Bio-Engineered Skin and Soft Tissue Substitutes

Policy Number: MM.06.018
Original Effective Date: 06/01/2012
Line(s) of Business: HMO; PPO; QUEST Integration
Current Effective Date: 06/01/2015
Section: Surgery
Place(s) of Service: Outpatient/Office

I. Description

Summary

Bio-engineered skin and soft tissue substitutes may be derived from human tissue (autologous or allogeneic), nonhuman 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.

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

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 (ADM) products (ie, 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 ADM 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 not covered to fill in contour defects and prevent Frey syndrome after parotidectomy.

Fistula Repair

One RCT was identified that used an ADM product that has not been cleared for marketing in the United States. Therefore, the use of this product for fistula repair is not covered.

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 not covered.

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-RCT. 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

RCTs have demonstrated the efficacy of Apligraf and Dermagraft over the standard of care, and of EpiFix in comparison with Apligraf. 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

RCTs 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 RCT, 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 an HDE. As this is a rare disorder and it is unlikely that there will be RCTs, OrCel is considered medically necessary for this indication.

This policy does not address products used in the treatment of burns, tendon/ligament repair or products supplied in an inpatient setting.
II. Criteria/Guidelines

A. Allogeneic acellular dermal matrix products (i.e., AlloDerm, DermaMatrix, FlexHD, Graftjacket, AlloMax, or Strattice) are covered (subject to Limitations and Administrative Guidelines) in breast reconstructive surgery when:

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

B. Apligraf, Dermagraft, or Epifix is covered (subject to Limitations and Administrative Guidelines) for the treatment of chronic, non-infected, full-thickness diabetic lower extremity ulcers when all of the following criteria are met:

1. The ulcers have not adequately responded after six weeks of standard wound therapy*.
2. The patient is on a comprehensive diabetic management program
3. Compression bandages and/or graduated compression garments have been consistently applied; and
4. Leg elevation and exercise have been encouraged.

C. Apligraf, Epifix, or Oasis Wound Matrix is covered (subject to Limitations and Administrative Guidelines) for the treatment of chronic, non-infected, partial or full-thickness lower extremity skin ulcers due to venous insufficiency when all of the following criteria are met:

1. The ulcers have not adequately responded after six weeks of standard wound therapy*.
2. Compression bandages and/or graduated compression garments have been consistently applied; and
3. Leg elevation and exercise have been encouraged.

D. OrCel is covered (subject to Limitations and Administrative Guidelines) for the treatment of dystrophic epidermolysis bullosa.

* Standard wound therapy includes:
- Evaluation of wound with documentation of measurements (length, width and depth) at baseline and at least weekly by a licensed medical professional
- Application of moist topical dressings
- Debridement of necrotic tissue, if present
- Treatment of infection, if present
- Evaluation and provision of adequate nutrition
- Management of diabetes mellitus, if applicable
- Evaluation and management of peripheral artery disease, if applicable

III. Limitations

A. Bio-engineered skin and soft tissue substitutes have not been shown to improve health outcomes for all other conditions not listed under Criteria/Guidelines.
B. The following bio-engineered skin and soft tissue substitutes have not been shown to improve health outcomes, this includes, but is not limited to:

<table>
<thead>
<tr>
<th>Affinity 1</th>
<th>Allopatch HD</th>
<th>Alloskin AC</th>
<th>Allowrap DS or Dry</th>
</tr>
</thead>
<tbody>
<tr>
<td>AmnioBand, Guardian</td>
<td>Amnioexcel or Biodexel</td>
<td>Amniomatrix or Biodmatrix</td>
<td>Architect extracellular matrix</td>
</tr>
<tr>
<td>Arthroflex</td>
<td>Biodexel Dryflex</td>
<td>Biovance 1</td>
<td>Cymetra</td>
</tr>
<tr>
<td>Dermapure</td>
<td>Dermavest</td>
<td>E-Z Derm</td>
<td>Excellagen</td>
</tr>
<tr>
<td>Gammagraft</td>
<td>Grafix prime</td>
<td>Hyalomatrix</td>
<td>hMatrix</td>
</tr>
<tr>
<td>MariGen</td>
<td>MatriStem</td>
<td>Mediskin</td>
<td>Memoderm</td>
</tr>
<tr>
<td></td>
<td>Micromatrix and Wound Matrix</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neox</td>
<td>NeoX Flo or ClarixFlo</td>
<td>Nushield</td>
<td>Primatrix</td>
</tr>
<tr>
<td>Repriza</td>
<td>Revitalon</td>
<td>SurgiMend</td>
<td>Talymed</td>
</tr>
<tr>
<td>Tensix</td>
<td>Theraskin</td>
<td>TissuMend</td>
<td>Unite Biomatrix</td>
</tr>
<tr>
<td>XCM Biologic Tissue Matrix</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### IV. Administrative Guidelines

A. Precertification is required for the application of Apligraf, Dermagraft, OrCel, Epifix and Oasis. Complete HMSA’s Precertification request and mail or fax the form as indicated. Include the following information:

1. Clinical notes documenting patient’s compliance with a diabetic management program.
2. The exact location of the ulcer and initial ulcer size.
3. Duration and description of the standard treatments that were tried and failed.
4. Documentation of the presence of dystrophic epidermolysis bullosa if this is the indication.

B. Precertification is not required for acellular dermal matrixes or Strattice when used in breast reconstruction surgery. HMSA reserves the right to perform retrospective reviews using the above criteria to validate if services rendered met payment determination criteria.

C. Applicable HCPCS codes:

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q4101</td>
<td>Apligraf, per sq. cm.</td>
</tr>
<tr>
<td>Q4102</td>
<td>Oasis wound matrix, per sq. cm.</td>
</tr>
<tr>
<td>Q4106</td>
<td>Dermagraft, per sq. cm.</td>
</tr>
<tr>
<td>Q4107</td>
<td>Graftjacket, per sq. cm.</td>
</tr>
<tr>
<td>Q4116</td>
<td>AlloDerm</td>
</tr>
</tbody>
</table>
Bio-Engineered Skin and Soft Tissue Substitutes

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q4110</td>
<td>PriMatrix, per sq. cm.</td>
</tr>
<tr>
<td>Q4111</td>
<td>GammaGraft, per sq. cm.</td>
</tr>
<tr>
<td>Q4112</td>
<td>Cymetra, injectable</td>
</tr>
<tr>
<td>Q4113</td>
<td>Graftjacket Express, injectable, 1cc</td>
</tr>
<tr>
<td>Q4117</td>
<td>Hyalomatrix, per sq. cm.</td>
</tr>
<tr>
<td>Q4118</td>
<td>Matristem micromatrix, per sq.cm.</td>
</tr>
<tr>
<td>Q4119</td>
<td>Matristem wound matrix, per sq.cm.</td>
</tr>
<tr>
<td>Q4121</td>
<td>Theraskin, per sq.cm.</td>
</tr>
<tr>
<td>Q4123</td>
<td>Alloskin RT, per sq. cm.</td>
</tr>
<tr>
<td>Q4125</td>
<td>Arthroflex, per sq. cm.</td>
</tr>
<tr>
<td>Q4126</td>
<td>Memoderm, per sq. cm.</td>
</tr>
<tr>
<td>Q4127</td>
<td>Talymed, per sq. cm.</td>
</tr>
<tr>
<td>Q4129</td>
<td>Unite Biomatrix, per sq. cm.</td>
</tr>
<tr>
<td>Q4128</td>
<td>Allopatch HD per sq. cm.</td>
</tr>
<tr>
<td>Q4132</td>
<td>Grafix core, per sq. cm.</td>
</tr>
<tr>
<td>Q4133</td>
<td>Grafix prime, per sq.cm.</td>
</tr>
<tr>
<td>Q4134</td>
<td>hMatrix, per sq. cm.</td>
</tr>
<tr>
<td>Q4135</td>
<td>Mediskin, per sq. cm.</td>
</tr>
<tr>
<td>Q4136</td>
<td>EZ-derm, per sq. cm.</td>
</tr>
<tr>
<td>Q4137</td>
<td>Amnioexcel or Biodexcel, per sq. cm</td>
</tr>
<tr>
<td>Q4138</td>
<td>Biodfence Dryflex, per sq. cm</td>
</tr>
<tr>
<td>Q4139</td>
<td>AmnioMatrix or Biodmatrix, injectable, 1 cc</td>
</tr>
<tr>
<td>Q4140</td>
<td>Biodfence, per sq. cm</td>
</tr>
<tr>
<td>Q4141</td>
<td>Alloskin AC, per sq. cm</td>
</tr>
<tr>
<td>Q4142</td>
<td>XCM biologic tissue matrix, per sq. cm</td>
</tr>
<tr>
<td>Q4143</td>
<td>Repriza, per sq. cm</td>
</tr>
<tr>
<td>Q4147</td>
<td>Architect extracellular matrix, per sq. cm</td>
</tr>
<tr>
<td>Q4148</td>
<td>Neox 1k, per sq. cm</td>
</tr>
<tr>
<td>Q4149</td>
<td>Excellagen, 0.1 cc</td>
</tr>
<tr>
<td>Q4150</td>
<td>Allowrap DS or Dry 1 per sq. cm</td>
</tr>
<tr>
<td>Q4151</td>
<td>Amnioband, Guardian 1 per sq. cm</td>
</tr>
</tbody>
</table>
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. The various acellular dermal matrix (ADM) products can differ in a number of ways, including as species source (human, bovine, porcine), tissue source (e.g., dermis, pericardium, intestinal mucosa), additives (e.g., antibiotics or surfactants), hydration (wet or freeze dried) and required preparation (multiple rinses, rehydration).

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. 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. American Association of Tissue Banks (AATB) compliant tissue banks and Federal 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 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 is an acellular non-cross-linked human dermis allograft.
- DermaCell is an allogeneic ADM processed with proprietary technologies MATRACELL and PRESERVON.
- DermaMatrix is a freeze dried acellular dermal matrix (allograft) derived from donated human skin tissue. DermaMatrix Acellular Dermis is processed by the Musculoskeletal Transplant Foundation (MTF).
- DermaPure is a single layer decellularized human dermal allograft for the treatment of acute and chronic wounds.
- FlexHD is an acellular hydrated dermis derived from donated human allograft skin. The Musculoskeletal Transplant Foundation acquires and processes the tissue.
- Graftjacket Regenerative Tissue Matrix is an acellular regenerative tissue matrix that has been processed from screened donated human skin supplied from U.S. tissue banks. The allograft is processed minimally to remove the epidermal and dermal cells while preserving dermal structure.

PriMatrix 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 wound.

SurgiMend PRS is a xenogeneic ADM processed from fetal bovine dermis. This product is currently undergoing an FDA-regulated investigational device exemption (IDE) trial for breast reconstruction.
Amniotic Membrane

Amniotic membrane 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 FDA classifies it as banked human tissue and therefore, it does not require FDA approval. EpiFix and Amniofix are commercially available sources of dehydrated human amniotic membranes. EpiFix is provided in sheets and Amniofix is an injectable form of micronized amniotic membrane. Other amniotic membrane products are Affinity, Allowrap, AmnioBand, GUARDIAN, AmnioGraft, Biodefense, BioDDryFlex, Biovance, Dermavest, Neox Flo, Clarix Flo, Neox 1000, NuShield and Revitalon.

Collagen Scaffold

OASIS Wound Matrix 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 is a bilayered living cell therapy composed of an epidermal layer of living human keratinocytes and a dermal layer of living human fibroblasts. 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 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.

Theraskin is a cryopreserved human skin allograft composed of living fibroblasts and keratinocytes and an extracellular matrix in epidermal and dermal layers. Theraskin is derived from human skin allograft in compliance with the American Association of Tissue Banks (AATB) and U.S. Food and Drug Administration’s (FDA) guidelines. It is considered minimally processed human cell, tissue, and cellular- and tissue-based product (HCT/P) by the FDA.

OrCel is an absorbable allogeneic bilayered cellular matrix, made of bovine collagen, in which human dermal cells have been cultured. It was approved by the FDA pre-market approval 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 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.
VI. Rationale:

**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% 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 to breast reconstruction using traditional musculofascial flaps. Another meta-analysis that compared 19 studies using acellular dermal matrix (n=2,037) 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. 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. 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. 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, 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. 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. AlloDerm has been reported in nipple reconstructive surgery in a case series on 30 nipple reconstructive procedures performed at one institution. Use of AlloDerm has also been reported in a small series (n=3) to correct breast implant-related problems (malposition, symmastia, and rippling).

Other: Liu et al. reported postoperative complications in breast reconstruction with (n=266) or without (n=204) AlloDerm in 2011. 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.

Bindingnavele et al. reviewed charts of 41 patients (65 breasts) who had staged breast reconstruction with acellular cadaveric dermis to report postoperative complication rates. 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.

Strattice

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, use of AlloDerm 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 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 reestablishment of these landmarks is needed. The expanding body of literature for Strattice as well as the wide acceptance of its use by the reconstructive surgery community make it a medically necessary alternative to Alloderm under similar circumstances.

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). 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, ADM 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). Total complication rates for the 2 products were similar (19.1% for AlloDerm, 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 ADM was not a risk factor for any complication.

Brooke et al conducted a retrospective review of complication rates when AllDerm (n=49), DermaMatrix (n=110), or FlexHD (n=62) was used for tissue expander breast reconstruction. 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 ADM (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 ADM products.

SurgiMend (Fetal Bovine ADM) Versus AlloDerm (Human ADM)

Butterfield reported a retrospective comparison of 281 patients who underwent breast reconstruction with SurgiMend (79.0%) or AlloDerm (21.0%). AlloDerm was used at the beginning of the study while SurgiMend was used predominantly in the latter period due to ease of use and lower cost; the 2 groups were comparable on patient demographics, risk factors, and concurrent therapy. The rate of seroma, the most prevalent complication, was significantly lower for SurgiMend (8.3%) compared to AlloDerm (15.7%, p=0.044), however the necrosis rate was higher for SurgiMend (11.1% vs 3.4%, p=0.027), due entirely to a higher minor necrosis rate for SurgiMend (8.8% vs 1.1%). There were no significant differences in complication rates for hematoma, infection, major skin necrosis, or breast implant removal. SurgiMend is currently being studied in a randomized clinical trial compared to AlloDerm (NCT01781299) and in a non-randomized comparative trial of breast reconstruction with and without the use of SurgiMend (NCT01959867).

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. 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. 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. 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.

**Surgical Repair of Hernias**

**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. The first 41 procedures were performed using Surgisis Gold 8-ply mesh formed from porcine small intestine sub-mucosa, 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 two 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. 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. 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.

Reconstructive Tissue Matrix

The PRISM Study Group reported a multicenter double-blinded, randomized trial of porcine acellular dermal matrix for parastomal reinforcement in patients undergoing surgery for permanent abdominal wall ostomies.27 Patients were randomly assigned to undergo standard stoma construction with no reinforcement (n=58) or stoma construction with Reconstructive Dermal Matrix as parastomal reinforcement (n=55). At 24 months of follow-up (n=75), the incidence of parastomal hernias was similar for the 2 groups (13.2% of controls and 12.2% of the study group).

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

Laryngoplasty

There are several reports with short-term follow-up of micronized AlloDerm (Cymetra) injection for laryngoplasty. In 2005, Millstein 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. 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. 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. The study involved 24 centers in the US, 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 five 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 median time to complete closure was 65 days for Graftskin, significantly lower than the 90 days observed in the control group (p=0.0026). The rate of adverse reactions was similar between the two 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 Apligraf (Graftskin), in conjunction with good local wound care, met the TEC criteria for the treatment of diabetic ulcers that fail to respond to conservative management.

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. The design and patient population of this study were similar to the 208-subject US 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 two 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 two 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 to 10 months in the U.S. study). Reported adverse events by 12 weeks were comparable across treatment groups in the two 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 US 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 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. 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.

**Dermagraf**

A pivotal multi-center FDA-regulated trial randomized 314 patients with chronic diabetic ulcers to Dermagraf or control. Over the course of the 12-week study patients received up to 8 applications of Dermagraf. 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 Dermagraf group was 91% compared to 78% for the control group. Ulcers treated with Dermagraf closed significantly faster than ulcers treated with conventional therapy. No serious adverse events were attributed to Dermagraf. Ulcer infections developed in 10.4% of the Dermagraf patients compared to 17.9% of the control patients. Together, there was a lower rate of infection, cellulitis, and osteomyelitis in the Dermagraf-treated group (19% vs. 32.5%).

**Theraskin versus Dermagraf**

Sanders et al reported a small (n=23) industry-funded randomized comparison of Theraskin (human skin allograft with living fibroblasts and keratinocytes) versus Dermagraf (human-derived fibroblasts cultured on mesh) for diabetic foot ulcers. Wound size at baseline ranged from 0.5 to 18.02 cm2; the average wound size was about 5 cm2 and was similar for the 2 groups (p=0.51). Grafts were applied according to manufacturer’s instructions over the first 12 weeks of the study until healing, with an average of 4.4 Theraskin grafts (every 2 weeks) compared with 8.9 Dermagraf applications (every week). At week 12, complete wound healing was observed in 63.6% of ulcers treated with Theraskin and 33.3% of ulcers treated with Dermagraf (p=0.0498). At 20 weeks, complete wound healing was observed in 90.9% of the Theraskin-treated ulcers compared with 66.67% of the Dermagraf group (p=0.428). Additional study in a larger number of subjects is needed.

**EpiFix Amniotic Membrane**

EpiFix is an amniotic membrane extracellular collagen allograft comprised of an epithelial layer and two fibrous connective tissue layers. Amniotic membrane is banked human tissue regulated by the AATB and FDA. Four growth factors are present in EpiFix including epidermal growth factor (EGF), transforming growth factor - β (TGF-β), fibroblast growth factor (FGF) and platelet derived growth factor A & B (PDGF A & B). It is proposed to promote cellular migration to enhance soft tissue repair in acute and chronic wounds free of necrotic tissue and infection; partial- and full-thickness
wounds; venous, diabetic, pressure, and chronic vascular ulcers. Epifix comes in a wide variety of sizes eliminating waste and reducing cost.

Clinical trials reported ninety percent of wounds treated exhibited 100% uptake of the amniotic membrane graft without rejection after 1 week. An average of 50 percent reduction of wound volume and size was proven by weekly measurements. Clinical pain, signs of infection, and drainage post application was noticeably less among amniotic membrane graft patients. Postoperative course and maintenance is simple and direct, which allowed for better compliance.

A single site industry sponsored prospective, randomized comparative parallel study of amniotic membrane vs. standard management in the treatment of diabetic ulcers was published by Zelen C. in 2012. It was terminated early due to dramatic and significant improved outcomes in the Epifix group. At 6 weeks the Epifix arm had a 92% wound healing rate compared to only 8% for the conventional treatment arm. Though the authors conclude that further expanded studies should be considered, they point out that the dramatic improvement in outcomes coupled with the cost effective characteristic of the product already make it a viable clinical option for diabetic ulcers.

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. 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. 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 non-healing 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) and 7.0 weeks for control (range 2 – 12). Kaplan-Meier survivorship analysis for time to complete healing at 12 weeks showed a significantly lower non-healing 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.

**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. This was an industry-sponsored randomized controlled multicenter trial conducted at 9 outpatient wound care clinics and involved 73 patients with at least 1 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 post-hoc 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 2014, Kavros et al reported a prospective multicenter study of PriMatrix (a xenograft fetal bovine dermal collagen matrix) for the treatment of chronic diabetic foot ulcers in 55 patients. The average duration of ulcers prior to treatment was 286 ±353 days and the average area was 4.34 cm². Of the 46 patients who completed the study, 76% healed by 12 weeks with an average of 2 applications of PriMatrix. For the intention-to-treat population, 64% of wounds healed by 12 weeks.

In 2011, Karr published a retrospective comparison of PriMatrix (a xenograft fetal bovine dermal collagen matrix) and Apligraf in 40 diabetic foot ulcers. 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**

Falanga and colleagues reported a multicenter randomized trial of Apligraf (human skin equivalent) in 1998. 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 endpoints 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 (>1000 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 were 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.

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 el 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). Prespecified 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

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. 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 two 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 two extracellular matrix-based products, Oasis and Hyaloskin (extracellular matrix with hyaluronic acid). A total of 54 patients with mixed arterial/venous leg ulcers were assigned to the two 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 if
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. 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**

In 2011, Karr published a retrospective comparison of PriMatrix and Apligraf in 28 venous stasis ulcers. 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 and EpiFix 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**

OrCel is approved by a 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 if OrCel improves health outcomes for this condition.

**2014 Input**

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
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). 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 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 acellular dermal matrixes or Strattice 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.

**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 no covered.

**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 not covered.

**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 or comparative trials have demonstrated the efficacy of Apligraf, Dermagraft and Epifix in comparison to Apligraf. 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 or comparative trials have demonstrated the efficacy of Apligraf, Epifix 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. 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, this product is considered medically necessary for this indication.

All other uses of the tissue-engineered skin substitutes do not meet payment determination criteria.

**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. 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 American Society of Plastic Surgeons (ASPS) endorsed guidelines from the Wound Healing Society on the treatment of arterial insufficiency ulcers. 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. 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. 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. 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.

The 2006 guidelines 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. 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 bioengineered tissues have been approved to treat diabetic foot ulcers in
the U.S. Apligraf and Dermagraft; 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) 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.

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.

Beginning in 2014, CMS will not distinguish between different skin substitutes and will classify them as either high cost or low cost. 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.

VII. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.
This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VIII. References


52. Shah, AP. EpiFix, Human Amniotic Membrane Allograft for Treatment in Diabetic Wound Care Management. Clinical Symposium on Advances in Skin & Wound Care, 2010.


