-infection states and enable proactive bacterial and biofilm management may lead to better outcomes and support the viability of early excision. Further studies, however, are needed to prove the association of fluorescence imaging with other burn wound outcomes, including research that compares fluorescence imaging with other advanced microbe typification methods, or investigates variations in graft take between beds prepared using fluorescence guidance and those following standard care protocols.

Mayer et al. (2024) conducted a prospective, single-blind clinical trial to evaluate the diagnostic accuracy of clinical signs of biofilm (CSB), bacterial fluorescence imaging (MolecuLight™), and wound blotting (Saraya®, Osaka, Japan) against biofilm identification as validated by gold standard scanning electron microscopy (SEM) imaging and microbiology. In this study, 40 chronic hard-to-heal wounds underwent the following assessments: (1) clinical signs of biofilm (CSB), (2) biofilm blotting, (3) fluorescence imaging for localizing bacterial loads, wound scraping taken for (4) SEM to confirm matrix encased bacteria (biofilm), and (5) PCR (Polymerase Chain Reaction) and NGS (Next Generation Sequencing) to determine absolute bacterial load and species present. The authors used a combination of SEM and PCR microbiology to calculate the diagnostic accuracy measures of the CSB, biofilm blotting assay, and fluorescence imaging. Study data demonstrate that 62.5% of wounds were identified as biofilm-positive based on SEM and microbiological assessment. By employing this method to determine the gold truth, and thus calculate accuracy measures for all methods, fluorescence imaging demonstrated superior sensitivity (84%) and accuracy (63%) compared to CSB (sensitivity 44% and accuracy 43%) and biofilm blotting (sensitivity 24% and accuracy 40%). Biofilm blotting exhibited the highest specificity (64%), albeit with lower sensitivity and accuracy. Using SEM alone as the validation method slightly altered the results, but all trends held constant. The authors concluded that this trial provides the first comparative assessment of bedside methods for wound biofilm detection. The authors report the diagnostic accuracy measures of these more feasibly implementable methods versus laboratory-based SEM. Fluorescence imaging showed the greatest number of true positives (highest sensitivity), which is clinically relevant and provides assurance that no pathogenic bacteria will be missed. It effectively alerted regions of biofilm at the point-of-care with greater accuracy than standard clinical assessment (CSB) or biofilm blotting paper, providing actionable information that will likely translate into enhanced therapeutic approaches and better patient outcomes. This study has limitations. The biofilm prevalence reported here is likely an underestimation due to a small sample size. The microbiological analyses herein were semiquantitative, whereas quantitative analysis could have provided more insights, particularly in the cases that were inconclusive for biofilm. The threshold used in the microbiological analysis was set as 10^5 CFU/g of tissue due to processing lab standards. If this threshold had been set lower, the results of this analysis could provide more information. The MolecuLight™ device detects bacteria at a lower threshold (starting at 10^4 CFU/g), which differs from this threshold. Due to product supply constraints, only 35/40 subjects included were exposed to wound blotting. This meant that sensitivity and specificity were calculated with a slightly smaller sample size. When sample sizes are small, the confidence interval around the sensitivity and specificity widens, indicating greater uncertainty. Finally, while efforts were made to choose the most suitable validation method, there is currently no consensus on the definitive method for detecting biofilms. If an alternative diagnostic standard emerges in the future, it could impact the accuracy of the current bedside measures that have been selected.

Armstrong et al. (2023) conducted a post-hoc multicenter clinical trial analysis of 138 DFUs to evaluate fluorescence (FL)-imaging role in detecting biofilm-encased and planktonic bacteria in wounds at high loads. The sensitivity and specificity of clinical assessment and FL-imaging were compared across bacterial loads of concern (10^4 –10^9 CFU/g). Quantitative tissue culture confirmed the total loads. Bacterial presence was confirmed in 131/138 ulcers. Of these, 93.9% had loads > 10^4 CFU/g. In those wounds, symptoms of infection were largely absent and did not correlate with, or increase proportionately with, bacterial loads at any threshold. FL-imaging increased sensitivity for the detection of bacteria across loads 10^4 –10^9 ($p < .0001$), peaking at 92.6% for > 10^8 CFU/g. Imaging further showed that 84.2% of ulcers contained high loads in the peri-wound region. The authors anticipate that the definition of chronic inhibitory bacterial load (CIBL) will spark a paradigm shift in DFU wound assessment and management that encourages and enables earlier intervention along the bacterial-infection continuum, thereby preventing sequelae of infection and supporting improved DFU outcomes. The authors concluded that FL-imaging of bacterial burden has potential for facilitating early bacterial intervention, monitoring treatment effectiveness during and after debridement, aiding antimicrobial stewardship to limit antibiotic and antimicrobial dressing prescriptions, and improving wound healing outcomes. Clinicians had limited experience using FL-imaging in a clinical context before the study; this may have lowered the sensitivity of FL-imaging to detect bacteria at loads > 10^4 CFU/g (sensitivity previously reported to range from 72% to 100%). Limitations of the imaging technology described include a limited (1.5 mm) depth of excitation and the inability to detect non-porphyrin-producing bacteria,

including all species from the *Streptococcus, Enterococcus*, and *Finegoldia* genres, although these rarely occur mono-microbially in chronic wounds. Additional limitations are that this study focused primarily on high bacterial load as a contributor to wound pathogenicity, but there are additional systemic factors which delay DFU healing and increase infection risk (e.g., peripheral artery disease, poor glycemic control, neuropathy). As the number of datapoints for each bacterial load threshold ranges from n = 14 to 34, these results should be interpreted with caution. The clinical utility of the technology to improve patient-centered outcomes was not assessed in this study. Finally, there is risk of bias and a potential conflict of interest as this clinical trial was funded by MolecuLight, Inc.

Chen et al. (2023) conducted a meta-analysis to assess the effect of ultrasound-supported wound debridement (USSD) in subjects with diabetic foot ulcer (DFU). A comprehensive literature examination through January 2023 was implemented and 1873 linked studies were appraised. The picked studies contained 577 subjects with DFUs in the studies' baseline, 282 of them were using USSD, 204 were using standard care, and 91 were using a placebo. Odds ratio (OR) in addition to 95% confidence intervals (CIs) were used to calculate the consequence of USSD in subjects with DFUs by the dichotomous styles and a fixed or random effect model. The USSD applied to DFU caused a significantly higher wound healing rate compared with the standard care (OR, 3.08; 95% CI, 1.94–4.88, $p < .001$) with no heterogeneity ($I^2 = 0\%$) and the placebo (OR, 7.61; 95% CI, 3.11–18.63, $p = .02$) with no heterogeneity ($I^2 = 0\%$). The USSD applied to DFUs caused a significantly higher wound healing rate compared with the standard care and the placebo. Though precautions should be taken when commerce with the consequences as all of the picked studies for this meta-analysis was with low sample sizes. A limitation to this meta-analysis is potential selection bias because a number of the studies involved in the meta-analysis were not covered. In addition, bias may have been increased due to the inclusion of missing or erroneous data from prior studies. The findings of this study need to be validated by well-designed studies. Further investigation is needed before clinical usefulness of this procedure is proven. [Authors Rastogi et al. (2019), and Yao et al. (2014), who were previously cited in this policy, are included in this meta-analysis.]

Derwin et al. (2023) conducted a prospective observational study to investigate wound area reduction (WAR) outcomes in a complex wound population composed of non-healing acute and chronic wounds. The relationship between bacterial autofluorescence signals and WAR was investigated. Area measurements were collected both manually and digitally, and both methods were compared for accuracy. Twenty-six participants with 27 wounds of varying etiologies were observed twice weekly for two weeks. Digital wound measurement, wound bacterial status assessment, and targeted debridement were performed through a point-of-care fluorescence imaging device (MolecuLight® i: X, MolecuLight Inc, Toronto, Canada). The wound area reduction (WAR) rate was calculated using baseline and last visit measurements. Statistical analyses, including t-tests, Fisher exact tests, the Wilcoxon signed rank test for method comparison, and ANOVA for bacterial subgroups, were applied as pertinent. The overall average WAR was −3.80 cm2 , or a decrease of 46.88% (manual measurement), and −2.62 cm2, or a 46.05% decrease (digital measurement via MolecuLight® device). There were no statistically significant differences between the WAR of acute and chronic wounds ($p = 0.7877$). A stepwise correlation between the WAR and bacterial status classification per fluorescence findings was observed, where persistent bacteria resulted in worse WAR outcomes. An overestimation of wound area by manual measurement was 23% on average. The authors concluded that fluorescence imaging signals were linked to WAR outcome and could be considered predictive. Wounds exhibiting bacterial loads that persisted at the end of the study period had worse WAR outcomes, while those for which management was able to effectively remove them demonstrated greater WAR. Manual measurement of the wound area consistently overestimated wound size when compared to digital measurement. However, if performed by the same operator, the overestimation was uniform enough that the WAR was calculated to be close to accurate. Notwithstanding, single wound measurements are likely to result in overestimation. Limitations to this study include being conducted at a single site, and a small, heterogeneous sample in relation to the age and wound etiology. Therefore, caution is needed in generalizing the results. Further research with randomized controlled trials is needed to validate these findings.

Ramirez-GarciaLuna et al. (2023) conducted a multi-center prospective study of 66 outpatient wound care participants using hyperspectral imaging to collect visible light, thermography, and bacterial fluorescence images. Wounds were assessed and screened using the International Wound Infection Institute (IWII) checklist for clinical signs and symptoms (CSS) of infection. Principal component analysis was performed on the images to identify wounds presenting as infected, inflamed, or non-infected. The model could accurately predict all three wound classes (infected, inflamed, and non-infected) with an accuracy of 74%. They performed best on infected wounds (100% sensitivity and 91% specificity) compared to noninflamed (sensitivity 94%, specificity 70%) and inflamed wounds (85% sensitivity, 77% specificity). The authors concluded that combining multiple imaging modalities enables the application of models to improve wound assessment. Infection detection by CSS is vulnerable to subjective interpretation and variability based on clinicians' education and skills. Enabling clinicians to use point-of-care hyperspectral imaging may allow earlier infection detection and intervention, possibly preventing delays in wound healing and minimizing adverse events. Limitations to the research include a lack of systematic, objective infection measurements, such as tissue biopsies, as the classification of infected

vs. non-infected wounds was clinically done. The findings of this study need to be validated by well-designed studies. Further investigation is needed before clinical usefulness of this procedure is proven.

Rahma et al. (2022) conducted a single center (multidisciplinary outpatient clinic), prospective pilot, randomized controlled trial (RCT) to estimate comparative healing rates and decision-making associated with the use of bacterial autofluorescence imaging in the management of diabetic foot ulcers (DFUs). This RCT included participants with an active diabetic foot ulcer (DFU) and no suspected clinical infection. Consenting participants were randomly assigned 1:1 to either treatment as usual informed by autofluorescence imaging (intervention), or treatment as usual alone (control). The primary outcome was the proportion of ulcers healed at 12 weeks by blinded assessment. Secondary outcomes included wound area reduction at 4 and 12 weeks, patient quality of life, and change in management decisions after autofluorescence imaging. Between November 2017 and November 2019, 56 participants were randomly assigned to the control or intervention group. The proportion of ulcers healed at 12 weeks in the autofluorescence arm was 45% (n = 13 of 29) vs. 22% (n = 6 of 27) in the control arm. Wound area reduction was 40.4% (autofluorescence) vs. 38.6% (control) at 4 weeks and 91.3% (autofluorescence) vs. 72.8% (control) at 12 weeks. Wound debridement was the most common intervention in wounds with positive autofluorescence imaging. There was a stepwise trend in healing favoring those with negative autofluorescence imaging, followed by those with positive autofluorescence who had intervention, and finally those with positive autofluorescence with no intervention. The authors concluded that assessing the use of autofluorescence imaging in DFU management, their results suggest that a powered RCT is feasible and justified. Autofluorescence may be valuable in addition to standard care in the management of DFU. There are a number of limitations to this study. First, it was a pilot study and, therefore, was not powered to show a difference in the primary outcome. Although the results suggest an improvement in the primary outcome measure in the autofluorescence arm, the results must be viewed with some caution, and a fully powered study is required to determine whether there is definitive evidence that the use of autofluorescence to guide standard care is superior to standard care alone. Second, the randomization was performed using serial opaque envelopes by stratification group which may present a greater risk of selection bias. Finally, although all attempts were made to minimize differences in baseline characteristics and the provision of standard care between the randomization groups, there may have been differences in the treatment received and patient concordance based on knowledge of randomization strategy. Further investigation is needed before clinical usefulness of this procedure is proven.

In participants with longstanding diabetic foot ulcers (DFUs), Ai-Jalodi et al. (2021) conducted a multi-center, prospective pilot study evaluating the time to healing over 12 weeks. The aim of this study was to assess the efficacy and safety of a porcine peritoneum-derived matrix in DFU treatment. In addition to weekly assessments for wound size, investigators analyzed bacterial burden using the MolecuLight i:X (MLiX) wound imaging device and bacterial protease (BPA) testing. Participants received a weekly application of Meso Wound Matrix Scaffold (MWM), a lyophilized porcine peritoneum-derived matrix (DSM Biomedical Inc., Exton, PA, US) for up to eight weeks. Descriptive statistics were chosen for this analysis. A total of 12 male participants and three female participants with an average age of 57 years were enrolled over a two-month period. The average wound duration was 30 weeks. Due to unrelated health issues, four participants were withdrawn. For the study endpoint of complete wound closure at 12 weeks, six (55%) of the remaining 11 participants achieved complete closure, and four (36%) participants healed during the 8-week treatment period. The average number of cellular- and/or tissue-based product (CTP) applications was six. Participants who healed all had negative BPA by nine weeks and no fluorescence on MLiX, indicating low bacterial load. The authors concluded this small pilot study indicated that participants with longstanding DFUs may respond to a porcine peritoneal-derived CTP. In this study, the CTP appears to have inhibited bacterial growth in the wound; however, further research is needed. The limitations of this pilot study include the small sample size, the lack of a control arm, and the loss of four of the 15 participants to unrelated adverse events. The bacterial results require further study before drawing any conclusions. Further research with randomized controlled trials is needed to validate these findings.

A clinical evidence assessment by ECRI suggests the evidence for the use of the MolecuLight i:X Fluorescence Imaging System is inconclusive. Studies provide insufficient evidence to determine improvement in patient outcomes. 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; updated 2024). 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. The clinical utility of the technology to improve patient-centered outcomes was not assessed in this study.

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 participants 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. The authors conclude that these findings may pave the way for including bacterial fluorescence imaging use into the pediatric burn population. The clinical utility of the technology to improve patient-centered outcomes was however not assessed in this study.

Chew and associates (2020) stated that early diagnosis of wound infections is 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 participants 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 participants were included and data collected from 35 wounds; three 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 one 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 a bacterial fluorescence imaging device MolecuLight i:X and standard microbiological swabs. A total of 14 participants 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. Four out the 19 participants (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 participants 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 participants. 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. Participants over 18 were recruited with a variety of wounds; patients 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.

For information on current clinical trials studying the use of MolecuLight i:X and bacterial growth, go to www.clinicaltrials.gov. (Accessed March 20, 2025)

Clinical Practice Guidelines

Association for the Advancement of Wound Care (AAWC)

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 in 2015, 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 participants to make decisions about appropriate health care for venous ulcer (VU) clinical care.

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. (AAWC, 2015; Couch et al., 2017)

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)

In 2010, 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.

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)

National Institute for Health and Care Excellence (NICE)

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)

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 DFUs: 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 DFUs, on the advice of the multidisciplinary foot care service. Dermal or skin substitutes as an adjunct to standard care can be considered when treating DFUs, only when healing has not progressed, and on the advice of the multidisciplinary foot care service. (NICE, 2019; updated 2023)

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 April 23, 2025)

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 23, 2025)

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 23, 2025)

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 23, 2025)

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 23, 2025)

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 23, 2025)

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The foregoing Oxford policy has been adapted from an existing UnitedHealthcare national policy that was researched, developed and approved by UnitedHealthcare Medical Technology Assessment Committee. [2025T0521X]

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Policy History/Revision Information

Date	Summary of Changes
08/01/2025	**Supporting Information** • Updated *Clinical Evidence* and *References* sections to reflect the most current information • Archived previous policy version REHAB 031.18

Instructions for Use

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

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