



Kansas City

An Independent Licensee of the Blue Cross and Blue Shield Association

Bio-Engineered Skin and Soft Tissue Substitutes

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Next Review: 3/2015

Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for bio-engineered skin and soft tissue substitutes when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered

Breast reconstructive surgery using allogeneic acellular dermal matrix products* (i.e., AlloDerm®, AlloMax™, DermaMatrix™, FlexHD®, GraftJacket®) may be considered **medically necessary**,

- when there is insufficient tissue expander or implant coverage by the pectoralis major muscle and additional coverage is required,
- when there is viable but compromised or thin post-mastectomy skin flaps that are at risk of dehiscence or necrosis, or
- the infra-mammary fold and lateral mammary folds have been undermined during mastectomy and re-establishment of these landmarks is needed.

Treatment of chronic, non-infected, full-thickness diabetic lower extremity ulcers using the following tissue-engineered skin substitutes may be considered **medically necessary**.

- Apligraf®**
- Dermagraft®**

Treatment of chronic, non-infected, partial or full-thickness lower extremity skin ulcers due to venous insufficiency which have not adequately responded following a one month period of conventional ulcer therapy using the following tissue-engineered skin substitutes may be considered **medically necessary**.

- Apligraf®**
- Oasis™ Wound Matrix***

Treatment of dystrophic epidermolysis bullosa using the following tissue-engineered skin substitutes may be considered **medically necessary**.

- OrCel™ (for the treatment of mitten-hand deformity when standard wound therapy has failed and when provided in accordance with the Humanitarian Device Exemption (HDE) specifications of the FDA)****

Treatment of second and third degree burns using the following tissue-engineered skin substitutes may be considered **medically necessary**.

- 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 HDE specifications of the FDA)****
- Integra™**
- TransCyte™**

The use of AlloDerm® graft as an interpositional barrier following parotidectomy to reduce the incidence of Frey syndrome is considered **medically necessary**.

The use of AlloDerm® graft as an implant for reconstruction following removal of a malignant neoplasm is considered **medically necessary**.

*Banked Human Tissue

** FDA PMA approved

*** FDA 510(k) cleared

**** FDA-approved under a humanitarian device exemption (HDE)

When Policy Topic is not covered

All other uses of allogeneic skin substitutes not listed above are considered **investigational**.

All other skin substitutes not listed above are considered **investigational**, including, but not limited to:

- ACell® UBM Hydated Wound Dressing
- ACell® UBM Lyophilized Wound Dressing
- AlloPatch HD™
- AlloSkin™
- AlloSkin™ RT
- Amniofix®
- Aongen™ Collagen Matrix
- ArthroFlex™ (FlexGraft)
- Atlas Wound Matrix
- Avagen Wound Dressing
- Avaulta Plus™
- Biobrane®
- BioDfence/BioDfactor
- CellerateRX®
- Collagen Sponge (Innocoll)
- Collagen Wound Dressing (Oasis Research)
- Collaguard®
- CollaSorb™
- CollaWound™
- Collexa®
- Collieva®
- Conexa™
- Coreleader Colla-Pad
- CorMatrix®
- CRXa™
- Cymetra®
- Dermadapt™ Wound Dressing
- DressSkin
- Durepair Regeneration Matrix®
- Endoform Dermal Template™
- ENDURAgen™
- EpiFix®
- Excellagen
- E-Z Derm™
- FortaDerm™ Wound Dressing
- GammaGraft
- Grafix® core
- Grafix® prime
- GraftJacket® Regenerative Tissue Matrix

- GraftJacket® Xpress, injectable
- HA Absorbent Wound Dressing
- Helicoll
- Hyalomatrix® (Laserskin®)
- Hyalomatrix® PA
- hMatrix®
- Integra™ Flowable Wound Matrix
- Integra™ Bilayer Wound Matrix
- Jaloskin®
- MatriDerm®
- MatriStem® Burn Matrix
- MatriStem® Micromatrix
- MatriStem® Wound Matrix
- Matrix Collagen Wound Dressing
- Matrix HD™
- MediHoney®
- Mediskin®
- MemoDerm™
- Oasis® Burn Matrix
- Oasis® Ultra Tri-Layer Matrix
- Permacol™
- PriMatrix™
- Primatrix™ Dermal Repair Scaffold
- Puros® Dermis
- Repliform®
- Repriza™
- SIS Wound Dressing II
- SS Matrix™
- Stimulen™ Collagen
- StrataGraft
- Strattice™ (xenograft)
- Suprathel®
- SurgiMend®
- Talymed®
- TenoGlide™
- TheraForm™ Standard/Sheet
- TheraSkin®Unite™
- Unite® Biomatrix
- Veritas® Collagen Matrix

Considerations

Application of skin replacements and skin substitutes is reported with CPT codes 15040-15278. Codes 15040-15261 are specific to autografts and tissue-cultured autografts, codes 15271-15278 are specific to skin substitute grafts.

Effective in 2012, there is a specific add-on CPT code for the use of these materials as an implant:

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

The HCPCS codes for these products that are used in outpatient and office settings are listed in the code table. There are also HCPCS modifiers to indicate whether the skin substitute is or is not used as a graft (i.e., surface use vs. use as an implant):

- JC: Skin substitute used as a graft
- JD: Skin substitute not used as a graft

Description of Procedure or Service

Bio-engineered skin and soft tissue substitutes may be derived from human tissue (autologous or allogeneic), non-human tissue (xenographic), synthetic materials, or a composite of these materials. Bio-engineered skin and soft tissue substitutes are being evaluated for a variety of conditions, including breast reconstruction and to aid healing of lower extremity ulcers and severe burns. Acellular dermal matrix products are also being evaluated in the repair of a variety of soft tissues.

Background

Bio-engineered skin and soft tissue substitutes may be either acellular or cellular. Acellular products (i.e., cadaveric human dermis with cellular material removed) contain a matrix or scaffold composed of materials such as collagen, hyaluronic acid, and fibronectin. Cellular products contain living cells such as fibroblasts and keratinocytes within a matrix. The cells contained within the matrix may be autologous, allogeneic, or derived from other species (e.g., bovine, porcine). Skin substitutes may also be composed of dermal cells, epidermal cells, or a combination of dermal and epidermal cells, and may provide growth factors to stimulate healing. Tissue-engineered skin substitutes can be used as either temporary or permanent wound coverings.

There are a large number of potential applications for artificial skin and soft tissue products. One large category is non-healing wounds, which potentially encompasses diabetic neuropathic ulcers, vascular insufficiency ulcers, and pressure ulcers. A substantial minority of such wounds do not heal adequately with standard wound care, leading to prolonged morbidity and increased risk of mortality. For example, non-healing lower extremity wounds represent an ongoing risk for infection, sepsis, limb amputation and death. Bio-engineered skin and soft tissue substitutes have the potential to improve rates of healing and reduce secondary complications.

Other situations in which bio-engineered skin products might substitute for living skin grafts include certain post-surgical states such as breast reconstruction, in which skin coverage is inadequate for the procedure performed, or for surgical wounds in patients with compromised ability to heal. Second- and third-degree burns are another situation in which artificial skin products may substitute for auto- or allografts. Certain primary dermatologic conditions that involve large areas of skin breakdown, such as bullous diseases, may also be conditions in which artificial skin products can be considered as substitutes for skin grafts. Acellular dermal matrix products are also being evaluated in the repair of other soft tissues including rotator cuff repair, following oral and facial surgery, hernias, and a variety of other conditions.

Regulatory Status

There are a large number of artificial skin products that are commercially available or in development. The following summary of commercially available skin substitutes describes those products that have substantial relevant evidence on efficacy. This list demonstrates the wide range of types of products available:

Acellular Dermal Matrix

Allograft acellular dermal matrix products derived from donated human skin tissue are supplied by U.S. AATB-compliant tissue banks using the standards of the American Association of Tissue Banks (AATB) and U.S. Food and Drug Administration's (FDA) guidelines. The processing removes the cellular components (i.e., epidermis and all viable dermal cells) that can lead to rejection and infection. Acellular dermal matrix products from human skin tissue are regarded as minimally processed and not significantly changed in structure from the natural material; the FDA classifies it as banked human tissue and therefore does not require FDA approval.

- AlloDerm® (LifeCell Corporation) is an acellular dermal matrix (allograft) tissue-replacement product that is created from native human skin and processed so that the basement membrane and cellular matrix remain intact. An injectable micronized form of AlloDerm (Cymetra) is also available.
- AlloMax™ Surgical Graft (Bard Davol) is an acellular non-cross-linked human dermis allograft. (AlloMax was previously marketed as NeoForm™.)

- DermaMatrix (Synthes) is an acellular dermal matrix (allograft) derived from donated human skin tissue. DermaMatrix Acellular Dermis is processed by the Musculoskeletal Transplant Foundation® (MTF®).
- GraftJacket® Regenerative Tissue Matrix (KCI) is an acellular regenerative tissue matrix that has been processed from screened donated human skin supplied from U.S. tissue banks. The allograft is minimally processed to remove the epidermal and dermal cells, while preserving dermal structure.

PriMatrix (TEI Biosciences) is a xenogeneic acellular dermal matrix processed from fetal bovine dermis. It is indicated through the U.S. Food and Drug Administration's (FDA) 510(k) process for partial and full-thickness wounds; diabetic, pressure, and venous stasis ulcers; surgical wounds; and tunneling, draining, and traumatic wounds.

Amniotic Membrane

Human amniotic membrane, or amnion, is the inner most layer of the 3 layers forming the fetal membrane. It is harvested immediately after birth, cleaned, sterilized, and either fresh frozen or dehydrated. Human amniotic membrane is considered to be minimally processed and not significantly changed in structure from the natural material; the U.S. Food and Drug Administration (FDA) classifies it as banked human tissue and therefore, it does not require FDA approval. Epifix® (MiMedix) is a commercially available source of dehydrated human amniotic membrane.

Collagen Scaffold

OASIS™ Wound Matrix (Cook Biotech) is a xenogeneic collagen scaffold derived from porcine small intestinal mucosa. It was cleared by the FDA's 510(k) process in 2000 for the management of partial- and full-thickness wounds including pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled undermined wounds, surgical wounds, trauma wounds, and draining wounds.

Living Cell Therapy

Apligraf® (Organogenesis) is a bi-layered living cell therapy composed of an epidermal layer of living human keratinocytes and a dermal layer of living human fibroblasts. Apligraf® is supplied as needed, in 1 size, with a shelf-life of 10 days. It was FDA-approved in 1998 for use in conjunction with compression therapy for the treatment of non-infected, partial- and full-thickness skin ulcers due to venous insufficiency and in 2001 for full-thickness neuropathic diabetic lower extremity ulcers nonresponsive to standard wound therapy.

Dermagraft® (Advanced Tissue Sciences) is composed of cryopreserved human-derived fibroblasts and collagen applied to a bioabsorbable mesh. Dermagraft has been approved by the FDA for repair of diabetic foot ulcers and for use in the treatment of wounds related to dystrophic epidermolysis bullosa.

Epicel® (Genzyme Biosurgery) is a cultured epithelial autograft and is FDA-approved under a humanitarian device exemption (HDE) for the treatment of 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 due to the severity and extent of their burns.

OrCel™ (Forticell Bioscience) (formerly called Composite Cultured Skin) is an absorbable allogeneic bi-layered cellular matrix, made of bovine collagen, in which human dermal cells have been cultured. It was approved by the FDA premarket approval (PMA) for healing donor site wounds in burn victims and under a humanitarian device exemption (HDE) for use in patients with recessive dystrophic epidermolysis bullosa undergoing hand reconstruction surgery to close and heal wounds created by the surgery, including those at donor sites.

Biosynthetic

Biobrane®/Biobrane-L (Smith and Nephew) is a biosynthetic wound dressing constructed of a silicon film with a nylon fabric partially imbedded into the film. The fabric creates a complex 3-dimensional

structure of tri-filament thread, which chemically binds collagen. Blood/sera clot in the nylon matrix, adhering the dressing to the wound until epithelialization occurs.

Integra® Dermal Regeneration Template (Integra LifeSciences) is a bovine, collagen/glycosaminoglycan dermal replacement covered by a silicone temporary epidermal substitute. It is FDA-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 physiologic condition of the patient. Integra™ Matrix Wound Dressing and Integra™ meshed Bilayer Wound Matrix are substantially equivalent skin substitutes that are FDA-510(k) approved for other indications.

TransCyte™ (Advanced Tissue Sciences) consists of human dermal fibroblasts grown on nylon mesh, combined with a synthetic epidermal layer and was approved by the FDA in 1997. TransCyte is intended to be used as a temporary covering over burns until autografting is possible. It can also be used as a temporary covering for some burn wounds that heal without autografting.

Rationale

The policy was developed based on a literature search using MEDLINE in November 2007 for use of an allogeneic tissue-engineered skin substitute (AlloDerm) in breast reconstructive surgery. At the time this policy was created, the available data on use of this technology were limited. In particular, there were no comparative studies to evaluate possible changes of the reconstructive time or to evaluate changes in esthetics. In addition, the duration of follow-up was limited, so the impact on longer-term complications such as severe contractures could not be determined. Finally, criteria to determine those who were candidates for use of this procedure had not been established.

Clinical input was obtained for the 2008-2009 update of this policy. It was concluded that given the extensive data from case series, as well as the clinical input obtained about the usefulness of this procedure in providing inferolateral support for breast reconstruction, this procedure was changed to medically necessary in breast reconstruction when there is insufficient tissue expander or implant coverage by the pectoralis major muscle and additional coverage is required; when there is viable but compromised or thin post-mastectomy skin flaps that are at risk of dehiscence, or necrosis or when the infra-mammary fold and lateral mammary folds have been undermined during mastectomy and re-establishment of these landmarks is needed.

In 2011 this policy was expanded to address additional bio-engineered skin and soft tissue substitutes and other indications. The most recent literature update for this policy was performed through September 4, 2013. Following is a summary of key literature to date.

Breast Reconstruction

AlloDerm

Systematic Reviews: Two systematic reviews from 2012 found an increased rate of complications with acellular dermal matrix-assisted breast reconstruction. One meta-analysis of 16 retrospective studies found a higher likelihood of seroma (pooled odds ratio [OR]=3.9; 95% confidence interval [CI], 2.4-6.2), infection (pooled OR=2.7; 95% CI, 1.1-6.4) and reconstructive failure (pooled OR=3.0; 95% CI, 1.3-6.8) when compared with breast reconstruction using traditional musculofascial flaps. (2) Another meta-analysis that compared 19 studies using acellular dermal matrix (n=2037) with 35 studies using submuscular reconstruction (n=12,847) found an increased risk of total complications (relative risk [RR]=2.05; 95% CI, 1.55-2.70), seroma (RR=2.73; 95% CI, 1.67-4.46), infection (RR=2.47; 95% CI, 1.71- 3.57), and reconstructive failure (RR=2.80; 95% CI, 1.76-4.45) with acellular dermal matrix. (3) These meta-analyses are limited by the poor quality of included studies and significant heterogeneity.

Randomized Controlled Trials: In 2012, McCarthy et al. reported a multicenter blinded randomized controlled trial of AlloDerm in 2-stage expander/implant reconstruction. (4) Seventy patients were

randomized to AlloDerm acellular dermal matrix-assisted tissue expander/implant reconstruction or to submuscular tissue expander/implant placement. There were no significant differences between the groups in the primary outcomes of immediate postoperative pain (54.6 AlloDerm and 42.8 control on a 100-point visual analog score) or pain during the expansion phase (17.0 AlloDerm and 4.6 control), or in the secondary outcome of rate of tissue expansion (91 days AlloDerm and 108 days control) and patient-reported physical well-being. There was no significant difference in adverse events, although the total number of adverse events was small. Phase 2 of the study will evaluate long-term outcomes.

Controlled Studies: Preminger and colleagues evaluated the impact of AlloDerm on expansion rates in immediate tissue expander/implant reconstruction in a retrospective matched cohort study. (5) Forty-five patients had reconstruction with AlloDerm and 45 had standard reconstruction. Subjects were matched for expander size (+/-100 mL), history of irradiation, and indication for mastectomy. There were no significant differences in initial filling volume, mean number of postoperative expansions, mean rate of postoperative tissue expansion, or in the incidence of postoperative complications. Aesthetic outcomes were not addressed. In 2008, Colwell and Breuing reported on 10 patients who had mastopexy with dermal slings, 5 patients were given AlloDerm and 5 were given autologous tissue. (6) Patients maintained projection and breast base width after 6 months to 3 years.

Uncontrolled Studies: A number of case series have also demonstrated that this approach can provide tissue coverage of implants and tissue expanders. (7, 8) AlloDerm has been reported in nipple reconstructive surgery in a case series on 30 nipple reconstructive procedures performed at one institution. (9) Use of AlloDerm has also been reported in a small series (n=3) to correct breast implant-related problems (malposition, symmastia, and rippling). (10)

Other: Liu et al. reported postoperative complications in breast reconstruction with (n=266) or without (n=204) AlloDerm in 2011. (11) Radiation therapy, body mass index (BMI), intraoperative use of tumescent solution, and medical comorbidities were similar between the 2 groups, but there were twice as many smokers and the implants were larger in the AlloDerm group. There was a trend for a higher rate of major infections that required prosthesis removal in the AlloDerm group (4.9% vs 2.5%, p=0.172) and a statistically significant increase in overall wound infection rate (6.8% vs 2.5%). The overall surgical complication rate was significantly higher in the AlloDerm group (19.5% vs 12.3%). Multivariate analysis indicated that the use of acellular dermal matrix, smoking, higher BMI, higher initial volume, and bigger implant size were associated with a higher overall surgical complication rate. This study is limited by the retrospective analysis and differences between groups at baseline.

Bindingavele et al. reviewed charts of 41 patients (65 breasts) who had staged breast reconstruction with acellular cadaveric dermis to report postoperative complication rates. (12) Rates for wound infection, expander removal, hematoma, and seroma were 3.1%, 1.5%, 1.5%, and 4.6%, respectively. The authors concluded that based on low rates of complications and good cosmetic outcomes, the technology should be in the repertoire of plastic surgeons and that follow-up is required to evaluate long-term outcomes.

AlloDerm versus DermaMatrix or FlexHD

A 2013 retrospective review by Liu et al. compared complication rates following breast reconstruction with AlloDerm or FlexHD in 382 consecutive women (547 breasts). (13) Eighty-one percent of the sample were immediate reconstructions; 165 used AlloDerm, and 97 used FlexHD. Mean follow-up was 6.4 months. Compared with breast reconstruction without use of AlloDerm or FlexHD, acellular dermal matrix had a higher rate of delayed healing (20.2% vs 10.3%), although this finding might be related to differences in fill volumes. In univariate analysis, there were no significant differences in complications (return to the operating room, surgical site infection, seroma, hematoma, delayed healing, or implant loss) between AlloDerm and FlexHD. In multivariate analysis, there were no significant differences between AlloDerm or FlexHD for the return to the operating room, surgical site infection, seroma, or delayed healing. Independent risk factors for implant loss included the use of FlexHD, single-stage reconstruction, and smoking. Another retrospective review from 2013 compared complication rates

following use of AlloDerm (n=136) or FlexHD (n=233) in a consecutive series of 255 patients (369 breasts). (14) Total complication rates for the 2 products were similar (19.1% for AlloDerm and 19.3% for FlexHD). Analysis by type of complication showed no significant difference between the 2, and regression analysis controlling for differences in baseline measures found that the type of acellular dermal matrix was not a risk factor for any complication.

Brooke et al. conducted a retrospective review of complication rates when AlloDerm (n=49), DermaMatrix (n=110), or FlexHD (n=62) was used for tissue expander breast reconstruction. (15) Clinically significant complications were defined as cellulitis, abscess, seroma, expander leak or puncture, skin necrosis, wound dehiscence, or hematoma. The total clinically significant complication rate was 22% with AlloDerm, 15% with DermaMatrix, and 16% with FlexHD (not significantly different). Infectious complication rates for the 3 products were the same at 10%. When compared with breast reconstruction without an acellular dermal matrix (n=64), there was no significant difference in the total complication rate (17% vs 11%), but there was a trend toward a higher incidence of infectious complications (10% vs 2%, p=0.09)

This small amount of evidence from retrospective comparative studies does not show any difference in outcomes among different types of acellular dermal matrix (ADM) products.

Interpositional Graft after Parotidectomy

AlloDerm

In 2003, Sinha et al. reported the use of AlloDerm acellular human dermal matrix as an interpositional physical barrier to prevent the development of Frey syndrome (gustatory sweating) after parotidectomy. (16) Thirty patients were divided into 3 groups; it was not described if the assignments were randomized. One group underwent superficial parotidectomy with reconstruction of the defect with AlloDerm, a second group had superficial parotidectomy without placement of an interpositional barrier, and the third group underwent deep-plane rhytidectomy without disruption of the parotid fascia. At minimum 1-year follow-up, there was a subjective incidence of Frey syndrome in 1 patient treated with AlloDerm and 5 patients in group 2. The objective incidence of Frey syndrome, measured with the Minor starch-iodine test, was 2 patients treated with AlloDerm and 8 patients in group 2. None of the patients in group 3 who underwent deep-plane rhytidectomy without disruption of the parotid fascia had subjective or objective Frey syndrome. There were no adverse effects.

A 2008 publication from Asia compared use of allogeneic acellular dermal matrix (RENOV) in 168 patients who had superficial or partial parotidectomy. (17) Sixty-four patients received an acellular dermal matrix and 104 patients had superficial or partial parotidectomy alone. The size of the graft depended on the amount of tissue required to restore the normal facial contour. The method of assignment to the 2 groups was not described. At a median follow-up of 16 months (range, 11-27), the subjective incidence of Frey syndrome was 2% in the acellular dermal matrix group compared with 61% in controls. Objective assessment, performed in 30 patients randomly selected from each group, found an incidence of Frey syndrome in 2 patients (7%) treated with acellular dermal matrix and 24 patients (80%) in the control group. One patient in the acellular dermal matrix group and 18 patients in the control group developed a parotid fistula.

DermaMatrix

DermaMatrix is an acellular dermal matrix that differs from AlloDerm in several ways; it can be stored at room temperature (vs. refrigerated), it has a shelf-life of 3 years (vs. 2 years), and it can be rehydrated in 3 minutes (vs. 30 minutes).

Athavale et al. evaluated complications of AlloDerm and DermaMatrix in a retrospective review of 100 patients treated between 2001 and 2009 at a single U.S. institution. (18) Exclusion criteria for the study included presence of malignancy on final surgical pathology report, incomplete medical records, previous history of radiation therapy to the head and neck region, and additional procedures to the region of the parotid gland. Initially, only AlloDerm was used; this changed to a 20/80 ratio of

AlloDerm/DermaMatrix due to more readily available stock of DermaMatrix. Complications were defined as any outcome that required procedural intervention for resolution (seroma/sialocele formation, infected fluid collection, and/or serosanguinous fluid collection). The authors identified 8 complications in 31 DermaMatrix implants (26%) compared with 5 complications in 69 AlloDerm implants (7%). The complication rate did not differ for total parotidectomies but was higher for DermaMatrix compared to AlloDerm for subtotal parotidectomies (37% vs 8%). Nearly half of all complications were seroma/sialocele formation.

Randomized, double-blind, controlled trials with longer follow-up are needed to evaluate this procedure.

Tendon Repair

GraftJacket

In 2012, Barber et al. reported an industry-sponsored multi-center randomized controlled trial of augmentation with GraftJacket acellular human dermal matrix for arthroscopic repair of large (>3 cm) rotator cuff tears involving 2 tendons. (19) Twenty-two patients were randomized to GraftJacket augmentation, and 20 patients were randomized to no augmentation. At a mean follow-up of 24 months (range, 12 to 38 months) the American Shoulder and Elbow Surgeons (ASES) score improved from 48.5 to 98.9 in the GraftJacket group and from 46.0 to 94.8 in the control group ($p=0.035$). The Constant score improved from 41 to 91.9 in the GraftJacket group and from 45.8 to 85.3 in the control group ($p=0.008$). The University of California, Los Angeles score was not significantly different between the groups. Gadolinium-enhanced magnetic resonance imaging (MRI) scans showed intact cuffs in 85% of repairs in the GraftJacket group and 40% of repairs in the control group. However, no correlation was found between MRI findings and clinical outcomes. Rotator cuff retears occurred in 3 patients (14%) in the GraftJacket group and 9 patients (45%) in the control group. Although these results are promising, additional study with a larger number of patients is needed.

Fistula Repair

Acellular Dermal Matrix

A study from Asia compared a xenogeneic acellular dermal matrix (J-I type, J.Y. Life Tissue Engineering Co., China) with endorectal advancement flap (ERAF) for the treatment of complex anorectal fistula in a randomized study with 90 consecutive patients. (20) Follow-up was performed at 2 days, 2, 4, 6, 12 weeks, and 5 months after surgery. Success was defined as closure of all external opening, absence of drainage without further intervention, and absence of abscess formation. Success was observed in 82.2% of the acellular dermal matrix group. Fistula recurred in 2 (4.45%) patients in the acellular dermal matrix group compared with 13 (28.89%) patients in the ERAF group. Healing time was reduced (7.5 vs 24.5 days), and quality of life was rated higher in the acellular dermal matrix group (85.9 vs 65.3). No significant difference was observed in the incontinence and anal deformity rate between the 2 groups. This product is not cleared for marketing in the U.S., although the manufacturing process was reported to be similar to Surgisis AFP.

Surgical Repair of Hernias

A 2011 systematic review included 30 level III and level IV articles on acellular dermal matrix (ADM) for abdominal wall reconstruction. (21) No randomized controlled trials or high-quality comparative studies (level I or II) were identified. Examples of the level III studies are described next.

AlloDerm

Gupta et al. compared the efficacy and complications associated with the use of AlloDerm and Surgisis bioactive mesh in 74 patients who underwent ventral hernia repair in 2006. (22) The first 41 procedures were performed using Surgisis Gold 8-ply mesh formed from porcine small intestine submucosa, and the remaining 33 patients had ventral hernia repair with AlloDerm. Patients were seen 7-10 days after discharge from the hospital and at 6 weeks. Any signs of wound infection, diastasis, hernia recurrence, changes in bowel habits, and seroma formation were evaluated. The use of the AlloDerm mesh

resulted in 8 hernia recurrences (24%). Fifteen of the AlloDerm patients (45%) developed a diastasis or bulging at the repair site. Seroma formation was only a problem in 2 patients.

In 2007, Espinosa-de-los-Monteros and colleagues retrospectively reviewed 39 abdominal wall reconstructions with AlloDerm performed in 37 patients and compared them with 39 randomly selected cases. (23) They reported a significant decrease in recurrence rates when human cadaveric acellular dermis was added as an overlay to primary closure plus rectus muscle advancement and imbrication in patients with medium-sized hernias. However, no differences were observed when adding human cadaveric acellular dermis as an overlay to patients with large-size hernias treated with underlay mesh.

A 2013 study compared AlloDerm with FlexHD for complicated hernia surgery. (24) From 2005 to 2007, AlloDerm was used to repair large (>200 cm²) symptomatic complicated ventral hernia that resulted from trauma or emergency surgery (n=55). From 2008 to 2010, FlexHD was used to repair large complicated ventral hernia in patients meeting the same criteria (n=40). The 2 groups were comparable at baseline. At one-year follow-up, all of the AlloDerm patients were diagnosed with hernia recurrence (abdominal laxity, functional recurrence, or true recurrence) requiring a second repair. Eleven patients (31%) in the FlexHD group required a second repair. This comparative study is limited by the use of nonconcurrent comparisons, which is prone to selection bias and does not control for temporal trends in outcomes.

The limited evidence available at this time does not support the use of AlloDerm in hernia repair.

Oral Surgery

AlloDerm

In 2008, Novaes and de Barros described 3 randomized trials from their research group that examined use of acellular dermal matrix in root coverage therapy and alveolar ridge augmentation. (25) Two trials used acellular dermal matrix in both the study and control groups and are not described here. A third trial compared acellular dermal matrix with subepithelial connective tissue graft in 30 gingival recessions (9 patients). At 6 months postsurgery, the acellular dermal matrix showed recession reduction of 1.83 mm while subepithelial connective tissue graft showed recession reduction of 2.10 mm; these were not significantly different.

A nonrandomized cohort study compared Alloderm with the gold standard of split thickness skin grafts in 34 patients who underwent oral cavity reconstruction following surgical removal of tumors. (26) Patients were enrolled after surgical treatment for evaluation at a tertiary care center and divided into 2 cohorts according to the reconstruction method used, which was based on surgeon preference. Twenty-two patients had been treated with Alloderm, and 12 had been treated with split thickness skin grafts. The location of the grafts (Alloderm vs. autograft) were on the tongue (54% vs 25%), floor of mouth (9% vs. 50%), tongue and floor of mouth (23% vs 8%), buccal (9% vs 0%), or other (5% vs 17%). More patients in the Alloderm group were treated with radiation therapy (45% vs 17%), and the graft failure rate was higher (14% vs 0%). Radiation therapy had a significantly negative impact for both groups. Histology on a subset of the patients showed increased inflammation, fibrosis, and elastic fibers with split thickness skin grafts. Functional status and quality of life were generally similar in the 2 groups. Interpretation of these results is limited by the differences between the groups at baseline.

Laryngoplasty

There are several reports with short-term follow-up of micronized AlloDerm (Cymetra) injection for laryngoplasty. In 2005, Milstein et al. reported mean 11.2 month follow-up (range, 1 to 35 months) of Cymetra injection in 20 patients with unilateral vocal-fold paralysis. (27) Pre- and post-operative digital voice samples and video stroboscopy were rated on a 4-point scale by a panel of 3 voice experts who were blinded to the pre- or postoperative status. Compared with preoperative measures, Cymetra improved voice quality (from 3.23 to 1.65), glottal closure (from 3.21 to 1.42), and degree of vocal-fold bowing (from 2.38 to 1.36). Quality-of-life measures and patients' self-perceptions of vocal quality were

also improved. In 5 patients (25%), the effect was temporary, and in 8 patients (40%) who had follow-up of 1 year or longer, the improvement was maintained. Longer-term study in a larger number of patients is needed to determine the durability of this procedure and to evaluate the safety of repeat injections.

Tympanoplasty

Vos et al. reported a retrospective non-randomized comparison of AlloDerm versus native tissue grafts for type I tympanoplasty in 2005. (28) Included in the study were 108 patients (25 AlloDerm, 53 fascia reconstruction, and 30 fascia plus cartilage reconstruction) treated between 2001 and 2004. One surgeon had performed 96% of the AlloDerm tympanoplasties. Operative time was reduced in the AlloDerm group (82 minutes for AlloDerm, 114 minutes for fascial cases, and 140 minutes for fascia plus cartilage). There was no significant difference in the success rate of the graft (88% for AlloDerm, 89% for fascia grafts, 96.7% for cartilage plus fascia). There was no significant difference in hearing between the groups at follow-up (time not specified). Longer-term controlled study in a larger number of patients is needed to determine the durability of this procedure.

Diabetic Lower Extremity Ulcers

Apligraf

In 2001, Veves and colleagues reported on a randomized prospective study on the effectiveness of Graftskin (Apligraf), a living skin equivalent, in treating noninfected nonischemic chronic plantar diabetic foot ulcers. (29) The study involved 24 centers in the U.S.; 208 patients were randomly assigned to ulcer treatment either with Graftskin (112 patients) or saline-moistened gauze (96 patients, control group). Standard state-of-the-art adjunctive therapy, including extensive surgical debridement and adequate foot off-loading, was provided in both groups. Graftskin was applied at the beginning of the study and weekly thereafter for a maximum of 4 weeks (maximum of 5 applications) or earlier if complete healing occurred. At the 12-week follow-up visit, 63 (56%) Graftskin-treated patients achieved complete wound healing compared with 36 (38%) in the control group ($p=0.0042$). The Kaplan-Meier method median time to complete closure was 65 days for Graftskin, significantly lower than the 90 days observed in the control group ($p=0.003$). The rate of adverse reactions was similar between the 2 groups with the exception of osteomyelitis and lower-limb amputations, both of which were less frequent in the Graftskin group. The authors concluded that application of Graftskin for a maximum of 4 weeks resulted in a higher healing rate when compared with state-of-the-art treatment and was not associated with any significant side effects. This study was reviewed in a 2001 TEC Assessment, which concluded that Graftskin (Apligraf), in conjunction with good local wound care, met the TEC criteria for the treatment of diabetic ulcers that fail to respond to conservative management. (30)

In 2010, Steinberg and colleagues reported on a study of 72 subjects from Europe and Australia that assessed the safety and efficacy of Apligraf in the treatment of non-infected diabetic foot ulcers. (31) The design and patient population of this study were similar to the 208-subject U.S study (described above), which led to FDA-approval of Apligraf for the treatment of diabetic foot ulcers. For these studies, subjects with a non-infected neuropathic diabetic foot ulcer present for at least 2 weeks were enrolled in these prospective, multicenter, randomized controlled, open-label studies that compared Apligraf use in conjunction with standard therapy (sharp debridement, standard wound care, and off-loading) against standard therapy alone. Pooling of data was performed because of the similarity and consistency of the 2 studies. Efficacy and safety results were consistent across studies independent of mean ulcer duration that was significantly longer in the European study (21 months, compared with 10 months in the U.S. study). Reported adverse events by 12 weeks were comparable across treatment groups in the 2 studies. Efficacy measures demonstrated superiority of Apligraf treatment over control-treated groups in both studies. Combining the data from both studies, 55.2% (80/145) of Apligraf subjects had complete wound closure by 12 weeks, compared to 34.3% (46/134) of control subjects ($p=0.0005$), and Apligraf subjects had a significantly shorter time to complete wound closure ($p=0.0004$). The authors concluded that both the EU and U.S. studies exhibited superior efficacy and

comparable safety for subjects treated with Apligraf compared to control subjects, and the studies provide evidence of the benefit of Apligraf in treating diabetic foot ulcer (DFU).

In 2010, Kirsner and colleagues reported on analysis of 2,517 patients with diabetic neuropathic foot ulcers who were treated between 2001 and 2004. (32) The study was a retrospective analysis using a wound-care database; the patients received advanced biological therapy i.e., Apligraf (446 patients), Regranex, or Procuren. In this study, advanced biological therapy was used, on average, within 28 days from the first wound clinic visit and associated with a median time to healing of 100 days. Wounds treated with engineered skin (Apligraf) as the first advanced biological therapy were 31.2% more likely to heal than wounds first treated with topical recombinant growth factor ($p < 0.001$) and 40.0% more likely to heal than those first treated with platelet releasate ($p = 0.01$). Wound size, wound grade, duration of wound, and time to initiation of advanced biological therapy affected the time to healing.

Dermagraft

A pivotal multi-center FDA-regulated trial randomized 314 patients with chronic diabetic ulcers to Dermagraft or control. (33) Over the course of the 12-week study, patients received up to 8 applications of Dermagraft. All patients received pressure-reducing footwear and were encouraged to stay off their study foot as much as possible. At 12 weeks, the median percent wound closure for the Dermagraft group was 91% compared to 78% for the control group. Ulcers treated with Dermagraft closed significantly faster than ulcers treated with conventional therapy. No serious adverse events were attributed to Dermagraft. Ulcer infections developed in 10.4% of the Dermagraft patients compared with 17.9% of the control patients. Together, there was a lower rate of infection, cellulitis, and osteomyelitis in the Dermagraft-treated group (19% vs. 32.5%).

GraftJacket Regenerative Tissue Matrix

Brigido et al. reported a small ($n = 40$) randomized pilot study of GraftJacket compared with conventional treatment for chronic non-healing diabetic foot ulcers in 2004. (34) Control patients received conventional therapy with debridement, wound gel with gauze dressing, and off-loading. GraftJacket patients received surgical application of the scaffold using skin staples or sutures and moistened compressive dressing. A second graft application was necessary after the initial application for all patients in the GraftJacket group. Preliminary 1-month results showed that after a single treatment, ulcers treated with GraftJacket healed at a faster rate than conventional treatment. There were significantly greater decreases in wound length (51% vs. 15%), width (50% vs. 23%), area (73% vs. 34%), and depth (89% vs. 25%). All of the grafts incorporated into the host tissue.

In 2009, Reyzelman et al. reported an industry-sponsored multicenter randomized study that compared a single application of GraftJacket versus standard of care in 86 patients with diabetic foot ulcers. (35) Offloading was performed using a removable cast walker. Ulcer size at presentation was 3.6 cm² in the GraftJacket group and 5.1 cm² in the control group. Eight patients, 6 in the study group and 2 in the control group, did not complete the trial. At 12 weeks, complete healing was observed in 69.6% of the GraftJacket group and 46.2% of controls. After adjusting for ulcer size at presentation, a statistically significant difference in nonhealing rate was calculated, with odds of healing 2.0 times higher in the study group. Mean healing time was 5.7 weeks versus 6.8 weeks for the control group. The authors did not report if this difference was statistically significant. The median time to healing was 4.5 weeks for GraftJacket (range, 1–12 weeks) and 7.0 weeks for control (range 2–12 weeks). Kaplan-Meier method survivorship analysis for time to complete healing at 12 weeks showed a significantly lower nonhealing rate for the study group (30.4%) compared with the control group (53.9%). The authors commented that a single application of GraftJacket, as used in this study, is often sufficient for complete healing. This study is limited by the small study population, differences in ulcer size at baseline, and the difference in the percentage of patients censored in each group. Questions also remain about whether the difference in mean time to healing is statistically or clinically significant. Additional trials with a larger number of subjects are needed to evaluate if GraftJacket Regenerative Tissue Matrix improves health outcomes in this population.

EpiFix Amniotic Membrane

In 2013, Zelen et al. reported an industry-sponsored, non-blinded, randomized controlled trial comparing use of EpiFix (n=13) with standard of care (SOC; moist wound therapy, n=12) for diabetic foot ulcers of at least 4 weeks' duration. (36) EpiFix was applied every 2 weeks if the wound had not healed, with weekly dressing changes comprised of nonadherent dressing, moisture retentive dressing, and a compression dressing. Standard moist wound dressing was changed daily. After 4 weeks of treatment, EpiFix treated wounds had reduced in size by a mean of 97.1% compared with 32.0% for the SOC group. Healing rate, defined as complete epithelialization of the open area of the wound, was 77% for EpiFix compared with 0% for SOC. After 6 weeks of treatment, wounds were reduced by 98.4% with EpiFix treatment compared with -1.8% for standard care. The healing rate was 92% with EpiFix compared with 8% with standard treatment alone. Results of this small study are encouraging, but preliminary. Confirmation of these results in a larger trial is needed.

Oasis Wound Matrix

Niezgoda and colleagues compared healing rates at 12 weeks for full-thickness diabetic foot ulcers treated with OASIS Wound Matrix, an acellular wound care product, versus Regranex Gel. (37) This was an industry-sponsored randomized controlled multicenter trial conducted at 9 outpatient wound care clinics and involved 73 patients with at least one diabetic foot ulcer. Patients were randomized to receive either Oasis Wound Matrix (n=37) or Regranex Gel (n=36) and a secondary dressing. Wounds were cleansed and debrided, if needed, at a weekly visit. The maximum treatment period for each patient was 12 weeks. After 12 weeks of treatment, 18 (49%) Oasis-treated patients had complete wound closure compared with 10 (28%) Regranex-treated patients. Oasis treatment met the non-inferiority margin, but did not demonstrate that healing in the Oasis group was statistically superior (p=0.055). Post-hoc subgroup analysis showed no significant difference in incidence of healing in patients with type 1 diabetes (33% vs. 25%) but a significant improvement in patients with type 2 diabetes (63% vs. 29%). There was also an increased healing of plantar ulcers in the Oasis group (52% vs. 14%). These posthoc findings are considered hypothesis-generating. Additional study with a larger number of subjects is needed to evaluate the effect of Oasis treatment in comparison with the current standard of care.

PriMatrix

In 2011, Karr published a retrospective comparison of PriMatrix (a xenograft fetal bovine dermal collagen matrix) and Apligraf in 40 diabetic foot ulcers. (38) The first 20 diabetic foot ulcers matching the inclusion and exclusion criteria for each graft were compared. Included were diabetic foot ulcers of 4 weeks' duration, at least 1 sq cm and depth to subcutaneous tissue, healthy tissue at the ulcer, adequate arterial perfusion to heal, and able to off-load the diabetic ulcer. The products were placed on the wound with clean technique, overlapping the edges of the wound, and secured with sutures or staples. The time to complete healing for PriMatrix was 38 days with 1.5 applications compared to 87 days with 2 applications for Apligraf. Although promising, additional study with a larger number of subjects is needed to evaluate the effect of PriMatrix treatment in comparison with the current standard of care.

Lower Extremity Ulcers due to Venous Insufficiency

Apligraf

Apligraf is a living cell therapy composed of living human keratinocytes and fibroblasts. Falanga and colleagues reported a multicenter randomized trial of Apligraf (human skin equivalent) in 1998. (39) A total of 293 patients with venous insufficiency and clinical signs of venous ulceration were randomized to compression therapy alone or compression therapy and treatment with Apligraf. Apligraf was applied up to a maximum of 5 (mean 3.3) times per patient during the initial 3 weeks. The primary end points were the percentage of patients with complete healing by 6 months after initiation of treatment and the time required for complete healing. At 6 months' follow-up, the percentage of patients healed was increased with Apligraf (63% vs. 49%), and the median time to complete wound closure was reduced (61 vs 181 days). Treatment with Apligraf was found to be superior to compression therapy in healing larger (>1,000 mm²) and deeper ulcers and ulcers of more than 6 months' duration. There were no symptoms or signs of rejection, and the occurrence of adverse events was similar in both groups. This

study was reviewed in a 2001 TEC Assessment, which concluded that Apligraf (graftskin), in conjunction with good local wound care, met the TEC criteria for the treatment of venous ulcers that fail to respond to conservative management. (30)

Dermagraft

Dermagraft is a living cell therapy composed of cryopreserved human fibroblasts cultured on a bioabsorbable mesh. Dermagraft has been approved by the FDA for repair of diabetic foot ulcers. Use of Dermagraft for venous ulcers is an off-label indication. In 2013, Harding et al. reported an open-label multi-center randomized controlled trial that compared Dermagraft plus compression therapy (n=186) versus compression therapy alone (n=180). (40) The study had numerous inclusion/exclusion criteria that restricted the study population to patients who had nonhealing ulcers with compression therapy but had capacity to heal. Intent-to-treat analysis revealed no significant difference between the 2 groups in the primary outcome measure, the proportion of patients with completely healed ulcers by 12 weeks (34% Dermagraft vs 31% control). Pre-specified subgroup analysis revealed a significant improvement in the percent of ulcers healed for ulcers of 12 months or less in duration (52% vs 37%) and for ulcers of 10 cm or less (47% vs 39%). There were no significant differences in the secondary outcomes of time to healing, complete healing by week 24, and percent reduction in ulcer area.

Oasis Wound Matrix

Oasis Wound Matrix is a xenogeneic collagen scaffold derived from porcine small intestinal mucosa. In 2005, Mostow et al. reported an industry-sponsored multicenter (12 sites) randomized trial that compared weekly treatment with Oasis Wound Matrix versus standard of care in 120 patients with chronic ulcers due to venous insufficiency that were not adequately responding to conventional therapy. (41) Healing was assessed weekly for up to 12 weeks, with follow-up performed after 6 months to assess recurrence. After 12 weeks of treatment, there was a significant improvement in the percentage of wounds healed in the Oasis group (55% vs. 34%). After adjusting for baseline ulcer size, patients in the Oasis group were 3 times more likely to achieve healing than those in the standard care group. Patients in the standard care group whose wounds did not heal by the 12th week were given the option to cross over to Oasis treatment. None of the healed patients treated with Oasis wound matrix and seen for the 6-month follow-up experienced ulcer recurrence.

A research group in Europe has described 2 comparative studies of the Oasis matrix for mixed arterial venous and venous ulcers. In a 2007 quasi-randomized study, Romanelli et al. compared the efficacy of 2 extracellular matrix-based products, Oasis and Hyaloskin (extracellular matrix with hyaluronic acid). (42) A total of 54 patients with mixed arterial/venous leg ulcers were assigned to the 2 arms based on order of entry into the study; 50 patients completed the study. Patients were followed up twice a week, and the dressings were changed more than once a week, only when necessary. After 16 weeks of treatment, complete wound closure was achieved in 82.6% of Oasis-treated ulcers compared with 46.2% of Hyaloskin-treated ulcers. Oasis treatment significantly increased the time to dressing change (mean of 6.4 vs. 2.4 days), reduced pain on a 10-point scale (3.7 vs 6.2), and improved patient comfort (2.5 vs. 6.7).

In a 2010 trial, Romanelli et al. compared Oasis with a moist wound dressing in 23 patients with mixed arterial/venous ulcers and 27 patients with venous ulcers. (43) The study was described as randomized, but the method of randomization was not described. After the 8-week study period, patients were followed up monthly for 6 months to assess wound closure. Complete wound closure was achieved in 80% of the Oasis-treated ulcers at 8 weeks, compared to 65% of the standard of care group. On average, Oasis-treated ulcers achieved complete healing in 5.4 weeks as compared with 8.3 weeks for the standard of care group. Treatment with Oasis also increased the time to dressing change (5.2 vs 2.1 days) and the percentage of granulation tissue formed (65% vs 38%).

PriMatrix

PriMatrix is a xenogeneic acellular dermal matrix. In 2011, Karr published a retrospective comparison of PriMatrix and Apligraf in 28 venous stasis ulcers. (38) The first 14 venous stasis ulcers matching the inclusion and exclusion criteria for each graft were compared. Included were venous stasis ulcers of 4

weeks' duration, at least 1 sq cm and depth to subcutaneous tissue, healthy tissue at the ulcer, adequate arterial perfusion to heal, and able to tolerate compression therapy. The products were placed on the wound with clean technique, overlapping the edges of the wound, and secured with sutures or staples. The time to complete healing for PriMatrix was 32 days with 1.3 applications compared to 63 days with 1.7 applications for Apligraf. Although promising, additional study with a larger number of subjects is needed to evaluate the effect of PriMatrix treatment in comparison with the current standard of care.

Section Summary. Randomized controlled trials have demonstrated the efficacy of Apligraf and Oasis Wound Matrix over the standard of care. Use of these products may be considered medically necessary for lower extremity ulcers due to venous insufficiency. In a moderately large randomized controlled trial, Dermagraft was not shown to be more effective than controls in the primary or secondary end points for the entire population and was slightly more effective than controls (an 8%-15% increase in healing) only in subgroups of patients with ulcer duration of 12 months or less or size of 10 cm or less. Additional study with a larger number of subjects is needed to evaluate the effect of PriMatrix treatment in comparison with the current standard of care.

Dystrophic Epidermolysis Bullosa

Dermagraft had been FDA approved by a Humanitarian Device Exemption (HDE) for the treatment of dystrophic epidermolysis bullosa. The manufacturer has since withdrawn Dermagraft from HDE status.

OrCel is approved by an HDE for use in patients with dystrophic epidermolysis bullosa undergoing hand reconstruction surgery to close and heal wounds created by the surgery, including those at donor sites.

As this is a rare disorder, it is unlikely that there will be randomized controlled trials to evaluate whether OrCel improves health outcomes for this condition. Dermagraft is no longer considered medically necessary for this indication, due to the withdrawal of HDE status.

In 2003, Fivenson et al. reported the off-label use of Apligraf in 5 patients with recessive dystrophic epidermolysis bullosa who underwent syndactyly release. (44)

Dermagraft, OrCel, and Apligraf are all living cell therapies. Apligraf is a bilayered cell therapy composed of living human keratinocytes and fibroblasts, while OrCel is a bilayered cellular matrix made of bovine collagen in which human dermal cells (fibroblasts and keratinocytes) have been cultured. Dermagraft is composed of cryopreserved human-derived fibroblasts and collagen on a bioabsorbable mesh.

Ocular Burns

A 2012 Cochrane review evaluated the evidence on amniotic membrane transplantation (AMT) for acute ocular burns. (45) Included in the review was a single randomized controlled trial from India of 68 patients with acute ocular burns who were randomized to treatment with AMT and medical therapy or medical therapy alone. In the subset of 36 patients with moderate ocular burns who were treated within 7 days, 13/20 (65.0%) of control eyes and 14/16 (87.5%) of AMT-treated eyes had complete epithelialization by 21 days. There was a trend ($p=0.09$) toward a reduced risk ratio of failure of epithelialization in the treatment group. Mean LogMAR [logarithm of the minimum angle of resolution] final visual acuities were 0.06 in the treatment group and 0.38 in the control group. In the subset of patients with severe ocular burns treated within 7 days, 1/17 (5.9%) of AMT-treated eyes and 1/15 (6.7%) control eyes were epithelialized by day 21. Final visual acuity was 1.77 logMAR in the treated eyes and 1.64 in the control group (not significantly different). The risk of bias was considered to be high because of differences between the groups at baseline and because outcome assessors could not be masked to treatment. The review determined that conclusive evidence supporting the treatment of

acute ocular surface burns with AMT is lacking. It should also be noted that the amniotic membrane used in this study was fresh frozen and is not commercially available.

Non-Ocular Burns

Biomembrane

A small (n=46) quasi-randomized trial compared treatment with amniotic membrane (Biomembrane) versus polyurethane membrane (Tegaderm) for patients with second- or third-degree burns covering less than 50% total body surface area. (46) Treatment with amniotic membrane significantly reduced occurrence of infection (4.3%) compared with treatment with polyurethane (13.0%). Pain during dressing was reduced in the group treated with amniotic membrane (43.5% vs 60.9%), while the frequency of healing within the 11-20 day follow-up was greater (47.8% vs 39.1%). It was not reported if the evaluators in this quasirandomized study were blinded to treatment condition. In addition, this study did not have a control group treated with medical therapy alone.

Epistel

Epistel is FDA-approved under an HDE for the treatment of deep dermal or full-thickness burns comprising a total body surface area of greater than or equal to 30%. It is unlikely that there will be randomized controlled trials (RCTs) to evaluate whether Epistel® will improve health outcomes for this condition. One case series described the treatment of 30 severely burned patients with Epistel®. (47) The cultured epithelial autografts were applied to a mean 37% of total body surface area. Epistel® achieved permanent coverage of a mean 26% of total body surface area, an area greater than that covered by conventional autografts (a mean 25%). Survival was 90% in these severely burned patients.

EpiFix

Although several small trials from the Middle East and Asia have evaluated locally harvested and processed amniotic membrane, no randomized controlled trials were identified with the commercially available EpiFix amniotic membrane.

Integra Dermal Regeneration Template

A 2013 study compared Integra versus split-thickness skin graft or viscose cellulose sponge (Cellonex), using 3 test sites of 10 cm by 5 cm on each of 10 burn patients. (48) The surrounding burn area was covered with meshed autograft. Biopsies were taken from each site on days 3, 7, 14, and 21, and at 3 months and 12 months. The tissue samples were stained and examined for markers of inflammation and proliferation. The Vancouver Scar Scale (VSS) was used for scar assessment. At 12-month follow-up, the 3 methods resulted in similar clinical appearance, along with similar histologic and immunohistochemic findings.

Branski et al. reported a randomized trial of Integra compared with a standard autograft-allograft technique in 20 children with an average burn size of 73% total body surface area (71% full-thickness burns) in 2007. (49) Once vascularized (about 14-21 days), the Silastic epidermis was stripped and replaced with thin (0.05-0.13 mm) epidermal autograft. There were no significant differences between the Integra group and controls in burn size (70% vs 74% total body surface area), mortality (40% vs 30%), and length of stay (41 vs 39 days – all respectively). Long-term follow-up revealed a significant increase in bone mineral content and density (24 months) and improved scarring in terms of height, thickness, vascularity, and pigmentation (12 months and 18-24 months) in the Integra group. No differences were observed between the groups in the time to first reconstructive procedure, cumulative reconstructive procedures required during 2 years, and the cumulative operating room time required for these procedures. The authors concluded that Integra can be used for immediate wound coverage in children with severe burns without the associated risks of cadaver skin.

In 2003, Heimback and colleagues reported a multicenter (13 U.S. burn care facilities) postapproval study involving 222 burn injury patients (36.5% total body surface area, range 1%-95%) who were treated with Integra® Dermal Regeneration Template. (50) Within 2 to 3 weeks, the dermal layer regenerated, and a thin epidermal autograft was placed. The incidence of infection was 16.3%. Mean

take rate (absence of graft failure) of Integra was 76.2%; the median take rate was 98%. The mean take rate of epidermal autograft placed over Integra was 87.7%; the median take rate was 95%.

OrCel

There is limited evidence to support the efficacy of OrCel compared to the standard of care for the treatment of split-thickness donor sites. Still et al. examined the safety and efficacy of bilayered OrCel to facilitate wound closure of split-thickness donor sites in 82 severely burned patients. (51) Each patient had 2 designated donor sites that were randomized to receive a single treatment of either OrCel or the standard dressing (Biobrane-L). The healing time for OrCel sites was significantly shorter than for sites treated with a standard dressing, enabling earlier recropping. OrCel sites also exhibited a non-significant trend for reduced scarring. Additional studies are needed to evaluate the effect of this product on health outcomes.

TransCyte

In 2001, Lukish et al. compared 20 consecutive cases of pediatric burns greater than 7% total body surface area that underwent wound closure with TransCyte with the previous 20 consecutive burn cases greater than 7% total body surface area that received standard therapy. (52) Standard therapy consisted of application of antimicrobial ointments and hydrodebridement. Only one child in the TransCyte group required autografting (5%), compared with 7 children in the standard therapy group (35%). Children treated with TransCyte had a statistically significant decreased length of stay compared with those receiving standard therapy, 5.9 days versus 13.8 days, respectively.

Amani et al. compared results from 110 consecutive patients with deep partial-thickness burns who were treated with Transcyte with data from the American Burn Association Patient Registry. (53) Significant differences were found in patients who were treated with dermabrasion and Transcyte compared to the population in the Registry. Patients with 0%-19.9% total body surface area burn treated with dermabrasion and Transcyte had length of stay of 6.1 days versus 9.0 days ($p < 0.001$). Those with 20%-39.9% total body surface area burn had length of stay of 17.5 days versus 25.5 days. Patients who had 40%-59.9% total body surface area burn had length of stay of 31 versus 44.6 days. The authors found this new method of managing patients with partial-thickness burns to be more efficacious and to significantly reduce length of stay compared to traditional management.

Traumatic Wounds

Use of Integra Dermal Regeneration Template has been reported in small case series (<20 patients) for the treatment of severe wounds with exposed bone, joint and/or tendon. (54-56) No controlled trials were identified.

Other

In addition to indications reviewed above, off-label uses of bio-engineered skin substitutes have included surgical wounds, pressure ulcers, split-thickness skin donor sites, inflammatory ulcers such as pyoderma gangrenosum and vasculitis, scleroderma digital ulcers, postkeloid removal wounds, genetic conditions, and variety of other conditions. (57) In addition, products that have been FDA approved/cleared for one indication (e.g., lower extremity ulcers) have been used off-label in place of other FDA approved/cleared products (e.g., for burns). (58) No controlled trials were identified for these indications. Therefore, they are considered investigational.

Clinical Input Obtained Through Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests for input on use of AlloDerm in breast reconstruction surgery, input was received from one physician specialty society (2 physicians) and one academic medical center while this policy was under review in 2008. All reviewers indicated that this procedure should be available for use during breast reconstruction surgery.

2011

In response to requests, input was received from 3 physician specialty societies and 2 academic medical centers while this policy was under review in 2011. A majority of reviewers supported the indications and products as described in this policy. Clinical input was requested regarding the use of an interpositional spacer after parotidectomy. Support for this indication was mixed. Some reviewers suggested use of other products and/or additional indications; however, the input on these products/indications was not uniform. The reviewers provided references for the additional indications; these were subsequently reviewed.

2014

In response to requests, input was received from 3 physician specialty societies and 4 academic medical centers while this policy was under review in 2014. In addition to questions on medical necessity for different indications, input was specifically requested on the equivalency of products within the different categories (e.g., acellular dermal matrix, living cell therapy, xenogenic collagen scaffold, and amniotic membrane). Five reviewers addressed the use of acellular dermal matrix products for breast reconstruction, and most considered the various acellular dermal matrix products (AlloDerm, AlloMax, DermaMatrix, FlexHD, and GraftJacket) to have similar outcomes when used for breast reconstructive surgery, although differences in firmness and stretch of the products were noted. Six reviewers addressed questions on bio-engineered skin and soft tissue substitutes for diabetic and venous lower extremity ulcers. Responses were mixed, although a majority of reviewers considered living cell therapies to be equivalent for these indications. A majority of reviewers did not consider xenogenic acellular dermal matrix products (e.g., PriMatrix) or amniotic membrane (e.g., EpiFix) to be medically necessary for any indication.

Summary

Bio-engineered skin and soft tissue substitutes are being evaluated for a variety of conditions. Overall, the number of bio-engineered skin and soft-tissue substitutes is large, but the evidence is limited for any specific product. Relatively few products have been compared with the standard of care, and then only for some indications. A few comparative trials have been identified for use in lower extremity ulcers (diabetic or venous) and for treatment of burns. In these trials, there is a roughly 15% to 20% increase in the rate of healing. Several other products/indications are supported by either clinical input or by an FDA humanitarian device exemption (HDE).

Breast Reconstruction

Given the extensive data from controlled cohorts and case series, as well as the clinical input obtained about the usefulness of this procedure in providing inferolateral support for breast reconstruction, use of allogeneic acellular dermal matrix products (i.e., AlloDerm, AlloMax, DermaMatrix, FlexHD, GraftJacket) may be considered medically necessary in breast reconstruction when there is insufficient tissue expander or implant coverage by the pectoralis major muscle and additional coverage is required; when there is viable but compromised or thin postmastectomy skin flaps that are at risk of dehiscence or necrosis, or when the inframammary fold and lateral mammary folds have been undermined during mastectomy and re-establishment of these landmarks is needed.

Interpositional Graft after Parotidectomy

Two lower quality controlled trials were identified that demonstrated a reduction in the incidence of Frey syndrome with use of an interpositional acellular dermal matrix graft. Neither study described the method of group assignment or blinding of patients and assessors. In addition, clinical input regarding the use of an interpositional spacer after parotidectomy was not uniform. Therefore, bio-engineered skin and soft tissue substitutes are considered investigational to fill in contour defects and prevent Frey syndrome after parotidectomy.

Tendon Repair

One small randomized controlled trial was identified that found improved outcomes with GraftJacket acellular human dermal matrix for rotator cuff repair. Although these results are promising, additional study with a larger number of subjects is needed. Therefore, this use is considered investigational.

Fistula Repair

One randomized controlled trial was identified that used an acellular dermal matrix product that has not been cleared for marketing in the U.S. Therefore, the use of this product for fistula repair is considered investigational.

Surgical Repair of Hernias

The limited evidence available does not support the efficacy of any tissue-engineered skin substitute for surgical repair of hernias. Therefore, this use is considered investigational.

Oral Surgery

Use of acellular human dermal matrix (AlloDerm) has been reported for root coverage therapy and oral cavity reconstruction following surgical removal of tumors. Although AlloDerm may possibly result in less scar contracture, results to date have not shown an improvement over the standard of care. Therefore, this use is considered investigational.

Laryngoplasty

The effect of micronized AlloDerm (Cymetra) in laryngoplasty has been reported in case series. Longer-term controlled study in a larger number of patients is needed to determine the durability of this procedure and to evaluate the safety of repeat injections.

Tympanoplasty

AlloDerm has been compared with native tissue grafts in a non-randomized controlled study. There was no significant difference in the success rate of the graft (88% for AlloDerm, 89% for fascia grafts, 96.7% for cartilage plus fascia), and there was no significant difference in hearing between the groups at follow-up. Longer-term controlled study in a larger number of patients is needed to determine the durability of this procedure.

Diabetic Lower Extremity Ulcers

Randomized controlled trials have demonstrated the efficacy of Apligraf and Dermagraft over the standard of care. Use of these products may be considered medically necessary for the treatment of diabetic lower extremity ulcers. Additional study with a larger number of subjects is needed to evaluate the effect of PriMatrix treatment in comparison with the current standard of care.

Lower Extremity Ulcers Due to Venous Insufficiency

Randomized controlled trials have demonstrated the efficacy of Apligraf and Oasis Wound Matrix over the standard of care. Use of these products may be considered medically necessary for lower extremity ulcers due to venous insufficiency. In a large randomized controlled trial, Dermagraft was not shown to be more effective than controls in the primary or secondary end points for the entire population, and was slightly more effective than controls (an 8%-15% increase in healing) only in subgroups of patients with ulcer duration of 12 months or less or size of 10 cm or less. Additional study with a larger number of subjects is needed to evaluate the effect of PriMatrix treatment in comparison with the current standard of care.

Dystrophic Epidermolysis Bullosa

OrCel has received approval via a Humanitarian Device Exemption (HDE). As this is a rare disorder and it is unlikely that there will be randomized controlled trials, OrCell is considered medically necessary for this indication.

Ocular Burns

Evidence is insufficient to evaluate the efficacy of human amniotic membrane for ocular burns. This is considered investigational.

Non-Ocular Burns

Epicel is FDA-approved under an HDE for the treatment of deep dermal or full-thickness burns comprising a total body surface area of greater than or equal to 30%. This treatment may be considered medically necessary according to the HDE indications.

Comparative studies have demonstrated improved outcomes for Integra Dermal Regeneration Template and Transcyte for the treatment of burns; therefore, these are considered medically necessary.

Traumatic Wounds

Use of Integra Dermal Regeneration Template has been reported in small case series (<20 patients) for the treatment of severe wounds with exposed bone, joint, and/or tendon. Controlled trials are needed to evaluate this product/indication.

All other uses of the bio-engineered skin and soft-tissue substitutes are considered investigational.

Practice Guidelines and Position Statements

Review of the literature for 2013 guidelines from the American Society of Plastic Surgeons (ASPS) found that evidence suggests that the use of acellular dermal matrix, although increasingly common in postmastectomy expander/implant breast reconstruction, can result in increased risk of complications in the presence of certain risk factors. (59) The ASPS notes that cellular dermal matrix is currently used to increase soft tissue coverage, support the implant pocket, improve contour and reduce pain with expansion. However, evidence to support these improved surgical outcomes are limited. Some evidence suggests that use of acellular dermal matrix is associated with increased postoperative complications, specifically related to infection and seroma. Overall, the ASPS found that evidence on acellular dermal matrix products in postmastectomy expander/implant breast reconstruction is varied and conflicting, and gave a Grade C recommendation based on level III evidence that surgeons should evaluate each clinical case individually and objectively determine the use of acellular dermal matrix.

In 2006, the ASPS endorsed guidelines from the Wound Healing Society on the treatment of arterial insufficiency ulcers. (60) The guidelines state that extracellular matrix replacement therapy appears to be promising for mixed ulcers and may have a role as an adjuvant agent in arterial ulcers, but further study is required. (Level IIIC) "Despite the existence of animal studies, case series, and a small number of random control trials to support biomaterial use for pressure ulcers, diabetic ulcers, and venous ulcers; there are no studies specifically on arterial ulcers. Therefore, studies in arterial ulcers must be conducted before the recommendation can be made."

The ASPS endorsed guidelines from the Wound Healing Society on the treatment of venous ulcers in 2006. (61) The guidelines state that various skin substitutes or biologically active dressings are emerging that provide temporary wound closure and serve as a source of stimuli (e.g., growth factors) for healing of venous ulcers. Guideline #7b.1 states that there is evidence that a bilayered artificial skin (biologically active dressing), used in conjunction with compression bandaging, increases the chance of healing a venous ulcer compared with compression and a simple dressing (Level I).

The ASPS also endorsed guidelines from the Wound Healing Society on the treatment of diabetic ulcers in 2006. (62) The guidelines state that healthy living skin cells assist in healing diabetic foot ulcers by releasing therapeutic amounts of growth factors, cytokines, and other proteins that stimulate the wound bed. Guideline #7.2.2 states that living skin equivalents may be of benefit in healing diabetic foot ulcers. (Level I)

The 2007 guidelines from the ASPS on chronic wounds of the lower extremity state that maintaining a moist environment, while simultaneously removing soluble factors detrimental to wound healing might logically provide optimal conditions for wound healing. (63) Classic dressings include gauze, foam, hydrocolloid, and hydrogels. Fluid-handling mechanisms include absorption, gelling, retention and vapor transmission. Bioactive dressings include topical antimicrobials, bioengineered composite skin equivalent, bilaminar dermal regeneration template, and recombinant human growth factor.

The 2011 guidance from the United Kingdom's National Institute for Health and Clinical Excellence recommends not to use dermal or skin substitutes for the inpatient management of diabetic foot problems, unless part of a clinical trial. (64)

The 2006 clinical consensus statement [previously called clinical practice guideline] on diabetic foot disorders from the American College of Foot and Ankle Surgeons (ACFAS) state that bioengineered tissues have been shown to significantly increase complete wound closure in venous and diabetic foot ulcers. (65) Tissue-engineered skin substitutes can function both as biologic dressings and as delivery systems for growth factors and extracellular matrix components through the activity of live human fibroblasts contained in their dermal elements. Currently, two bio-engineered tissues have been approved to treat diabetic foot ulcers in the U.S.: Apligraf™ (Organogenesis Inc., Canton, MA), and Dermagraft™ (Smith & Nephew, Inc., London, UK); both have demonstrated efficacy in randomized, controlled trials. Apligraf™ has been shown to significantly reduce the time to complete wound closure in venous and diabetic ulcers. Regenerative tissue matrix (GraftJacket™, Wright, Arlington, TN) is a new therapy used in diabetic foot ulcers, although it had not undergone any randomized clinical trials at the time of this guideline. This allograft skin is minimally processed to remove epidermal and dermal cells while preserving the bioactive components and structure of dermis. This results in a framework that supports cellular repopulation and vascularization. Oasis™, composed of structural cellular components and growth factors utilized to promote natural tissue remodeling, recently completed a randomized trial that showed non-inferiority to becaplermin gel in the healing of diabetic foot ulcers. Integra™ dermal regeneration template, a collagen-chondroitin sponge overlaid with silicone originally developed for burns, has been shown to be ideally suited to chronic and pathologic wounds.

The 2012 guidelines from the Infectious Diseases Society of America (IDSA) state that for selected diabetic foot wounds that are slow to heal, clinicians might consider using bioengineered skin equivalents (weak recommendation, moderate evidence) growth factors (weak, moderate), granulocyte colony-stimulating factors (weak, moderate), hyperbaric oxygen therapy (strong, moderate), or negative pressure wound therapy (weak, low). (66) It is emphasized that none of these measures have been shown to improve resolution of infection and that they are expensive, not universally available, may require consultation with experts, and reports supporting their utility are mostly flawed.

A 2012 Technology Assessment from the Agency for Healthcare Research and Quality (AHRQ) does not make a formal recommendation for bioengineered skin and soft tissue substitutes. (1) The Assessment notes that autologous tissue grafting is an invasive and painful procedure and often the extent of damaged skin is too large to be covered by autologous tissue graft alone. A variety of skin substitutes and alternatives are designed to replace the damaged epithelial and dermal layers of skin, and many of the conditions and biological factors needed in the healing process may be provided by the substitute skin products.

Medicare National Coverage

Centers for Medicare and Medicaid Services (CMS) has issued the following national coverage determination: Porcine (pig) skin dressings are covered, if reasonable and necessary for the individual patient as an occlusive dressing for burns, donor sites of a homograft, and decubiti and other ulcers. (67)

Beginning in 2014, CMS will not distinguish between different skin substitutes and will classify them as either high cost or low cost. (68) CMS will package skin substitutes of the same class into the associated surgical procedures for hospital outpatient departments and ambulatory surgical centers. A

separate payment might be made if the item is furnished on a different date of service as the primary service.

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Billing Coding/Physician Documentation Information

Note: CPT 15777 would be correct coding when used for Frey's syndrome and in reconstruction post neoplasm removal (other than skin cancers).

- 15271** Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
- 15272** Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
- 15273** Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
- 15274** Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
- 15275** Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
- 15276** Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
- 15277** Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
- 15278** Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal

to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)

- 15777** Implantation of biologic implant (eg, acellular dermal matrix) for soft tissue reinforcement (eg, breast, trunk) (List separately in addition to code for primary procedure)
- C9354** Acellular pericardial tissue matrix of nonhuman origin (Veritas), per sq cm
- C9358** Dermal substitute, native, nondenatured collagen, fetal bovine origin (SurgiMend Collagen Matrix), per 0.5 sq cm
- C9360** Dermal substitute, native, nondenatured collagen, neonatal bovine origin (SurgiMend Collagen Matrix), per 0.5 sq cm
- C9363** Skin substitute (Integra Meshed Bilayer Wound Matrix), per square cm
- C9364** Porcine implant, Permacol, per sq cm
- Q3028** Injection, interferon beta-1a, 1 mcg for subcutaneous use
- Q4100** Skin substitute, not otherwise specified
- Q4101** Apligraf®, per sq cm
- Q4102** Oasis wound matrix, per sq cm
- Q4103** Oasis burn matrix, per sq cm
- Q4104** Integra bilayer matrix wound dressing (BMWD), per sq cm
- Q4105** Integra dermal regeneration template (DRT), per sq cm
- Q4106** Dermagraft®, per sq cm
- Q4107** GRAFTJACKET, per sq cm
- Q4108** Integra matrix, per sq cm
- Q4110** PriMatrix, per sq cm
- Q4111** GammaGraft, per sq cm
- Q4112** Cymetra, injectable, 1 cc
- Q4113** GraftJacket® xpress, injectable, 1cc
- Q4114** Integra flowable wound matrix, injectable, 1 cc
- Q4115** AlloSkin, per square centimeter
- Q4116** AlloDerm®, per square centimeter
- Q4117** Hyalomatrix, per square centimeter
- Q4118** Matristem micromatrix, 1 mg
- Q4119** Matristem wound matrix, per square centimeter
- Q4120** Matristem burn matrix, per square centimeter
- Q4121** Theraskin, per square centimeter
- Q4122** DermACELL, per sq cm
- Q4123** AlloSkin RT, per sq cm
- Q4124** OASIS ultra tri-layer wound matrix, per sq cm
- Q4125** Arthroflex, per sq cm
- Q4126** MemoDerm, per sq cm
- Q4127** Talymed, per sq cm
- Q4128** FlexHD or AllopatchHD, per sq cm
- Q4129** FlexHD or AllopatchHD, per sq cm
- Q4130** Strattice TM, per sq cm
- Q4131** EpiFix, per sq cm
- Q4132** Grafix core, per sq cm
- Q4133** Grafix prime, per sq cm
- Q4134** hMatrix, per sq cm
- Q4135** Mediskin, per sq cm
- Q4136** E-Z Derm, per sq cm
- Q4137** Amnioexcel or biodexcel, per sq cm
- Q4138** Biodfence dryflex, per sq cm
- Q4139** Amniomatrix or biodmatrix, injectable, 1 cc
- Q4140** Biodfence, per sq cm
- Q4141** Alloskin AC, per sq cm
- Q4142** XCM biologic tissue matrix, per sq cm

- Q4143** Repriza, per sq cm
- Q4145** Epifix, injectable, 1 mg
- Q4146** Tensix, per sq cm
- Q4147** Architect extracellular matrix, per sq cm
- Q4148** Neox 1k, per sq cm
- Q4149** Excellagen, 0.1 cc

Effective January 1, 2012 CPT codes 15170, 15171, 15175, 15176, 15300, 15301, 15320, 15321, 15330, 15331, 15335, 15336, 15340, 15341, 15360, 15361, 15365, 15366, 15400, 15401, 15420, 15421, 15430 and 15431 were deleted and replaced with CPT codes 15271-15278.

Additional Policy Key Words

N/A

Policy Implementation/Update Information

- 6/1/08 New policy; considered investigational.
 - 1/8/09 Interim update. Policy statement revised to indicate procedure may be considered medically necessary with criteria. Coding updated. The change is effective 1/8/2009.
 - 8/1/09 Coding update only.
 - 1/1/10 No policy statement changes.
 - 1/1/11 No policy statement changes. Coding updated.
 - 8/11/11 Policy updated and scope expanded to include indications previously addressed in policy 7.01.510 Skin Substitutes for Wound Healing; policy statements added for other indications; title changed to "Tissue-Engineered Skin Substitutes."
 - 1/1/12 Coding updated.
 - 3/1/12 Title changed to "Bio-Engineered Skin and Soft Tissue Substitutes". MatrixDerm® and StrataGraft added to list of investigational skin substitutes. Added use of AlloDerm® graft as an implant for reconstruction following removal of a malignant neoplasm is considered medically necessary
 - 9/1/12 No policy statement changes.
 - 3/1/13 Policy statement revised on Dermagraft. No longer considered medically necessary for dystrophic epidermolysis bullosa due to withdrawal of HDE [humanitarian device exemption] status. Other policy statements unchanged.
 - 3/1/14 First policy statement expanded to include other acellular dermal matrix products. Updated investigational list. HCPCS codes updated.
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