BIOENGINEERED SKIN SUBSTITUTES

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INSTRUCTIONS:

“Medical Policy assists in administering UCare benefits when making coverage determinations for members under our health benefit plans. When deciding coverage, all reviewers must first identify enrollee eligibility, federal and state legislation or regulatory guidance regarding benefit mandates, and the member specific Evidence of Coverage (EOC) document must be referenced prior to using the medical policies. In the event of a conflict, the enrollee’s specific benefit document and federal and state legislation and regulatory guidance supersede this Medical Policy. In the absence of benefit mandates or regulatory guidance that govern the service, procedure or treatment, or when the member’s EOC document is silent or not specific, medical policies help to clarify which healthcare services may or may not be covered. This Medical Policy is provided for informational purposes and does not constitute medical advice. In addition to medical policies, UCare also uses tools developed by third parties, such as the InterQual Guidelines®, to assist us in administering health benefits. The InterQual Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice. Other Policies and Coverage Determination Guidelines may also apply. UCare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary and to provide benefits otherwise excluded by medical policies when necessitated by operational considerations.”
### POLICY DESCRIPTION:

This document addresses the use of human skin substitutes (also referred to as artificial skin) for the treatment of acute and chronic non-healing wounds and soft tissue grafting. The goals are to provide temporary wound coverage, provide complete wound closure, reduce time to healing, lessen pain, minimize postoperative contracture, improve aesthetics and functional abilities, obviate the need for more extensive treatments such as skin grafting or amputation, and improve overall quality of life.

### COVERAGE RATIONALE / CLINICAL CONSIDERATIONS:

#### REASONABLE AND MEDICALLY NECESSARY:

**Apligraf®** is considered **MEDICALLY NECESSARY** for either of the following indications:
- Venous insufficiency skin ulcers with all the following characteristics:
  - Chronic, non-infected, partial or full-thickness ulcers due to venous insufficiency,
  - Standard therapeutic compression also in use,
  - At least one month of conventional ulcer therapy (such as standard dressing changes, and standard therapeutic compression) has been ineffective.
- Diabetic foot ulcers with all the following characteristics:
  - Full-thickness neuropathic diabetic foot ulcers,
  - Extends through the dermis but without tendon, muscle, joint capsule, or bone exposure,
  - At least four weeks of conventional ulcer therapy (such as surgical debridement, complete off-loading and standard dressing changes) has been ineffective.

**Biobrane®** is considered **MEDICALLY NECESSARY** for the treatment of burn wounds when all of the following criteria are met:
- The treatment is specific to noninfected partial-thickness burn wounds and donor site wounds,
- Excision of the burn wound is complete (e.g., nonviable tissue are removed) and homeostasis achieved,
- Sufficient autograft tissue is not available at the time of excision, OR
- Autograft is not desirable due to the individual's physiologic condition (e.g., individual has multisystem injuries such that creating new wounds may cause undue stress).

**Dermagraft®** is considered **MEDICALLY NECESSARY** when used for either of the following indications:
- The treatment of full-thickness diabetic foot ulcers of greater than six weeks duration that has not adequately responded to standard therapy, that extend through the dermis, but without tendon, muscle, joint capsule, or bone exposure; OR
- When used on wounds with dystrophic epidermolysis bullosa.

**Epicel™** is considered **MEDICALLY NECESSARY** for the treatment of deep dermal or full-thickness burns when all of the following medical necessity criteria are met:
- The burns comprise 30 percent or greater of total body surface area,
- When used in conjunction with split-thickness autografts or alone in individuals for whom split-thickness autografts may not be an option due to the severity and extent of their burns,
- Approval has been obtained for the use of Epicel™ in accordance with the above US Food and Drug Administration (FDA)-labeled indications under the Humanitarian Device Exemption (HDE).
**GRAFTJACKET® Regenerative Tissue Matrix** is considered **MEDICALLY NECESSARY** for treatment of full-thickness diabetic foot ulcers greater than four-week duration that extend through the dermis, but without tendon, muscle, joint capsule or bone exposure.

**Integra™ Bilayer Matrix Wound Dressing, Dermal Regeneration Template, and Meshed Bilayer Wound Matrix**, artificial skin substitutes products, are considered **MEDICALLY NECESSARY** in the post-excisional treatment of severe burns (full-thickness, 3rd degree), or (deep partial-thickness, 2nd degree) when autografting is not feasible due to the individual’s weakened physiological condition where there is a limited amount of their own skin to use or they are too ill to have more wound sites created.

**OrCel™**, a composite skin substitute, is considered **MEDICALLY NECESSARY** for either of the following uses:
- Dystrophic epidermolysis bullosa in children who are undergoing reconstructive hand surgery.
- Full-thickness (3rd degree) and partial-thickness (2nd degree) thermal burns.
- Healing donor site wounds in burn victims.

**TransCyte™**, a biosynthetic skin substitute dressing, is considered **MEDICALLY NECESSARY** for the following uses:
- Temporary wound covering to treat surgically excised full-thickness (3rd degree) and deep partial-thickness (2nd degree) thermal burn wounds in persons who require such a covering before autograft placement.
- The treatment of middermal to indeterminate depth burn wounds that typically require debridement and that may be expected to heal without autografting.

**INVESTIGATIONAL AND NOT MEDICALLY NECESSARY:**

- When criteria above are not met, or for any other application not listed, the use of Apligraf®, Biobrane®, Dermagraft®, Epicel®, GRAFTJACKET® Regenerative Tissue Matrix, Integra Bilayer Matrix Wound Dressing®, OrCel®, and TransCyte® are considered **EXPERIMENTAL/INVESTIGATIONAL AND NOT MEDICALLY NECESSARY**.

- The use of all other allogeneic, xenographic, synthetic and composite skin substitutes products for wound healing or soft tissue grafting, not addressed in the Coverage Determination section, including but not limited to the following products, is considered **INVESTIGATIONAL AND NOT MEDICALLY NECESSARY**:
  - AlloDerm®
  - AlloMax™
  - Allopatch HD™
  - Alloskin™
  - Alloskin RT™
  - AmnioFix™
  - Arthrolflex™
  - Avaulta Plus™
  - C-QUR™
  - CellerateRX®
  - CollaFix™
  - Collamend™
  - Conexa™
- CorMatrix®
- CRXa™
- Cuffpatch™
- Cymetra®
- Dermacell™
- Dermamatrix®
- Endoform™
- ENDURagen™
- Epidex®
- EpiFix™
- E-Z Derm™
- Flex HD®
- Gammagraft™
- GORE BIO-A® Fistula Plug
- Grafix® CORE
- Grafix® PRIME
- Graftjacket™ Xpress injectable
- Hyalomatrix®
- Inforce®
- Integra™ Neural Wrap
- Matriderm®
- Matristem®
- MediHoney®
- Medeor™
- Mediskin®
- Memoderm™
- Menaflex™ Collagen Meniscus Implant
- Meso BioMatrix™
- Neoform Dermis™
- Neuragen®
- NeuraWrap™
- Neuroflex™
- NeuroMatrix™
- Oasis Wound Matrix™
- OrthADAPT™
- Pelvicol®
- Pelvisoft®
- Permacol™
- PTFE felt™
- PriMatrix™
- Promogran™
- Puracol®
- SportMesh™
- Strattice™
- SurgiMend®
Clinical Considerations:

**Contraindications include:**
- Evidence of arterial occlusive disease, i.e., ankle-brachial index (ABI) < 0.65.
- Evidence of infection in ulcer(s) targeted for treatment.
- Exudate consistent with heavy bacterial contamination, or necrotic tissue that would interfere with graft take and healing.
- Active Charcot disease.
- Hypersensitivity or allergy to any components of the skin substitutes.

The efficacy and safety of these skin substitutes in patients who are pregnant or lactating, have uncontrolled diabetes, or are currently being treated with corticosteroids, immunosuppressants, or chemotherapy have not been established (Sabolinski et al., 1996; Falanga et al., 1998; Falanga and Sabolinski, 1999).

**Evaluation/Risk Assessment/Screening**
- Initial and continuous pressure ulcer risk assessment using reliable scales
- Nutritional assessment with a validated measure
- Document medical and surgical history
- Assessment of psychosocial conditions and quality of life
- Environmental assessment
- Physical examination, including wound assessment
- Diagnostic tests

**Prevention/Rehabilitation**
- Skin inspection and maintenance
- Hydration and nutrition plan of care
- Rehabilitative and restorative programs
- Positioning standards of care to manage pressure ulcers
- Off-loading equipment including chairs, intensive care, and operating rooms
- Interdisciplinary team approach
- Education

**Management/Treatment**
- Remove/alleviate all causes of pressure ulcer damage
**Debride, cleanse, and dress the wound**
- Advanced or adjuvant interventions
- Surgical interventions
- Documentation of response
- Palliative care

**Follow-Up Care**
The individual should be self-sufficient with follow-up care or have the required support system to participate in the follow-up care associated with skin substitutes.

**BACKGROUND:**
Skin wounds can be caused by a variety of different events, including thermal burns, venous stasis, ischemia, pressure, trauma, or surgery, and as a result of an underlying skin disorder such as epidermolysis bullosa (EB). According to the American Burn Association (ABA), an estimated 1 million burn injuries occur annually in the United States. Burn injuries result in approximately 4500 deaths, 45,000 hospitalizations, and 700,000 emergency room visits per year. The average size of a burn injury among patients admitted to burn centers is approximately 14% of the total body surface area (TBSA). Partial-thickness, or second-degree, burns are those in which there is damage to the epidermis and the upper portion of the dermis. Serious burns are treated by split-thickness autographs (STGs), which include part of the dermis, and are obtained from such areas as the inner thigh or buttocks, and placed on the wound.

Chronic wounds, including venous ulcers, diabetic foot ulcers, and pressure sores, are a major public health problem in the United States; the total prevalence of these wounds has been estimated to range from 3 to 6 million. Difficult-to-heal wounds lead to high rates of morbidity and mortality, negative effects on quality of life, and high healthcare costs. Lower extremity ulcers affect approximately 1% of the adult population and approximately 3.6% of persons older than 65 years. While lower extremity ulcers have numerous causes, such as venous disease, arterial disease, mixed venous-arterial disease, diabetic neuropathy, trauma, immobility, and vasculitis, over 90% of the lesions are related to venous or arterial disease and neuropathy.

**SKIN GRAFTING.**
There are currently a wide variety of products available for soft tissue grafting and wound treatment. These products may be derived from allogeneic, xenographic, synthetic, or a combination of any or all of these types of materials.

**Autologous skin grafts** also referred to as autografts, are permanent covers that use skin from different parts of the individual's body. These grafts consist of the epidermis and a dermal component of variable thickness. A split-thickness skin graft (STSG) includes the entire epidermis and a portion of the dermis. A full-thickness skin graft (FTSG) removes all the layers of the skin. Although autologous skin grafts are the optimum choice for wound coverage, areas of skin for harvesting may be limited, particularly in cases of large burns; in addition, the procedures are invasive and painful. **Allografts** (which use skin from another human [e.g., cadaver]) and **xenografts** (which use skin from another species [e.g., porcine or bovine]) may also be employed as temporary skin replacements, but they must later be covered by an autograft.

**BIOENGINEERED SKIN SUBSTITUTES.**
Because of problems inherent with autografts, allografts, and xenografts, bioengineered skin substitutes
have been developed. These are products used for non-healing wound treatment and soft tissue grafting on patients with life threatening full-thickness (3rd degree) or deep partial-thickness (2nd degree) burns, surgical wounds, diabetic ulcers, venous ulcers, and epidermolysis bullosa. These products are manufactured by starting with a few human cells in which tissue engineers simulate the environments that allow cells to develop into viable tissue. The specific procedure varies by company, but it generally involves seeding the selected cells onto some type of matrix, where they are then provided with the proteins and growth factors necessary for them to grow and multiply into the desired tissue.

A variety of biosynthetic and tissue-engineered human skin equivalents (HSE) are manufactured under an array of trade names and marketed for various purposes. All of these products are procured, produced, manufactured or processed in sufficiently different manners that they cannot be addressed and evaluated as equivalent products.

Bioengineered skin substitutes are classified into the following types:

- Cultured epithelial autografts
- Human skin allografts derived from donated human cadaver tissue
- Allogenic matrices derived from human neonatal fibroblasts
- Composite matrices derived from human keratinocytes, fibroblasts, and bovine or porcine collagen
- Acellular matrices derived from porcine or bovine collagen

**CULTURED EPITHELIAL AUTOGRATFS (CEAs):** Examples include, but may not be limited to:

- **Epicel™** (cultured epidermal autograft [CEA]) (Genzyme Tissue Repair; Cambridge, MA). Sheets of skin cells intended to replace the epidermis on severely burned patients. The patient’s own skin cells are grown or cultured from a postage-stamp sized sample of the patient’s own healthy skin. The skin cells are grown on a layer of irradiated mouse cells, making Epicel® a xenotransplantation product. (Genzyme Corp., 2007).
- **EpiDex™** (DFH Pharmaceuticals, Inc.; Fort Worth, TX) is a fully differentiated autologous epidermal equivalent derived from outer root sheath keratinocytes that is grown directly from plucked hair follicles. Cell cultures expand for five to six weeks, after which time the product is applied non-surgically. One study was insufficiently powered to allow assumptions about its effect on the population. In a second study, there was no significant difference between the groups in the frequency of complete ulcer closure or time to complete closure. At this time, EpiDex™ has no FDA designation.
- **Hyalomatrix**® (Laserskin®) (Fidia Advanced Biopolymers; Abano Terme, Italy). A bioresorbable dermal substitute made of HYAFF®, a long-acting derivative of hyaluronic acid providing a microenvironment purportedly suitable for optimal tissue repair and accelerated wound healing. Specifically intended for the treatment of deep burns and full-thickness wounds; also provides a wound preparation support for the implantation of autologous skin grafts.

**HUMAN SKIN ALLOGRAFTS DERIVED FROM DONATED HUMAN CADAVER TISSUE:** Examples include, but may not be limited to:

- **AlloDerm®** (Life Cell Corp.; The Woodlands, TX). AlloDerm is an acellular dermal matrix designed to serve as a biologic scaffold for normal tissue remodeling. Processed from human cadaver skin with the cells responsible for immune response and graft rejection removed. The remainder is a matrix or framework of natural biological components, ready to enable the body to mount its own tissue regeneration process. (Jones et al., 2002).
- **Alloskin™** (AlloSource Inc.; Centennial, CO). An allograft derived from epidermal and dermal cadaveric...
tissue and suggested for wound care.

- **Cymetra®** (Life Cell Corp.; The Woodlands, TX). An injectable form of AlloDerm® that has been processed into micronized particles; suggested for the correction of soft-tissue defects, such as injection laryngoplasty.

- **GammaGraft™** (Promethean LifeSciences, Inc.; Pittsburgh, PA). GammaGraft™ is an irradiated composite allograft that can be stored at room temperature. According to the manufacturer, GammaGraft™ is indicated in various types of wounds and is used primarily as a temporary dressing that may require multiple applications.

- **GRAFTJACKET® Regenerative Tissue Matrix** (Wright Medical Technology; Arlington, TN). This is a product derived from cadaver skin from which the epidermis and all cellular components are removed while preserving the matrix and biochemical factors. Graftjacket is to be used for the repair or replacement of damaged or inadequate integumental tissue or for other homologous uses of human integument (Wright Medical Technology Inc., 2008). It is suggested for diabetic foot ulcers.

- **GRAFTJACKET® EXPRESS Scaffold** (Wright Medical Technology; Arlington, TN). This allograft is a micronized (finely ground) decellularized soft tissue scaffold indicated for the repair or replacement of damaged or inadequate integumental tissue, specifically deep, dermal wounds that exhibit tunneling and extension from the wound base that may move into the tendon and bone.

- **TheraSkin®** (Soluble Solutions, Newport News, Va.). A biologically active cryopreserved human skin allograft with both epidermis and dermis layers; the cellular and extracellular composition provides a supply of growth factors, cytokines and collagen to supposedly promote wound healing.

**ALLOGENIC MATRICES DERIVED FROM HUMAN NEONATAL FIBROBLASTS:** Examples include, but may not be limited to:

- **AlloMax™** (Bard Davol, Inc.). A sterile regenerative human collagen matrix suggested for soft tissue repair, including hernia and abdominal wall reconstruction, and post-mastectomy breast reconstruction.

- **Celaderm®** (Advanced BioHealing; Westport, CT) is a cultured epithelial allograft that contains metabolically active human foreskin-derived allogeneic keratinocytes. At this time, this product has no FDA designation.

- **Dermagraft®** (Advanced BioHealing; Westport, CT / Smith & Nephew, Inc.; La Jolla, CA). This product is a living dermal replacement that employs human neonatal foreskin fibroblasts. The mesh is a biodegradable material that disappears after being in place for three to four weeks. It is used in the treatment of full-thickness diabetic foot ulcers of greater than six weeks duration that extends through the dermis, but without tendon, muscle, joint capsule, or bone exposure. It is also used for treatment of wounds in individuals with dystrophic epidermolysis bullosa (DEB).

**COMPOSITE MATRICES DERIVED FROM HUMAN KERATINOCYTES, FIBROBLASTS AND BOVINE OR PORCINE COLLAGEN:** Examples include, but may not be limited to:

- **Apligraf®** (Organogenesis, Inc.; Canton, MA). Formerly marketed as Graftskin. Much like human skin as it has two primary layers: the epidermal (outer) layer consists of live keratinocytes, while the dermal (inner) layer contains living fibroblasts. Also referred to as human skin equivalent.

- **OrCel™** (formally Composite Cultured Skin) (Ortec International, Inc.; New York, NY). A bi-layered skin substitute that uses human epidermal keratinocytes and dermal fibroblasts that are cultured into two separate layers on a bovine collagen sponge. As healing occurs at the site of the wound, the OrCel® dissolves and the patient’s own skin cells then replace the OrCel® cells to create a new skin surface.
• **TransCyte™** (formerly Dermagraft TC™ [Dermagraft Transitional Covering]) (Advanced BioHealing; Westport, CT). A human fibroblast-derived temporary skin substitute consisting of a polymer membrane and neonatal human fibroblast cells cultured under aseptic conditions in vitro on a nylon mesh. Purportedly, as fibroblasts proliferate within the nylon mesh, they secrete human dermal collagen, matrix proteins and growth factors.

**ACELLULAR MATRICES DERIVED FROM PORCINE, OVINE, OR BOVINE COLLAGEN:** Examples include, but may not be limited to:

- **Biobrane®** (UDL Laboratories Inc.; Rockford, IL) (formerly a product of Mylan/Bertek Laboratories). This product is an acellular dermal matrix constructed using collagen (porcine type 1) that is incorporated with both silicone and nylon, and mechanically bonded to a flexible knitted nylon fabric. The semipermeable membrane is comparable to human skin as it controls the loss of water vapor, allows for drainage of exudates, and provides permeability to topical antibiotics. The nylon/silicone membrane provides a flexible adherent covering for the wound surface.

- **Endoform™** Dermal Template (Mesynthes Ltd, Wellington, New Zealand). This product is an extracellular matrix derived from sheep collagen (forestomach) and intended for single use in the treatment of wounds.

- **EZ Derm™** (Brennen Medical, Inc.; St. Paul, MN). A porcine derived xenograft in which the collagen has been chemically cross-linked with aldehyde (a chemical compound) purportedly to provide strength and durability.

- **Integra® Dermal Regeneration Template** (Integra LifeSciences Corp.; Plainsboro, NJ) is a bi-layered extracellular matrix of fibers of cross-linked bovine collagen and chondroitin-6-sulfate (a component of cartilage) with silicone backing. Once an organized regeneration of dermal tissue is formed (neodermis), the disposable silicone sheet is removed and an ultrathin autograft is placed over the neodermis.

- **Integra™ Bilayer Matrix Wound Dressing and Integra™ Meshed Bilayer Wound Matrix** (Integra LifeSciences Corp.; Plainsboro, NJ). A biodegradable porous matrix of cross-linked bovine tendon collagen and glycosaminoglycan intended to provide a scaffold for cellular invasion and capillary growth. Wound closure is typically complete within 30 days.

- **Integra™ Flowable Wound Matrix** (Integra LifeSciences Corp.; Plainsboro, NJ) is comprised of granulated cross-linked bovine tendon collagen and glycosaminoglycan, which is hydrated with saline for injection into difficult to access wound sites and tunneled wounds.

- **Matristem® Wound Matrix** (ACell Inc. Jessup, MD) is a porcine-derived, single or multi-layer, extracellular matrix sheet. This product is used for the management of 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-Moh’s surgery, podiatric, wound dehiscence), trauma wounds (e.g., abrasions, lacerations, second degree burns, skin tears), and draining wounds.

- **Matristem Micromatrix®** (ACell Powder Wound Dressing) (ACell Inc. Jessup, MD) is composed of porcine collagen from urinary bladder matrix that is lyophilized to be used as a topical application. This product is marketed as a wound healing powder that helps regenerate hair in the donor and recipient regions of hair transplant individuals.

- **Matristem® Burn Matrix** (ACell Inc. Jessup, MD) is a porcine-derived, single or multi-layer, extracellular matrix sheet.

- **Oasis Wound Matrix™** (Cook Biotech, Inc; West Lafayette, IN). A naturally derived ECM, created from...
the submucosal layer of porcine small intestine; proposed to support the body's healing process by providing an acellular scaffold that accommodates remodeling of host tissue. This product also contains other biologically active components that may stimulate healing such as glycosaminoglycans, proteoglycans, fibronectin, and growth factors (Mostow et al., 2005).

- **Oasis Burn Matrix™** (Cook Biotech, Inc; West Lafayette, IN) is a product derived from porcine small intestinal submucosa (SIS). This product is intended for the management of second degree burns and donor sites.

- **PriMatrix™ Dermal Repair Scaffold** (TEI Biosciences Inc.; Boston, MA) (formerly DressSkin). A naturally derived, ECM created from the submucosal layer of porcine small intestine; proposed to support the body's healing process by providing an acellular scaffold that accommodates remodeling of host tissue. Primatrix is designed to incorporate collagen into the wound bed and stimulate rapid tissue granulation and native collagen production. This biological matrix is appropriate for treatment of a variety of different types of wounds, including skin ulcers, second-degree burns, surgical wounds, trauma wounds, post-Mohs surgical wounds, and tunneled wounds (TEI Biosciences, 2008).

### REGULATORY STATUS:

1. **U.S. FOOD AND DRUG ADMINISTRATION (FDA):**

   Depending on the purpose of the product and how it functions, skin substitutes are regulated by the FDA premarket approval (PMA) process, 510(k) premarket notification process, or the FDA regulations for banked human tissue.

   Products that are classified by the FDA as an interactive wound and burn dressing are approved under the PMA process as a class III, high-risk device and require clinical data to support their claims for use. These devices may be used as a long-term skin substitute or a temporary synthetic skin substitute. They actively promote healing by interacting directly or indirectly with the body tissues. Examples of these devices include Apligraf® (Organogenesis Inc., Canton, MA) and Dermagraft® (Advanced BioHealing, Inc., LaJolla, CA).

   Other wound care devices are approved by the 510(k) process, and their primary purpose is to protect the wound and provide a scaffold for healing. They may or may not be integrated into the body tissue. Some devices are rejected by the body after approximately ten days to several weeks and removed prior to definitive wound therapy or skin grafting. Integra™ Bilayer Matrix Wound Dressing (BMWD) (Integra LifeSciences Corp., Plainsboro, NJ) and Oasis® Wound Matrix (Cook Biotech, Inc., West Lafayette, IN) are examples of these devices.

   Donated skin that requires minimal processing and is not significantly changed in structure from its natural form is classified by the FDA as banked human tissue. It is not considered a medical device, and does not require PMA or 510(k) approval. Donated skin is regulated by the American Association of Tissue Banks (AATB) and the FDA guidelines for banked human tissue. AATB oversees a voluntary accreditation program and the FDA focuses on preventing the transmission of communicable diseases by requiring donor screening and testing. Tissue establishments must register with the FDA and list each cell or tissue produced. An example of a banked human tissue product is AlloDerm, an acellular dermal matrix (FDA, 2004; Department of Health and Human Services, 2001).

   - **AlloDerm®** (Life Cell Corp.; The Woodlands, TX). AlloDerm® is regulated as human tissue and subject to the rules and regulations of banked human tissue, regulated by the American Association of Tissue Banks (AATB); hence, it is not subject to FDA pre-notification approval (LifeCELL.
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Corporation, 2008).

- **Alloskin™** (AlloSource Inc.; Centennial, CO). FDA regulation of human tissue does not include review and approval for safety and effectiveness.

- **Apligraf®** (Organogenesis, Inc.; Canton, MA). Apligraf gained FDA PMA based on its efficacy with venous ulcers. Apligraf® also has FDA PMA for use in the treatment of diabetic foot ulcers.

- **Biobrane®** (UDL Laboratories Inc.; Rockford, IL). This product holds an FDA 510(k) approval for the treatment of clean partial-thickness burn wounds and donor site wounds.

- **Celaderm®** (Advanced BioHealing; Westport, CT). At this time, this product has no FDA designation, and no published study outcomes were found in the literature. Individuals are currently being enrolled in an FDA-approved study to evaluate the safety of Celaderm® in humans and to assess its potential for acceleration of healing of venous leg ulcers.

- **Cymetra®** (Life Cell Corp.; The Woodlands, TX). The FDA considers Cymetra® banked human tissue because it is minimally processed and not significantly changed in its structure from the natural material.

- **Dermagraft®** (Advanced BioHealing; Westport, CT / Smith & Nephew, Inc.; La Jolla, CA). Dermagraft® has received FDA premarket approval (PMA) for use in the treatment of full-thickness diabetic foot ulcers of greater than six weeks duration that extend through the dermis, but without tendon, muscle, joint capsule, or bone exposure.

- **Endoform™** Dermal Template (Mesynthes Ltd, Wellington, New Zealand). Endoform™ received an FDA 510(k) Premarket Notification from the FDA. The product is similar to Integra™ and Oasis,™ which were cited as predicate devices. Indications are similar to other acellular matrix products and include the following: treatment of 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-Moh’s surgery, post-laser surgery, podiatric, wound dehiscence, trauma wounds (e.g., abrasions, lacerations, second-degree burns, and skin tears), and draining wounds.

- **Epicel™** (Genzyme Tissue Repair; Cambridge, MA). The FDA considers Epicel™ to be a cultured epidermal autograft, dressing, wound, and burn interactive that does not require an FDA designation. For burns, Epicel™ has been approved by the FDA under the humanitarian device (HDE) designation for use in individuals who have deep dermal or full-thickness burns comprising a total body surface area of greater than or equal to 30 percent.

- **EpiDex™** (DFH Pharmaceuticals, Inc.; Fort Worth, TX). At this time, EpiDex™ has no FDA designation.

- **EZ Derm™** (Brennen Medical, Inc.; St. Paul, MN). EZ Derm™ has FDA 510(k) approval for the treatment of partial-thickness burns and venous, diabetic, and pressure ulcers.

- **GammaGraft™** (Promethean LifeSciences, Inc.; Pittsburgh, PA). At this time, it has No FDA designation.

- **Graftjacket®**: **Graftjacket Matrix, Graftjacket Xpress Scaffold, and Graftjacket Ulcer Repair Matrix** (Wright Medical Technology; Arlington, TN): These products are made from human donor skin, which undergoes a process that removes the epidermis and dermal cells, thereby creating an acellular dermis. Similar to AlloDerm, human cells or tissues intended for implantation, transplantation, infusion, or transfer into a human recipient are regulated as human cell, tissue,
and cellular- and tissue-based products; hence, it is not subjected to FDA pre-notification approval (FDA, 2009).

- **Hyalomatrix®** (Laserskin®) (Fidia Advanced Biopolymers; Abano Terme, Italy). This product has received FDA 510(k) approval and is indicated for the management of wounds in the granulation phase (e.g., pressure ulcers, venous and arterial leg ulcers, diabetic ulcers, surgical incisions, second-degree burns, skin abrasions, lacerations, partial-thickness grafts and skin tears, and wounds and burns treated with meshed grafts).

- **Integra® Dermal Regeneration Template** (Integra LifeSciences Corp.; Plainsboro, NJ). Integra® has an FDA PMA for treatment of life-threatening, full-thickness or deep partial-thickness thermal injuries where sufficient autograft is not available at the time of excision or not desirable due to the physiologic condition of the individual. This product also has an FDA PMA for repair of scar contractures.

- **Integra™ Bilayer Matrix Wound Dressing and Integra™ Meshed Bilayer Wound Matrix** (Integra LifeSciences Corp.; Plainsboro, NJ). FDA has approved these products for indications that include management of partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, surgical wound (donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second degree burns, and skin tears), and draining wounds.

- **Integra™ Flowable Wound Matrix** (Integra LifeSciences Corp.; Plainsboro, NJ). According to the FDA 510(k) summary, this product is equivalent in function and intended use to the Integra™ Matrix Wound Dressing.

- **Matristem Micromatrix®** (ACell Inc. Jessup, MD). Matristem Micromatrix® has also received 510k Premarket Notification for the same indications as Matristem® Wound Matrix. This product is marketed as a wound healing powder that helps regenerate hair in the donor and recipient regions of hair transplant individuals.

- **Matristem® Wound Matrix** (ACell Inc. Jessup, MD). Matristem® Wound Matrix has received FDA Premarket Notification for the management of 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-Moh's surgery, podiatric, wound dehiscence), trauma wounds (e.g., abrasions, lacerations, second degree burns, skin tears), and draining wounds.

- **Oasis® Wound Matrix: Oasis Wound Matrix** is regulated by the FDA as a Class II (moderate risk) device. This product received FDA 510(k) approval (K061711), granted to Cook Biotech Inc. on July 19, 2006. It is an animal-derived extracellular matrix that is supplied sterile and is intended for single use in the management of various wounds such as partial and full-thickness wounds, pressure, venous, diabetic, and chronic vascular ulcers, tunneled/undermined wounds, surgical wounds, trauma wounds, and draining wounds (FDA 2006b). The product is identical to an earlier product developed by Cook Biotech Inc. (SIS wound dressing II, K993948, issued January 6, 2000) (FDA, 2000). The FDA approved a name change to Oasis Wound Matrix to acknowledge that it contains glycosaminoglycans and other matrix components not found in other purified collagen-alone materials that can stimulate cell differentiation in cell culture assay, an indicator of bioactivity (Schaum and Farley, 2006).

- **OrCel™** (Ortec International, Inc.; New York, NY). OrCel™ has received FDA PMA for the treatment of fresh, clean split-thickness donor site wounds. OrCel™ has received an HDE for the treatment of
surgical wounds and donor sites associated with mitten-hand deformities in individuals who have recessive dystrophic epidermolysis bullosa (RDEB).

- **PriMatrix™ Dermal Repair Scaffold** (TEI Biosciences Inc.; Boston, MA) (formerly DressSkin). This product received initial FDA 510(k) approval (K061407), granted to TEI Biosciences Inc. on June 29, 2006. This product is indicated for the management of wounds, including partial- and full-thickness wounds, pressure, diabetic, and venous ulcers, second-degree burns, surgical wounds, trauma wounds, tunneled/undermined wounds, and draining wounds (FDA, 2006a).

- **Promogran®**: Promogran Matrix Wound Dressing received FDA 510(k) approval (K014129), granted to Johnson & Johnson Medical Ltd. on February 14, 2002. Promogran is indicated for use in patients with diabetic ulcers, venous ulcers, ulcers caused by mixed vascular etiologies, full- and partial-thickness wounds, donor sites and other bleeding surfaces, abrasions, traumatic wounds, and dehisced surgical wounds (FDA, 2002).

- **TheraSkin®** (Soluble Solutions, Newport News, Va.). The FDA has classified TheraSkin™ as banked human tissue and, therefore, is subject to the rules and regulations of banked human tissue.

- **TransCyte™** (Advanced BioHealing; Westport, CT). TransCyte™ received FDA PMA as a temporary wound covering for surgically excised full-thickness and deep partial-thickness burn wounds in individuals who require such a covering prior to autograft placement.

- **Xelma®**: Xelma has not yet received premarket approval from the FDA.

2. **CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS):**

   The Local Coverage Article (LCD A40531) covers the use of skin substitutes and related products in the treatment of lower extremity ulcer disease. The LCD does not pertain or otherwise apply to the use of any skin substitutes or related products in the treatment of burns, skin cancer, or for true reconstructive surgery.

   **Indications:**

   Application of Bioengineered Skin Substitutes will be covered when the following conditions are met and documented as appropriate for the individual patient:

   1. Presence of neuropathic diabetic foot ulcers for greater than four (4) weeks' duration.
   2. Presence of venous stasis ulcers of greater than three (3) months' duration that have failed to respond to documented conservative measures for greater than two (2) months' duration.
   3. Presence of neuropathic diabetic foot ulcers that have failed to respond to documented conservative measures for greater than one (1) month's duration. These measures must include appropriate steps to off-load pressure during treatment.
   4. Presence of partial or full-thickness ulcers.
   5. Measurements of the initial ulcer size, the size following cessation of any conservative management and the size at the beginning of skin substitute treatment.

   In all cases, the ulcer must be free of infection and underlying osteomyelitis. Documentation must be provided that these conditions have been successfully treated and resolved prior to instituting skin substitute treatment.

3. **MINNESOTA DEPARTMENT OF HUMAN SERVICES (DHS):**

   Minnesota DHS has guidance regarding specialized wound treatment technology and specifically addresses platelet rich plasma systems (e.g., AutoloGel, Magellan); negative pressure wound therapy devices, and Electro-magnetic/ultrasound therapy. DHS does not address Bioengineered Skin
Substitutes in its Provider Manual or other specific provider references.

**Criteria for Specialized Wound Treatment for Chronic Wounds**

Authorization for specialized wound therapy for chronic wounds will be considered when a wound does not respond to standard wound treatment for at least a 30 day period. For all wounds, documentation and a comprehensive treatment plan, before requesting authorization for a specialized wound therapy product, is required and includes the following:

- **Wound type, including:**
  - Etiology and stage when appropriate
  - Date of onset
  - Evaluation
  - Previous wound care and assessments done by a licensed medical professional

- **Weekly wound measurements to assess the appropriateness of current wound treatment.** If no improvement to the wound, the wound treatment must be changed. This must be done by nursing staff in the skilled facility or by a licensed medical professional in the home setting.

- **Application of dressings to maintain a continuously moist wound environment must have been tried prior to requesting a specialized wound therapy product (gel dressings).**

- **Impregnated dressings have been tried when applicable (e.g., sodium, antimicrobial, collagen petroleum).**

- **Debridement of necrotic tissue - mechanical, surgical/chemical.**

- **Evaluation and provision for adequate nutritional status.** Include both prealbumin and albumin levels. Ideally, albumin levels are 3.5 – 5. If albumin levels are below 3.5, specialized wound therapy may be approved if prealbumin levels are 20-40, show improvement over the previous 30 days and if there is a nutritional plan in place written by an appropriate professional. Specialized wound therapy will not be authorized for albumin levels below 2.8. Baseline albumin and prealbumin levels are required and as medically necessary thereafter. If albumin levels are below 3.5, enteral nutritional support may be covered. Refer to Enteral Nutritional Products policy.

- **Moisture and incontinence have been addressed and appropriately managed.**

- **Compliance issues are addressed (i.e., missed medical appointments, refusing dressing changes, repositioning, smoking, poor nutritional intake or choices).**

- **Medical intervention/correction of underlying conditions** that may hinder the healing process of the wound (i.e., local or distant infections are addressed).

- **Assessment of medications** that may delay healing (i.e. systemic steroids, immunosuppressive drugs).

- **Evaluation of arterial sufficiency when appropriate.**

- **Licensed professional (RN, LPN, PT) services in place for treatment in the home.**

- **Document how this request is appropriate for the type of wound being treated.**

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**CLINICAL EVIDENCE:**

There are currently a wide variety of products available for soft tissue grafting and wound treatment. These products may be derived from allogeneic, xenographic, synthetic, or a combination of any or all of these
types of materials. All of these products are procured, produced, manufactured or processed in sufficiently different manners that they cannot be addressed and evaluated as equivalent products. Therefore, each product must be reviewed and judged on the basis of the available scientific evidence specific to that product. Unfortunately, the majority of these products have no peer-reviewed, published studies available to assist in the evaluation of their safety and efficacy. In such circumstances, products are considered investigational and not medically necessary based on a lack of data addressing both the safety and efficacy of the product in question. For other products, there may be one or more published studies of varying quality. Below is a summary of the findings of the most recent, most significant, or most rigorous studies available for each product. Many studies have been omitted because they were considered poorly designed or too small to adequately demonstrate efficacy for a more general population.

CONCLUSIONS:
The overall body of published evidence regarding the safety and efficacy of biological tissue-engineered skin substitutes is limited, and at the present time does not clearly demonstrate a benefit of these products compared with optimal standard wound care. None of the available studies provided an adequate direct comparison of the different biological tissue-engineered skin substitute products. Additional research, including well-designed randomized controlled or comparative studies, is needed to establish the safety, efficacy, and comparative effectiveness of the different skin substitute products and to define appropriate patient selection criteria.

APPLICABLE CODES:

The Current Procedural Terminology (CPT®) codes and HCPCS codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered health service. The inclusion of a code does not imply any right to reimbursement or guarantee claims payment. Other medical policies and coverage determination guidelines may apply.

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>C9354</td>
<td>Acellular pericardial tissue matrix of nonhuman origin (Veritas), per sq cm</td>
</tr>
<tr>
<td>C9358</td>
<td>Dermal substitute, native, nonadenatured collagen, fetal bovine origin (SurgiMend Collagen Matrix), per 0.5 sq cm</td>
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<tr>
<td>C9360</td>
<td>Dermal substitute, native, nonadenatured collagen, neonatal bovine origin (SurgiMend Collagen Matrix), per 0.5 sq cm</td>
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<tr>
<td>C9363</td>
<td>Skin substitute (Integra Meshed Bilayer Wound Matrix), per square cm</td>
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<td>C9364</td>
<td>Porcine implant, Permacol, per sq cm</td>
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<td>C9366</td>
<td>EpiFix, per sq cm</td>
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<td>C9367</td>
<td>Skin substitute, Endoform Dermal Template, per sq cm</td>
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<td>C9368</td>
<td>Grafix core, per square centimeter</td>
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<td>Q4100</td>
<td>Skin substitute, not otherwise specified</td>
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<td>Integra bilayer matrix wound dressing (BMWD), per sq cm</td>
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<td>Integra dermal regeneration template (DRT), per sq cm</td>
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<tr>
<td>15002-15005</td>
<td>Surgical preparation codes for skin replacement surgery</td>
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<tr>
<td>15271</td>
<td>Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area</td>
</tr>
<tr>
<td>15272</td>
<td>Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)</td>
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<tr>
<td>15273</td>
<td>Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children</td>
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<td>15274</td>
<td>Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)</td>
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<td>15275</td>
<td>Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area</td>
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15276  Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)

15277  Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children

15278  Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)

15777  Implantation of biologic implant (e.g., acellular dermal matrix) for soft tissue reinforcement (e.g., breast, trunk) (List separately in addition to code for primary procedure)

ICD-9 Procedure Code | Description
---|---
86.67  | Free skin graft; Dermal regenerative graft

CPT® is a registered trademark of the American Medical Association.

REFERENCES:
13. Hayes, Winifred S. Search and Summary. Strattice™ reconstructive tissue matrix(LifeCell Corporation) for hernia


52. Falanga V, Sabolinski M. A bilayered living skin construct (APLIGRAF) accelerates complete closure of hard-to-heal
67. Guyatt GH, Sackett DL, Cook DJ. Users’ guides to the medical literature. II. How to use an article about therapy or prevention. B. What were the results and will they help me in caring for my patients? Evidence-Based Medicine Working Group. JAMA. 1994;271(1):59-63.


86. Wound, Ostomy and Continence Nurses Society (WOCN) [website]. Wound Ostomy and Continence Nurses Society Guidance on Oasis Skin and Wound Status M0 Items. Revised July 2006. Available at:

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