KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Wound Care Treatments

- Autologous Platelet Derived Wound Healing Factors for Non Healing Cutaneous Wounds (Procuren)
- Electrical Stimulation and Electromagnetic Therapy
- Low Frequency, Noncontact, Nonthermal Ultrasound Wound Therapy
- Maggot Debridement Therapy (MDT)
- Medihoney Dressing for Wound Management
- Noncontact Normothermic Wound Therapy
- OASIS Wound Dressing
- Tissue Engineered Skin Substitutes
- Warm-Up Wound Therapy

A Separate Criteria Document Exists for the Following:
Negative Pressure Wound Therapy Pumps (NPWT)
Platelet Rich Plasma Injections for the Treatment of Non-Healing Fractures and Tendinopathy

Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	• Electrical Stimulation (ES) and Electromagnetic Therapy for the Treatment of Wounds (270.1) • Non-Contact Normothermic Wound Therapy (NNWT) (270.2) • Treatment of Decubitus Ulcers (270.4) and Medicare manual, section 270. • Porcine Skin and Gradient Pressure Dressings (270.5) • Infrared Therapy Devices (270.6) • Blood-Derived Products for Chronic Non-Healing Wounds (270.3) • Autologous Platelet-Rich Plasma
Local Coverage Determinations (LCD)	L33831 Surgical Dressings See Non-Covered Services (L35008)
Local Coverage Article	Surgical Dressings – (A54563)
KPWA Medical Policy	Due to the absence of a NCD, LCD, or other coverage guidance, KPWA has chosen to use their own Clinical Review Criteria for Skin Engineered Substitutes for medical necessity determinations when these products are used in the outpatient hospital or office setting. Use the Non-Medicare Criteria below.

Skin Substitutes – HCPCS Q4100 – Q4182

- **In the Ambulatory Care Setting** - Medicare considers these codes wound care dressings in the ASC - Ambulatory Care Setting and not separately billable. They do not need to go for Medical Review. See the

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- **In the outpatient hospital or clinic setting** - Medicare considers these codes billable in the outpatient hospital setting or office setting. Please use the Non-Medicare criteria below for medical necessity determinations.

For Non-Medicare Members

Treatment	Criteria Used
Autologous Platelet Derived Wound Healing Factors for Non-Healing Cutaneous Wounds (Autologel, Procuren, SafeBlood)	MCG* A-0630
Noncontact Normothermic Wound Therapy	MCG* A-0351 **If requesting this service, please send the following documentation to support medical necessity:** • Last 6 months of clinical notes from requesting provider &/or specialist
Electrical Stimulation and Electromagnetic Therapy	MCG* A-0242 **If requesting this service, please send the following documentation to support medical necessity:** • Last 6 months of clinical notes from requesting provider &/or specialist
Medihoney Dressing for Wound Management Warm-Up Wound Therapy Low Frequency, Noncontact, Non Thermal Ultrasound Wound Therapy	There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.
Maggot Debridement Therapy (MDT)	No medical necessity review required for this service.

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Treatment	Criteria Used

Tissue-engineered skin substitute may be indicated for **ONE or more of the following**:

1. Diabetic ulcers, as indicated by **ALL of the following**:
   - Treated foot has adequate blood supply as evidenced by either the presence of a palpable pedal pulse or an ankle-brachial index (ABI) of ≥ 0.70)
   - Receiving conventional wound care and optimal glycemic management to continue during treatment
   - Diabetes mellitus (type 1 or type 2)
   - Full-thickness foot ulcer with location on plantar, medial, or lateral area, and no exposure of tendon, muscle, capsule, or bone (Full thickness ulcer extends thru dermis and epidermal layers. Subcutaneous fat may be visible but bone, tendon or muscle are not exposed.)
   - Ulcer history, as indicated by **ONE or more of the following**:
     - Duration greater than 3 weeks (prior to Apligraf, (Graftskin))
     - Duration greater than 6 weeks (prior to Dermagraft)
   - No allergy to bovine products
   - No response to conventional therapy, including **ALL of the following**:
     - No weight-bearing (off loading, so there is no pressure on the wound)
     - Optimal glycemic management (HbA1c of 7% (0.07) or less)
     - Saline-moistened dressings
     - Sharp debridement
   - No wound infection
   - No slough or eschar in the wound bed

Only the following products are approved for treatment of diabetic ulcers – Dermagraft Q4106, Apligraf Q4101, Oasis Wound Matrix Q4102, Oasis Ultra Tri-Layer Matrix Q4124, GraftJacket Regenerative Tissue Matrix Q4107 Epifix Amniotic Membrane Q4131, TheraSkin® Q4121

2. Venous insufficiency ulcers, as indicated by **ALL of the following**:
   - Treated foot has adequate blood supply as evidenced by either the presence of a palpable pedal pulse or an ankle-brachial index (ABI) of ≥ 0.70)
   - Receiving concurrent conventional wound care, to include compression of extremity (e.g. compression stocking, ace bandage, lymphedema pump – if meets criteria)Receiving concurrent optimal glycemic management, if patient is also diabetic
   - Duration greater than 1 month
   - Full-thickness ulcer due to venous insufficiency
   - No allergy to bovine products
   - No response to conventional therapy, including **ALL of the following**:
     - Saline-moistened dressings
     - Sharp debridement
     - No wound infection
     - Compression
   - No slough or eschar in the wound bed

Only the following products are approved for treatment of venous insufficiency ulcers - Oasis Wound Matrix Q4102, Apligraf Q4101, Epifix Amniotic Membrane Q4131, Oasis® Ultra Tri-Layer Matrix Q4124, TheraSkin® Q4121

Apligraf®

When the above medical necessity criteria are met, the following conditions of coverage apply:

- treatment is limited to one initial application
- additional applications at a minimum of one week intervals, for up to a maximum of four in 12 weeks are considered medically necessary when evidence of wound healing is present (e.g., signs of epithelialization and reduction in ulcer size)

Additional applications beyond 12 weeks are considered not medically necessary regardless of wound status.

Dermagraft® and Epifix Amniotic Membrane Q4131

When the above medical necessity criteria are met, the following conditions of coverage apply:

- treatment is limited to one initial application
- additional applications for up to a maximum of eight in 12 weeks when there is evidence of wound healing (e.g., signs of epithelialization and reduction in ulcer size)
- Additional applications beyond 12 weeks are considered not medically necessary regardless of wound status.

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Treatment	Criteria Used

In regards to the following products, there is insufficient evidence in the published medical literature to show that these skin substitutes are more efficacious or provide better longer outcomes than the preferred products for the conditions listed above:

- Active barrier
- ActiveMatrixAcuseal
- Adherus Dural Sealant;
- Affinity
- AlloMax for indications other than breast reconstruction; for AlloMax for breast reconstruction, see Breast Reconstruction or Breast Prostheses criteria
- Allopatch for soft tissue augmentation and all other indications;
- Alloskin RT;
- Alloskin;
- AlloSource cryopreserved human cadaver skin;
- Allowrap – Aetna (Cigna)
- Allowrap DS
- Amnioband
- AmnioCare;
- Amnioclear
- Amnioclear LTC flowable
- AmnioExCel;
- AmnioFix;
- Amniomatrix;
- AmnioMTM;
- AmnioShield;
- Amniotic fluid injection for corneal wound healing and for prevention of adhesions after orthopedic surgery;
- Amnio wound
- Amniox (human embryonic membrane) for tarsel tunnel repair and all other indications;
- Architect ECM;
- Architect PX;
- Architect™ Biomatrix;
- Artelon (poly[urethane urea] elastomer) for anterior cruciate ligament reconstruction, rotator cuff repair, trapezio-metacarpal joint osteoarthritis and all other indications;
- Arthres GraftRope for acromio-clavicular joint separation reconstruction;
- Arthroflex (FlexGraft);
- Autologous fat for the treatment of scars;
- Avance nerve graft
- Avotermin for improvement of skin scarring;
- Axogen 2 nerve wrap;
- Biodesign® (Surgisis®) Hiatal Hernia Matrix;
- Biodesign® (Surgisis®) Inguinal Hernia Matrix;
- Biodesign® (Surgisis®) RVP Recto-Vaginal Fitsula Plug;
- BioDexcel;
- BioDfactor/BioDfence human amniotic allograft;
- BioFix
- Biostat Biologx fibrin sealant for wound healing and all other indications;
- Biotape reinforcement matrix for soft tissue augmentation and all other indications;
- Biovance
- CellerateRX;
- Clarix® Flo Integumental;
- Clarix® Regenerative Matrix;
- CollaFix;
- Conexa reconstructive tissue matrix;
- CorMatrix Patch for cardiac tissue repair and all other indications;
- C-QUR biosynthetic mesh;

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Treatment	Criteria Used

- CRXa;
- CryoSkin®
- Cymetra injectable allograft for wound healing
- Dermacell;
- DermaClose RC continuous external tissue expander for facilitation of wound closure and all other indications;
- Dermagraft for chronic foot ulcer secondary to necrotizing fasciitis;
- DermaMatrix for wound healing and other indications other than breast reconstruction; for DermaMatrix for breast reconstruction, see Breast Reconstruction or Breast Prostheses criteria
- Dermapure
- DermaSpan;
- Dermavest
- DryFlex (human amnion allograft) for shoulder repair and all other indications;
- Duraform™
- DuraGen Plus dural regeneration matrix for surgical repair of soft tissue deficiencies and all other indications;
- DuraGuard;
- DuraMatrix™
- DuraSeal;
- Durepair Regeneration Matrix®;
- Endoform;
- ENDURAGen;
- Epidex;
- EPIFLO transdermal continuous oxygen therapy for wound healing;
- Equine-derived decellularized collagen products (e.g., OrthADAPT, Unite, and Unite® Biomatrix);
- Evicel fibrin sealant for repair of cerebrospinal fluid leakage and all other indications;
- Excellagen®;
- E-Z Derm for wound healing and all other indications;
- FlexHD acellular dermal matrix for wound healing; for FlexHD for breast reconstruction, see Breast Reconstruction or Breast Prostheses criteria
- FloGraft;
- Floweramnioflo
- Floweramniopatch
- Flowerderm
- Fortaderm Antimicrobial;
- Fortaderm™;
- Gammagraft skin substitute for wound healing and all other indications;
- Gore Bio A Tissue reinforcement
- GORE BIO-A Fistula Plug;
- Grafix Core and Grafix Prime;
- Graftjacket express injectable allograft for wound healing and all other indications;
- Guardian;
- Hyalomatrix (hMatrix);
- HydroFix;
- Inforce;
- Integra Neural Wrap for peripheral nerve repair and all other indications
- Integra Wound Matrix and Integra Flowable Wound Matrix for the management of wounds including partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (e.g., donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (e.g., abrasions, lacerations, second-degree burns, skin tears) and draining wounds and all other indications;
- Integra™ Flowable Wound Matrix;
- LiquidGen;
- Marigen
- Matriderm;

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Treatment	Criteria Used
• MatriStem wound micromatrix powder; • Matrix HD™ • Medeor; • MediHoney; • Mediskin™ • Memoderm; • Menaflex Collagen Meniscus Implant - see Collagen Meniscus Implant criteria • Meso BioMatrix; • Neoform Dermis for wound healing; for NeoForm for breast reconstruction - see Breast Reconstruction or Breast Prostheses criteria • Neox 100; • Neox 1K; • Neox® Wound Matrix; • Neoxflo; • Neopatch • Neuragen; • NeuraWrap • Neuroflex; • NeuroMatrix collagen nerve cuff for peripheral nerve repair and all other indications • NeuroMend collagen nerve wrap for peripheral nerve repair and all other indications • NuCel liquid wound covering; • NuShield, NuShield Orthopaedics, and NuShield Spine; • Oasis burn matrix for wound healing and all other indications; • Orcel® • OrthADAPT Bioimplant (type I collagen scaffold) for tendon repair and all other indications; • OrthADAPT™ Bioimplant • OsseoGuard; • Ovation; • PalinGen membrane for wound healing; • PalinGen® Flow • PalinGen® Xplus • Parietex Composite (PCO) Mesh for the treatment of genito-urinary (e.g., uterine or vaginal vault) prolapse; • Peri-Guard Repair Patch; • Peri-Strips Dry, and Peri-Strips Dry with Veritas Collagen Matrix; • Permacol Biologic Implant for soft tissue surgical repairs, including hernia repair, muscle flap reinforcement, rectal prolapse (including intussusception), rectocele repair, abdominal wall defects, plastic and reconstructive surgery, complex abdominal wall repair and all other indications; • Porcine-derived decellularized collagen products (e.g., Collamend, Cuffpatch, Pelvicol, and Pelvisoft); • Porcine-derived decellularized fetal skin products (e.g., Mediskin); • Porcine-derived polypropylene composite wound dressing (e.g., Avaulta Plus); • Preclude® Dura Substitute • Preclude® Pericardial Membrane • Preclude® Vessel Guard • PriMatrix acellular dermal tissue matrix for wound healing and all other indications; • Promogran; • PTFE felt; • Puracol; • PX50® /PX50® Plus • Radiofrequency stimulation devices (e.g., Provant Wound Closure System, MicroVas Vascular Treatment System) for wound healing; • Repriza®; • Restore® Orthobiologic Soft Tissue Implant; • Revita • Revitalon; • Seamguard;	

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Treatment	Criteria Used
• SERI™ Surgical Scaffold • Silver-coated wound dressings (e.g., Acticoat, Actisorb, and Silversorb) for wound healing and all other indications; • SJM™ Pericardial Patch with EnCap™ AC Technology • Solana allograft; • SportMatrix; • SportMesh; • SteriShield™; • Strattice tissue matrix for wound healing; for Strattice for breast reconstruction - see Breast Reconstruction or Breast Prostheses criteria • Suprathel; • SurgiMend for plastic and reconstructive surgery, muscle flap reinforcement, hernia repair, reinforcement of soft tissues repaired by sutures or suture anchors, during tendon repair surgery (including reinforcement of the rotator cuff, patellar, Achilles, biceps, quadriceps, or other tendons), and all indications other than breast reconstruction; for SurgiMend for breast reconstruction - see Breast Reconstruction or Breast Prostheses criteria • Surgisis (including Surgisis AFP Anal Fistula Plug, Surgisis Gold Hernia Repair Grafts, and Surgisis Biodesign); • Talymed; • TenoGlide tendon protector sheet (Tendon WrapTM tendon protector) for the management and protection of tendon injuries and all other indications; • TenSix (acellular dermal matrix) for tendon repair and all other indications; • TissueMend for the repair or reinforcement of soft tissues repaired by sutures or suture anchors during tendon repair surgery, including reinforcement of the rotator cuff, patellar, Achilles, biceps, quadriceps, or other tendons, and all other indications; • Tornier BioFiber Absorbable Biological Scaffold, and Tornier Collagen Coated BioFiber Scaffold; • Transcyte • Unite® Biomatrix; • Vascu-Guard®; • Vaso Shield; • Veritas collagen matrix for use as an implant in the surgical repair of soft tissue deficiencies and all other indications; • VersaShield™ • Vitagel surgical hemostat for wound healing and all other indications; • WoundEx® Flow • WoundEx® Membrane • XCM Biologic; • Xelma; • XenMatrix • X-Repair	

The following information was used in the development of this document and is provided as background only. It is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Chronic wounds, wounds with long healing time, and wounds with frequent recurrence are a major health problem. They are a problem for the patient who suffers from them, the clinician who treats them, and the health care system that is overburdened by their cost. It is estimated that chronic wounds affect approximately 2% of the American population at an estimated cost of US $20 billion per year. Many factors can impede wound healing, including chronic disease, venous insufficiency, arterial insufficiency, neuropathy, nutritional deficiencies and local features such as pressure, edema, and infection (Fonder, 2008, Rizzi 2010).

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No single regimen is universally accepted as the best modality for treating chronic wounds. They are managed through conventional wound care procedures performed by primary care providers, community nurses, pharmacists, and others. In the early 2000s, the concept of wound bed preparation has been proposed as a means of providing a structured and systemic approach to the management of chronic wounds. It is believed to accelerate endogenous healing and/or facilitate the effectiveness of other therapeutic measures. Wound bed preparation involves ongoing wound debridement, management of exudates, and resolution of bacterial imbalance (Schulz 2003, Ramundo 2008).

Wound debridement is defined as the removal of devitalized or contaminated tissue as well as foreign material from the wound bed until healthy tissue is exposed. Efficient debridement reduces the necrotic burden, achieves healthy granulation tissue, and reduces wound contamination and tissue destruction. This can be performed by different enzymatic, autolytic, sharp/surgical, biological, and mechanical techniques. Each has its own advantages and limitations, and the methods that are most efficient at removal of debris, may at the same time be the most detrimental to fragile new growth (Schulz 2003, Beitz, 2005, Ramundo 2008).

Tissue-engineered skin substitutes (i.e., human skin equivalents [HSE]), also referred to as artificial skin, are bioengineered skin products and may be either acellular or cellular. Acellular (i.e., cadaveric human dermis with cellular material removed) products contain a matrix or scaffold composed of materials such as collagen, hyaluronic acid, and fibronectin. The construction of the matrix allows easy access by host cells during the healing process. Cellular products contain living cells such as fibroblasts and keratinocytes within a matrix. The cells contained within a matrix may be allogeneic (i.e., obtained from another individual) or autologous (i.e., obtained from the same individual). Some products are derived from other species (e.g., bovine, porcine) and are referred to as a xenograft. Skin substitutes are generally comprised of epidermal cells, dermal cells or may be composites (i.e., a combination of dermal and epidermal). The substitutes can be used as either temporary or permanent wound coverings. Grafting techniques utilized to apply skin substitutes include autografting (i.e., tissue transplanted from one part of the body to another), allografting (i.e., transplant from one individual to another of the same species), and xenografting (i.e., a graft from one species to another unlike species). Skin substitutes have been proposed for the treatment of multiple conditions including breast reconstruction and chronic wounds nonresponsive to standard therapy.

During breast reconstruction, acellular dermal skin substitutes (i.e., AlloDerm, AlloMax) are primarily used in the setting of tissue expander and breast implant reconstruction. Patients should be in overall good health and have no underlying condition that would restrict blood flow or interfere with the normal healing process (e.g., uncontrolled diabetes, hypertension, previous surgery). These matrixes may be indicated when there is insufficient tissue expander or implant coverage by the pectoralis major muscle and additional coverage is required, as may be the case in a very thin patient; if there is viable but compromised or thin post-mastectomy skin flaps that are at risk of dehiscence or necrosis; or if there is a need to re-establish the inframammary fold and lateral mammary fold landmarks. When used in appropriate candidates, these skin substitutes are proposed to improve control over placement of the inframammary fold and final breast contour, enhance use of available mastectomy skin, reduce the number of expander fills necessary, reduce time to complete expansion and eventual implant exchange, potential improved management of a threatened implant, reduce the need for explantation and the potential for reduction in the incidence of capsular contracture. However, there are ongoing concerns regarding the increased risk of seroma and infection, a higher risk of an implant having to be removed, and tissue flap death.

Evidence and Source Documents

Autologous Platelet Derived Wound Healing Factors for Non Healing Cutaneous Wounds (Procuren) Bilaminate Skin Substitutes
Electrical Stimulation and Electromagnetic Therapy
Low Frequency, Noncontact, Nonthermal Ultrasound Wound Therapy Maggot Debridement Therapy (MDT)
Medihoney Dressing for Wound Management OASIS
Wound Dressing
Warm-Up Wound Therapy

Medical Technology Assessment Committee

Autologous Platelet Derived Wound Healing Factors for Non Healing Cutaneous Wounds (Procuren)

BACKGROUND

Wound healing is a dynamic process that involves a complex interaction of several cellular and biochemical

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events. Tissue repair begins with a clot formation and platelet degranulation which release the growth factors necessary for wound repair. Generally, the process of normal healing takes few days to 2 weeks and involves three phases that may overlap in time: 1. inflammatory phase, 2. proliferative phase, and 3. remodeling phase. If any of these phases is compromised, healing will be delayed. Treatment of chronic non-healing cutaneous wounds has challenged health care providers for generations, and various strategies including devices, biologics and drug have been used to accelerate the healing process. These agents are designed to affect one of processes involved in healing (Robson 1999). Advances in biology of wound healing, showed that macrophages and platelets are the chief regulatory cells in the repair process. Platelets are known for their role in haemostasis where they help prevent blood loss at site of vascular injury. They adhere, aggregate, and form a procoagulant surface leading to thrombin generation and fibrin formation. Activated platelets release potent locally acting growth factors substances that initiate division and migration of fibroblasts and formation of new capillaries promoting wound healing (Knighton 1986, Fu 2005). Becaplermin, a topical treatment with platelet derived growth factor as its active ingredient was approved by the FDA in 1997 to treat diabetic foot and leg ulcers that extend into the subcutaneous tissue or beyond and have adequate blood supply. Platelet derived growth factor (Procuren) for the treatment of non-healing cutaneous wounds was reviewed by MTAC in February 1999, and failed MTAC evaluation criteria due to the lack of scientific evidence to determine its safety and efficacy. It is being re-reviewed based on requests for coverage from Eastern WA. ***Bone Fracture Healing (GEM 21STM)*** Bone fracture healing is a biological process that involves both local and systemic acute phase reactants. The physiological events occurring at the site of injury include hematoma formation, recruitment and transformation of mesenchymal cells, induction of angiogenesis, and the production and remodeling of the extracelluar matrix. Radiographic healing of a bone fracture is normally achieved in 4-13 months depending on type and location of the fracture. The rate of bone union also depends on several other factors as patient's health, compliance, nutritional status, stability of the fracture and others. Disruption of any of these factors would lead to delayed or non-union of the fracture. It was reported that approximately 10% of the bone fractures in the US are complicated by impaired healing, which has a high impact on the quality of life and burden of health costs. Several compounds and technologies have been, and are being developed to enhance fracture healing and accelerate repair. These include prostaglandins, gene therapy, growth hormone, parathyroid hormone, and growth factors. Among the growth factors studied are the bone morphologic proteins, transforming growth factor B, vascular endothelial growth factor, and platelet derived growth factor (PDGF) (Axelrad 2007, Hollinger 2008). In vitro and animal studies indicate that PDGF has the potential of accelerating the bone healing process. The experimental studies showed that PDGF receptors increase in osteoblasts as they mature, but that the response varies inversely to the number of receptors. This indicates that there is an optimal concentration and time during bone regeneration to deliver the PDGF in order to be effective (Axelrad 2007). The GEM 21STM a device for bone grafting material containing a therapeutic tri-calcium phosphate or PDGF was approved by the FDA for peridontally related defects in November 2005. ***Tendinopathy*** Tendinopathy is a general term that is used to describe a tendon injury. It is characterized by pain, stiffness, and loss of strength in the affected area. Treatments for tendinopathy include, but are not limited to: rest, anti-inflammatory medication, analgesia, orthotics, physical therapy, and local steroid injections. Another more recent technology that has been proposed for the treatment of tendinopathy is platelet rich plasma injections into the ailing tendon (Kampa 2010). Platelets are small nonneculeated bloods cells that are involved in wound healing. The exact mechanism by which platelet rich plasma promotes tendon healing is unclear; however, it is thought that the growth factors and cytokines contained in the platelets speed tissue regeneration and healing. Platelets contain alpha granules and dense granules, which when stimulated release growth factors and cytokines. The alpha granules release: platelet-derived growth factor, transforming growth factor-beta, vascular endothelial growth factor, epidermal growth factor, insulin-like growth factor I and II, and fibroblast growth factor. These factors play an important role in cellular proliferation, chemotaxis, cellular differentiation, extracellular matrix production, and angiogenesis. The dense granules contain adenosine, serotonin, histamine, and calcium, which play a role in tissue modulation and regeneration (Foster 2009, Maffulli 2010). Platelet rich plasma is derived from anti-coagulated autologous whole blood, which is centrifuged to concentrate platelets in plasma. Normal platelet counts in the blood range from 150,000-350,000 µL. The goal of the devices used to create platelet rich plasma is to raise the concentration to at least one million platelets per µL. After separation, the platelet rich plasma must be clotted to allow for delivery to the desired site. This clotting leads to platelet activation, resulting in the release of growth factors and cytokines. Bovine thrombin, calcium chloride, and type I collagen are different agents used to stimulate platelet activation (clotting) (Foster 2009). One of the advantages of this approach is that because the platelet rich plasma is derived from the patient's own blood there is a low chance of rejection. However, the optimal dose range has not been defined. The injection of platelet rich plasma is a procedure and therefore notregulated by the FDA. However, several devices used in the preparation of platelet rich plasma have received FDA approved.

02/10/1999: MTAC REVIEW
Autologous Platelet Derived Wound Healing Factors for Non Healing Cutaneous Wounds (Procuren)

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Evidence Conclusion: The published evidence on the effect of Procuren for treating non-healing cutaneous wounds consists of two small randomized controlled trials, one of which reports improvements in wound healing for Procuren as compared to placebo and the other trial reports worse outcomes with Procuren. The available evidence does not allow any conclusion about the effects of Procuren on non-healing cutaneous wounds.
Articles: Knighton DR, et al. Stimulation of repair in chronic, nonhealing cutaneous ulcers using platelet-derived wound healing formula. Surgery, Gyn, Obstet 1990;170:56-60.The use of platelet derived growth factors for the treatment of non-healing cutaneous wounds is approved by the FDA and therefore GHC Criteria 1 is met.

There is insufficient scientific evidence that Procuren is medically effective and therefore *Kaiser Permanente Medical Technology Assessment Criteria.*

06/04/2008: MTAC REVIEW
Autologous Platelet Derived Wound Healing Factors for Non Healing Cutaneous Wounds (Procuren)
Evidence Conclusion: Wound Healing (Procuren) The reviewer's conclusion in the previous MTAC report of 1999 was, "The published evidence on the effect of Procuren™ for treating non-healing cutaneous wounds consists of two small randomized controlled trials, one of which reports improvements in wound healing for Procuren™ as compared to placebo, and the other trial reports worse outcomes with Procuren™. The available evidence does not allow any conclusion about the effects of Procuren™ on non-healing cutaneous wounds." The literature search for the current review did not reveal any additional evidence that would determine the efficacy and safety of platelet derived growth factor for the treatment of non-healing cutaneous wounds. Bone Fracture Healing (GEM 21STM) There insufficient published evidence to determine the efficacy and safety of autologous platelet derived wound healing factors for the treatment of non-healing fractures.
Articles: *Wound Healing* The search yielded around 100 articles. Many were review articles or publications not related to the current review. No meta-analyses of empirical studies, randomized or non-randomized controlled studies, published after the last review, were identified. *Bone Fracture Healing* The literature search did not reveal any empirical studies on the use of PDGF for bone fractures. The published studies were all related to the use of PDGF for of dental implants, periodontal wounds, defects, or bone turnover during periodontal repair. None was selected for critical appraisal.

The use of Autologous Platelet Derived Wound Healing Factors in the treatment of Non-Healing Wounds does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

The use of Autologous Platelet Derived Wound Healing Factors in the treatment of Non-Healing Fractures does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

02/14/2011: MTAC REVIEW
Autologous Platelet Derived Wound Healing Factors for Non Healing Cutaneous Wounds (Procuren)
Evidence Conclusion: *Achilles tendinopathy* A recent double-blind, placebo-controlled RCT evaluated the effects of adding a platelet rich plasma (PRP) injection to an eccentric exercise program in 54 patients with chronic midportion Achilles tendinopathy. The primary outcome measures were pain and activity level, measured using the Victorian Institute of Sports Assessment-Achilles (VISA-A). In both groups, VISA-A scores improved significantly after 24 week; however, there was no significant difference in VISA-A score between the two groups. With regard to safety, no microbial growth was found in the collected PRP samples, and no complications (infections, hematomas, or ruptures) were reported after the treatment (de Vos 2010). *Lateral epicondylitis (tennis elbow)*
A double-blind RCT that included 100 subjects compared the efficacy of a platelet rich plasma injection to a corticosteroid injection for the treatment of lateral epicondylitis in patients who had failed non-operative treatment. In addition to a platelet rich plasma injection or a corticosteroid injection subjects also participated in an eccentric exercise program. The primary outcome measures were pain, measured using the visual analog scale (VAS), and disability, measured using the disability of the arm, shoulder, hand (DASH) outcome measure. Successful treatment was defined as more than a 25% reduction in VAS or DASH without a re-intervention after 1 year.
According to the VAS, treatment was successful for 73% of subjects in the platelet rich plasma group and 49% in the corticosteroid group ($P<0.001$). When using the DASH, treatment was successful for 73% of subjects in the platelet rich plasma group and 51% in the corticosteroid group ($P=0.005$). This trial did not address safety. Results from this study should be interpreted with caution as there are several methodological limitations (Peerbooms 2010).
Conclusion: There is insufficient evidence to support the use of platelet rich plasma injection for the treatment of Achilles tendinopathy. There is evidence from one small RCT that supports the use of this technology for patients with lateral epicondylitis; however, because of methodological limitations results from this trial are insufficient to determine the safety and efficacy of this procedure. Several trials are currently underway to determine the safety and efficacy of platelet rich plasma injections for the treatment of tendinopathy.

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Articles: Studies were selected for review if they included at least 25 subjects and assessed either the safety or efficacy of platelet rich plasma injections for the treatment of tendinopathy. Studies were excluded if they lacked a valid comparison group. Two RCTs were selected for review. The following studies were critically appraised: de Vos RJ, Weir A, van Schie HTM, et al. Platelet-rich plasma injection for chronic Achilles tendinopathy. JAMA 2010; 303:144-149. See Evidence Table. Peerbooms JC, Sluimer J, Bruijn DJ, and Gosens T. Positive effect of an autologous platelet concentrate in lateral epicondylitis in a double-blind randomized controlled trial. Am J Sports Med 2010; 38:255-262. See Evidence Table.

The use of Autologous Platelet Derived Wound Healing Factors in the treatment of Tendinopathy does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Bilaminate Skin Substitutes

BACKGROUND

Venous ulcers are a chronic recurring condition associated with long-standing venous hypertension of the lower extremities. They occur in approximately 1-3 patients per thousand in the general population with the incidence rising to 20 per thousand in individuals over 80 years old. The chronicity of care required to treat this condition involves significant time and resources and often treatment is unsuccessful in producing complete venous ulcer healing. Typical treatments include frequent dressing changes, compression bandages, antibiotic and antiseptic use, and mechanical debridement. One proposed treatment of chronic venous ulcers involves covering the ulcer with a natural bilayer skin substitute that is hypothesized to protect the wound and promote healing.

08/11/1999: MTAC REVIEW

Bilaminate Skin Substitutes

Evidence Conclusion: The best, published article reporting original data on the effect of using Apligraf on non-healing venous ulcers is a randomized controlled trial of 309 patients recruited from 5 wound treatment centers. The results of this randomized controlled trial indicate that venous ulcers resolve more quickly when treated with compression and human skin equivalent than when treated with compression alone. The results also suggest that patients treated with compression/human skin equivalent are more likely to have complete healing of a venous ulcer than those who are treated only with compression. The bias introduced by the failure to perform an intention-to-treat analysis could explain some of the differences between treatment groups. The results cannot be generalized to patients with conditions that are associated with poor wound healing or to patients with large venous ulcers. Additionally, the probability of ulcer recurrence after 12 months for patients treated with compression/human skin equivalent relative to that of patients treated only with compression remains unknown. This study has not defined the risk of clinically relevant immunologic rejection of human skin equivalent for patients with venous ulcers.

Articles: Falanga, V et al, *Arch. Dermatol*. 1998;134:292-300 See Evidence Table.

The use of Apligraf human skin equivalent for the treatment of non-healing venous ulcers has been approved by the FDA and therefore meets GHC criteria 1. There is sufficient scientific evidence that Apligraf is medically effective and therefore *Kaiser Permanente Medical Technology Assessment Criteria*.

Electrical Stimulation and Electromagnetic Therapy

BACKGROUND

Chronic wounds have been traditionally known as wounds that take prolonged time to heal, do not heal completely, or recur frequently. There is no agreed upon definition for chronic wounds; Lazarus et al (1994) defined them as wounds of at least 8 weeks in duration that have failed to proceed through an orderly and timely process that produces anatomic and functional integrity. Troxler et al (2006) defined them as wounds that fail to heal with ‘standard therapy’ in an orderly and timely manner. More recently Fonder and colleagues (2008) defined chronic skin wounds as break in the skin of long duration (>6 weeks), or frequent recurrence. Generally, the process of normal healing takes few days to 2 weeks and involves three phases that may overlap in time: 1. inflammatory phase, 2. proliferative phase, and 3. remodeling phase. If any of these phases is compromised, healing will be delayed. Chronic wounds are predominantly due to chronic venous insufficiency, atherosclerosis, pressure sores, or peripheral neuropathy. Chronic ulceration can affect any anatomic region of the body, but the majority is seen in the lower limbs. Pressure sores also known as pressure ulcers are the most common of all chronic wounds, and venous ulcers account for the majority of leg ulcers (70-85%). Diabetic foot ulcers and ischemic ulcers contribute to a significant proportion of the rest (Eaglestein 1997, Simon 2004, Jones 2007, Fonder 2008). Management of chronic wounds has challenged health care providers for generations, and various strategies have been used to accelerate the healing process. Standard care includes debridement of necrotic or infected tissue, maintenance of a moist wound environment, control of infection, wound dressing, nutritional

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support, and treatment of concurrent conditions that may delay healing. Adjuncts to wound care include several established or emerging therapies. These include compression therapy, pressure relieving beds or cushions, hyperbaric oxygen therapy, topical negative pressure devices, growth factors, skin substitutes, and topical or systemic medications. Selection of therapy is based on the individual patient's clinical condition, and type and cause of wound. A whole range of other adjunctive treatment modalities, such as laser, ultrasound, and electricity have also been applied to chronic wounds (Cullum 2000, de Araujo 2003, Fonder 2008). Electrical stimulation (ES) or electrotherapy for wound healing is defined as the application of electrical current from electrodes placed directly within a wound or on skin in a close proximity to it. ES has been a topic for research for decades, and is often used by physical therapists to promote healing. There are four basic treatment regimens for ES therapy: low intensity direct current (LIDC), high voltage pulsed current (HVPC), alternating current (AC), and transcutaneous electrical nerve stimulation (TENS). Electromagnetic therapy is a related therapy but is distinct from other forms of electrotherapy in that it uses an electromagnet to generate the electric current. It has a field effect not a direct effect or a form of irradiation. It covers a wide range of wavelengths including radio-waves and X-rays. Short wave diathermy (SWD) is a non-ionizing radiation present in the radio-waves portion of the electromagnetic spectrum. The frequency of the short- wavelength radio-waves ranges from 10 to 100 MHz. The radiofrequency wave band of 27.12 MHz is used for therapeutic effect in continuous SWD. Electromagnetic therapy can also be delivered in short bursts of energies called Pulsed Short Wave Diathermy or PSWD (gardener 1999, Ojingwa 2002, Stiller 1992, Olyaee 2006, Callaghan 2008). In vitro and animal studies have showed that electrical stimulation can increase the DNA and collagen synthesis, direct epithelial, fibroblast, and endothelial cell migration into wound sites, inhibit growth of some wound pathogens, and increase tensile strength of wound scar (Bassett 1974, Gordon 2007). Several devices have been used off-label to deliver ES or electromagnetic therapy to cutaneous wounds. The FDA approved electric stimulators as Class III devices for deep brain and bone stimulation, and cleared them as class II devices for muscle stimulation. Electromagnetic devices were also FDA cleared for the treatment of selected medical conditions including relief of pain, muscle contracture, joint contractures, and others. None of the ES or electromagnetic devices has been cleared by the FDA, to date, for the treatment of wounds. The objective of this review is to determine whether electric stimulation and /or electromagnetic therapies are effective adjunctive treatments for chronic skin wounds. The technology has not been previously reviewed by MTAC for this indication.

04/09/2008: MTAC REVIEW

Electrical Stimulation and Electromagnetic Therapy

Evidence Conclusion: There is limited evidence on the effect of electric stimulation (ES) or electromagnetic (EM) therapy on the healing of chronic wounds. The body of evidence on ES therapy mainly consists of small randomized and nonrandomized controlled trials that used the therapy off-label to treat chronic wounds, as well as a meta-analysis that pooled the results of 15 randomized and nonrandomized studies. The literature on EM therapy was more limited. There were very few small trials that also used the therapy off- label. Due to this limited number of studies, the authors of the Cochrane reviews were unable pool the results in a meta-analysis. Although a number of the published RCTs were randomized, controlled, blinded, and had clinical outcomes, all had their limitations: they were too small, with short follow-up durations, and with no standardized dose, frequency, or duration for the electric stimulation (ES) or electromagnetic (EM) therapy. Moreover, several studies used the change in ulcer size rather than incidence of /or time to complete healing as their outcome. No adjustments were made for potential confounding factors, and analyses were not based on intention to treat. The results of these trials suggest that electrotherapy might be associated with improved healing, but the evidence is insufficient to draw any conclusions on the benefits of therapy on complete healing or health outcomes. Gardener and colleagues' (1999) pooled the results of nine small RCTs to quantify the effect of ES on chronic wound healing.

They showed a healing rate of 22% per week among patients treated with ES therapy compared to 9% healing rate per week among the controls. There were several differences among the studies included in the patients' characteristics, types of wounds, and devices used to deliver the ES therapy, as well as dose, frequency and duration of therapy. The two Cochrane reviews on EM therapy (Ravaghi 2006, and Manesh 2006) on venous leg ulcers, and pressure ulcers respectively, could not pool the results due to the limited number of included trials. In conclusion, there is insufficient evidence to determine whether the use of ES or EM therapy as adjunctive treatments would lead to healing of chronic wounds or improve the patients' health outcomes.

Articles: The literature search revealed over 90 articles. Several were reviews or non-related to the current report. There was a meta-analysis of randomized and non-randomized controlled studies on ES therapy for chronic wounds, and two small RCTs that were not included in the meta-analysis. There were also two Cochrane reviews on electromagnetic therapy for treating pressure ulcers and venous leg ulcers. The reviews however did not pool the results in meta-analyses due to the limited number of studies. A review by TEC of Blue Cross Blue Shield on electric stimulation and electromagnetic therapy for chronic skin ulcers (2005), and an ECRI report (1996) on electrical stimulation for the treatment of chronic wounds were also identified by the search. The meta-analysis and the two

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more recent RCTs on ES, as well as the two Cochrane reviews on electromagnetic therapy were critically appraised. Gardener SE, Frantz R, Schmidt FL. Effect of electrical stimulation on chronic wound healing: a meta-analysis. Wound Rep Reg 1999;7:495-503. See Evidence Table. Ravaghi H, Flemming K, Cullum NA, et al. Electromagnetic therapy for treating venous leg ulcers. (Review). Cochrane Database of Systematic Reviews 2006, Issue 2. Art. No.:CD002933. DOI:10.1002/14651858. CD002933.pub3. See Evidence Table. Manesh O, Flemming K, Cullum NA, et al. Electromagnetic therapy for treating pressure ulcers. (Review). Cochrane Database of Systematic Reviews 2006, Issue 2. Art. No.:CD002930. DOI:10.1002/14651858. CD002930.pub3. See Evidence Table. Peters EJ, Lavery LA, Armstrong DG, et al. Electrical stimulation as an adjunct to heal diabetic foot ulcers: a randomized clinical trial. Arch Phys Med Rehabil. 2001;82:721-725, See Evidence Table. Houghton PE, Kinacaid CB, Lovell M, et al. Effect of electrical stimulation on chronic leg ulcer size and appearance. Phys Ther 2003;83:17-28 See Evidence Table.

The use of Electrical stimulation and electromagnetic therapy in the treatment of chronic skin wounds does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Low Frequency, Noncontact, Nonthermal Ultrasound Wound Therapy

BACKGROUND

Chronic wounds, wounds with long healing time, and wounds with frequent recurrence are a major health problem. They are a problem for the patient who suffers from them, the clinician who treats them, and the health care system that is overburdened by their cost. It is estimated that chronic wounds affect approximately 2% of the American population at an estimated cost of US $20 billion per year. Many factors can impede wound healing, including chronic disease, venous insufficiency, arterial insufficiency, neuropathy, nutritional deficiencies and local features such as pressure, edema, and infection (Fonder, 2008, Rizzi 2010). No single regimen is universally accepted as the best modality for treating chronic wounds. They are managed through conventional wound care procedures performed by primary care providers, community nurses, pharmacists, and others. In the early 2000s, the concept of wound bed preparation has been proposed as a means of providing a structured and systemic approach to the management of chronic wounds. It is believed to accelerate endogenous healing and/or facilitate the effectiveness of other therapeutic measures. Wound bed preparation involves ongoing wound debridement, management of exudates, and resolution of bacterial imbalance (Schulz 2003, Ramundo 2008). Wound debridement is defined as the removal of devitalized or contaminated tissue as well as foreign material from the wound bed until healthy tissue is exposed. Efficient debridement reduces the necrotic burden, achieves healthy granulation tissue, and reduces wound contamination and tissue destruction. This can be performed by different enzymatic, autolytic, sharp/surgical, biological, and mechanical techniques. Each has its own advantages and limitations, and the methods that are most efficient at removal of debris, may at the same time be the most detrimental to fragile new growth (Schulz 2003, Beitz, 2005, Ramundo 2008). Noncontact, low frequency ultrasound therapy was recently introduced as a modality for promoting wound healing through wound cleansing and maintenance debridement. The therapy is thought to produce a number of biophysical effects that are associated with wound healing. These include increased protein and collagen synthesis, angiogenesis, production of growth hormone by macrophages, endothelial production of nitric oxide synthesis; and leukocyte adhesion. One of the main mechanisms of action for ultrasound therapy, as shown by in vitro studies, is achieved through the process of cavitation. This involves the production and vibration of micron-sized bubbles within the coupling medium and fluids in the tissues. As the bubbles collect and condense, they are compressed before moving to the next area. This movement and compression can potentially cause changes in the cellular activities of the tissues subjected to the ultrasound. Acoustic streaming is another mechanism by which ultrasound generates biologic activity producing a unidirectional movement of fluid along and around cell membranes. A more recent hypothesis known as the frequency resonance theory uses the above concepts at the protein and genetic level, and result in a broad range of cellular effects that promote healing. Ultrasound energy is also believed to have a direct bactericidal action caused by the cavitation effects produced by the ultrasound waves (Ennis 2005 Ramundo 2008). The sound waves generated by the therapeutic ultrasound devices have lower frequencies than those generated by diagnostic devices (25-40 kHz vs. 200,000-400,000 kHz respectively). Ultrasound MIST therapy devices use saline to couple the ultrasound energy to tissue within the wound bed. This is accomplished by the noncontact non-thermal application of a fine oxygenated fluid (sterile saline) stream spray to the wound bed through which the ultrasound energy is transmitted from the applicator tip to the wound tissue. This noncontact ultrasound is believed to provide cellular stimulation, increase blood flow, and reduce bioburden with much less pain or thermal effect than other direct contact devices. It is usually applied three times a week for a duration dependent on the wound dimensions. The therapy should be performed in a closed environment area to avoid spread of microbes, and the clinician delivering the therapy should wear protective gear (Ramundo 2008, FDA webpage). Ultrasound MIST therapy (Celleration, Inc, Eden Prairie, MN), was cleared by the FDA in 2004 to promote healing of wounds through wound cleansing and maintenance debridement by the removal of yellow slough, fibrin, tissue exudates and bacteria. Its use is contraindicated for malignant wounds, radiation wounds, for tissue previously treated with radiation, and for

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patients with bleeding disorders, or thrombophlebitis.

02/01/2010: MTAC REVIEW

Low Frequency, Noncontact, Nonthermal Ultrasound Wound Therapy

Evidence Conclusion: The literature search revealed two published RCTs on the low frequency noncontact ultrasound therapy for the treatment of wounds. The two trials were funded by the manufacturer. In one trial, Ennis and colleagues, 2005, compared the ultrasound therapy to a sham device for the treatment of patients with diabetic foot ulcers. Patients in the two treatment groups also received wound conventional therapy. The trial was randomized and controlled, and had clinically important outcome. However, it had several methodological flaws which limit generalization of its results. The study had a very low completion rate (41%) due to dropouts or violations of the protocol, and the ulcers in the sham treatment group were significantly lager in size and with a longer duration than those in the investigational group, which are potential sources of bias and confounding. The results show significant difference in the wound closure favoring the ultrasound therapy group when the analysis included only those who completed the trials, but no significant differences were observed when the analysis was based on intention to treat. Kavros and colleagues, 2007, compared the effects of the ultrasound therapy plus standard wound care to standard wound care alone in 70 patients with non-healing ischemic lower-extremity wounds. The trial was also randomized and controlled, but was not blinded, and the outcomes were mainly based on measurements which are subject to potential error, and observational bias. Moreover, the authors did not discuss if there were any dropouts, rate of compliance, or adverse events associated with the intervention. Overall, the results of the trial show that patients managed with MIST therapy in addition to standard treatment, achieved a significantly higher >50% wound closure rate in 12 weeks than those managed with standard therapy alone. A secondary analysis of the trial showed that patients with critical limb ischemia with baseline TcPO2 <20 with dependency were significantly less likely to achieve >50% healing by week 12, using standard treatment with or without MIST therapy. In conclusion, the published literature does not provide sufficient evidence to determine that non-thermal, noncontact, low frequency ultrasound therapy “Mist therapy “ is safe to use, or that it has similar or better outcomes than those achieved by other debridement methods or standard wound care management procedures.

Articles: The literature search yielded two RCTs, on the low frequency ultrasound therapy using the MIST therapy system for the treatment of chronic wounds, one non-randomized retrospective comparative study and prospective case series. The two RCTs were critically appraised. Ennis WJ, Formann P, Mozen N, et al. Ultrasound therapy for recalcitrant diabetic foot ulcers: Results of a randomized, double-blind, controlled, multicenter study. Ostomy Wound Management.2005;51:24-39. See Evidence Table. Kavros SJ, Miller JL, Hanna SW. Treatment of ischemic wounds with noncontact, low-frequency ultrasound The Mayo Clinic experience, 2004-2006. Adv skin Wound Care 2007;20:221-226. See EvidenceTable.

The use of Low frequency, noncontact, nonthermal ultrasound therapy for the treatment of wounds does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Maggot Debridement Therapy (MDT)

BACKGROUND

Chronic wounds, wounds with long healing time or frequent recurrence, are major health care and quality of life burdens. Approximately 1-2% of individuals in the United States are likely to be affected by leg ulceration at some time in their life. Many factors can impede wound healing, including chronic disease, vascular insufficiency, nutritional deficiencies and local features such as infection, pressure and edema (Fonder et al., 2008). Preparation of the wound bed is an important component of optimal healing. Proper preparation includes debridement of nonviable tissue, management of inflammation and infection, and establishment of proper moisture balance. Wound debridement serves several purposes. It removes necrotic tissue which can present physical barriers to healing, decreases the potential for infection, enhances the ability to assess wound depth, and helps to remove bacteria that may prevent healing (Beitz, 2005). Debridement methods include hydrogels, enzymatic agents, dextranomer polysaccharide beads or paste, adhesive zinc oxide tape, and sharp debridement. A systematic review of studies on different debridement methods concluded that there was insufficient evidence to recommend one method of debridement over another (Bradley et al., 1999). Maggot debridement therapy (MDT) is another method for wound debridement. Maggot or larval therapy has been used in some form for centuries, including treating battle wounds in Napoleon’s army in the 1550s. Dr. William Baer, often called the founder of modern maggot therapy, observed the effects of maggots on the wounds of soldiers during World War I and he later refined the technique to use sterile maggots under controlled conditions. MDT increased in popularity after WWI and, by the 1930s, was widely used in the U.S. and Europe. Its use decreased after the advent of antibiotics in the 1940s. As of the late 1990s there has been resurgence in interest due to antibiotic resistance, particularly methicillin-resistant Staphylococcus areureus (MRSA) and the lack of other reliably effective methods (Gupta,

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2008). Modern MDT involves the use of specially bred larvae, most commonly of the green-bottle fly Lucilia sericata species. Larvae 1-2 mm long larvae hatch from eggs in 12-24 hours and, when they feed on necrotic tissue in the moist environment of wounds, they mature in 4-5 days, at which time they measure about 10mm. Larvae need to be sterile to prevent contamination, and should be used within 8 hours of hatching or stored in refrigerator at 8-10o C to slow their metabolism. They require an optimal body temperature, moist environment and adequate oxygen supply. The general procedure is to introduce larvae to the wound at a density of 5-8 per cm2 and cover with a containment dressing that allows oxygen to pass through. Dressings are generally changed once a day to avoid build-up of secretions, and the larvae are changed every 2-3 days. Wounds commonly require 2-6 treatment cycles for complete debridement (Gupta et al., 2008; Chan et al., 2007; FDA materials). The exact mechanisms by which maggots debride wounds are not fully understood. It is generally believed that there is a combination of: 1) Mechanical action: probing from the maggots' pair of mandibles/hooks may facilitate debridement; 2) Enzymatic action: Three proteolytic enzymes have been identified in maggot excretions/secretions (ES) that can degrade extracellular matrix components, including laminin and fibronectin. The ES also have antibacterial substances which appear to have an inhibitory effect on Gram-positive and Gram-negative bacteria including MRSA. Maggots may also secrete cytokines which aid in wound healing; 3) Digestion: Maggots appear to ingest bacteria and kill them in their alimentary tract (Chan et al., 2007). There are no reports that MDT is associated with major adverse effects or complications. Minor discomfort has been reported, and excessive pressure on the wound may kill some of the maggots, resulting in uneven healing. There is also the issue of social acceptance of larval therapy, the widely-cited "yuck" factor, for patients and providers. In 2004, FDA cleared Medical Maggots (Monarch Labs, Irvine, CA) for commercial production as a Class II medical device. The approved indication is debridement of non-healing necrotic skin and soft tissue wounds.

04/06/2009: MTAC REVIEW
Maggot Debridement Therapy (MDT)
Evidence Conclusion: There is fair evidence from one RCT that wound debridement is significantly faster with maggot debridement therapy than hydrogel, but that there is no significant difference in time to complete wound healing (Dumville et al., 2009). In the RCT, median time to healing was 236 days in the larvae therapy groups and 245 in the hydrogel group. Time to debridement was 14 days in the group receiving loose larvae, 28 days in the bagged larvae group and 72 days in the hydrogel group. The efficacy of maggot therapy for debridement is supported by the results of a retrospective cohort study, and several case series. The RCT found significantly higher reports of ulcer-related pain in the larvae therapy groups in the 24 hours before removal of the first treatment compared to hydrogel, and did not report on pain during subsequent treatments. There is insufficient evidence on the efficacy of maggot therapy for MRSA eradication compared to standard wound care approaches. The number of MRSA-positive wounds in the RCT was too small to draw conclusions about eradication.
Articles: The search yielded two RCTs, one of which had a sample size of 12 patients and was excluded from further review. There was also one non-randomized comparative study and several case series. The larger RCT, cohort study and the three largest case series (n>50) were critically appraised. Citations are as follows: Dumville JC, Worthy G, Bland JM et al. Larval therapy for leg ulcers (VenUS II): randomized controlled trial. BMJ 2009; 338; online first. See Evidence Table. Sherman RA. Maggot versus conservative debridement therapy for the treatment of pressure ulcers. Wound Rep Reg 2002; 10: 208-214. See Evidence Table. Steenvoorde P, Jacob CE, Van Doorn L, Oskam J. Maggot debridement therapy of infected ulcers: patient and wound factors influencing outcome- a study on 101 patients with 117 wounds. Ann R Coll Surg Engl 2007; 89: 596-602. See Evidence Table. Wolff H, Hansson C. Larval therapy- an effective method of ulcer debridement. Clin Exper Dermatol 2003; 134-137. See Evidence Table. Courtenay M, Church JCT, Ryan TJ. Larva therapy in wound management. J Royal Soc Med 2000; 93: 72-73. See Evidence Table.

The use of maggot debridement therapy for the treatment of chronic and infected wounds does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Medihoney Dressing for Wound Management
BACKGROUND
Honey has been used in wound care for thousands of years. The ancient Egyptians, Greeks, Romans, Chinese, and other early cultures used it as a remedy for wounds either alone or in combination with other ingredients. Its healing benefits were passed from generation to generation, and honey is still traditionally used in many parts of the world. Recently there has been a resurgent interest by the medical profession in using topical honey for wound treatment, mainly due to the increasing number of bacterial strains developing resistance to antibiotics. It is only in the last few decades that researchers started to investigate honey's mechanism of action in wound healing (Molan 2008, Lay-flurrie 2008). Honey is a viscous supersaturated sugar solution derived from nectar gathered and modified by the honeybee. It contains approximately 30% glucose, 40% fructose, 5% sucrose, 20% water and

many other substances as amino acids, vitamins, minerals, and enzymes. In-vitro and animal studies indicate that honey has several therapeutic potentials. Its high osmolarity due to the sugar content causes bacterial cell wall shrinkage and inhibition of growth. Many bacteria grow and multiply in a neutral pH environment (6.5-7.0), and cannot thrive in the acidic pH of honey which ranges from 3.2 to 4.2. Researchers have reported that it in additionto its antibacterial properties, honey enhances tissue growth by drawing fluid from the underlying circulation providing both a moist environment and topical nutrition to the tissues. They also found that honey leads to cytokine release, promote autolytic debridement, deodorize malodorous wounds, and stimulates anti-inflammatory activity that reduces pain, edema, and exudate, and minimizes scarring (Molan 1999, Sato 2000, White 2005, Bell 2007). There are many different types of honey but the Manuka honey, a monofloral honey derived from the leptospermum tree species known as tea trees in Australia and New Zealand, has received particular interest for wound healing. Some researchers claim that it has a broad spectrum antibacterial activity and is exceptionally effective for several bacterial species that commonly infect surgical wounds as Staphylococcus aureus and Pseudomonas aeroginosa (Lusby 2002, Visavadia 2008).Therapeutic honey is typically raw and does not undergo heat treatment like culinary honey. It is sterilized by gamma irradiation which destroys any bacterial spores while retaining its biologic activities. Honey dressings are available in various commercial preparations such as honey gel ointment, honey-impregnated tulle dressings, honey impregnated calcium alginate dressings, and honey-based sheet hydrogel dressings (Molan 1999, Lusby 2002 Visavadia 2008, Eddy 2008, Lay-flurrie 2008). Derma Sciences Medihoney Dressing with Active Manuka Honey received FDA approval for providing a moist environment conducive to wound healing. These are tulle dressings comprised of 95% Active Manuka Honey and 5% calcium alginate, and are offered in several sizes including 0.5, 1, and 1.5 ounces. According to the FDA, Medihoney dressings are indicated for the management of light to moderately exuding wounds as: diabetic foot ulcers, venous or arterial leg ulcers, partial or full thickness pressure ulcers/sores, first and second partial thickness burns, and traumatic and surgical wounds. Honey dressings should be avoided in patients with a known history of allergy to either honey or bee venom. It was also reported (Lay-flurrie 2008) that patients with diabetes should have their blood sugar monitored as they may be at higher risk of hyperglycemia due to the sugar content of honey.

12/01/2008: MTAC REVIEW
Medihoney Dressing for Wound Management
Evidence Conclusion: To date, there are no published high quality studies to support the use honey in wound dressings. Jull and colleagues performed a systematic review (Cochrane review) of 19 randomized and quasi-randomized trials to determine the efficacy of honey on the healing of acute and chronic wounds. The meta-analysis had generally valid methodology. However, its strength is only as good as the trials it includes, and the majority was of low methodological quality. Moreover, 11 of the 19 studies were conducted by one and the same author in a single center. There was significant clinical and statistical heterogeneity between the studies which did not enable pooling of the results in the meta-analysis. Overall, the results of subgroup meta-analyses only showed a significant benefit of honey dressings (2 trials, n=992) in reducing time to complete healing of mild to moderate partial thickness burns vs. conventional dressings. The Jull et al's RCT, 2008 compared the effect of Manuka honey dressings to usual care for the treatment of venous ulcers. It was randomized, controlled and multicenter, and analysis was based on intention to treat. However, the trial was open-label, and a range of dressings were used in the control group, which are potential sources of bias. Its results showed no statistically significant differences between the honey dressing and the usual care in rate or time to complete healing. On the other hand, honey dressings were associated with significantly higher rates of overall adverse events, ulcer pain (NNH=7), and ulcer deterioration (NNH=10). Gethin and colleagues' trial compared Manuka honey to hydrogel dressings used for the treatment of venous ulcers. The trial was unblinded, small, and did not recruit the predetermined number of patients required to provide sufficient statistical power. The results of the trial showed no statistically significant differences between the Manuka honey and hydrogel therapy in desloughing the wound (percent of wound area covered by slough), or rate of slough removal in venous ulcers at 4 weeks. There was however, a higher rate of ulcer healing in the Manuka honey group (44%) vs. the hydrogel group (33%) with a risk ratio of 1.38, and NNT =9 in 12 weeks. The authors did not discuss how they defined wound healing. Conclusion: There is insufficient good quality evidence to determine whether the use of Medihoney dressings would improve the rate of healing in acute wounds as burns and traumatic wounds. There is insufficient evidence to determine whether the use of Medihoney improves the rate of healing in chronic wounds including venous ulcers, arterial ulcers, diabetic ulcers, and pressure ulcers.
Articles: The search revealed over 120 articles on the use of honey for wound care. The number of published articles dropped to just over 20 articles when the search was limited to Manuka or Medihoney. Many were review articles or opinion pieces on the benefits of honey in wound management. There was a Cochrane review on honey as a topical treatment of wounds, and a number of RCTs on the use of honey in the treatment of acute wounds due to burns. The majority of the latter trials were conducted in one center, and by one and the same author. The

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literature on the use of honey for chronic ulcers was limited. There were three RCTs on honey dressings for venous ulcers, two of which were conducted by the same investigators (Gethin and colleagues 2008) among the same group of patients, but reported different outcomes. No randomized controlled trials on the use of honey in diabetic foot ulcers, ischemic, or pressure ulcers were identified. There were only very small non-randomized trials, case series and case reports. The Cochrane review and the three trials on the use of honey for venous ulcers were critically appraised: Jull AB, Rodgers A, Walker N. Honey as a topical treatment for wounds Cochrane Database of Systematic Reviews 2008, Isssue4. Art No.:CD005083.DOI10.1002/14651858.CD005083pub2: 16:1085-1100. See Evidence Table. Jull A, Walker N, Parag V, et al. Randomized clinical trial of honey- impregnated dressings for venous leg ulcers. Br J Surg 2008; 85:175-182 See Evidence Table. Gethin G, Cowman S. Manuka honey vs. hydrogel –a prospective, open label, multicenter, randomized controlled trial to compare desloughing efficacy and healing outcomes in venous ulcers. J Clin Nurs 2008; August 23 See Evidence Table. Gethin G, Cowman S. Bacteriological changes in sloughing venous leg ulcers treated with Manuka honey or hydrogel: an RCT. J wound Care 2008;17:241-247 See Evidence Table.

The use of medihoney dressing in the treatment of wound management does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

OASIS Wound Dressing

BACKGROUND

OASIS® Wound Matrix (Cook Biotech, Inc.) is a biosynthetic skin substitute that is derived from porcine small intestine submucosa. This material is approximately 0.15 mm thick and consists primarily of a collagen-based extracellular matrix. However, unlike other purified collagen wound care products, biologically important components of the extracellular matrix such as glycosaminoglycans, proteoglycans, fibronectin, basic fibroblast growth factor, and transformind growth factor β are retained in the small intestine submucosa (Barber 2008, Chern 2009, Limová 2010). OASIS® Wound Matrix has a shelf life of 24 months and is FDA approved for use in patients with various partial- and full-thickness wounds such trauma wounds, ulcers, tunneled/undetermined wounds, draining wounds, and surgical wounds. It is not approved for use in patients with third-degree burn or with known allergies to porcine materials. According to the manufacturer's Web site, side-effects of OASIS Wound Matrix include: infection, chronic inflammation, allergic reaction, excessive redness, pain, swelling, and blistering. Additionally, the initial application of the wound dressing may be associated with transient, mild, localized inflammation (Cook Biotech, Inc 2011).

10/11/2000: MTAC REVIEW
OASIS Wound Dressing

Evidence Conclusion: Given the fact that there are no peer-reviewed articles on this topic, there is insufficient (no) evidence to determine the efficacy of this type of the Oasis Cook® wound care dressing.
Articles: Articles were selected based on study type. There were no peer-reviewed articles, so no articles were reviewed. Informational materials on the company's Web site (www.cookgroup.com) were reviewed, but no evidence tables were created.

The use of OASIS Wound Dressing in the treatment of non-healing partial thickness dermal wound does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

06/20/2011: MTAC REVIEW
OASIS Wound Dressing

Evidence Conclusion: *OASIS® versus usual care* - The first RCT included 50 subjects and compared the efficacy and tolerability of OASIS® Wound Matrix versus petrolatum-impregnated gauze in patients with difficult to heal mixed arterial/venous or venous leg ulcers. Results from this study suggest that patients treated with OASIS® have faster healing times, were more likely to experience complete wound closure, and required fewer dressing changes compared to usual care. Additionally, after 8 weeks patients treated with OASIS® had significantly more granulation tissue compared to usual care. No adverse events were observed in either treatment group. Results from this study should be interpreted with caution as it had several methodological limitations (Romanelli 2010). *OASIS® versus Hyaloskin®* - The second RCT included 54 subjects and compared the effectiveness of OASIS® Wound Matrix versus Hyaloskin® for the treatment of mixed arterial/venous leg ulcers. Results from this study suggest that patients treated with OASIS® Wound Matrix were more likely to experience wound closure compared to patients treated with Hyaloskin®. Additionally, patients treated with OASIS® Wound Matrix reported greater comfort, less pain, and required fewer dressing changes. No adverse events were observed in either treatment group. Results from this study should be interpreted with caution as it had several methodological limitations (Romanelli 2007). *OASIS® plus compression therapy versus compression therapy alone* - The third RCT included

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120 subjects and compared the effectiveness of OASIS® Wound Matrix plus compression versus compression therapy alone for the treatment of chronic leg ulcers. The primary outcome was complete wound closure. Results from this study suggest that subjects who received OASIS® Wound Matrix plus compression therapy were significantly more likely to experience complete wound closure compared to standard care plus compression therapy. There was no significant difference in adverse events between the two groups. The most frequently occurring complications were allergic reaction or intolerance to secondary dressing and wound infection. Results from this study should be interpreted with caution as it had several methodological limitations (Mostow 2005).
Conclusion: Evidence from three RCTs suggest that OASIS® Wound Matrix may be a safe and effective treatment for leg ulcers; however, results from these studies should be interpreted with caution as all of the trials had methodological limitations. For example, two of the trials were funded by the manufacturers of OASIS® Wound Matrix. Only one study performed an intent-to-treat analysis and assessed power and none of the studies provided confidence intervals.
Articles: The literature search revealed several RCTs that evaluated the safety and efficacy of OASIS® Wound Matrix for the treatment of various partial- and full-thickness wounds. Three recent RCTs were selected for review. Two of these studies were performed by the same investigator. Another trial was excluded because it did not have sufficient power (Niezgoda 2005). The following studies were critically appraised:
Romanelli M, Dini V, and Bertone M. Randomized comparison of OASIS® Wound Matrix versus moist wound dressing in the treatment of difficult-to-heal wounds of mixed arterial/venous etiology. *Adv Skin Wound Care 2010;* 23:34-38. See Evidence Table. Romanelli M, Dini V, Bertone M, et al. OASIS® Wound Matrix versus Hyaloskin® in the treatment of difficult-to-heal wounds of mixed arterial/venous aetiology. *Int Wound J 2007;* 4:3-7. See Evidence Table. Mostow EN, Hataway D, Dalsing M, et al. Effectivness of an extracellular matrix graft (OASIS® Wound Matrix) in the treatment of chronic leg ulcers. *J Vasc Surg 2005;* 41:837-843. See Evidence Table.

The use of OASIS Wound Dressing in the treatment of non-healing partial thickness dermal wound does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Warm-Up Wound Therapy

BACKGROUND
Noncontact normothermic wound therapy (The Warm-up therapy system) is used for the treatment of partial- and full-thickness wounds such as pressure ulcers, venous ulcers, diabetic ulcers, surgical wounds, and arterial wounds. Noncontact normothermic wound therapy is intended to speed the healing of wounds and venous ulcers by warming the wound and thereby increasing blood flow and allowing sufficient moisture in the wound to help cells grow and divide.The Warm-up therapy system consists of the following components: a noncontact wound cover, a temperature control unit with an AC adapter and a warming card. The non-contact wound cover is placed over the wound; the cover is raised so it does not touch the wound. It is designed to maintain warmth and humidity and to absorb exudate. There is space to insert the warming card into the wound cover. The temperature control unit, which is portable, controls the temperature of the warming card. The manufacturer recommends three warming sessions per day, heating the wound to 38^{o}C (Augustine Medical Web site). Anodyne Therapy is another treatment for increasing the rate of wound healing; it is also used to treat patients with peripheral neuropathy. Treatment consists of monochromatic near-infrared photo energy (MIRE). The recommended course of treatment is 12 sessions of MIRE. For patients with peripheral neuropathy, the intention is to increase local circulation and restore sensation. MIRE has been shown to increase nitric oxide (NO) in the blood and plasma of normal adults (Horwitz, 1999). An elevation in NO may be beneficial for wound healing and increased circulation.

10/08/2003: MTAC REVIEW
Warm-Up Wound Therapy
Evidence Conclusion: *Noncontact Normothermic Therapy (Warm-up wound therapy)* - Combining the evidence from the current and previous MTAC reviews, four randomized controlled trials comparing Warm-up wound therapy to standard care were critically appraised (McCulloch and Kloth in the current review, Warwick and Price from the 2002 review). All of the studies were subject to selection bias due to the limited sample sizes (the treatment groups are likely to be dissimilar on characteristics that may affect outcome). The Price study had the strongest methodology and did not find a statistically significant difference in healing rates in an intention to treat analysis; the study may have been underpowered. The other three RCTs found statistically significant improvement in healing according to one or more outcome variables, but were subject to biases including improper randomization, lack of intention to treat analysis, potential data manipulation and funding by the manufacturer.
Articles: *Noncontact Normothermic Therapy* - The search yielded 8 articles. There were four new RCTs, sample sizes were n=16, n=20, n=36 and n=40. The two RCTs with the larger sample sizes were critically appraised:
McCulloch J, Knight A. Noncontact normothermic wound therapy and offloading in the treatment of neuropathic

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foot ulcers in patients with diabetes. *Ostomy/Wound Management* 2002; 48: 38-44. See Evidence Table. Kloth LC, Berman JE, Nett M et al. A randomized controlled clinical trial to evaluate the effects of noncontact normothermic wound therapy on chronic full-thickness pressure ulcers. *Adv SkinWound Care* 2002; 15: 270-276. See Evidence Table.

The use of Warm-up Wound Therapy in the treatment of partial and full-thickness wounds does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

04/10/2002: MTAC REVIEW

Warm-Up Wound Therapy

Evidence Conclusion: Two relatively small RCTs evaluating the efficacy of noncontact normothermic wound therapy (Warm-up® Therapy System) for accelerating the healing rate of pressure ulcers were reviewed. The Price study, which had the stronger methodology, found no significant differences in healing rates in an intention to treat analysis. Patients receiving Warm-up wound therapy took an average of 5 fewer days for their wound to be reduced to 25% of original size. This difference was not have been statistically significant but the study may have been under-powered. Whitney found a statistically significant improvement in the linear rate of healing using Warm-up wound therapy. However, the Whitney study had substantial threats to validity (e.g. no power analysis, substantial dropout; no intention to treat analysis). The absolute difference in healing was 0.008 cm/day. The clinical significance of this difference in healing rates needs to be considered. The two RCTs reviewed had pressure ulcers as the outcome; no conclusions can be drawn about the effectiveness of this treatment for other types of wounds.

Articles: The search yielded 6 articles on this treatment, all of which were empirical and had small sample sizes (most had sample sizes of 20 or less). There were three RCTs with clinical outcomes. One had n=13 and was not reviewed. The other two RCTs (n=40 and n=58) were critically appraised: Whitney JD, Salvadalena G, Higa L, Mich M. Treatment of pressure ulcers with noncontact normothermic wound therapy: healing and warming effects. J WOCN 2001;28:244-52. See Evidence Table. Price P, Bale S, Crook H, Harding KGH. The effect of a radiant heat dressing on pressure ulcers. J Wound Care 2000;9:201-205. See Evidence Table.

The use of Warm-up Wound Therapy in the treatment of partial and full-thickness wounds does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Date Created	Date Reviewed	Date Last Revised
11/25/2002	03/02/2010P[MDCRPC], 01/04/2011P[MDCRPC] ,11/01/2011P[MDCRPC], 09/04/2012P[MDCRPC], 07/02/2013P[MDCRPC], 05/06/2014P[MPC], 12/02/2014P[MPC], 10/06/2015[MPC], 08/02/2016[MPC], 06/06/2017[MPC], 04/03/2018[MPC]	09/27/2018

[MPC] Medical Policy Committee

Revision History	Description
07/29/2015	Added Medicare language for skin substitutes
10/06/2015	Added new products to indications and non-coverage
08/02/2016	Added new products to the exclusion/non-coverage list
05/02/2017	MPC approved to utilize KP criteria for Skin-Engineered substitutes for Medicare members
01/23/2018	Added the 2018 new HCPC codes Q4176-82
09/27/2018	Added C9360, C9361, C9363, C9364

Codes

CPT:

Skin Substitutes: Q4101**;** Q4102; Q4106; Q4107; Q4121; Q4124 Q4131

Skin Substitutes (not covered): Q4100; Q4103; Q4104; Q4105; Q4108; Q4110; Q4111; Q4112; Q4113; Q4114; Q4115; Q4116; Q4117; Q4118; Q4119; Q4120; Q4122; Q4123; Q4125; Q4126; Q4127; Q4128; Q4129; Q4130; Q4132; Q4133; Q4134; Q4135; Q4136; Q4137; Q4138; Q4139; Q4140; Q4141; Q4142; Q4143; Q4145; Q4146; Q4147; Q4148; Q4149; Q4150; Q4151; Q4152; Q4153; Q4154; Q4155; Q4156; Q4157; Q4158; Q4159; Q4160, Q4161, Q4162, Q4163, Q4164, Q4165, Q4166, Q1467, Q1468, Q1469, Q1470, Q1471, Q4172, Q4173, Q4174, Q4175, Q4176, Q4177, Q4178, Q4179, Q4180, Q4181, Q4182, C9349, C9358, C9360, C9361, C9363, C9364

Autologous Platelet Derived Would Healing Factors for Non Healing Cutaneous Wounds (Procuren): G0460, 0232T, P9020, S9055

Electrical Stimulation and Electromagnetic Therapy: E0761; E0769; G0281, G0282, G0295; G0329

Low Frequency, Noncontact, Non Thermal Ultrasound Wound Therapy: 97610

Maggot Debridement for Chronic and Infected Wounds: No specific codes

MediHoney Dressing for Wound Management: No specific codes

Normothermic Wound Therapy: A6000; E0231; E0232

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Warm-up Therapy:

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