



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

**Subject Tissue-Engineered Skin
Substitutes and Platelet-
Derived Growth Factors**

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- Bone Graft Substitutes for Use in Bone Repair
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- Hyperbaric Oxygen Therapy, Systemic & Topical
- Negative-Pressure Wound Therapy/Vacuum-Assisted Closure (VAC) for Non-Healing Wounds
- Plantar Fasciitis Treatments
- Pulsed Electromagnetic Therapy
- Scar Revision

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2011 CIGNA

Coverage Policy

CIGNA covers each of the following products* as medically necessary for the specific indications noted:

- **AlloDerm®** when used in association with a covered, medically necessary breast reconstruction procedure
- **AlloMax™** when used in association with a covered, medically necessary breast reconstruction procedure
- **Apligraf®** for EITHER of the following indications when standard wound therapy has failed:
 - chronic, noninfected, full-thickness lower extremity ulcer due to diabetic neuropathy
 - chronic, noninfected, partial- or full-thickness venous stasis ulcer

- **Becaplermin (Regranex®) when used as an adjunct treatment for a diabetic neuropathic ulcer of the lower extremity that extends into the subcutaneous tissue or beyond**
- **Biobrane®/Biobrane® L silicone-collagen membrane for the temporary covering of a partial-thickness burn wound**
- **Dermagraft® for EITHER of the following indications when standard wound therapy has failed:**
 - chronic, full-thickness, lower extremity ulcer due to diabetic neuropathy
 - wound from dystrophic epidermolysis bullosa when provided in accordance with the Humanitarian Device Exemption specifications of the U.S. Food and Drug Administration (FDA)
- **Epicel® for the treatment of deep dermal or full-thickness burns comprising a total body surface area of greater than or equal to 30% when provided in accordance with the Humanitarian Device Exemption specifications of the FDA**
- **Integra® Dermal Regeneration Template, Integra™ Bilayer Matrix Wound Dressing, Integra™ Matrix Wound Dressing and Integra™ Meshed Bilayer Wound Matrix for the postexcisional treatment of a full-thickness or deep partial-thickness burn**
- **NeoForm™ Dermis when used in association with a covered, medically necessary breast reconstruction procedure**
- **Oasis® Wound Matrix for EITHER of the following indications when standard wound therapy has failed:**
 - chronic, partial or full-thickness, lower extremity venous ulcer
 - chronic, partial or full-thickness, lower extremity diabetic ulcer
- **Orcel™ for the treatment of a mitten-hand deformity in an individual with epidermolysis bullosa when standard wound therapy has failed and when provided in accordance with the Humanitarian Device Exemption specifications of the FDA**
- **Transcyte® for the temporary covering of a partial- or full-thickness burn wound when standard wound therapy has failed**

CIGNA does not cover any of the products* listed above for ANY unlisted indication because each is considered experimental, investigational, or unproven.

CIGNA does not cover ANY of the following products* because each is considered experimental, investigational, or unproven for any indication (this list may not be all-inclusive):

- AlloSkin™
- ArthroFlex™ (FlexGraft®)
- Autologous Platelet-Derived Growth Factors (e.g., AutoloGel™ and Autologous Platelet Grafting™)
- BioDfence/BioDfactor
- Biodesign™ (Surgisis®) AFP™ Anal Fistula Plug
- Biodesign™ (Surgisis®) Inguinal Hernia Matrix
- Biodesign™ (Surgisis®) RVP™ Recto-Vaginal Fistula Plug
- Conexa™
- Cymetra™
- DermaMatrix Acellular Dermis
- Durepair Regeneration Matrix®
- Endoform Dermal Template™
- EZ Derm™
- FlexHD® Acellular Hydrated Dermis

- GammaGraft
- GORE BIO-A® Fistula Plug
- GraftJacket® Regenerative Tissue Matrix
- GraftJacket® Xpress
- Hyalomatrix® PA
- Integra™ Flowable Wound Matrix
- MatriStem®
- Matrix HD™
- Oasis® Burn Matrix
- OrthADAPT™ Bioimplant
- Permacol™
- PriMatrix
- Restore® Orthobiologic Soft Tissue Implant
- SportMesh™
- Strattice™ Reconstructive Tissue Matrix
- SurgiMend® Collagen Matrix
- TheraSkin®
- TissueMend

***Note: Refer to the table in Appendix A for a list of products and the associated CPT and HCPCS codes.**

General Background

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 (Ho, et al., 2005; Sibbald, et al., 2005). 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 chronic wounds nonresponsive to standard therapy. Other products have been FDA approved for the treatment of epidermolysis bullosa.

A chronic wound is defined as a wound that does not heal in the time expected based upon the patient's age, comorbidities, and wound etiology. Different types of chronic wounds include venous ulcers, lower extremity diabetic neuropathic ulcers, and burn wounds. Treatment depends on the type of wound, wound location, and wound size. Standard wound therapy includes: cleansing and debridement of the wound; compression therapy, such as compression stockings, Unna boots, elastic wraps, or orthotic compression devices; topical medications; nutritional support; pain control; skin grafting; and other surgical interventions.

Epidermolysis bullosa (EB) is a rare genetic disease that causes the skin to be fragile making it easily injured and prone to blistering. Standard of care is primarily supportive and includes prevention of infection, protection of the skin against trauma, attention to nutritional deficiencies and dietary complications, and minimization of deformities and contractures.

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 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 (BMWWD) (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, 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).

Skin Substitutes and Growth Factors

The safety and efficacy of the skin substitutes and growth factors listed below are supported by the evidence in the published peer-reviewed scientific literature and/or are established treatment options for the discussed indications.

AlloDerm[®] - Breast Reconstruction

AlloDerm (LifeCell Corporation, Branchburg, NJ) is an acellular dermal matrix allograft classified as banked human tissue by the FDA because it is minimally processed and not significantly changed in structure from the natural material. AlloDerm is an established treatment option and is supported by the evidence in the published peer-reviewed scientific literature for tissue repair during postmastectomy breast reconstruction (Chun, et al., 2010; Spear, et al., 2008; Bindingnavele, et al., 2007; Breuing and Colwell, 2007; Zienowicz, et al., 2007; Glasberg, et al., 2006; Salzberg, 2006; Breuing, et al., 2005; Nahabedian, 2005; Gamboa-Bobadilla, 2006).

AlloDerm – Other Indications

AlloDerm has been proposed as a treatment option for various other conditions including abdominal wall reconstruction and/or hernia repair, tympanoplasty, lower eyelid surgery, Frey's syndrome (a complication of parotid excision), various oral surgery procedures including gingival recession, empty nose syndrome, burns and postburn scar contractures. In addition, AlloDerm has been investigated for placement over implantable cardioverter-defibrillators and cardiac pacemakers to prevent skin erosion, scalp reconstruction and hand resurfacing. Studies are primarily in the form of case series or retrospective reviews with small patient populations (n=6-58) and short-term follow-ups (e.g., 3–68 months). Comparative studies to established therapies with randomization are lacking. There is insufficient evidence in the published peer-reviewed scientific literature to support the efficacy of AlloDerm for these indications.

Literature Review

Abdominal Wall Reconstruction: Case series (n=10) (DeMoya, et al., 2008) and retrospective reviews (Lee, et al., 2009; Bellows, et al., 2007; Patton, et al., 2007; Schuster, et al., 2006) (n=18-67) with 2–16 months follow-up have evaluated the use of AlloDerm during contaminated abdominal wall reconstructive surgery. Diagnosis included infected fascia with dehiscence, complex ventral hernia, and dehiscence and/or evisceration. Typically the wounds were contaminated or dirty. Hernia recurrence rates up to 64% were reported. Complication rates were as high as 43% and included wound infections, fistulas, wound dehiscence, graft infection, postoperative intra-abdominal bleeding, and evisceration. Some cases required repeat surgery and/or removal of the AlloDerm. The authors reported that 100% of the patients experienced either significant abdominal laxity or a hernia following the application of AlloDerm (De Moya, et al., 2008); due to the high overall rate of hernia recurrence when the wound was left open, they could not support the use of AlloDerm unless the wound could be closed postoperatively (Shuster, et al., 2006); ongoing studies are required to address further refinements of

surgical technique and to analyze long-term outcomes related to the durability (Patton, et al., 2007); and lastly, long-term outcomes are unknown and are critical to “fully establish the durability and functional properties of remodeling of AlloDerm grafts when used as tissue prosthesis during abdominal wall repair” (Bellows, et al., 2007).

Burn Wounds: Yim et al. (2010) conducted a case series (n=64) to evaluate AlloDerm for the treatment of burn wounds on joint areas. The patients had cultured epithelial autografts applied initially following wound excision. AlloDerm was applied to 16 knee joints, 24 elbow joints, eight shoulder joints, six wrist joints and ten fingers. Follow-up ranged from 1–3 years, and 31 patients (55 joints) were available for final follow-up. Out of the 55 joints, 24 joints (43.6%) showed no limitations in passive range of joint motion, 12 joints (21.8%) showed limitations less than 10%, 16 joints (29.1%) showed 10%–19% limitation and three joints (5.5%) showed limitations greater than 20%. There was no significant difference in the scar thickness between areas where AlloDerm was applied and where it was not applied. The trans-epidermal water loss and erythema values were significantly better in the areas treated with AlloDerm ($p < 0.001$, each). Limitations of the study include the small patient population, patients lost to follow-up, and lack of a control group and randomization.

Frey's syndrome: It has been proposed that AlloDerm can alleviate the gustatory sweating associated with Frey's syndrome following parotid excision. In a prospective case series, Sinha et al. (2003) evaluated the effectiveness of AlloDerm as an interpositional physical barrier to prevent Frey's syndrome after parotidectomy. Thirty patients were divided into three groups of ten. Group 1 underwent superficial parotidectomy with placement of an AlloDerm graft. Group 2 had superficial parotidectomy without placement of an interpositional barrier. Group 3 underwent deep-plane rhytidectomy without disruption of the parotid fascia. At the one-year follow-up, patients were questioned about gustatory sweating. Subjective Frey's syndrome was reported in one patient in Group 1 and five patients in Group 2, which was statistically significant ($p < 0.05$). The incidence of objective Frey's syndrome was noted in two patients in Group 1 and eight patients in Group 2 and was also statistically significant ($p < 0.05$). No major postoperative complications were noted. According to the authors, the use of AlloDerm as an interpositional barrier may decrease the incidence of Frey's syndrome, but two concerns arose. First, although recurrence of benign parotid disease is very rare, the difficulties in reoperation are unknown. Secondly, long-term maintenance of soft tissue augmentation is unpredictable due to the inability to assess the amount of graft resorption ahead of time. They suggested long-term follow-up of a large study to address these questions.

Govindaraj et al. (2001) conducted a randomized controlled trial (n=64) to evaluate the role of AlloDerm in preventing parotidectomy gustatory sweating. Group 1 patients (n=32) underwent a superficial lobe parotidectomy, and group II (n=32) patients underwent a superficial lobe parotidectomy with placement of AlloDerm within the parotid bed. Follow-up was greater than six months in all patients and consisted of evaluation for gustatory sweating using a questionnaire. Thirty patients (15 patients from each group) were randomly assigned to be evaluated by the Minor's Starch-Iodine Test (MIST) as an objective measure of gustatory sweating. All questionnaires were returned and demonstrated subjective sweating in three of 32 patients in Group I (9.3%) and in one of 32 patients in Group II (3.1%). The objective incidence, measured by the MIST test, revealed a 40% incidence of Frey's syndrome in Group 1 (6/15) and a 0% incidence in Group II. The complication rate was 9% in Group I (3/32) and 25% in Group II (8/32). According to the authors, the AlloDerm patients experienced a higher rate of wound and seroma formation which may be explained by the AlloDerm obstructing the fluid absorption.

Hernia Repair: Case series (n=11–70) (Bluebond-Langner, et al., 2008; Misra, et al., 2008; Aycocock, et al., 2007) and retrospective reviews (n=37–165) (Diaz, et al., 2009; Lee, et al., 2008; Jin, et al., 2007) evaluated the application of AlloDerm during hernia repairs (e.g., parastomal hernia, hiatal hernia, incisional hernia, ventral hernia). Follow-ups ranged from 8–37 months. Complication rates were as high as 44%. Diaz, et al. (2000) reported a 17.1% overall hernia recurrence rate, 40% surgical site infections, and 11.6% postoperative fistulas. Other studies reported postoperative ileus (24.2%), wound seroma (12.9%), and intrabdominal abscess (9.6%). In one study, seven of nine patients required reoperation due to postoperative abdominal wall laxity which was associated with infection and larger defects. Outcomes varied based on the type of surgical procedure performed, the type and number of AlloDerm sheets used, presence or absence of fecal contamination, and patient comorbidities (e.g., diabetes mellitus). The evidence in the published peer-reviewed scientific literature does not support the efficacy of AlloDerm for hernia repair.

Lower Eyelid Surgery: AlloDerm is proposed as an alternative to hard palate grafting used in the surgical repair of lower eyelid retraction following blepharoplasty. Two retrospective reviews compared the outcomes of hard palate mucosa to AlloDerm. Although not statistically significant, Li et al. (2005) (n=35) reported that hard palate patients had better elevation and lower failure rate than AlloDerm patients. Taban et al. (2005) (n=21) reported that no improvement was seen in five of the procedures. Sullivan and Dailey (2003) evaluated the graft contraction rate of AlloDerm compared with hard palate graft in 14 patients (19 grafts). A statistically significant difference in mean graft contraction between the AlloDerm group and the hard palate graft group was observed (57% and 16%, respectively; $p < 0.005$). The mean one-year follow-up graft contraction rate was 57% with AlloDerm compared to 16% with the hard palate graft. Five patients with a mildly contracted socket treated with AlloDerm either failed or had partial success due to graft contraction. The authors concluded that AlloDerm contracts significantly more than hard palate grafts resulting in less successful outcomes.

Oral Surgery: AlloDerm has been proposed for closure of oral harvest sites, oral cavity reconstruction, and the treatment of gingival recession. Jamal et al. (2010) conducted a randomized controlled trial to compare AlloDerm (n=10) closure to primary closure (n=10) of oral harvest sites for buccal mucosa grafts for urethroplasty. A single graft was harvested from one cheek. Based on questionnaire scores, there were no significant differences in postoperative oral pain, neurosensory deficits, or mouth tightness between the two groups. Although the difference was not statistically significant, there was a trend in the AlloDerm group toward more difficulty with mastication at three weeks, and three-, six-, and 12-month follow-ups. A significant difference was reported in cheek swelling at three weeks with 80% of the AlloDerm group compared to 30% of the primary closure group ($p = 0.01$). The authors noted that AlloDerm “proved to be an effective means of closing the harvest site, but offered no significant advantages when compared with primary closure” and its use appeared to be “an unnecessary step”.

In a prospective nonrandomized study, Girod et al. (2009) compared the efficacy of AlloDerm (n=22) to split thickness skin graft (STSG) (n=12) in patients who underwent surgical resection of oral cavity tumors followed by reconstruction. The surgeries were performed by two different surgeons. The time from date of surgery to enrollment in the study was 22 months for the AlloDerm group and 12 months for the STSG group. There was a higher pre- and post-operative prevalence of radiotherapy exposure in the AlloDerm (45%) compared to the STSG group (17%). A higher graft failure rate was seen in the AlloDerm group (14% vs. 0%), but was not statistically significant. There was a significant difference in the distribution of graft sites with more tongue patients in the AlloDerm group and more floor-of-mouth patients in the STSG group. AlloDerm grafts resulted in a more normal appearing mucosal surface. Although the AlloDerm patients scored higher on the Global Health Status, Functional, and Symptom scores on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items/Head and Neck 35 (EORTC QLQ-C30/H&N35) tool, the differences were not significant. Histopathology comparisons (n=12) showed less fibrous tissue and keratinization of the epithelium in the AlloDerm patients.

Mahajan et al. (2007), in a randomized controlled trial, evaluated the effectiveness of AlloDerm in the treatment of gingival recession. Fourteen patients were randomly assigned to the AlloDerm group (AlloDerm and coronally positioned flap [CPF]; n=7) or the CPF group (CPF alone; n=7). The defect coverage in the AlloDerm group was 97.14% compared to 77.42% in the CPF group, which was statistically significant ($p < 0.05$). CPF produced statistically significant better results ($p < 0.03$) in patient comfort. There were no significant differences between the two groups in the remaining clinical outcomes and overall patient satisfaction.

A randomized study by Rahmani and Lades (2006) compared AlloDerm to conventional grafting. Fourteen patients with 20 gingival recessions of Miller’s grade I and II were included in the study. Outcomes were measured at baseline and at six months after surgery and included: recession height, recession width, probing depth, attached gingiva, keratinized gingiva, and clinical attachment level. Differences in the mean change between the two groups were not significant in any of the parameters.

AlloMax™

AlloMax Surgical Graft (Bard Davol, Inc. Warwick, RI) is an acellular non-cross-linked human dermis allograft. Because AlloMax is a natural human product it is classified as banked human tissue and does not require FDA approval. It is regulated by the American Association of Tissue Banks and the FDA guidelines for banked human tissue. The AlloMax Surgical Graft for Breast Reconstruction (previously marketed as NeoForm™) is proposed for post-mastectomy breast reconstruction and is an established skin substitute for this indication (Bard, 2011).

The AlloMax Surgical Graft for Hernia and Abdominal Wall Repair is proposed for hernia or other complex abdominal wall repairs when a synthetic prosthesis is contraindicated or inappropriate. There is insufficient evidence in the published peer-reviewed scientific literature to support the safety and efficacy of AlloMax for hernia and abdominal wall repair. Studies have primarily been in the form of case reports for hernia repair (e.g., hiatal hernia, incisional hernia) and abdominal wall reconstruction (Bard, 2011).

Apligraf®

Apligraf (Organogenesis Inc., Canton, MA) (also known as Graftskin), a bilayered living skin equivalent, is FDA PMA approved for use in conjunction with compression therapy for the treatment of non-infected, partial and full-thickness skin ulcers due to venous insufficiency and for full-thickness neuropathic diabetic lower extremity ulcers nonresponsive to standard wound therapy. Apligraf is an accepted treatment modality for chronic, noninfected, full-thickness lower extremity venous stasis ulcers and for lower extremity ulcers due to diabetic neuropathy that are nonresponsive to medical management. Randomized controlled trials (Steinberg, et al., 2010; Edmonds, et al., 2009; Curran and Plosker, 2002; Veves, et al., 2001) support the safety and efficacy of Apligraf for these indications.

Becaplermin

Becaplermin (Regranex) (Ortho-McNeil Pharmaceutical, Raritan, NJ) is an aqueous gel with recombinant human platelet-derived growth factor. It is approved by the FDA under the biologics license application as an adjunct to good ulcer care practices for the treatment of diabetic foot ulcers that extend into the subcutaneous tissue or beyond and have an adequate blood supply. Systematic reviews and randomized controlled trials support the safety and efficacy of the use of Becaplermin as an adjunct to standard care in the treatment of diabetic lower extremity ulcers (Buchberger, et al., 2010; Steed, 2006; Rees, et al., 1999; Smiell, et al., 1999). (For additional information, refer to the I Coverage Policy Becaplermin [Regranex®]).

Biobrane®/Biobrane®-L

Biobrane/Biobrane-L (Smith and Nephew, Inc., Largo, FL) are synthetic, bilaminar, collagen-based composites. Under the FDA PMA approval, Biobrane is indicated for use as a temporary covering of partial-thickness burn wounds until autografting is clinically appropriate. Randomized controlled trials and retrospective reviews support the safety and efficacy of Biobrane for the treatment of partial-thickness burns (Lang, et al., 2005; Lal, et al., 2000).

Biobrane has also been proposed for the treatment of toxic epidermal necrolysis, paraneoplastic pemphigus, dermabrasion, skin graft harvesting, laser resurfacing, and other types of chronic wounds that cannot be immediately closed (e.g., open sternotomy, venous ulcers), but there is insufficient evidence to support Biobrane for these indications (Whitaker, et al., 2008).

Dermagraft®

Dermagraft (Advanced BioHealing, Inc., LaJolla, CA) is a cryopreserved dermal substitute approved by the FDA PMA process for the treatment of lower extremity full-thickness diabetic ulcers, of longer than six weeks' duration, that extend through the dermis, and are refractory to standard wound care management. Randomized controlled trials and case series have demonstrated improved outcomes when Dermagraft was used for the treatment of these ulcers (Marston, et al., 2003; Omar, et al., 2004; Sibbald, et al. 2005).

Dermagraft is also FDA approved by the Humanitarian Device Exemption (HDE) process for the treatment of dystrophic epidermolysis bullosa (EB). As EB is a rare disorder, it is unlikely that there will be a sufficient body of evidence to demonstrate conclusively that Dermagraft is better than the standard of care for this condition.

Epicel

Epicel (Genzyme Biosurgery, Cambridge, MA) is a cultured epidermal autograft (CEA) that is FDA approved under the HDE process for patients who have deep dermal or full-thickness burns comprising a total body surface area of greater than or equal to 30%. It may be used in conjunction with split-thickness autografts or alone in patients for whom split-thickness autografts may not be an option (FDA, 2007).

As the FDA approval is an HDE, it is unlikely that there will be a sufficient body of evidence to demonstrate conclusively the efficacy of Epicel for the treatment of burns. One case series (Carsin, et al., 2000) detailed the

treatment of 30 severely burned patients with Epicel over a five-year period. A permanent coverage of a mean of 26% of total body surface area, similar to that of conventional autografts, was reported.

Integra®

Integra Dermal Regeneration Template (Integra LifeSciences Corp., Plainsboro, NJ) is a bovine, collagen-based temporary epidermal substitute that is FDA PMA approved for use in postexcisional treatment of life-threatening full-thickness or deep partial-thickness thermal injury where sufficient autograft is not available at the time of excision or not desirable because of the physiological condition of the patient (FDA, 2002). Integra™ Bilayer Matrix Wound Dressing, Integra™ Matrix Wound Dressing, and Integra™ Meshed Bilayer Wound Matrix, are substantially equivalent skin substitutes that are FDA 510(k) approved for the management of partial- and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, surgical wounds (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 (FDA, 2008).

Results of randomized controlled trials, case series and retrospective reviews support the safety and efficacy of Integra Dermal Regeneration Template as a treatment option for burn patients (Lee, et al., 2008; Branski, et al., 2007; Fette, 2005; Groos, et al., 2005; Klein, et al., 2005; Heitland, et al., 2004; Heimbach, et al., 2003).

Case reports, case series, pilot studies and retrospective reviews have reported the application of Integra for the treatment of other conditions including: giant congenital melanocytic nevi, scalp reconstruction, burn scar revision, and dermatologic procedures (e.g., removal of squamous cell carcinoma, malignant melanomas, and keloids). Studies included small patient populations (n=8-30), short-term follow-ups and did not compare Integra to standard methods of treatment. There is insufficient evidence in the published peer-reviewed scientific literature to support Integra for the treatment of these conditions.

Neoform™ Dermis

Neoform Dermis (Mentor Corp., Santa Barbara, CA) is a solvent-dehydrated, gamma-irradiated preserved human allograft dermis indicated for use as a soft tissue graft for horizontal and vertical soft tissue augmentation of thickness and length, such as breast reconstruction (Mentor, 2005). NeoForm is classified as banked human tissue by the FDA. Although evidence in the published, peer-reviewed scientific literature supporting the use of this product in breast reconstruction is limited, Neoform Dermis is an established skin substitute used for tissue expansion in breast reconstruction following a mastectomy. Neoform is no longer available for distribution.

Oasis® Wound Matrix

Oasis Wound Matrix (Cook Biotech Inc., West Lafayette, IN) is a porcine-derived, acellular collagen matrix. Oasis is 510(k) FDA approved for the management of partial and full thickness wounds including pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled undermined wounds, surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, skin tears), and draining wounds (FDA, 2006).

Randomized controlled trials support the use of Oasis for the treatment of chronic partial and full-thickness lower extremity venous or diabetic ulcers when conventional wound therapy fails. The studies compared Oasis to standard wound therapy, Regranex Gel or hyaluronic acid dressing. Treatment with Oasis resulted in better outcomes and lower recurrence rates (Romanelli, et al., 2010; Romanelli, et al., 2007; Niezgodna, et al., 2005; Mostow, et al., 2005; Demling, et al., 2004).

OrCel™

OrCel (Forticell Bioscience, Inc., New York, NY) (formerly called Composite Cultured Skin [CCS]) is an allogeneic, bilayered cellular matrix with FDA PMA approval for the treatment of split-thickness donor site wounds in burn patients. FDA-HDE approval was granted for use as an adjunct in the treatment of mitten-hand deformity surgery of epidermolysis bullosa. As epidermolysis bullosa is a rare disorder, it is unlikely that there will be a sufficient body of evidence to demonstrate conclusively that OrCel is better than the standard of care.

There is limited evidence to support the efficacy of OrCel compared to the standard of care for the treatment of split-thickness donor sites. Therefore, OrCel is considered investigational for this indication. In a matched-pairs study conducted by Still et al. (2003), the use of OrCel was compared to treatment with Biobrane L. Eighty-two severely burned patients each had two designated split-thickness donor sites of equivalent surface area and depth. Sites were randomized to receive a single treatment of either OrCel or the standard dressing, Biobrane-L.

Sites were evaluated for wound closure. The researchers found a statistically significant decrease in healing time with the use of OrCel compared to Biobrane L. There was a decrease in scarring associated with the use of OrCel, although it was not statistically significant. Additional clinical trials are needed to validate the findings of this study.

TransCyte

TransCyte (Smith & Nephew Inc., Largo, FL) (originally known as Dermagraft-TC) is a bilaminate, temporary skin substitute that is FDA PMA approved for the treatment of full- or partial-thickness burns. It is used as a temporary wound covering until autograft is possible. Randomized controlled trials and prospective case series support the safety and efficacy of TransCyte for the treatment of this type of burns (Amani, et al., 2006; Kumar, et al., 2004, Lukish, et al., 2001).

Other Skin Substitutes and Growth Factors

Additional skin substitutes and growth factors have been proposed for the treatment of multiple conditions as discussed below, but the evidence in the published peer-reviewed scientific literature does not support the safety and efficacy of the use of these substitutes and growth factors. The number of available studies is limited and involves small, heterogeneous patient populations, short-term follow-ups, minimal comparisons to the established treatment method for the condition, and/or lack of a control group. In some cases, reported outcomes are inconsistent, and a consensus on patient selection criteria and the appropriate surgical approach and techniques that should be used have not been established.

AlloSkin™

AlloSkin (Allosource, Centennial, CO) is an allograft composed of epidermal and dermal cadaveric tissue proposed for use with partial and full thickness wounds and is regulated by the American Association of Tissue Banks (AATB) and the FDA guidelines for banked human tissue (AlloSource, 2010). There is insufficient evidence in the published peer-reviewed scientific literature supporting the efficacy of AlloSkin.

ArthroFlex™ Acellular Bio-Implant for Soft Tissue Repair

ArthroFlex or FlexGraft® (LifeNet Health, Virginia Beach, VA) is a decellularized human allograft dermis implant proposed for shoulder reconstruction and Achilles tendon repair. The allograft is regulated by the American Association of Tissue Banks and the FDA guidelines for banked human tissue. Based on the size and thickness the product may be referred to as Aflex100, Aflex101, or Aflex200 (LifeNet Health, 2011). Data in the peer-reviewed scientific literature supporting the safety and effectiveness of Arthroflex are lacking.

Autologous Platelet-Derived Growth Factors (APDGF)

Autologous platelet-derived growth factors (APDGF) also referred to as platelet gel, platelet-rich plasma, platelet-rich concentrate, autogenous platelet gel, or platelet releasate, have been proposed for the treatment of multiple conditions to enhance healing. At the point of care, a collection and preparation system is used to prepare a small sample of the patient's blood to produce a platelet-rich plasma. The plasma is combined with other substances to form a platelet-rich gel that can be applied to the wound. The systems are FDA approved under the 510(k) notification process. Examples of approved devices include:

- AutoloGel (Cytomedix, Inc., Rockville, MD)
- Autologous Platelet Grafting™ (SafeBlood® Technologies, Inc., Little Rock, AR)
- CASCADE® Autologous Platelet System (Musculoskeletal Transplant Foundation [MTF], Edison, NJ)
- Fibrinet® (Cascade Medical Enterprises, Wayne, NJ)
- Gravitational Platelet Separation System (GPSII®) (Biomet Biologics, Inc., Warsaw, IN)
- Mini GPSII (Biomet Biologics, Inc., Warsaw, IN)
- SmartPreP® 2 APC+ system (Harvest Technologies Corporation, Plymouth, MA)
- Vitagel Surgical Hemostat (Orthovita, Inc., Malvern, PA)

APDGF has been proposed for the treatment of chronic wounds (e.g., lower extremity wounds, pressure ulcers, graft-versus-host disease [GVHD] ulcers); persistent epithelial defects of the cornea; periodontal disease; bone graft supplementation, regeneration, substitution and/or healing (e.g., lumbar fusion, iliac crest grafted maxilla); ingrown toenails; degenerative cartilage lesions; tendonitis; joint capsular injuries; plantar fasciitis; soft tissue trauma (e.g., tendon and ligament ruptures); fractures; osteoarthritis of the knee; as well as muscle injuries and disorders. Studies have also investigated the use of APDGF to enhance healing in various types of surgical procedures including blepharoplasty, mammoplasty, cleft lip and palate, maxillofacial surgery, dental

implantology, mandibular degree II furcation defects, sinus floor augmentation, pediatric tonsillectomy, cystectomy, finger amputation, epithelialization of skin donor sites, skin autografts, saphenectomy, hemithyroidectomy, inguinal hernia repair and other abdominal surgeries, chest surgery and anterior colporrhaphy. However, consensus on the terminology of the platelet products and standardization of the preparation of the platelet-leukocyte gel has not been established (Balbo, et al., 2010; Luaces-Rey, et al., 2010; Mishra, et al., 2009; Everts, et al., 2007). Overall, limitations of the studies include small patient populations, and lack of a control group and/or comparison to standard therapy. Outcomes have been conflicting or reported that the application of APDGF did not make a significant difference in inflammation, closure, healing, bleeding, bone ingrowth, implant stability, reduction in recovery time or postoperative pain. Some studies reported that initial appearing benefits were not maintained. There is insufficient evidence in the published, peer-reviewed scientific literature to support the effectiveness of platelet gel for these indications.

Literature Review

Anterior Cruciate Ligament Repair: In a randomized controlled trial (n=100), Nin et al. (2009) evaluated the efficacy of APDGF when used for the treatment of initial anterior cruciate ligament (ACL) reconstruction with bone-patellar tendon-bone allograft. Fifty of the patients were treated with platelet gel and 50 were not (i.e., control group). In the study group during the surgical procedure, the ligament was covered with APDGF and sutured over itself. The gel was also introduced after implantation of the graft prior to closing the wound. Follow-up ranged from 18 to 36 months (mean 24.3 months). Postoperatively, there were no statistically significant differences between the two groups in the perimeters of the kneecap, C-reactive protein levels, magnetic resonance imaging (MRI) appearance of the graft, and clinical evaluation scores including range of knee motion, muscle torque, visual analog scale, International Knee Documentation Committee scores, and KT-1000 arthrometer scores. The pivot shift test was negative in 94% of all patients. There was no discernable clinical or biomechanical effect of APDF for this patient population.

Radice et al. (2010) prospectively compared the effect of APDGF on MRI findings in first-time patients who received platelet gel (n=25) during repair of an isolated anterior cruciate ligament compared to patients (n=25) not treated with APDGF (i.e., control group). Patients received either a bone-patellar tendon-bone autograft (BPTB) or a hamstring autograft. Postoperatively, a statistically significant difference (p<0.001) was noted in the time it took to obtain a completely homogeneous intra-articular segment (i.e., a mean 179 days in the study group compared to 369 days in the control group). When only the BPTB graft cases were compared in both groups, a homogeneous graft was obtained in 109 days in the study group compared to 363 days in the control group. However, the sample size was too small to determine if this was statistically significant. Limitations of the study include the small patient population, inclusion of two different graft techniques and lack of randomization.

Vogrin et al. (2010) conducted a randomized controlled trial (n=50) to evaluate the effect of APDGF on postoperative knee stability following anterior cruciate ligament reconstruction for ligament rupture. Patients were divided into the study group (n=25) which received APDGF during surgical repair and the control group which was not treated with the platelet gel. The gel was applied locally following hamstring graft placement. Follow-up occurred at three and six months. Clinical evaluations were assessed using the Tegner activity score, Lyshol score and International Knee Documentation Committee (IKDC) score. Anteroposterior knee stability was measured using the KT-2000 arthrometer at 15, 20 and 30 pounds of force with knee flexion at 25 degrees and fixed patella at the same time. There was no significant difference in joint stability of the knee between the two groups at the three-month follow-up. At six months, there was a significant improvement (p=0.011) in the KT-2000 arthrometer scores in the study group compared to the control group. Limitations of the study include the small patient population, short-term follow-up and patients lost to follow-up (n=5).

Blepharoplasty: In 2006, Vick et al. conducted a randomized, controlled trial (n=33) to evaluate the effect of autologous platelet gel on postoperative edema and ecchymosis in one of the two eyes during bilateral blepharoplasty. Of the 33 patients, 28 (85%) completed the study. No significant differences between the treated and untreated sides were noted for discomfort and ecchymosis. A statistically significant difference was noted in photograding of edema on the treated side on day 1 (p=0.03), but the scores were equal on days three and seven. No clinically significant benefits to the use of autologous platelet gel during blepharoplasty were reported.

Breast Surgery: In a randomized controlled trial (n=111), Anzarut et al. (2007) studied the effectiveness of topical application of autologous platelet gel during breast surgery to reduce postoperative wound drainage in patients undergoing bilateral reduction mammoplasty. Each patient had one breast which received the gel and one breast which did not. No statistically significant differences in drainage, pain, size of open areas, clinical

appearance, degree of scar pliability, or scar erythema were noted. The data did not support the use of autologous platelet gel to improve outcomes after breast reduction mammoplasty.

Cervical Fusion: Feiz-Erfan et al. (2007) conducted a double-blind randomized study in which platelet gel was used to treat 50 patients who underwent anterior cervical fusion with allograft bone and internal fixation. Altogether, 81 disc levels were treated. Forty-two levels were assigned to the gel group and 39 levels were assigned to the control group. Follow-up evaluations occurred at 6 weeks, 12 weeks, one year and two years. There were no significant differences in fusion rates between the groups at any follow-up evaluation. The data presented did not support the use of platelet gel to improve fusion rates in patients undergoing anterior cervical fusion.

Degenerative Joint Disease: Kon et al. (2010) conducted a prospective case series (n=100 patients/115 knees) to evaluate the efficacy of APDGF in the treatment of monolateral or bilateral degenerative lesions of articular cartilage of the knee. Patients had experienced at least four months of pain or swelling of the knee and had radiographic findings of degenerative joint changes. Intra-articular injections were administered every 21 days, and follow-up occurred for 12 months. Compared to baseline, statistically significant improvements in the International Knee Documentation Committee (IKDC) objective scores were seen following APDGF injections at the six and 12 month follow-ups ($p < 0.0005$, each). However, a statistically significant worsening of scores was seen between six and twelve months ($p < 0.0005$). The same results were seen with the IKDC subjective scores with significant improvements at six- and 12-month follow-ups ($p < 0.005$, each), but significant worsening at the 12-month follow-up ($p = 0.02$). The Euroqol Visual Analogue Scale (EQ VAS) scores improved significantly at the six- and 12-month follow-ups compared to baseline ($p < 0.0005$, each), but had a tendency to worsen over time ($p = 0.2$), even though not statistically significant. Limitations of the study include the lack of a control group and randomization, short-term follow-up and the number of patients lost to follow-up or who did not complete the study (n=12).

Epicondylitis: Peerbooms et al. (2010) conducted a two-center randomized controlled trial to evaluate the treatment of chronic lateral epicondylitis in patients randomly assigned to receive an APDGF injection (n=51) or a corticosteroid injection (n=49) (control group). Six months prior to onset of the trial, patients had been unresponsive to cast immobilization, corticosteroid injections and/or physiotherapy. Primary outcomes included visual analog scores (VAS) and Disabilities of the Arm, Shoulder, and Hand (DASH) scores. A successful outcome was a more than 25% reduction in VAS or DASH scores without repeat treatment within the first year following injection. Follow-ups occurred for up to 52 weeks. Patients engaged in a stretching protocol and a muscle- tendon- strengthening program following the injections. The VAS and DASH scores were significantly better in the APDGF group compared to the corticosteroid injection group at the six-month ($p < 0.001$, $p = 0.03$, respectively) and one-year ($p < 0.001$, $p = 0.001$, respectively) follow-ups. Although the scores were better in the corticosteroid injection group initially, improvement declined. In contrast the APDGF group showed progressive improvement over time. After an average five months, five APDGF-treated patients required reintervention compared to 13 control group patients. Limitations of the study include the small patient populations and patients lost to follow-up or patients with inadequate data sets (n=8).

Hechtman et al. (2011) conducted a prospective case series to investigate the outcomes of a single injection of APDGF in patients (n=30 patients/31 elbows) with painful medial or lateral epicondylitis. Patients had pain for at least six months and were unresponsive to medical management, including steroid injections. Outcomes were based on clinical evaluation and visual analog scale for pain and patient self-evaluation of function and satisfaction. Each patient was used as their own control. The overall success rate was 90% with 28 patients achieving a 25% reduction in worst pain on one or more follow-up visits. There were significant improvements in pain scores and patient satisfaction scores compared to baseline ($p < 0.01$, each). However, range of motion and physician assessments (e.g., flexor or extensor origin tenderness) were not greatly impaired at baseline or significantly changed after treatment. One patient reported no improvement after six month. No adverse events were reported. Limitations of the study include the small patient population, short-term follow-up, most patient missed one or more follow-up visits, and lack of a formal control group and randomization.

Gingival Recession: Keceli et al. (2008) conducted a randomized controlled trial to evaluate the effectiveness of platelet gel used for the treatment of 40 patients with gingival recession. Patients were randomized to either connective tissue graft only or to connective tissue graft plus platelet gel. Outcomes were measured in terms of gingival index, plaque index, recession depth, probing depth, keratinized tissue width, recession width, clinical attachment level, and localization of mucogingival junction. Although significant improvements were seen within

each group following treatment, no statistically significant differences were seen in outcomes between the two groups at the six-week, six-month and 12-month postoperative follow-up visits. No benefits from application of the platelet gel were identified.

Long-Bone Nonunion: Prospective case series have investigated the efficacy of autologous platelet gel to enhance bony union in refractory atrophic nonunion of long bones. Chiang et al. (2007) reported that 11 of 12 patients with four femoral and eight tibial atrophic nonunion treated with PRP healed in 19.7 weeks showing increased bone mineral density and improvement in physical functioning, bodily pain, social functioning, and mental health scores. Mariconda et al. (2008) reported no improvement with the use of PRP (n=20) when compared to a control group treated at an earlier time without PRP for aseptic atrophic long-bone nonunion. There were no significant differences in radiographic consolidation between the two groups. The study failed to demonstrate clinical usefulness of platelet gel in this patient population.

Periodontal Intraosseous Defects: Kotsovilis et al. (2009) conducted a systematic review of randomized controlled trials (n=10 studies) to evaluate the efficacy of APDGF for the treatment of periodontal intraosseous defects. Seven trials had a parallel group design and three exhibited a split-mouth design. Four studies were conducted by the same research group. Various parameters of APDGF preparations and applications were used (e.g., type of centrifuge, pattern of centrifuge steps, baseline and treatment platelet concentration, growth factor concentration in platelets) and APDGF was combined with various types of bone grafts or substitutes, alloplastic materials, and/or guided tissue regeneration. According to the authors, overall primary and secondary outcomes failed to confer statistically significant additive benefits of APDGF in the therapy of periodontal intraosseous defects. There were no safety issues identified.

Sinus Augmentation Procedures: Arora et al. (2010) conducted a systematic review of randomized controlled trials (n=5 trials; 5–39 patients per trial) of at least six months duration to evaluate the efficacy of APDGF when used with bone and bone substitutes in sinus augmentation procedures. Limitations noted by the authors included heterogeneity of the study designs, small patient populations and inconsistent single outcome variables for sinus elevation. A meta-analysis of the data was not possible due to the heterogeneity of the outcome variables. The authors concluded that “the disparity in the study design, surgical techniques, and different outcome assessment variables used makes it difficult to assess the practical benefit of using APDGF in sinus grafting procedures.”

Tendon Repair: de Vos et al. (2010) conducted a single-center, double-blind, randomized controlled trial (n=54) to determine if autologous platelet gel would improve the pain and functional outcomes of patients with chronic midportion Achilles tendinopathy. Randomization was stratified by activity level to the study group (n=27; mean age 49 years) or to the saline injection placebo group (n=27; mean age 50 years). Both groups were also involved in an eccentric exercise program. Stratification into one of two treatment groups was based on the ankle activity score that objectively quantified ankle-related activity into a high activity group or a low activity group. The primary outcome measure was the self-reported Victorian Institute of Sports Assessment-Achilles (VISA-A) questionnaire, which quantified pain and activity levels. The secondary outcome measures were subjective patient satisfaction, return to sports, and adherence of the eccentric exercises. At the 24-week follow-up, the VISA-A score improved significantly in both groups (study group 21.7 points; placebo group 20.5 points), but the difference between the two groups was not significant, and there were no significant differences in the secondary outcomes. The injection of platelet gel did not result in greater improvements than placebo. Two author-noted limitations of the study were the amount of platelets and the quantity of activated growth factors in the platelet gel injections were unknown and the use of eccentric exercises.

In a technology assessment (2010), the California Technology Assessment Forum (CTAF) conducted a systematic review of the literature to evaluate the evidence on platelet-rich plasma injections for the treatment of Achilles tendinopathy. One randomized controlled trial (deVos, et al., 2010), one case series (n=14) and one case report met inclusion criteria. CTAF concluded that based on the evidence, “PRP injection added to standard eccentric exercise therapy does not appear to be an effective approach to the treatment of Achilles tendinopathy.”

Total Knee Arthroplasty: Peerbooms et al. (2009) conducted a randomized controlled trial (n=102) to evaluate the efficacy of platelet gel in wound healing following total knee arthroplasty. Patients were randomly assigned to a control group who received no platelet gel (n=52) or to the study group treated with platelet gel (n=50). Due to insufficient data, the final analysis included 32 study group patients and 41 control group patients. There were

no significant differences in the two groups based on comparison of postoperative wound scores, visual analog scale, Western Ontario MacMaster (WOMAC) questionnaire scores, knee function, use of analgesics, and the pre- and postoperative hemoglobin values. Results of the study indicated that the application of platelet gel “did not promote wound healing” and had “no effect on pain, knee function, or hemoglobin values.”

Wound Healing: The outcomes of randomized controlled trials and case series investigating the efficacy of autologous platelet gel in the treatment of wounds including lower extremity ulcers, pressure ulcers, diabetic ulcers, and venous ulcers have been mixed. Frykberg et al. (2010) conducted a prospective case series (n=49 patients/65 wounds) to evaluate the efficacy of APDGF on chronic, nonhealing wounds nonresponsive to standard therapy. The most prevalent wounds were pressure ulcers (n=21), venous ulcers (n=16) and diabetic foot ulcers (n=14). Inclusion criteria included open, cutaneous wounds, with a clean wound bed without signs of active infection. The mean wound duration without healing was 47.8 weeks. Following a mean 2.8 ± 2.4 weeks with 3.2 ± 2.2 applications of topical APDGF, reductions in wound volume (mean 51%), area (39.5%), undermining (77.8%), and sinus tract/tunneling (45.8%) were observed. An improvement was seen in 97% of wounds. Two wounds either remained unchanged or increased in size. Author-noted limitations of the study included the fact that the patients were not followed to the endpoint of complete healing and treatment and dressing change frequency varied. Other limitations include the small heterogeneous patient population, and lack of a control group or comparison to standard wound therapy.

Kazakos et al. (2009) performed a randomized controlled trial to evaluate the benefit of APDGF in the treatment of soft tissue acute wounds (n=59). The wounds included open fracture of the tibia (n=37), closed fracture of the tibia with skin necrosis (n=9), wide friction burns in the femur (n=11), and one each acute injury of the Achilles tendon and open bimalleolar fracture. The study group (n=27) was treated with topical APDGF and the control group (n=32) was treated with conventional dressings. Follow-up ranged from 2.5–21 months (mean six months). The wound healing rate was significantly faster in the study group at weeks 1, 2 and 3 ($p=0.003$, $p<0.001$ and $p<0.001$, respectively). The mean time to plastic reconstruction in the APDGF group was significantly shorter (21.26 days) compared the control group (40.59 days) ($p<0.001$). The control group reported higher pain scores at the end of the second and third weeks. No adverse events were observed. Limitations of the study include the small, heterogeneous patient population.

In a prospective double-blind randomized controlled trial (n=44), Litmathe et al. (2009) evaluated the efficacy of APDGF for the treatment of wound complications following cardiac surgery in high-risk patients for wound healing complications (e.g., obesity, diabetes, smokers, peripheral vascular disease, heart failure). All patients underwent either isolated coronary artery bypass grafting (CABG) or combined coronary surgery and valve replacement. APDGF was applied to the wound in the study group (n=22) but not in the control group (n=22). There were no statistically significant differences in sternal wound healing or wound healing at the vein harvesting sites. No beneficial effects of APDGF were noted in this study.

Driver et al. (2006) (n=40) reported that 68.4% of patients with nonhealing diabetic foot ulcers randomized to platelet gel healed compared to 42.9% in the control group. In a case series, McAleer et al. (2006) (n=24 patients; 33 nonhealing lower extremity wounds) reported that within ten months wound closure was obtained in 20 patients who were previously nonresponsive to conventional therapy. However, five wounds showed no improvement. Two randomized controlled trials reported no significant difference in outcomes in treatment of chronic venous ulcers (Senet, et al., 2003; Stacey, et al., 2000) (n=15, 42, respectively) using platelet gel. Additional randomized controlled trials with larger sample sizes are indicated to establish the role of platelet gel in the treatment of lower extremity ulcers.

Other Indications: Martinez-Zapata et al. (2009) conducted a systematic review of the literature to evaluate the safety and efficacy of autologous platelet gel in tissue regeneration reported in randomized controlled trials (n=20). The trials that met inclusion criteria included oral and maxillofacial surgery (n=11), chronic skin ulcers (n=7), and surgical wounds (n=2). In four oral and maxillofacial surgery studies (n=153), which included patients suffering from chronic periodontitis, a meta-analysis was completed. A significant improvement was seen in the depth reduction of gingival recession following the use of platelet gel. The clinical attachment level of a subgroup of patients with more severe disease was better than the results in patients with incipient illness. Meta-analysis revealed no significant differences in patients treated with platelet gel for chronic skin ulcers or surgical wounds. Because of the poor quality of the studies (e.g., small patient populations, large confidence intervals, lack of reporting of adverse events, and heterogeneous outcome measures), well-designed large randomized controlled trials are needed to validated the finding of this analysis.

BioDfence/BioDfactor®

BioDfence Resorbable Adhesion Barrier (Amedica Corp., Salt Lake City, UT) is a human amniotic tissue allograft that is resorbed into the body during healing. It is regulated by the American Association of Tissue Banks and the FDA guidelines for banked human tissue. BioDfence is proposed for use as a physical barrier between the dura and soft tissue of the paraspinal muscles to reduce fibroblast infiltration into the epidural space and postoperative scarring. A second product, also made from amniotic tissue, is the BioDfactor Structural Tissue Matrix. This matrix is in a liquid form that is intended for use in filling soft tissue defects or bone voids where the BioDfence is inadequate or inappropriate. There is insufficient evidence in the published peer-reviewed literature to support the safety and efficacy of BioDfence or BioDfactor.

Biodesign™ (Surgisis®) AFP™ Anal Fistula Plug

The Biodesign (Surgisis) AFP Anal Fistula Plug (Cook Biotech Inc., West Lafayette, IN) is a porcine-based acellular matrix and is contraindicated in patients who are sensitive to porcine materials (Cook Biotech Inc., 2009). The Surgisis AFP (i.e., SIS Fistula Plug) received 510(k) approval from the FDA in March 2005 for “implantation to reinforce soft tissue where a rolled configuration is required, for repair of anal, rectal, and enterocutaneous fistulas.”

Literature Review

Evidence in the published peer-reviewed scientific literature does not support the safety and efficacy of the Surgisis AFP. Studies have primarily been in the form of case series and retrospective reviews with small, heterogeneous patient populations, and short-term follow-ups. One randomized controlled trial reported better outcomes with endorectal advancement flap compared to AFP. Appropriate candidates for AFP have not been established. Outcomes varied based on the type of fistula, the presence of single vs. multi-track fistula, and whether or not the patient had undergone previous fistula surgical procedures. Poorer results were reported in patients who were smokers, diabetics, and/or had Crohn’s disease. Failure rates were reported as high as 59% and recurrence rates as high as 75%. Some studies reported a decline in the success rate over time. One of the most common reasons for failure was due to the plug expulsion. Studies also reported the occurrence of postoperative sepsis as high as 89%.

In a randomized controlled trial, Ortiz et al. (2009) compared the outcomes of Surgisis AFP (n=16) to endorectal advancement flap (ERAF) (n=16) for the treatment of patients with high fistula in ano of cryptoglandular etiology. Sixteen patients had previously undergone ERAF. Recruitment was stopped because of the high recurrence rate following AFP. Follow-up evaluations were performed by an independent observer for up to one year postoperatively. Within the first postoperative year, a statistically significant difference was seen in 12 AFP patients who had fistula recurrence compared to two ERAF patients ($p<0.001$). Nine of 16 patients who had undergone previous surgery, experienced fistula recurrence, and eight of the nine were in the AFP group. Postoperatively, one AFP patient experienced recurrence with abscess, three had plug dislodgement, and eight had persistent leakage around the plug. Two ERAF patients experienced recurrences. In this study, AFP was associated with a low rate of healing especially in patient with previous fistula surgery.

Schwandner et al. (2009) prospectively evaluated the efficacy of the Surgisis AFP in 60 patients with single transsphincteric anorectal fistulas. Vessel loop drainage was applied for at least eight weeks prior to plug insertion. Follow-up occurred for up to 12 months. Complete healing was observed in 37 cases (62%). At 26 weeks, 38% had unhealed fistulas. There were no significant differences in preoperative and postoperative continence scores. Two plugs were expelled on postoperative day one and reinserted without further complications.

In a prospective case series, Zubaidi and Al-Obeed (2009) evaluated the efficacy of the Surgisis AFP in patients (n=22 patients; 23 fistulas) with chronic and/or complicated anorectal fistulas that were not amenable to fistulotomy. Most of the fistulas were primary in nature and had not undergone previous surgical intervention. A draining seton was used in 11 cases. The plugs were sutured in place. Follow-up ranged from 6–18 months (mean 12 months). At the final follow-up, 19 of 22 (86%) patients had successful closure. Three fistulas failed to close.

Additional prospective case series have reported mixed outcomes. Garg, (2008) reported complete healing in 15 of 23 patients (71.4%) in 6–18 months. Better outcomes were reported in single track fistulas vs. multi-track fistulas. With a median follow-up of 6.5 months, Ky et al. (2008) (n=45) reported that plug success declined over

time, dropping from 84% to 54.6% at 12 months. Outcomes were significantly better in simple fissure closures compared to complex fissure closures ($p<0.02$), with first plug closures compared to repeat closures ($p=0.001$), and with patients without Crohn's disease ($p<0.02$). Schwandner et al. (2008) conducted a prospective study to analyze the efficacy of the Surgisis AFP for the closure of cryptoglandular and Crohn's disease-associated transphincteric anorectal fistulas. The overall success rate was 61% (12 of 18). The success rate for the cryptoglandular fistulas was 45.5% (5 of 11) and 85.7% (6 of 7) for the Crohn's associated fistulas. The failure rate was 27.8% at nine months.

Thekkinkattil et al. (2008) conducted a prospective case series ($n=43$) for the treatment of anorectal, rectovaginal and pouch vaginal fistula. Complete healing occurred in 44% of patients. Nonhealing in ten patients (22%) was due to dislodgement of the plug. Van Koperen et al. (2007) conducted a prospective, two-center clinical study in patients ($n=17$) with complex high perianal fistulas. This data suggested a 41% success rate using the anal fistula plug to treat complex high perianal fistulas. The most common reason for recurrence was plug expulsion (7 of the 10 recurrences).

Biodesign™ (Surgisis®) Inguinal Hernia Matrix

The Biodesign (Surgisis) Inguinal Hernia Matrix (SIS Hernia Repair Device, Surgisis Gold Hernia Repair Graft) (Cook Biotech Inc., West Lafayette, IN) is a porcine derived device. Per the FDA 510(k) (2006) approval, the device is "intended to be implanted to reinforce soft tissue where weakness exists. Indications for use include the repair of a hernia and body wall defect." There is insufficient data from clinical trials to support the efficacy of this matrix.

Ansaloni et al. (2009) conducted a blinded, randomized controlled trial to compare the safety and efficacy of the use of Inguinal Hernia Matrix (SIHM) ($n=35$) to polypropylene mesh ($n=35$) in Lichtenstein's repair of noncomplicated, primary inguinal hernias in men. The primary endpoint was the degree of postoperative pain using a visual analogue scale or a simple verbal scale. The investigators were unaware of the mesh used. The first 24 postoperative hours a significant number of patients in the SIHM group developed self-subsiding hyperpyrexia (temperature $> 38^\circ$) compared to the polypropylene group ($p<0.05$). During the three year follow-up period, a significant decrease in the incidence of postsurgical pain was not seen in the SIHM group, but a significantly lower degree of pain was detected at rest and on coughing at 1, 3, and 6 months, on movement at 1, 3, and 6 months and 1, 2, and 3 years, and use of pain medication at 1, 3, and 6 months ($p<0.05$, each). No significant differences were noted in pain localization and irradiation. One recurrence was noted in the polypropylene group. Both groups experienced hematomas and seromas that resolved without treatment within the first three postoperative months. The SIHM group had a trend in higher incidence of complications (especially seromas), but compared to the polypropylene group the difference wasn't significant. The authors noted that their sample size was "too small to prove absolute efficacy in terms of low recurrence rate". Additional prospective studies are needed to establish the safety and efficacy of Inguinal Hernia Matrix.

Biodesign™ (Surgisis®) RVP™ Recto-Vaginal Fistula Plug™

Biodesign (Surgisis) RVP Recto-Vaginal Fistula Plug (Cook Biotech Inc., West Lafayette, IN) is a surgical mesh skin substitute manufactured from porcine small intestinal submucosa. It is supplied in a tapered configuration with a button to allow increased retention. The button eventually falls off leaving the plug to seal the opening between the rectum and the vagina. The Plug is FDA-510(k) approved for "implantation to reinforce soft tissue for repair of recto-vaginal fistulas" (FDA, 2006). There is insufficient evidence in the published peer-reviewed scientific literature to establish the safety and efficacy of Surgisis RVP. Studies are primarily in the form of case series with small patient populations and short-term follow-ups (1–21 weeks). Failure rates were as high as 65% due to dislodgement of the plug (Gonsalves, et al., 2009).

Conexa™ Reconstructive Matrix

Conexa Reconstructive Matrix (Tornier, Inc., Edna, MN) is a porcine dermis tissue substitute that is FDA 510(k) approved as LifeCell Tissue Matrix (LTM) Surgical Mesh (LifeCell Corporation, Branchburg, NJ). According to the FDA (2008) the matrix is intended "for the reinforcement of soft tissue repaired by sutures or suture anchors during tendon repair surgery including reinforcement of rotator cuff, patellar, Achilles, biceps, quadriceps, or other tendons. Indications for use also include the repair of body wall defects which require the use of reinforcing or bridging material to obtain the desired surgical outcome. The device is not intended to replace normal body structure or provide the full mechanical strength to support tendon repair of the rotator cuff, patellar, Achilles, biceps, quadriceps, or other tendons. Sutures, used to repair the tear, and sutures or bone anchors used to attach the tissue to the bone, provide biomechanical strength for the tendon repair." Based on

the thickness of the matrix, this product is available as Conexa 100 and Conexa 200 (Tornier, 2010). There is insufficient evidence in the published peer-reviewed scientific literature supporting the safety and effectiveness of Conexa as studies have primarily been in the form of individual case reports (Stover, et al., 2009).

Cymetra™

Cymetra (LifeCell Corporation, Branchburg, NJ) is a micronized form of AlloDerm. It is processed from human tissue obtained from tissue banks and is therefore, classified by the FDA as human tissue for transplantation. The allograft tissue is processed into a particulate acellular dermal matrix, dried and placed in a syringe. It is to be used in transplantation for the repair or replacement of damaged or inadequate integumental tissues (e.g., injection laryngoplasty) (LifeCell, 2010). Cymetra is proposed for the treatment of vocal fold scars, presbyphonia, Parkinson-related dysphonia, and medialization of vocal folds following thyroplasty. Due to resorption, repeated injections may be indicated (Simpson, et al., 2008; Remacle and Lawson, 2007; Simpson, 2006). Cymetra is also proposed for use for smoothing deep wrinkles, nasolabial lines, lip enhancement, and repair of acne scarring.

Studies evaluating the efficacy of Cymetra injections for vocal fold immobility are primarily in the form of case studies or retrospective reviews with small patient populations (n=6–34) and short-term follow-ups. One review noted that Cymetra “may be a suitable option for the treatment of vocal fold immobility with a moderate gap.” They also stated that “patients must be advised that the stability of results is unpredictable” (Remacle and Lawson, 2007). Milstein et al. (2005) conducted a retrospective review of 20 patients treated with Cymetra for unilateral vocal fold paralysis. Following injections, significant improvements were seen in glottal closure ($p<0.001$), dysphonia ($p<0.001$), and self-perceived voice quality ($p<0.01$). Improvements following the injections were temporary for five patients, lasting three months for three patients. Eight patients had results that lasted one year or longer. Further investigation is warranted to assess long-term benefits.

DermaMatrix Acellular Dermis

DermaMatrix (Synthes Inc., West Chester, PA) is an allograft derived from human skin and is classified by the FDA as banked human tissue. This dermal collagen matrix is proposed for repair of facial soft tissue defects, eyelid or anophthalmic reconstruction, nasal reconstruction, septal perforation, parotidectomy, cleft palate repair, oral resurfacing, vestibuloplasty, radial forearm free flap repair, breast reconstruction postmastectomy, and abdominal wall repair. There is insufficient evidence in the published peer-reviewed scientific literature to establish the efficacy of DemaMatrix for tissue repair and reconstruction. Studies are primarily in the form of retrospective reviews with small patient populations.

Becker et al. (2009) conducted a retrospective review to compare the outcomes of DermaMatrix (n=25) to AlloDerm (n=25) in patients who underwent immediate expander-based breast reconstruction following unilateral (n=20) or bilateral mastectomy (n=10). The median follow-up for the AlloDerm group was 15 months and 13.5 months for the DermaMatrix group. The only significant difference in the operative and reconstructive course between the two groups was that the AlloDerm patients had drains in place 11 mean number of days compared to 13 mean number of days in the DermaMatrix group ($p=0.02$). The DermaMatrix group had one incidence of seroma and one infection/cellulites. There were no complications in the AlloDerm group.

Durepair® Regeneration Matrix

Durepair Regeneration Matrix is a biological fetal bovine collagen implant that is FDA 510(k) approved for the repair of defects in the dura mater. The scaffold is proposed to prevent cerebrospinal fluid leakage and allow healing of openings in the dura by the ingrowth of fibroblasts and blood vessels on the scaffold (FDA, 2004). Evidence from the published peer-reviewed scientific literature supporting the safety and efficacy of Durepair is lacking.

Endoform Dermal Template™

Endoform Dermal Template (Mesynthes Ltd, Wellington, New Zealand) is an ovine (sheep)-derived extracellular matrix that is FDA 510(k) approved for single use in the treatment of “partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (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” (FDA, 2010). The template is a temporary matrix that is completely replaced by the patient’s own tissue over time. There is insufficient evidence in the published peer-reviewed literature to support the safety and efficacy of Endoform.

EZ Derm™

EZ Derm (Brennen Medical, Inc., St. Paul, MN) is a porcine-derived, biosynthetic xenograft. The manufacturer-recommended indications for use are as a temporary wound covering for partial-thickness burns, donor sites, autograft sites and ulcers. Evidence in the published peer-reviewed scientific literature is insufficient to make a determination regarding the efficacy of EZ Derm.

FlexHD® Acellular Hydrated Dermis

FlexHD Acellular Hydrated Dermis (Musculoskeletal Transplant Foundation, Edison, NJ and Ethicon Inc., Somerville, NJ) is a matrix derived from donated human allograft skin. The product is regulated by the American Association of Tissue Banks and the FDA guidelines for banked human tissue. FlexHD is indicated for the replacement of damaged or inadequate integumental tissue or for the repair, reinforcement or supplemental support of soft tissue defects. There are two products, FlexHD Acellular Hydrated Dermis for Hernia Repair and FlexHD Acellular Hydrated Dermis for Breast Reconstruction. The implantation of FlexHD has also been reported to aid in the rehabilitation of patients with empty nose syndrome in an attempt to provide resistance for breathing and decrease the sensation of suffocation (Ethicon, 2011; Chhabra and Houser, 2009). Data supporting the safety and efficacy of FlexHD from published clinical trials are lacking.

GammaGraft

GammaGraft (Promethean Lifesciences Inc., Pittsburg, PA) is an irradiated human skin allograft harvested from cadaveric donors and contains epidermal and dermal layers of skin. It is a temporary graft proposed for the treatment of venous stasis ulcers; diabetic foot ulcers; full-thickness ulcers; Mohs surgery sites; skin graft donor sites; partial thickness wounds; burns; areas of dermabrasion; temporary coverage of exposed abdominal viscera, including small bowel and liver; exposed pericranium and cranium; fasciotomy sites; as a test on a wound bed before autografting; and areas of excision which are not closed pending final pathology report. GammaGraft is regulated by the FDA as human tissue because it is donated human skin and not an engineered product (Promethean Lifesciences, 2008). Evidence in the published peer-reviewed scientific literature does not support the efficacy of GammaGraft.

GORE BIO-A® Fistula Plug

The GORE BIO-A Fistula Plug (W.L. Gore & Associates, Inc., Elkton, MD) is FDA approved as a Class II, 510(k) synthetic bioabsorbable scaffold intended for use in the reinforcement of soft tissue for repair of anorectal fistulas. Cell migration into the scaffold and tissue is generated as the body gradually absorbs the synthetic material (FDA, 2009). There is insufficient evidence in the published peer-reviewed scientific literature to support the safety and efficacy of this device.

GraftJacket® Regenerative Tissue Matrix

GraftJacket Regenerative Tissue Matrix (Wright Medical Technology, Inc., Arlington, TN) is an acellular human dermal collagen template indicated for the repair or replacement of damaged or inadequate integumental tissue. GraftJacket Regenerative Tissue Matrix is regulated by the FDA as human tissue for transplantation and indicated for the treatment of diabetic foot ulcers. GraftJacket Regenerative Tissue Matrix MaxForce Extreme and GraftJacket Matrix Maxstrip are variations of the size and thickness of this tissue matrix. There are also products specific for hand surgery and shoulder surgery (Wright Medical Technologies, 2011).

Literature Review

GraftJacket has been investigated for wound healing and tendon/rotator cuff repair. Published studies have been primarily in the form of case reports, case series, and retrospective reviews. The limited number of randomized controlled trials included small, heterogeneous patient populations and short-term follow-ups. In some studies multiple post-operative therapies were used, making it difficult to determine the efficacy of GraftJacket.

Tendon/Rotator Cuff Repair: Bond et al. (2008) conducted a prospective case series to assess the short-term results of arthroscopic repair of irreparable rotator cuff tears using GraftJacket allografts to span the cuff deficiency. Sixteen patients were treated with the GraftJacket and were followed-up for 1–2 years. The mean University of California, Los Angeles score significantly increased from 18.4 preoperatively to 30.4 postoperatively ($p=0.0001$). The Constant score increased from 53.8 to 84.0 ($p=0.0001$). Statistically significant improvements were also seen in pain, forward flexion, and external rotation strength. Thirteen patients had full incorporation of the graft as documented on magnetic resonance imaging. There were no complications

reported. Limitations of the study include the small patient population, short-term follow-up and lack of a control group, comparison to standard therapy and randomization.

Wound Healing: Reyzelman et al. (2009) conducted a 12-week randomized controlled multi-center trial to compare the treatment of grades 1 and 2 diabetic ulcers, primarily on the foot. Patients were randomized to treatment with an application of GraftJacket Regenerative Tissue Matrix (n=47) or to standard wound care (n=39) including moist dressings with alginates, foams, hydrocolloids and/or hydrogels. Study patients were also treated with a silver-based dressing and hydrogel bolsters or moist gauze until complete epithelialization occurred. Complete healing occurred in 32 (69.6%) study group patients and 18 (46.2%) control group patients. Adverse events in the study group included one amputation, one wound abscess, and two graft dislodgements resulting in graft failures. Limitation of the study include is the small patient population and short-term follow-up.

In a randomized controlled study by Brigido (2006), 28 diabetic patients with nonhealing, full-thickness, lower extremity wounds that had been present for at least six months were treated with sharp debridement and randomized to application of GraftJacket tissue matrix with compression dressing or to a control treatment of wound gel with gauze dressing. By week 16, 12 of 14 patients treated with GraftJacket tissue matrix demonstrated complete wound closure compared to 4 of 14 patients in the control group. Long-term studies with larger patient populations are needed to support the outcomes of this study.

Martin et al. (2005) prospectively evaluated the outcomes of 17 diabetic patients with University of Texas grade 2A neuropathic foot wounds that were treated with GraftJacket. Outcomes evaluated were time to complete wound closure and the percentage of patients who received complete closure by 20 weeks. Of the wounds measuring a mean 4.6 cm², 82.4% healed in the 20-week time frame. Limitations of the study include the small patient population and lack of a control group and randomization.

GraftJacket® Xpress

GraftJacket Xpress (Wright Medical Technology, Inc., Arlington, TN), a flowable soft-tissue scaffold, is a powdered form of the GraftJacket tissue matrix. Using saline, it is reconstituted and injected into a wound. The scaffold is proposed for filling deep tunneling-type chronic wounds such as those found in chronic diabetic foot ulcers. The skin substitute is packaged in a syringe and intended for one time use. This product is regulated by the FDA as human tissue for transplantation.

There is insufficient evidence in the published peer-reviewed scientific literature to support the safety and efficacy of GraftJacket Xpress. Studies have primarily been in the form of retrospective reviews with small patient populations and short-term follow-ups (Brigido, et al., 2009).

Hyalomatrix PA®

Hyalomatrix PA (Fidia Advanced Biopolymers S.r.l., Padova, Italy) is a bilayered, biodegradable acellular dermal skin substitute composed of hyaluronic acid and a semipermeable silicone membrane that acts as a scaffold for cellular invasion and capillary ingrowth. The matrix is FDA 510(k) approved "for the management of wounds including: partial and full-thickness wounds; second and third-degree burns; pressure ulcers; venous ulcers; diabetic ulcers; chronic vascular ulcers; tunneled/undetermined wounds; surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence); trauma wounds (abrasions, lacerations, skin tears); and draining wounds" (FDA, 2007). There is insufficient evidence in the peer-reviewed scientific literature to support the safety and effectiveness of Hyalomatrix PA. Studies have primarily been in the form of retrospective reviews. Prospective randomized controlled trials comparing Hyalomatrix PA to standard therapy are indicated.

Integra™ Flowable Wound Matrix

Integra Flowable Wound Matrix (Integra Lifesciences Corp., Plainsboro, NJ) is an acellular bovine tendon collagen device that is 510(k) FDA approved for the treatment of advanced wound care. It is considered "substantially equivalent in function and intended use to Integra Matrix Wound Dressing" and is approved for the treatment of "partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, skin tears) and draining wounds" (FDA, 2007). The skin substitute is packaged in a syringe and intended for one time use. There is insufficient evidence in the published peer-reviewed scientific literature supporting the efficacy of Integra Flowable Wound Matrix.

MatriStem®

MatriStem (Acell®, Inc., Columbia, MD), also called urinary bladder matrix (UBM), is an acellular device derived from the urinary bladder of pigs. The matrix is FDA 510(k) approved 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 (donor sites/grafts, post-Moh’s surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second degree burns, skin tears) and draining wounds” (FDA, 2009). The matrix is resorbed and replaced with new tissue. MatriStem has also been proposed for the treatment of alopecia. Product types include the MatriStem Wound Care Matrix, MatriStem Plastic Surgery Matrix, MatriStem Burn Matrix, MatriStem Hernia Matrix, and MatriStem Micromatrix®, which consists of micronized particles that are sprinkled onto the wound and covered with a moist dressing. There is insufficient evidence in the published peer-reviewed scientific literature to support the safety and efficacy of MatriStem.

Matrix™ HD

Matrix HD (RTI Biologics, Inc., Alachua, FL), an acellular allograft human dermis of collagenous connective tissue, is proposed to support cellular revascularization and repopulation by the host tissue. Regulated by the American Association of Tissue Banks and the FDA guidelines for banked human tissue, the matrix has been used in the repair of the deltoid muscle, patellar tendon, Achilles tendon, and shoulder capsule, as well as elbow capsule reconstruction, and fascia repair in the calf. It is also proposed as a wound covering (RTI Biologics, 2011). Evidence supporting the safety and efficacy of Matrix D from published clinical trials is lacking.

Oasis® Burn Matrix

Oasis Burn Matrix (Cook BioTech, Inc., West Lafayette, IN) is a porcine-derived acellular collagen matrix that is FDA 501(k) approved under the Oasis Wound Matrix device approval. The Burn Matrix is indicated for the treatment of partial-thickness burns. It is not indicated for the treatment of third degree burns (FDA, 2006; Healthpoint, 2007). There is insufficient evidence in the published peer-reviewed literature to support the safety and efficacy of Oasis Burn Matrix for the treatment of burns. Studies have primarily been in the form of case reports.

OrthADAPT™ Bioimplant

OrthADAPT Bioimplant (Pegasus Biologics, Inc., Irving CA) is a decellularized, biologic scaffold made from equine pericardium (xenograft). It is FDA 510(k) approved “to reinforce soft tissue including but not limited to: defects of the abdominal and thoracic wall, muscle flap reinforcement, rectal and vaginal prolapse, reconstruction of the pelvic floor, hernias, suture-line reinforcement and other reconstructive procedures. The device is also intended for the reinforcement of soft tissues repaired by sutures or suture anchors during tendon repair surgery including reinforcement of rotator cuff, patellar, Achilles, biceps, quadriceps, or other tendons” (FDA, 2007; Coons and Barber, 2006).

Permacol™

The Permacol Crosslinked Porcine Dermal Collagen Surgical Mesh (Tissue Sciences Laboratories PLC, Hants, United Kingdom), a xenograft, is a fibrous flat sheet comprised of acellular porcine dermal collagen and elastin. It is 510(k) FDA approved for “use to provide soft tissue repair or reinforcement in plastic and reconstructive surgery of the face and head” (FDA, 2002). Permacol is also proposed for use in inguinal hernia repair, abdominal wall repair, colorectal surgery, and head and face reconstruction. In 2004, 510(k) FDA approval was given for Permacol® Surgical Implant “for use as a soft tissue patch to reinforce soft tissue where weakness exists and for the repair of damaged or ruptured soft tissue membranes. It is specifically indicated for the repair of abdominal wall defects and hernias, including but not limited to parastomal hernias. The Permacol® Surgical Implant T-piece is shaped for use in rectal intussusception repair and the Permacol® Surgical Implant Rectocele-pieces are shaped for use in rectocele repair (FDA, 2005). Other Permacol products include ENDURAGEN™ (distributed by Porex Corporation, Newnan, GA) specifically indicated for plastic and reconstructive surgery of the head and face, and Permacol™ Biologic Implant (distributed by Covidien, Mansfield, MA), a biologic mesh for hernia repair. The Permacol™ Injection agent is also available from Covidien.

Literature Review

The application of Permacol products has been investigated for multiple conditions including hernia repairs, Frey’s syndrome, nasal septal perforation, fecal incontinence and urodynamic stress incontinence. Case series,

case reports and retrospective reviews with small patient populations and short-term follow-ups lack the data needed to support the efficacy of Permacol in the treatment of these conditions.

Maeda et al. (2010) conducted a systematic review investigating perianal injectable bulking agents for the treatment of fecal incontinence. Two studies using Permacol injection agent with a total of 12 patients were identified. There is insufficient data to support Permacol for the treatment of fecal incontinence.

Hammond et al. (2008) conducted a prospective case series (n=15) to evaluate human host response to Permacol for the prevention of parastomal herniation. Permacol was used to reinforce the edges of the abdominal wall stoma to prevent degradation. At a median of seven months (range 1–8) following the primary surgery, twelve of the patients underwent stoma reversal, allowing biopsies of the implants. The implants were present and intact in 11 patients and were bordered with non-fibrous, well-vascularized connective tissue with mild-to-moderate adherence. In another case series (Shaikh, et al., 2007) 20 patients underwent abdominal surgery with Permacol for chronic abdominal wall defects from large incisional hernias (n=8) or acute abdominal wall defects from visceral edema or tumor resection (n=12). Median follow-up was 18 months. The number of grafts used ranged from one to seven. Twelve patients had uneventful recoveries and were discharged within seven days. Seven patients developed complications including necrosis of the edges of the skin flaps, localized wound infections, superficial wound dehiscence, seromas, and wound sinus. There were three recurrent defects.

Frey's Syndrome: In a prospective case series, Papadogeorgakis et al. (2008) investigated the use of Permacol (n=19) in the prevention of Frey's syndrome and face-contouring deformities following parotid tumor surgery. Vacuum suction drains were used in all patients. Follow-up visits ranged from 28–36 months. None of the patients developed Frey's syndrome or complained of sweating, heat, or redness of the skin. All patients experienced "satisfactory aesthetic results with full facial contouring." Three patients developed salivary mucoceles and one case of facial nerve paralysis was reported following removal of the facial nerve.

Urodynamic Stress Incontinence: Bano et al. (2005) conducted a randomized controlled trial to compare the use of Permacol injection (n=25) to silicone injection (Macroplastique) (n=25) in the treatment of urodynamic stress incontinence in women. Following injection, two women treated with Permacol had urinary retention requiring catheterization for one week compared to three women in the Macroplastique injection group requiring catheterization for 24 hours to three days. Regarding pad loss at six months, 15 Permacol patients remained dry (62.5%), seven were unchanged, one was worse and one relapsed. In the Macroplastique group, nine were dry, seven were unchanged, five were worse and two relapsed. Fourteen Permacol patients had a reduction in the Stamey scoring system and 14 in the King's College Hospital Quality of Health Questionnaire scores compared to ten and seven, respectively, in the Macroplastique.

Other Indications: Permacol has also been investigated for use in lip augmentation; facial augmentation; nasal wall deformity; orbital floor implants; as a substitute for tendon graft to repair rotator cuff tears; abdominal compartment syndrome; inguinal, Littre's, and paraesophageal hernia repairs; hernias in contaminated fields; as well as, various urological, gynecological and plastic surgery indications (Bachman and Ramshaw, 2008; Hammond, et al., 2008; Hsu, et al., 2008; Papadogeorgakis, et al., 2008; Teicher, et al., 2008). The studies were primarily case reports or small case series (n≤10).

PriMatrix

PriMatrix (TEI Biosciences, Inc., Boston, MA) is an acellular dermal tissue matrix derived from fetal bovine dermis. It is 510(k) FDA approved for the "management of wounds that include: "partial and full thickness wounds; pressure, diabetic, and venous ulcers; second-degree burns; surgical wounds-donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence; trauma wounds-abrasions, lacerations, and skin tears; tunneled/undermined wounds and draining wounds" (FDA, 2008). There is insufficient evidence in the published peer-reviewed scientific literature supporting the efficacy of Primatrix.

Restore® Orthobiologic Soft Tissue Implant

Restore Orthobiologic Soft Tissue Implant is an FDA 510(k) porcine small intestinal submucosa (SIS) device. Per the FDA it is "intended to reinforce soft tissue where weakness exists, specifically for the reinforcement of soft tissue repaired by sutures or suture anchors during tendon repair surgery, including reinforcement of the rotator cuff, patella, Achilles, biceps, quadriceps, and other tendons." It may also be used during general tissue reconstruction of the periosteum. The device is proposed to be reabsorbed and replaced by the patient's own

tissue (FDA, 2007). There is insufficient evidence in the published peer-reviewed literature to support the safety and efficacy of Restore. Published studies consist primarily of case reports and in vitro studies.

SportMesh™

SportMesh (Biomet Sports Medicine, Warsaw, IN) is a synthetic device made from Artelon® (Artimplant, AB, Vastra Frolunda, Sweden) fibers. The device is a biodegradable temporary scaffold that is proposed to allow the body's cells to regenerate and heal. SportMesh is FDA 510(k) approved for "use in general surgical procedures for reinforcement of soft tissue where weakness exists" and "for reinforcement of soft tissues that are repaired by suture or suture anchors, limited to the supraspinatus, during rotator cuff repair surgery" (FDA, 2006). A second product, SportsMesh or Artelon Tissue Reinforcement mesh, is also FDA 510(k) approved based on the SportMesh predicate device for the same indications. Data supporting the safety and efficacy of SportMesh is lacking. Studies have primarily been in vitro or in the form of case reports with small patient populations (n=4) and short-term follow-ups (i.e., two weeks) (Huss, et al., 2008).

Strattice™ Reconstructive Tissue Matrix

Strattice Reconstructive Tissue Matrix (LifeCell Corporation, Branchburg, NJ) is a xenographic tissue matrix derived from porcine dermis. It is FDA 510(k) approved as LTM-RC surgical mesh "for use as a soft tissue patch to reinforce soft tissue where weakness exists and for the surgical repair of damaged or ruptured soft tissue membranes. The implant is intended for the reinforcement of soft tissues repaired by sutures or suture anchors, during rotator cuff surgery. Indications for use also include the repair of hernias and/or body wall defects which require the use of reinforcing or bridging material to obtain the desired surgical outcome" (FDA, 2007). There is insufficient evidence in the published peer-reviewed scientific literature supporting the efficacy of Strattice.

SurgiMend® Collagen Matrix

SurgiMend or SurgiMend Collagen Matrix (TEI Biosciences Inc., Boston, MA) is an acellular dermal tissue matrix derived from fetal or neonatal bovine dermis. The matrix acts as a scaffold that is progressively integrated, remodeled, and replaced by the functional host tissue. Approved as a Class II, FDA 510(k) device, SurgiMend is "intended for implantation to reinforce soft tissue where weakness exists and for the surgical repair of damage or ruptured soft tissue membranes" specifically for plastic and reconstructive surgery, muscle flap reinforcement, and hernia repair (e.g., abdominal, inguinal, femoral, diaphragmatic, scrotal, umbilical, incisional) (FDA, 2009). Other products include SurgiMend Inguinal Hernia Repair Matrix proposed for use in inguinal hernia repair and SurgiMend PRS for breast reconstruction.

Studies, primarily in the form of case reports, have evaluated SurgiMend for breast reconstruction; treatment of necrotic heel decubitus ulcers; repair of recurrent ventral hernia, enterocutaneous fistula, Achilles tendon, rupture of tibialis anterior tendon, posterior tibiotalar ligament, damaged cartilage; tendon-lengthening procedures; foot and ankle tendon reattachment procedures; and to promote biologic regeneration of tendon tissue around a supporting suture to prevent a large tissue gap (Cromwell, et al., 2009; TEI Biosciences, 2009). There is insufficient evidence in the published peer-reviewed scientific literature to support the safety and efficacy of Surgimend.

TheraSkin®

TheraSkin (LifeNet Health, Inc., Virginia Beach, VA) is a human skin allograft with epidermis and dermis layers. As a human skin product, TheraSkin is regulated by the American Association of Tissue Banks and the FDA guidelines for banked human tissue. Proposed indications for TheraSkin include ulcers (i.e., diabetic foot ulcers, venous stasis ulcers, stage II and greater pressure ulcers) and dehisced surgical burns with or without exposed tendon, muscle or bone. It is also proposed for the treatment of wounds that might otherwise require autografts. The allograft is to be used in conjunction with conventional therapies (Soluble Solutions, 2011). There is insufficient evidence in the published peer-reviewed scientific literature to support the safety and efficacy of TheraSkin. Studies have primarily been in the form of retrospective reviews (Landsman, et al., 2011) with small patient populations (n=188), heterogeneity of wound types (i.e., venous leg ulcers and diabetic foot ulcers) and sizes, and lack of follow-up to wound closure in all patients.

TissueMend Soft Tissue Repair Matrix

TissueMend Soft Tissue Repair Matrix (TEI Biosciences, Inc., Boston, MA), an acellular bovine collagen matrix, is 510(k) FDA approved for "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". It is a remodelable scaffold replaced by the patient's own soft tissue during the healing process (FDA, 2006; Coons and Barber, 2006). Data from clinical trials to establish the efficacy of this matrix are lacking.

Literature Review – Systematic Review and Meta-Analysis

In a Rapid Respond Report on biological mesh, the Canadian Agency for Drugs and Technologies in Health (CADTH) (2010) presented a summary of findings on biological mesh for breast reconstruction, pelvic organ prolapse, mucogingival surgery, inguinal hernia repair, urethroplasty, diabetic foot ulcers, and decompressive hemicraniectomy. The report included systematic reviews, meta-analyses, technology assessments, randomized and non-randomized clinical trials, economic studies and guidelines. CADTH stated that "overall, there was insufficient clinical evidence to thoroughly assess the comparative efficacy of biological and synthetic mesh product. " "In addition to the complexity of having many indications and few studies, there is an abundance of different mesh products available and an absence of evidence regarding differences in safety and efficacy." In conclusion, CADTH stated "there is insufficient evidence to clearly establish the place in therapy of biological mesh products." Examples of commercially available products noted by CADTH included:

- AlloDerm
- FlexHD[®]
- GraftJacket
- DermaMatrix
- Repliform[®] (LifeCell Corp, Branchburg, NJ)
- Suspend[®] (Mentor, Santa Barbara, CA)
- Tutoplast[®] (Tutogen Medical Inc., West Paterson, NJ)
- Permacol[™]
- CollaMend[™] (Bard Davol, Inc., Warwick, RI)
- XenMatrix[™] (Brennen Medical, St. Paul, MN)
- Strattice[®]
- Pelvicol[™] (CR Bard, Inc., Murray Hill, NJ)
- FortaGen (Organogenesis, Canton, MA)
- Surgisis[®]
- SurgiMend[™]
- Veritas[®] Collagen Matrix (Synovis Surgical Innovations, St. Paul, MN)
- Tutopatch[®] (Tutogen Medical Inc., West Paterson, NJ)
- UroPatch[™] (Shelhigh, Inc. Union, NJ)

Chen et al. (2009) conducted a systematic review of biological and synthetic scaffolds used for tendon and ligament repairs. Out of 378 identified articles, 47 clinical trials met inclusion criteria. Of the 47 articles, 16 clinical trials included four commercial biological scaffolds (i.e., five included the use of Restore, six used GraftJacket, four used Zimmer (formerly Permacol), and one study included both Restore and GraftJacket. After review of the data, the authors reported the following:

- Restore – "Restore or scaffolds from small intestine submucosal are ineffective in the reinforcement of large rotator cuff tears and currently not recommended for use in cuff tendon repair." They identified other scaffolds made from small intestine submucosal (i.e. Oasis, Surgiss, and CuffPatch[™] [Organogenesis, Inc., Canton, MA]) and stated that "extra care should be taken to monitor adverse events when applied in patients."
- GraftJacket – "Satisfactory results have been described using GraftJacket for skin lesion and abdominal wall repair". No reports of inflammatory response, edema or postoperative infection have been reported and patients seemed to tolerate it well. However, recurrent tears were noted in 30% of patients in two studies.
- Zimmer (Permacol) – Two retrospective reviews (n=10 each) reported increased pain relief and range-of-motion following implantation, but two other smaller studies reported recurrent tears, aggravated pain and decrease range-of-motion. Foreign body reaction was noted in several of the patients.
- TissueMend – No published animal or clinical studies were found. They noted that TissueMend has been reported to contain higher genetic materials compared to other products which raises concern re human application.
- OrthADAPT – No published animal or clinical studies could be found

According to Chen et al., the studies in this systematic review were primarily in the form of case reports, case series, or retrospective reviews and limited by small patient populations (n=1–30), short term follow-ups (3 months–5 years) and lack of comparison to established methods of treatment. One of the major concerns with these products is biocompatibility and inflammatory response associated with foreign body rejection. The authors also noted that many scaffolds were FDA approved without proper animal studies or evidence-based clinical trials.

A meta-analysis of 23 studies (n=2000), including 17 randomized clinical trials (i.e., nine trials included diabetic foot ulcers, seven trials included venous leg ulcers, and one trial involved mixed, nonhealing foot ulcers), was conducted by Ho et al. (2005) to “examine the clinical safety and efficacy of artificial skin grafts for patients with chronic skin wounds, such as diabetic foot ulcers and venous leg ulcers.” The trials compared the clinical outcomes of the use of artificial skin grafts plus medical management versus medical management alone. Artificial grafts included Dermagraft, Apligraf, and keratinocyte allograft. Artificial skin grafts in conjunction with conventional therapy promoted rapid and frequent healing in diabetic foot ulcers when compared to conventional treatment alone. The benefits were seen within 11–12 weeks. Treatment using grafts was not as successful with venous ulcers (i.e., outcomes were statistically insignificant), but the studies were diverse and limited. They also reported that skin grafts did not curtail adverse events (e.g., infection, cellulitis and osteomyelitis).

Professional Societies/Organizations

Based on data from a prospective, multicenter registry of 245 patients who underwent surgical intervention for anal fistula, the New England Regional Society of the American Society of Colon and Rectal Surgeons (Hyman, et al., 2009) reported that the best healing rates occurred following fistulotomy (87%) and the worse healing rates occurred following anal fistula plug (32%) (p=0.001). They stated that randomized controlled trials comparing various treatment options for anal fistulas “are clearly needed.”

Summary

There are numerous tissue-engineered skin substitute products available on the market. Various products are approved by the U.S. Food and Drug Administration (FDA) for specific indications (e.g., diabetic foot ulcers, temporary covering of partial-thickness or full-thickness burn wounds, and wounds from dystrophic epidermolysis), and are supported by evidence in the published peer-reviewed scientific literature. Becaplermin is currently the only growth factor supported by evidence in the peer-reviewed literature for the treatment of chronic wounds (i.e., lower extremity diabetic neuropathic ulcers).

Although the published evidence supporting the role of AlloDerm, AlloMax and Neoform Dermis in breast reconstruction procedures is not robust, limited data from several small studies, as well as acceptance and limited use of these products by certain specialists in the practicing community indicate that these products may improve outcomes in a carefully selected subset of patients. Based on the current peer-reviewed literature, the role of AlloDerm, AlloMax and NeoForm Dermis for any indication other than breast reconstruction has not been established.

Due to the limited number of studies with small heterogeneous patient populations, variable outcomes and study designs, and a lack of comparison to established treatment options, evidence in the published peer-reviewed scientific literature does not support the safety and efficacy of other skin substitutes or autologous platelet-derived growth factors for any indication.

Appendix A
Product/CPT/HCPCS Code Crosswalk

Product	CPT® Code	HCPCS Code
Covered When Medically Necessary		
AlloDerm (coverage limited to breast reconstruction)	15330-15331	G0040; G0441; Q4116
AlloMax (coverage limited to breast reconstruction)	15330-15331	Q4100
Apligraf (Graftskin)	15340-15341	Q4101
Becaplermin (Regranex)	No specific code	S0157
Biobrane/Biobrane L	15400-15421	Q4100
Dermagraft	15360-15366	Q4106
Epicel	15150-15157	Q4100
Integra Dermal Regeneration Template	15170-15176	Q4105
Integra Bilayer Matrix Wound Dressing	15170-15176	Q4104
Integra Matrix Wound Dressing	15170-15176	Q4108
Integra Meshed Bilayer Wound Matrix	15170-15176	C9363
NeoForm Dermis (coverage limited to breast reconstruction)	15330-15331	Q4100
Oasis Wound Matrix	15430-15431	Q4102
Orcel	15340-15341	Q4100
Transcyte	15360-15366	Q4100
Experimental, Investigational or Unproven and Not Covered		
AlloSkin	15150-15157	Q4115
ArthroFLEX (FlexGraft)	15330-15331	Q4100
Autologous Platelet-Derived Growth Factors	No specific code	S9055
BioDfence/BioDfactor	15340-15341	Q4100
Biodesign (Surgisis) AFP Anal Fistula Plug	15430-15431; 46707	Q4100
Biodesign (Surgisis) Inguinal Hernia Matrix	15430-15431	Q4100
Biodesign (Surgisis) RVP Recto-Vaginal Fistula Plug	15430-15431	Q4100
Conexa	15400-15421	Q4100
Cymetra	15330-15336	Q4112
DermaMatrix Acellular Dermis	15330-15336	Q4100
Durepair Regeneration Matrix	15430-15431	Q4100
Endoform Dermal Template	15400-15421	Q4100
EZ Derm	15400-15421	Q4100
FlexHD Acellular Hydrated Dermis	15330-15331	Q4100
GammaGraft	15330-15331	Q4111
GORE BIO-A Fistula Plug	15430-15431; 46707	Q4100
GraftJacket® Regenerative Tissue Matrix	15330-15336	Q4107
GraftJacket Xpress	15330-15336	Q4113
Hyalomatrix PA	15170-15176	Q4117
Integra Flowable Wound Matrix	15170-15176	Q4114
Matristem	15400-15421	Q4118; 4119; Q4120
Matrix HD	15330-15331	Q4100
Oasis Burn Matrix	15430-15431	Q4103
OrthADAPT Bioimplant	15430-15431	Q4100
Permacol	15400-15421	Q4100; C9364
PriMatrix	15430-15431	Q4110
Restore Orthobiologic Soft Tissue Implant	15430-15431	Q4100
SportMesh	15170-15176	Q4100
Strattice Reconstructive Tissue Matrix	15430-15431	Q4100
SurgiMend Collagen Matrix	15430-15431	C9358; C9360
TheraSkin	15150-15157	Q4121
TissueMend	15430-15431	Q4109

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

AlloDerm®

Covered when medically necessary:

CPT®* Codes	Description
15330	Acellular dermal allograft, trunk, arms, legs; first 100 sq cm or less, or 1% of body area of infants and children
15331	Acellular dermal allograft, trunk, arms, legs; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)

HCPCS Codes	Description
Q4116	Alloderm, per square centimeter

ICD-9-CM Diagnosis Codes	Description
174.0–174.9	Malignant neoplasm of female breast
175.0–175.9	Malignant neoplasm of male breast
198.81	Secondary malignant neoplasm of other specified sites; breast
232.5	Carcinoma in situ of skin of trunk, except scrotum
233.0	Carcinoma in situ of breast
611.83	Capsular contracture of breast implants
611.89	Other specified disorders of breast
612.0-612.1	Deformity and disproportion of reconstructed breast
996.52	Mechanical complication of other specified prosthetic device, implant, and graft; due to graft of other tissue, not elsewhere classified
996.54	Mechanical complication of other specified prosthetic device, implant, and graft; due to breast prosthesis
996.69	Infection and inflammatory reaction due to internal prosthetic device, implant, and graft; due to other internal prosthetic device, implant, and graft
996.79	Other complications of internal (biological) (synthetic) prosthetic device, implant, and graft; due to other internal prosthetic device, implant, and graft
V10.3	Personal history of malignant neoplasm; breast
V45.71	Acquired absence of breast
V50.41	Prophylactic organ removal: breast
V51.0	Encounter for breast reconstruction following mastectomy
V84.01	Genetic susceptibility to malignant neoplasm of breast

Experimental/Investigational/Unproven/Not Covered:

ICD-9-CM Diagnosis Codes	Description
	All other codes

AlloMax™**Covered when medically necessary:**

CPT®* Codes	Description
15330	Acellular dermal allograft, trunk, arms, legs; first 100 sq cm or less, or 1% of body area of infants and children
15331	Acellular dermal allograft, trunk, arms, legs; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)

HCPCS Codes	Description
Q4100†	Skin substitute, not otherwise specified

†**Note:** Covered when medically necessary when used to report a tissue-engineered skin substitute and/or platelet-derived growth factor listed as covered in this policy.

ICD-9-CM Diagnosis Codes	Description
174.0–174.9	Malignant neoplasm of female breast
175.0–175.9	Malignant neoplasm of male breast
198.81	Secondary malignant neoplasm of other specified sites; breast
232.5	Carcinoma in situ of skin of trunk, except scrotum
233.0	Carcinoma in situ of breast
611.83	Capsular contracture of breast implants
611.89	Other specified disorders of breast
612.0-612.1	Deformity and disproportion of reconstructed breast
996.52	Mechanical complication of other specified prosthetic device, implant, and graft; due to graft of other tissue, not elsewhere classified
996.54	Mechanical complication of other specified prosthetic device, implant, and graft; due to breast prosthesis
996.69	Infection and inflammatory reaction due to internal prosthetic device, implant, and graft; due to other internal prosthetic device, implant, and graft
996.79	Other complications of internal (biological) (synthetic) prosthetic device, implant, and graft; due to other internal prosthetic device, implant, and graft
V10.3	Personal history of malignant neoplasm; breast
V45.71	Acquired absence of breast
V50.41	Prophylactic organ removal: breast
V51.0	Encounter for breast reconstruction following mastectomy
V84.01	Genetic susceptibility to malignant neoplasm of breast

Experimental/Investigational/Unproven/Not Covered:

ICD-9-CM Diagnosis Codes	Description
	All other codes

Apligraf® (Graftskin)**Covered when medically necessary:**

CPT®*	Description
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Codes	
15340	Tissue cultured allogeneic skin substitute; first 25 sq cm or less
15341	Tissue cultured allogeneic skin substitute; each additional 25 sq cm, or part thereof (List separately in addition to code for primary procedure)

HCPCS Codes	Description
Q4101	Apligraf, per square centimeter

ICD-9-CM Diagnosis Codes	Description
249.60 - 249.61	Secondary diabetes mellitus with neurological manifestations
250.60- 250.63	Diabetes with neurological manifestations
250.70- 250.73	Diabetes with peripheral circulatory disorders
250.80- 250.83	Diabetes with other specified manifestations, type II or unspecified type, not stated as uncontrolled
440.23	Atherosclerosis of the extremities with ulceration
454.0	Varicose veins of lower extremities with ulcer
454.2	Varicose veins of lower extremities with ulcer and inflammation
459.31	Chronic venous hypertension with ulcer
459.33	Chronic venous hypertension with ulcer and inflammation
459.81	Venous (peripheral) insufficiency, unspecified
707.10- 707.19	Ulcer of lower limbs, except pressure ulcer

Experimental/Investigational/Unproven/Not Covered:

ICD-9-CM Diagnosis Codes	Description
	All other codes

Becaplermin (Regranex®)

Covered when medically necessary:

HCPCS Codes	Description
G0440	Application of tissue cultured allogeneic skin substitute or dermal substitute; for use on lower limb, includes the site preparation and debridement if performed; first 25 sq cm or less
G0441	Application of tissue cultured allogeneic skin substitute or dermal substitute; for use on lower limb, includes the site preparation and debridement if performed; each additional 25 sq cm
S0157	Becaplermin gel 0.01%, 0.5 gram

ICD-9-CM Diagnosis Codes	Description
249.60 - 249.61	Secondary diabetes mellitus with neurological manifestations
250.60-	Diabetes with neurological manifestations

250.63	
250.70-250.73	Diabetes with peripheral circulatory disorders
250.80-250.83	Diabetes with other specified manifestations, type II or unspecified type, not stated as uncontrolled
440.23	Atherosclerosis of the extremities with ulceration
707.10-707.19	Ulcer of lower limbs, except pressure ulcer

Experimental/Investigational/Unproven/Not Covered:

ICD-9-CM Diagnosis Codes	Description
	All other codes

Biobrane®/Biobrane L®

Covered when medically necessary:

CPT®* Codes	Description
15400	Xenograft, skin (dermal), for temporary wound closure, trunk, arms, legs; first 100 sq cm or less, or 1% of body area of infants and children
15401	Xenograft, skin (dermal), for temporary wound closure, trunk, arms, legs; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
15420	Xenograft skin (dermal), for temporary wound closure, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; first 100 sq cm or less, or 1% of body area of infants and children
15421	Xenograft skin (dermal), for temporary wound closure, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)

HCPCS Codes	Description
Q4100†	Skin substitute, not otherwise specified

†**Note:** Covered when medically necessary when used to report a tissue-engineered skin substitute and/or platelet-derived growth factor listed as covered in this policy.

ICD-9-CM Diagnosis Codes	Description
941.00 - 941.59	Burn of face, head, and neck
942.00 - 942.59	Burn of trunk
943.00 - 943.59	Burn of upper limb, except wrist and hand
944.00 - 944.59	Burn of wrist(s) and hand(s)
945.00 - 945.59	Burn of lower limb(s)
946.0 - 946.5	Burns of multiple specified sites

948.00 - 948.99	Burns classified according to extent of body surface involved
949.0 - 949.5	Burn, unspecified site

Experimental/Investigational/Unproven/Not Covered:

ICD-9-CM Diagnosis Codes	Description
	All other codes

Dermagraft®

Covered when medically necessary:

CPT®*	Description
15360	Tissue cultured allogeneic dermal substitute; trunk, arms, legs; first 100 sq cm or less, or 1% of body area of infants and children
15361	Tissue cultured allogeneic dermal substitute; trunk, arms, legs; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
15365	Tissue cultured allogeneic dermal substitute, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; first 100 sq cm or less, or 1% of body area of infants and children
15366	Tissue cultured allogeneic dermal substitute, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)

HCPCS Codes	Description
Q4106	Dermagraft, per square centimeter

ICD-9-CM Diagnosis Codes	Description
249.60 - 249.61	Secondary diabetes mellitus with neurological manifestations
250.60- 250.63	Diabetes with neurological manifestations
250.70- 250.73	Diabetes with peripheral circulatory disorders
250.80- 250.83	Diabetes with other specified manifestations, type II or unspecified type, not stated as uncontrolled
440.23	Atherosclerosis of the extremities with ulceration
707.10- 707.19	Ulcer of lower limbs, except pressure ulcer
757.39	Other specified congenital anomaly of skin

Experimental/Investigational/Unproven/Not Covered:

ICD-9-CM Diagnosis Codes	Description
	All other codes

Epicel®**Covered when medically necessary:**

CPT®* Codes	Description
15150	Tissue cultured epidermal autograft, trunk, arms, legs; first 25 sq cm or less
15151	Tissue cultured epidermal autograft, trunk, arms, legs; additional 1 sq cm to 75 sq cm (List separately in addition to code for primary procedure)
15152	Tissue cultured epidermal autograft, trunk, arms, legs; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
15155	Tissue cultured epidermal autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; first 25 sq cm or less
15156	Tissue cultured epidermal autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; additional 1 sq cm to 75 sq cm (List separately in addition to code for primary procedure)
15157	Tissue cultured epidermal autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)

HCPCS Codes	Description
Q4100 [†]	Skin substitute, not otherwise specified

†Note: Covered when medically necessary when used to report a tissue-engineered skin substitute and/or platelet-derived growth factor listed as covered in this policy.

ICD-9-CM Diagnosis Codes	Description
941.00 - 941.59	Burn of face, head, and neck
942.00 - 942.59	Burn of trunk
943.00 - 943.59	Burn of upper limb, except wrist and hand
944.00 - 944.59	Burn of wrist(s) and hand(s)
945.00 - 945.59	Burn of lower limb(s)
946.0 - 946.5	Burns of multiple specified sites
948.00 - 948.99	Burns classified according to extent of body surface involved
949.0 - 949.5	Burn, unspecified site

Experimental/Investigational/Unproven/Not Covered:

ICD-9-CM Diagnosis Codes	Description
	All other codes

Integra® Dermal Regeneration Template, Integra™ Bilayer Matrix Wound Dressing, Integra™ Matrix Wound Dressing and Integra™ Meshed Bilayer Wound Matrix

Covered when medically necessary:

CPT®* Codes	Description
15170	Acellular dermal replacement, trunk, arms, legs; first 100 sq cm or less, or 1% of body area of infants and children
15171	Acellular dermal replacement, trunk, arms, legs; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
15175	Acellular dermal replacement, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; first 100 sq cm or less, or 1% of body area of infants and children
15176	Acellular dermal replacement, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)

HCPCS Codes	Description
Q4104	Integra bilayer matrix wound dressing (bmwd), per square centimeter
Q4105	Integra dermal regeneration template (drt), per square centimeter
Q4108	Integra matrix, per sq cm
C9363	Skin substitute (Integra Meshed Bilayer Wound Matrix), per square cm

ICD-9-CM Diagnosis Codes	Description
941.00 - 941.59	Burn of face, head, and neck
942.00 - 942.59	Burn of trunk
943.00 - 943.59	Burn of upper limb, except wrist and hand
944.00 - 944.59	Burn of wrist(s) and hand(s)
945.00 - 945.59	Burn of lower limb(s)
946.0 - 946.5	Burns of multiple specified sites
948.00 - 948.99	Burns classified according to extent of body surface involved
949.0 - 949.5	Burn, unspecified site

Experimental/Investigational/Unproven/Not Covered:

ICD-9-CM Diagnosis Codes	Description
	All other codes

NeoForm-Dermis™

Covered when medically necessary:

CPT^{®*} Codes	Description
15330	Acellular dermal allograft, trunk, arms, legs; first 100 sq cm or less, or 1% of body area of infants and children
15331	Acellular dermal allograft, trunk, arms, legs; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)

HCPCS Codes	Description
Q4100 [†]	Skin substitute, not otherwise specified

†Note: Covered when medically necessary when used to report a tissue-engineered skin substitute and/or platelet-derived growth factor listed as covered in this policy.

ICD-9-CM Diagnosis Codes	Description
174.0–174.9	Malignant neoplasm of female breast
175.0–175.9	Malignant neoplasm of male breast
198.81	Secondary malignant neoplasm of other specified sites; breast
232.5	Carcinoma in situ of skin of trunk, except scrotum
233.0	Carcinoma in situ of breast
611.83	Capsular contracture of breast implants
611.89	Other specified disorders of breast
612.0-612.1	Deformity and disproportion of reconstructed breast
996.52	Mechanical complication of other specified prosthetic device, implant, and graft; due to graft of other tissue, not elsewhere classified
996.54	Mechanical complication of other specified prosthetic device, implant, and graft; due to breast prosthesis
996.69	Infection and inflammatory reaction due to internal prosthetic device, implant, and graft; due to other internal prosthetic device, implant, and graft
996.79	Other complications of internal (biological) (synthetic) prosthetic device, implant, and graft; due to other internal prosthetic device, implant, and graft
V10.3	Personal history of malignant neoplasm; breast
V45.71	Acquired absence of breast
V50.41	Prophylactic organ removal: breast
V51.0	Encounter for breast reconstruction following mastectomy
V84.01	Genetic susceptibility to malignant neoplasm of breast

Experimental/Investigational/Unproven/Not Covered:

ICD-9-CM Diagnosis Codes	Description
	All other codes

Oasis[®] Wound Matrix

Covered when medically necessary:

CPT^{®*} Codes	Description
15430	Acellular xenograft implant; first 100 sq cm or less, or 1% of body area of infants and children
15431	Acellular xenograft implant; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for

	primary procedure)
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HCPCS Codes	Description
Q4102	Oasis wound matrix, per sq cm

ICD-9-CM Diagnosis Codes	Description
249.60 - 249.61	Secondary diabetes mellitus with neurological manifestations
250.60-250.63	Diabetes with neurological manifestations
250.70-250.73	Diabetes with peripheral circulatory disorders
250.80-250.83	Diabetes with other specified manifestations, type II or unspecified type, not stated as uncontrolled
440.23	Atherosclerosis of the extremities with ulceration
454.0	Varicose veins of lower extremities with ulcer
454.2	Varicose veins of lower extremities with ulcer and inflammation
459.31	Chronic venous hypertension with ulcer
459.33	Chronic venous hypertension with ulcer and inflammation
459.81	Venous (peripheral) insufficiency, unspecified
707.10-707.19	Ulcer of lower limbs, except pressure ulcer

Experimental/Investigational/Unproven/Not Covered:

ICD-9-CM Diagnosis Codes	Description
	All other codes

Orcel™

Covered when medically necessary:

CPT®*	Description
15430	Acellular xenograft implant; first 100 sq cm or less, or 1% of body area of infants and children
15431	Acellular xenograft implant; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)

HCPCS Codes	Description
Q4100†	Skin substitute, not otherwise specified

†**Note:** Covered when medically necessary when used to report a tissue-engineered skin substitute and/or platelet-derived growth factor listed as covered in this policy.

ICD-9-CM Diagnosis Codes	Description
757.39	Other specified congenital anomaly of skin

Experimental/Investigational/Unproven/Not Covered:

ICD-9-CM Diagnosis Codes	Description
	All other codes

Transcyte®**Covered when medically necessary:**

CPT®*	Description
15360	Tissue cultured allogeneic dermal substitute; trunk, arms, legs; first 100 sq cm or less, or 1% of body area of infants and children
15361	Tissue cultured allogeneic dermal substitute; trunk, arms, legs; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
15365	Tissue cultured allogeneic dermal substitute, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; first 100 sq cm or less, or 1% of body area of infants and children
15366	Tissue cultured allogeneic dermal substitute, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)

HCPCS Codes	Description
Q4100†	Skin substitute, not otherwise specified

†**Note:** Covered when medically necessary when used to report a tissue-engineered skin substitute and/or platelet-derived growth factor listed as covered in this policy.

ICD-9-CM Diagnosis Codes	Description
941.00 - 941.59	Burn of face, head, and neck
942.00 - 942.59	Burn of trunk
943.00 - 943.59	Burn of upper limb, except wrist and hand
944.00 - 944.59	Burn of wrist(s) and hand(s)
945.00 - 945.59	Burn of lower limb(s)
946.0 - 946.5	Burns of multiple specified sites
948.00 - 948.99	Burns classified according to extent of body surface involved
949.0 - 949.5	Burn, unspecified site

Experimental/Investigational/Unproven/Not Covered:

ICD-9-CM Diagnosis Codes	Description

	All other codes
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Other Tissue-Engineered Skin Substitutes and Platelet-Derived Growth Factors

Experimental/Investigational/Unproven/Not Covered:

CPT®* Codes	Description
15335	Acellular dermal allograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; first 100 sq cm or less, or 1% of body area of infants and children
15336	Acellular dermal allograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
46707	Repair of anorectal fistula with plug (eg: porcine small intestine submucosa [SIS])
0232T	Injection(s), platelet rich plasma, any site, including image guidance, harvesting and preparation when performed

HCPCS Codes	Description
C9358	Dermal substitute, native, non-denatured collagen, collagen, fetal bovine origin, (SurgiMend collagen matrix), per 0.5 square centimeters
C9360	Dermal substitute, native, nondenatured collagen, neonatal bovine origin (SurgiMend Collagen Matrix), per 0.5 square cm
C9364	Porcine implant, Permacol, per square centimeter
Q4107	Graftjacket, per square centimeter
Q4103	Oasis burn matrix, per sq cm
Q4109	Skin substitute, tissuemend, per square centimeter (Code deleted 12/31/2010)
Q4110	Primatrix, per square centimeter
Q4111	Gammagraft, per sq cm
Q4112	Cymetra, injectable, 1cc
Q4113	Graftjacket express, injectable, 1cc
Q4114	Integra flowable wound matrix, injectable, 1cc
Q4115	Alloskin, per square centimeter
Q4117	Hyalomatrix, per square centimeter
Q4118	MatriStem micromatrix, 1 mg
Q4119	MatriStem wound matrix, per sq cm
Q4120	MatriStem burn matrix, per sq cm
Q4121	TheraSkin, per sq cm
S9055	Procuren or other growth factor preparation to promote wound healing

ICD-9-CM Diagnosis Codes	Description
	All codes

*Current Procedural Terminology (CPT®) © 2010 American Medical Association: Chicago, IL.

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	5/15/2008	0068	Tissue-Engineered Skin Substitutes and Growth Factors

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